CSIRO

E-cigarettes, smoking and health

A Literature Review Update

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Important disclaimer

Foreword

This report was funded by the Australian Commonwealth Department of Industry, Innovation and Science. It was produced by a team led by the Commonwealth Scientific and Industrial Research Organisation (CSIRO), and included external scientist consultants.

The terms of reference for the task were specifically to:

- Review all available evidence applicable to the impacts of the use of e-cigarettes, personal vaporisers and nicotine on individual and population health. This is addressed in Part 1 of the report.

- Review all available evidence applicable to the use of e-cigarettes, personal vaporisers and nicotine on rates of smoking. This is addressed in Part 2 of the report.

- Assess the impacts on health of allowing the use of e-cigarettes and personal vaporisers in countries where they have been permitted. This is addressed in Part 3 of the report.

- Review the impact of e-cigarettes and personal vaporisers on individual health as an alternative to smoking. This is addressed in Part 4 of the report.

- Identify any potential for e-cigarettes to reduce rates of smoking in Australia. This is addressed in Part 5 of the report.

- Compare rates of tobacco smoking in countries where e-cigarettes and similar smoking alternatives are available with rates in countries where such products are not available. This is addressed in Part 6 of the report.

In the course of the review, scientific literature relating to the use of e-cigarettes (for example use within population groups, and motivation for use) was reviewed and this contextual information is included in Part 7 of the report.

Extensive tables describing the studies reviewed are positioned at the end of each part of this report.

Executive Summary

Part 1: Review all available evidence applicable to the impacts of the use of e-cigarettes, personal vaporisers and nicotine on individual and population health.

Health risks of e-cigarettes – human studies

- Because of the lack of long-term studies, there continues to be no evidence that e-cigarette use is associated with clinical cardiovascular disease.
- Carcinogenic compounds and carcinogenic metabolites arising from e-cigarette use are demonstrated to be present in e-cigarette users, and arise through e-cigarette use in animal studies. However the risk of the development of cancer or other health effects from the levels arising from e-cigarettes use is unclear.
- The use of e-cigarettes may impair lung function however the independent effect of e-cigarettes is unclear because of potential confounding by conventional cigarette smoking.
- Case studies have suggested that e-cigarette use interferes with, or delays, wound healing. While these reports are suggestive, evidence from case studies should be verified using appropriately designed studies.

Health risks of e-cigarettes – injuries

- It is clear that e-cigarettes can explode and cause serious projectile and thermal injuries.
- Intentional or accidental ingestion of e-fluids can cause serious injury or death.

Health risks of e-cigarettes – animal studies

- E-cigarette vapour can cause significant damage to frog embryos, rats and mice. Adverse outcomes include increased release of pro-inflammatory cytokines, emphysematous lung destruction, renal, hepatic and heart fibrosis among rodents exposed to e-cigarettes vapours or IV e-cigarette liquids compared with those exposed to room air.
- E-cigarette vapour exposure also had significant effects on the offspring of exposed pregnant mice and frog embryos including increased release of pro-inflammatory cytokines, sleep disturbances and craniofacial defects.
- The implications of animal studies for human health is speculative.

Health risks of e-cigarettes – in vitro studies

- In vitro studies on e-cigarette vapour, liquid and extracts indicate the potential for human health risks including cell death, increased oxidative stress, reduced lung function, changes in inflammatory response, altered gene expression and increase of cellular risk factors for cardiovascular disease.

- There is a lack of clarity about the direct implications of the in vitro findings for human health.

> Conclusion: the evidence available suggests that regular use of e-cigarettes is likely to have adverse health consequences. There is a lack of clarity about the magnitude of adverse health effects, and the quantity of e-cigarette use required to trigger adverse health effects.

Part 2: Review all available evidence applicable to the use of e-cigarettes, personal vaporisers and nicotine on rates of smoking.

Gateway Effect – use of e-cigarettes leading to initiation of conventional cigarette smoking

- The evidence for a strong positive relationship between use of e-cigarettes and later cigarette smoking amongst youth continues to accumulate. The evidence is consistent in observational studies and across different countries.
- A plausible biological pathway from use of e-cigarettes to conventional cigarette smoking operates through developing addiction to nicotine. The use of e-cigarettes with higher concentrations of nicotine is observed to have a stronger association to later conventional cigarette use.
- A positive association is observed between the initiation of conventional smoking following use of non-nicotine e-cigarettes (however it is much weaker than the association with nicotine containing e-cigarettes). This highlights the possibility for other causal mechanisms besides the development of nicotine addiction linking e-cigarette use to the initiation of cigarette smoking.
- There is insufficient evidence to draw any conclusion about whether the use of e-cigarettes results in the use of other substances such as marijuana.
- Almost all investigations of 'gateway effect' focus on young people.

Smoking cessation

- Observational studies indicate that e-cigarettes are preferred as a smoking cessation method in some, but not all, populations.
- There is good evidence from clinical trials that e-cigarettes may reduce withdrawal symptoms in smokers after a short period of cigarette abstinence. The results of the trials have limited application because most trials are short term.
- There is currently no evidence that quit rates for smoking have decreased as a result of e-cigarette use. Long-term success with cessation was not measured in trials.
- Results from randomised controlled trials indicate that nicotine-containing e-cigarettes are more effective at reducing the amount of conventional smoking than nicotine-free e-cigarettes or no e-cigarettes.
- There is limited evidence comparing the effectiveness of e-cigarettes for smoking cessation with other smoking cessation methods.

Conclusion: In many countries where appropriate evidence is available, it appears that e-cigarette use occurs with cigarette use. However the evidence is consistent in suggesting that use of e-cigarettes by non-smoking youth predicts future smoking. While many smokers and former smokers state a preference for e-cigarettes as a smoking cessation method, the effectiveness of this method compared with other smoking cessation methods is not known.

Part 3: Assess the impacts on health of allowing the use of e-cigarettes and personal vaporisers in countries where they have been permitted.

- Country-level difference in impact on health of e-cigarettes is difficult to demonstrate because:
    o the use of e-cigarettes is low in all countries,

    o diseases and health conditions often have a long latent period, while the history of use of e-cigarettes is relatively short

    o diseases and health conditions are often due to multiple factors combined, and it is hard to disentangle the independent effects of these determinants which may be changing at different rates in different parts of the population.

- The United States (US) accounted for 56% of the global e-cigarette market in 2015. US studies show that there is no apparent change in the trend of age-adjusted Chronic Obstructive Pulmonary Disease deaths in the US over the period of 2000-2014, and no change in the trend for the prevalence of age-adjusted hypertension from 1999-2016.

- There is no break in the trend towards more former smokers, measured by the Quit ratio (the ratio of former smokers to ever smokers) in the US which is slowly increasing over 2005-2016.

- Population modelling of the health impacts of e-cigarettes is greatly hampered by lack of knowledge of the health effects of e-cigarettes. Models which have been developed give a positive or a negative overall health impact of e-cigarettes on a population depending on the parameters used. The health impact for a population will vary according to the prevalence of conventional smokers in the population.

Conclusion: based on the current evidence it is not possible to determine whether e-cigarettes have a positive or a negative effect on health in countries where they are permitted.

Part 4: Review the impact of e-cigarettes and personal vaporisers on individual health as an alternative to smoking.

- There is some evidence that blood pressure of smokers is lowered over a month when e-cigarettes are used instead of conventional cigarettes.
- In the short-term, there is evidence of small improvements in lung function in smokers who use e-cigarettes.
- The level of specific carcinogenic compounds and resulting metabolites is lower in humans after e-cigarette use compared to conventional cigarette use.
- The range of toxic compounds arising from normal use is not the same for e-cigarettes and conventional cigarettes. For e-cigarettes, potentially toxic compounds also arise from the e-fluid which varies in composition, and from the heating elements (which typically contribute metal vapour for example).
- Nicotine absorption and nicotine dependency for e-cigarettes users appears to depend on how the e-cigarettes are used. This is probably because the way in which the devices are used in terms of puffs and intensity can determine the amounts of nicotine inhaled, in addition to the nicotine concentration of the e-fluid.

Conclusion: when e-cigarettes are used by smokers instead of conventional cigarettes there is evidence for improvement in individual health. However, use of e-cigarettes may also introduce independent health risks, and 'dual use' (using both e-cigarettes and conventional cigarettes) is popular.

Part 5: Identify any potential for e-cigarettes to reduce rates of smoking in Australia.

- The prevalence of regular smoking in Australia has been declining since at least 1945, from very high levels, particularly in men.
- The most recent national data indicates that 14% of Australian adults are current regular smokers.
- E-cigarette use in Australia has generally increased from 2013 and 2016, however the prevalence of current regular use is below 8% amongst all adolescent and adult age groups.
- People who have used e-cigarettes on one or more occasions over their lifetime are termed 'ever users'. Among 'ever users' of e-cigarettes, the largest percentage is people who have used e-cigarettes only once or twice. This group is larger than current users and ex-users for all age groups, but is particularly large in adolescents and younger adults.
- E-cigarette use beyond once or twice is very uncommon amongst people who are not current or ex cigarette smokers.

- The most common reason for using e-cigarettes among adolescents and younger adults is 'out of curiosity', while among older adults the reasons for use are more likely to be related to tobacco smoking (to cease smoking, to reduce the number of cigarettes smoked, or to avoid recommencing smoking).

Conclusion: It is a critical research question to determine the effectiveness of e-cigarettes compared to other smoking cessation methods among Australian smokers generally, and also among specific groups with a high smoking rate. The rate at which young people and adults in Australia start smoking as a result of using e-cigarettes should be assessed and monitored to fill a research gap. On present evidence, it is not possible to determine whether less restrictive access to e-cigarettes would reduce rates of smoking in Australia.

Part 6: Compare rates of tobacco smoking in countries where e-cigarettes and similar smoking alternatives are available with rates in countries where such products are not available.

- There does not appear to be a consistent relationship across countries between current e-cigarette use rate and either male current smoking rate or female current smoking rate.
- There is a positive and moderately strong relationship across countries between rate of 'ever use' of e-cigarettes rate and female current smoking rate. The weaker positive relationship for male current smoking rate is not statistically significant.
- The use of e-cigarettes does not seem to be related to the type of regulation that governs its use. However, development of particular regulation has many determinants and the widespread use of e-cigarettes is relatively recent, and at different stages of initiation in different countries.

Conclusion: There does not appear to be a consistent pattern of rate of e-cigarette use compared to tobacco smoking across countries. However, while tobacco smoking is a well-established practice that varies widely between countries, e-cigarette use has spread across countries in the recent past with different rate of device availability, marketing, familiarity and regulations. It is plausible that a between-country relationship for tobacco smoking and e-cigarette use could develop in the future.

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Acknowledgments

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Acronyms

2-HPMA	2-Hydroxypropyl mercapturic acid
3-HPMA	3-Hydroxpypropyl mercapturic acid
AAMA	Acrylamide
AE	Adverse events
AI	Augmentation Index
AL	Attachment loss
ALDH3A1	Aldehyde dehydrogenase 3A1
AOR	Adjusted odds ratio
ASH	Action on Smoking Health
BAL	Brochoalveolar lavage
BCEP	Bis(2-chloroethyl) phosphate
BDCPP	Bis(1,3-dichloro-2-propyl) phosphate
Beas2B	Bronchial epithelial cells
BOP	Bleeding on probing
BP	Blood pressure
bpm	Beats per minute
CC	Conventional cigarette
CES-D	Center for Epidemiological Studies-Depression Scale
CFU	Colony forming units
CHS	Southern California Children's Health Survey
CI	Confidence interval
CNEMA	2-Cyanoethylmercapturic acid
CO	Carbon monoxide
COHb	Carboxyhemoglobin
COPD	Chronic obstructive pulmonary disease
Cr	Chromium
CS	Conventional cigarette smokers
CT scan	Computed tomography scan
CVD	Cardiovascular disease

DALY	Disability-adjusted life year
DBP	Diastolic blood pressure
DBUP	Dibutyl phosphate
DMBT1	Deleted in malignant brain tumors 1
DPhP	Diphenyl phosphate
DPPIV	Dipeptidyl peptidase-4
EBC	Exhaled breath condensate
EC	Electronic-cigarette
ECG	Electrocardiogram
ENDS	Electronic nicotine delivery systems
EVP	Electronic vapour product
FCTC	Framework convention on tobacco control
FDG	F-fluorodeoxyglucose
FDG-PET/CT	F-fluorodeoxyglucose positron emission tomography/computed tomography
FEF	Forced expiratory flow
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FOT	Forced oscillation technique
FRAP	Ferric reducing antioxidant power
f res	Resonance Frequency
FTND	Fagerstrom Test for Nicotine Dependence
FVC	Forced vital capacity
GCLC	Glutamate-cysteine ligase
GM	Geometric mean
GMR	Geometric mean ratio
GPX2	Glutathione peroxidase
HEMA	Ethylene oxide
HF	High frequency
HFL-1	Human foetal lung fibroblast
HMPMA	Hydroxy methyl propylmercapturic acid
HO1	Heme oxygenase 1
HR	Heart rate
HRCT	High resolution computed tomography

HRV	Heart rate variability
HS	Healthy smokers
HTP	Heated tobacco products
HYRBS	Healthy Youth Risk Behaviour Survey
ICAM-1	Intercellular adhesion molecule 1
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IL-8	Interleukin-8
IOS	Impulse oscillometry system
LAA-x	Low attenuation areas in the lungs (defined as a percentage of total lung voxels less than -x Hounsfield Units on inspiratory CT)
LC-MS	Liquid chromatography-mass spectrometry
LF	Low frequency
LGBTQ	Lesbian Gay Bisexual Transgender Queer
LYSC	Endoproteinase Lysosome-C
MCP-1	Monocyte chemoattractant protein-1
MDA	Malondialdehyde
MDS-TBR	Most diseased segment-tissue to background ratio
MIP-1α	Macrophage inflammatory protein - 1α
MIP-1β	Macrophage inflammatory protein - 1β
MNWS	Minnesota Nicotine Withdrawal Scale
MPO	Myeloperoxidase
MT	Missing teeth
MTF	Monitoring the Future
MWS-R	Minnesota Nicotine Withdrawal Scale
NATS	National Adult Tobacco Survey
NDSS	Nicotine Dependency Syndrome Scale
NE	Neutrophil elastase
NEQ	Nicotine equivalents
NET	Neutrophil extracellular traps
NETosis	Neutrophil extracellular trap activation and release
NHIS	National Health Interview Survey
Ni	Nickel

NK	Natural killer cells
NNAL	Product formed after NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) enters the body
NNK	Nicotine-derived nitrosamine ketone – also known as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NQO1	NAD(P)H Quinone dehydrogenase 1
Nrf2	Nuclear factor erythroid 2-related factor
NRT	Nicotine replacement therapy
NS	Never smokers
nu	Normalised units
NYTS	National Youth Tobacco Survey
OEHHA REL	Office of Environmental Health Hazard Assessment Reference Levels
OML	Oral mucosal lesion
OPFR	Organophosphate flame retardants
PAFR	Platelet activating factor receptor
PAH	Polyaromatic hydrocarbon
PATH	Population Assessment of Tobacco and Health
PD	Probing depth
PECAM-1	Platelet endothelial cell adhesion molecule-1
PEF	Peak expiratory flow
PG	Propylene glycol
PI	Plaque index
PMA	Benzene metabolites
Project M-PACT	Marketing and Promotions across Colleges in Texas Project
PWV	Pulse wave velocity
QSU	Questionnaire of Smoking Urges
QTcB	Heart rate-corrected QT interval
RB-ILD	Respiratory bronchiolitis-associated interstitial lung disease
RHI	Reactive hyperaemia index
ROS	Reactive oxygen species
rs	Spearman's rank correlation coefficient
SALSUS	Scottish Schools Adolescent Lifestyle and Substance Use Survey
SBP	Systolic blood pressure

SD	Standard deviation
SEM	Standard error of the mean
SHS	Second-hand smoke
STP	Smokeless tobacco product
supF	Gene found in Escherichia coli
SUV max	Maximum standardized uptake value
TATAMS	Texas Adolescent Tobacco and Marketing Surveillance System
TCEP	Tris(2-chloroethyl) phosphate
THP-1	Tamm-Horsfall Protein 1
TNF-α	Tumor necrosis factor-α
TSNA	Tobacco-specific nitrosamines
TUS-CPS	Tobacco Use Supplement-Current Population Survey
UK	United Kingdom
US	United States
VCAM-1	Vascular cell adhesion protein 1
VG	Vegetable glycerol
VOC	Volatile organic compounds (toxicants)
WHO	World Health Organization

Methods of this review

Purpose of the review

This report follows an evidenced-based approach into the use of e-cigarettes and personal vaporisers and an assessment of their potential to influence individual and population health, particularly relative to tobacco use and other tobacco cessation methods.

Specifically, the inquiry:

- Reviews all available evidence applicable to the impacts of the use of e-cigarettes, personal vaporisers and nicotine on individual and population health. (Part 1)

- Reviews all available evidence applicable to the use of e-cigarettes, personal vaporisers and nicotine on rates of smoking. (Part 2)

- Assesses the impacts on health of allowing the use of e-cigarettes and personal vaporisers in countries where they have been permitted. (Part 3)

- Reviews the impact of e-cigarettes and personal vaporisers on individual health as an alternative to smoking. (Part 4)

- Identifies any potential for e-cigarettes to reduce rates of smoking in Australia. (Part 5)

- Compares rates of tobacco smoking in countries where e-cigarettes and similar smoking alternatives are available with rates in countries where such products are not available. (Part 6)

Overview

Two recent comprehensive reviews were produced in 2018 by the US Academies of Sciences (Stratton, Kwan et al. 2018) and Public Health England (McNeill A 2018).

The conclusions from the US Academies of Sciences review, titled 'Public Health Consequences of e-Cigarettes' are summarised in Appendix A.

The purpose of the report was to:

a) conduct a critical, objective, and evidence-based review of the scientific evidence that addresses the various competing views on the public health consequences of e-cigarettes,

b) make recommendations for the improvement of this research, and

c) highlight gaps that are a priority for future research.

The scientific literature search for the report was conducted between 1 February 2017 and 31 August, 2017 in 6 databases – PubMed, Scopus, Web of Science, PsycINFO (ProQuest), Ovid (Medline), and Embase (Ovid). The following key terms were used: ecigarette, e-cigarettes, electronic cigarette, electronic cigarettes, electronic nicotine delivery, electronic nicotine device, vape, vaping, and e-liquid. Searches in PubMed and Medline also used the Medical Subject Headings (MeSH) term 'electronic cigarettes.' After identifying literature, titles and abstracts of the search results were reviewed to identify studies for inclusion in the review. Studies that met the inclusion criteria were sorted by population (human, in vivo, animal, and in vitro) and outcomes for committee review and quality assessment.

The purpose of the UK report was to summarise evidence to underpin policy and regulation of e-cigarettes and novel nicotine delivery systems. The conclusions from relevant parts of the Public Health England report, titled 'Evidence review of e-cigarettes and heated tobacco products' are summarised in Appendix B.

The report was an update of a previous review, and searched the peer reviewed literature on e-cigarettes produced between 1 January 2015 and 18 August 2017. The search covered the following databases: Pubmed, Embase, PsychInfo, MEDLINE, Web of Science and CINAHL. The key search terms used were e-cigarette, Electronic cigarettes, ENDS, electronic nicotine delivery systems, Vaping, Vape. Literature was included where it reported on e-cigarettes, published new evidence or data from research studies, presented a new synthesis of existing evidence, detailed case studies relevant to e-cigarettes, analysed policy and was published in English. Reports were excluded where they did not present new data, were editorial or opinion based in nature (i.e. did not contain new data), syntheses or research findings, were not peer-reviewed or were published before 1 January 2015. Additional literature known to the authors was included where it was able to provide context.

These recent authoritative reviews are used as benchmarks to compare the findings of the most recent relevant studies that are identified in the present review. The WHO Framework Convention on Tobacco Control (FCTC) report 2016 also provides a useful overview, as does the US Surgeon General's 2016 Report on e-Cigarette Use among Youth and Young Adults (US Dept of Health and Human Services 2016, World Health Organization 2016).

Method

A library services professional conducted a literature search over the period 6-14 March 2018. The search was for literature published from 1 January 2017 until the date of the search. A further search was conducted on 11 May 2018 to identify scientific literature published after the date of the earlier search. The databases searched were Scopus, and Web of Science. The search terms used were: e-cigarettes, electronic cigarettes, ENDS, electronic nicotine delivery system, vape and vaping.

A total of 1,514 articles were identified in the initial search, and 48 articles in the May search. The title was used to categorise articles into 'health outcomes of e-cigarettes' (sub-categorised as injuries, human studies, animal studies and in vitro studies), 'use of e-cigarettes', 'prevalence of e-cigarettes', 'smoking cessation', and 'gateway effect of e-cigarettes'. Web-based searches were undertaken to ascertain other sources of information regarding the country specific prevalence rate of e-cigarette use and of conventional smoking. Topic areas were assigned to specific individuals who retrieved the full articles and assessed them for review based on the abstract and body of the report. Articles that were assessed as appropriate for review were read in full and specific information was abstracted into pre-specified tables. This information was described, synthesised and interpreted in the body of each report. Where relevant, each writer was asked to consider what the new studies added to the existing recent reviews, and the extent to which they were consistent with the previous conclusions.

PART 1: Health impact of e-cigarettes and personal vaporisers

Executive summary

There is a level of complexity to the consideration of the health effects of e-cigarettes. There have not been long-term studies of the health effects because the widespread use of e-cigarettes in some countries has been over years rather than decades. Furthermore, e-cigarette devices have been changing and there is wide variation in the fluids vaporised in these devices.

The direct health effects of e-cigarettes are likely to differ according to how they are used, and what groups use them. An important consideration is the health impact for people where they are substituted for another behaviour such as conventional cigarette smoking. An initial view is that the risks of conventional smoking may be replaced by the risks of e-cigarette use – i.e. that people who are currently smoking cigarettes may completely replace this behaviour with use of e-cigarettes. On further examination, many people who smoke conventional cigarettes and choose to use e-cigarettes will use both. The health effects are then likely to depend on what happens with each behaviour, although there is the possibility that there is also a synergistic effect. Whilst ideally the adoption of e-cigarette use by a cigarette smoker might be expected to reduce the frequency of cigarette smoking, there are also other possibilities.

The health outcomes included in this report cover studies on the health effects of e-cigarettes considered in isolation to other behaviours. Studies assessing the health effects of e-cigarettes in conventional cigarette smokers are discussed in Part 4: Impact of e-cigarettes for smokers where the competing health risks of e-cigarettes and conventional smoking will be considered.

Health risks of e-cigarettes – human studies

- Because of a lack of long-term studies, there continues to be no evidence of e-cigarette use to be associated with clinical cardiovascular disease.
- Carcinogenic compounds and carcinogenic metabolites arising from e-cigarette use are demonstrated to be present in e-cigarette users, and in animal studies. However the risk of the development of cancer or other health effects from the levels found is unclear.
- Use of e-cigarettes may impair lung function although the independent effect of e-cigarettes is unclear because of potential confounding by conventional cigarette smoking.
- Case studies, which do not provide strong evidence, have suggested that e-cigarette use interferes with, or delays, wound healing. While these reports are suggestive, this has not yet been examined using appropriately designed studies.
- Studies have highlighted an association between e-cigarette use and depression which is not thought to be causal. Rather it identifies a population sub-group (i.e. people suffering depression) who may be vulnerable to the uptake and continued use of e-cigarettes.

Health risks of e-cigarettes – injuries

The studies reviewed in this section are mainly case studies and case series. However, the injuries incurred can be attributed directly to e-cigarettes. E-cigarettes can explode and cause serious projectile and thermal injuries. While uncommon events, if e-cigarettes were to increase in popularity without modification, injuries from e-cigarettes could be expected to increase in occurrence.

Intentional or accidental ingestion of e-fluids can cause serious injury or death.

Health risks of e-cigarettes – animal studies

Recent studies indicate that e-cigarette vapour can cause significant damage to frog embryos, rats and mice. Adverse outcomes include increased release of pro-inflammatory cytokines, emphysematous lung destruction, renal, hepatic and heart fibrosis among rodents exposed to e-cigarette vapour compared with those exposed to room air. E-cigarette vapour exposure also had significant effects on the offspring of exposed pregnant mice and on frog embryos including increased release of pro-inflammatory cytokines, sleep disturbances and craniofacial defects.

Health risks of e-cigarettes – in vitro studies

In vitro studies on e-cigarette vapour, liquid and extracts strongly indicated potential health risks including cell death, increased oxidative stress, reduced lung function, changes in inflammatory response, altered gene expression and increase of cellular risk factors for cardiovascular disease. There is a lack of clarity about the direct implications of the in vitro findings for human health.

1 Introduction

Electronic cigarettes or e-cigarettes refers to any a device with a heating element that produces an aerosol from a liquid that users can inhale. This definition excludes electronic devices that do not contain liquids and instead heat tobacco, such as those referred to as 'heat-not-burn' products.

E-cigarettes are a class of Electronic Nicotine Delivery Systems (ENDs) or Electronic Non-Nicotine Delivery Systems (ENNDs). Both are characterised by heating a solution (called an e-liquid) to create an aerosol which frequently contains flavouring compounds, usually dissolved into propylene glycol or/and glycerin (World Health Organization 2016).

A number of different devices have been developed, designated first to third generation devices, and evolution of devices is likely to continue. Variations in device performance and usage behaviours lead to a difference in exposure to active components such as nicotine. For example, the user's puffing style, the choice of e-liquid, the wattage and resistance of the device are all relevant variables determining the user's experience.

There are close to 8,000 reported e-liquid flavours. In the United States, most adults reported using e-cigarettes that contain nicotine—91.2% of daily users, 88.2% of non-daily users, and 89.5% of both daily and non-daily users overall (Coleman, Rostron et al. 2017). Approximately two-thirds of current US users also reported using a non-tobacco flavoured brand; these flavours include menthol, mint, clove, spice, candy, fruit, chocolate, alcohol (e.g., wine or cognac), or other sweet flavours (Coleman, Rostron et al. 2017).

In 2015, about 56% of the global market was accounted for by the United States, 12% by the United Kingdom and a further 21% by China, Germany, France, Italy and Poland (3-5% each).

2 Human health outcome studies

2.1 Introduction

This section considers studies examining the relationship between e-cigarettes, health risk factors and health outcomes. It addresses part of the assigned task to 'review all available evidence applicable to the impacts of the use of e-cigarettes, personal vaporisers and nicotine on individual and population health.' The majority of the 27 studies identified focused on multiple risk factors for health outcomes. Review findings have been categorised according to the following 'health outcomes': cardiovascular system, exposure to carcinogens, respiratory system, lymphatic system, oral health, dermatology, wound healing, oxidative stress, nicotine exposure and dependency, effects of e-cigarettes on microbiota and modelling studies. One study may be referred to under several health outcome sections. At the end of each section, the findings of this review are compared with what is already known from other recent UK and US comprehensive reviews (McNeill A 2018, Stratton, Kwan et al. 2018). This section is concluded by highlighting new findings from this review and results that were not consistent with the findings of recent reviews.

2.1.1 Studies included and excluded

The published papers identified by title to be related to health effects of e-cigarettes, were examined in full. Papers were excluded from consideration in Part 1 for the following reasons:

- letter to the editor/erratum, editorial or commentary only, not an original study
- air quality study
- review article or book chapter, not an original study
- on e-cigarette ingredients/toxicology (with no health outcome)
- conference abstract only (with some full papers in the review) or other abstract without sufficient detail, or abstract/article not able to be accessed
- focus on factors associated with e-cigarette uptake, not health outcomes
- prevalence study on e-cigarette use
- on perceptions of e-cigarette safety
- on e-cigarette particle distribution (modelling)
- studies otherwise inappropriate for this section.

Of the 49 studies identified as evaluating the effects of e-cigarettes on human health outcomes, 22 studies either sampled from a population of cigarette smokers or dual users or compared the results to cigarette smokers rather than non-smokers. These studies have been excluded from this section, however, they are included in Part 4 which focuses on health outcomes in cigarette smokers. The remaining **27 studies** are reviewed in this chapter.

2.1.2 Levels of evidence and study designs

Of the **27 studies** included in this review of health risks/outcomes associated with e-cigarettes, there was generally a low level of evidence arising from the study designs, with most of the studies being cross-sectional studies (n=12). Modelling studies (n=5) and case reports (n=4) were the next most frequent type of study design. The study designs included:

- Randomised cross-over trials (3)
- Randomised controlled trials (1)
- Prospective cohort studies (1)
- Case control studies (1)
- Cross sectional studies (12)
- Case Reports (4), and
- Modelling studies (5).

2.1.3 Review findings on health outcomes

In this section the health outcome studies are considered after categorising by various health risks and outcomes.

2.2 Cardiovascular system

There were five studies that considered cardio-vascular health risk factors associated with e-cigarette use (Boas, Gupta et al. 2017, Moheimani, Bhetraratana et al. 2017, Moheimani, Bhetraratana et al. 2017, Polosa, Cibella et al. 2017, Staudt, Salit et al. 2018). Two were randomised trials (Moheimani, Bhetraratana et al. 2017, Staudt, Salit et al. 2018), one was a prospective cohort study (Polosa, Cibella et al. 2017), and two were cross-sectional studies (Boas, Gupta et al. 2017, Moheimani, Bhetraratana et al. 2017). These studies considered various cardiac indicators such as **heart rate** (HR), **blood pressure (BP)** and **cardiac sympathetic nerve activity**.

In a small US randomised trial, Staudt et al. examined the effects of e-cigarettes on a range of outcomes including blood pressure and heart rate (Staudt, Salit et al. 2018). Ten healthy participants with no history of smoking, e-cigarette use or use of any other tobacco product completed a range of tests including blood pressure and heart rate measures. One week later, participants attended an experimental session where they inhaled 10 puffs of an e-cigarette on two occasions with a 30 minute break in between. Participants were randomised to use either an e-cigarette with nicotine (n=7) or an e-cigarette without nicotine (n=3) during the experimental session. Baseline tests were repeated within 2 hours of the experimental session.

No significant changes in blood pressure or heart rate were observed following use of an e-cigarette with nicotine or an e-cigarette without nicotine. This study has a number of limitations including the small sample size reducing the power to detect associations, lack of adjustment for potential confounders and lack of a control group.

The prospective cohort study, conducted in Italy by Polosa et al., considered **blood pressure** and **heart rate** at baseline and at three follow-up visits across **three and a half years** (Polosa, Cibella et al. 2017). The study aimed to compare health indicators in a cohort of daily e-cigarette users who have never smoked and a sample of never smokers/non-users of e-cigarettes over a 3.5-year period. Subjects (mean age 29.7 ± 6.1 years) were recruited via vape shop owners referring customers to the study. The study was small (n=21) and followed daily e-cigarette users (smoking for ≥ 3 months) who had never smoked conventional cigarettes (n=9). The control group was 12 never smokers/never e-cigarette users.

The authors claim that there were no significant changes as a result of smoking e-cigarettes on the health outcomes measured, and no significant differences between the control group and the e-cigarette group. Limitations included a possible strong bias in recruitment methods, the very small sample size, the young age of the sample, and the types of e-cigarette used in the study. A small sample size limits the power of the study to detect a relationship. Potential confounders of the relationship between e-cigarette use and heart rate and BP were also not considered. It is possible that the follow up period was also not long enough to observe the effects of e-cigarettes on heart rate and BP or that these effects had occurred prior to baseline.

Notably, only six of the nine e-cigarette group subjects were vaping nicotine containing e-liquid (and even these were using lower strength of nicotine in liquid), whilst three of the nine were using zero nicotine in e-liquid by the end of the study. Some also switched from 'standard refillables' (e.g. EGO style products) to more advanced refillable devices (Provari, Innokin, Joyetech eVIC, Avatar Puff). One of the researchers had received lecture fees from European electronic cigarette industry and trade associations that were linked to vaping advocacy non-profit organisations.

Another small study conducted by Boas et al. (n=27), investigated the effect of e-cigarettes on activation of the **Splenocardiac Axis**[1], measured by increased metabolic activity in the hematopoietic and vascular tissues, among healthy young adults (21-45 years old) (Boas, Gupta et al. 2017). In this cross-sectional study, subjects were habitual e-cigarette only users who had used e-cigarettes for a **minimum of one year (n=9)**. There was also a conventional smoking group (n=9) and a control group of healthy nonusers of either product (n=9). F-fluorodeoxyglucose positron emission tomography/computer tomography (FDG-PET/CT) was performed to measure FDG uptake in the spleen, bone marrow and aorta. FDG uptake in skeletal muscle was also measured as a control.

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[1] an inflammatory signalling network underlying acute cardiac ischemia

FDG uptake was higher in the e-cigarette group compared to the control group in the spleen (SUV$_{max}$=1.73 ± 0.04 and 1.62 ± 0.07 in e-cigarette users and controls respectively; p=0.29), bone marrow (SUV$_{max}$=2.17 ± 0.12 vs 1.88 ± 0.06 respectively; p=0.09) and aorta (SUV$_{max}$=1.98 ± 0.07 vs 1.87 ± 0.07 respectively; p=0.27). The differences observed, however, were not significant, although that for bone marrow was close to statistical significance and may warrant further investigation considering the small sample size and limited power of the study. FDG uptake in skeletal muscle was not different between groups. No differences were observed in the metabolic activity of the aortic wall when measured by MDS-TBR. Plasma cotinine was weakly correlated with bone marrow activity (r=0.39, p=0.05). Again the major limitations of this study include the small sample size reducing the power of the study to detect differences between the groups and the lack of consideration of potential confounders of the relationship between e-cigarette use and activation of the splenocardiac axis.

Another small US cross-sectional case-control study by Moheimani et al. assessed whether habitual use of e-cigarettes (most days across **one year**) was associated with an **imbalance of cardiac autonomic tone** and increased oxidative stress and inflammation in a sample of healthy young adults (e-cigarette users: n=16, controls: n=18; age: 21 - 45, mean age 27.6 years) (Moheimani, Bhetraratana et al. 2017). The study analysed Heart Rate Variability (HRV) components for the high frequency (HF) (an indicator of vagal activity), the low frequency (LF) component (a mixture of both vagal and sympathetic activity) and the ratio of the LF to HF (which reflects the cardiac sympathovagal balance).

The study found that HRV components are shifted towards sympathetic predominance and decreased vagal tone among e-cigarette users, which is found in people with increased cardiovascular risk, including conventional cigarette smokers. The HF component was significantly decreased in the e-cigarette users compared to the non-user controls (mean 46.5 [3.7] normalised units (nu) vs 57.8 [3.6] nu, p=0.04). The LF component (mean 52.7 [4.0] nu vs 39.9 [3.8] nu, p=0.03), and the LF to HF ratio (mean 1.37 [0.19] vs 0.85 [0.18], p=0.05) were significantly increased in the e-cigarette users compared with non-user controls, consistent with sympathetic predominance, even in the absence of recent e-cigarette use (as verified by the absence of detectable nicotine in the plasma). Plasma cotinine levels (an estimate of e-cigarette use) were significantly correlated with each of the HRV components: plasma cotinine levels were inversely related to HF component (r=-0.34, p=0.04) and directly related to the LF component (r=0.35, p=0.03) and LF to HF ratio (r=0.36, p=0.03). There was a nonlinear relationship between the number of tobacco cigarettes smoked per day and cardiovascular risk, which the authors suggest may indicate a low threshold above which underlying physiologic processes are saturated.

In a later US randomised cross-over study (Moheimani, Bhetraratana et al. 2017) the same authors aimed to determine the role of nicotine versus non-nicotine constituents present in e-cigarette emissions in causing increasing resting **cardiac sympathetic nerve activity** and increased susceptibility to oxidative stress. Subjects were healthy volunteers (n=33; age 21 - 45 years, mean age 26.3 years) who were not e-cigarette or tobacco users and underwent three **short term** exposure sessions of: e-cigarette with nicotine, e-cigarette without nicotine and sham smoking. Each exposure session was separated by a 4-week washout period.

The e-cigarette initially used was the Greensmoke cigalike device (with 1.2%, or 12mg/ml nicotine), and then, because only 5/15 subjects had detectable nicotine in plasma, the second-generation pen-like device (with 1.2% nicotine). It was reported that still no plasma nicotine was detectable in the first 6 subjects who used the second device for 10 minutes, so the exposure was increased to 30 minutes of use for the remaining 27 subjects.

Using the e-cigarette with nicotine (but not the e-cigarette without nicotine) led to a statistically significant and marked shift in cardiac sympatho-vagal balance toward sympathetic predominance: the HF component decreased, the LF component increased and the ratio of LF to HF increased. Whilst the systolic, diastolic and mean arterial blood pressure increased following the use of the e-cigarette with nicotine and decreased following the use of e-cigarette without nicotine or the sham control, changes were not statistically significant.

However, following the use of the e-cigarette with nicotine, plasma nicotine was significantly correlated with change in each of the heart rate variability (HRV) components: plasma nicotine was inversely related to the decrease in HF component (r_s=-0.25, p=0.02) and directly related to the increase in LF component (r_s=0.26, p=0.01) and the LF to HF ratio (r_s=0.27, p=0.008). Similarly, plasma nicotine was directly related to the increase in systolic blood pressure (r_s=0.21, p=0.04) and heart rate (r_s=0.21, p=0.04), but not to diastolic or mean blood pressure.

2.2.1   What the new studies add to what is already known about e-cigarettes

Cardiovascular disease

The WHO FCTC states that e-cigarettes may contribute to cardiovascular disease (World Health Organization 2016), whilst other reviews provide more mixed evidence. The US National Academies of Sciences, Engineering and Medicine Review (National Academy of Sciences) (Stratton, Kwan et al. 2018) conducted a review on the health effects of e-cigarettes with a search completed on 31 August 2017 (unlimited date for publications included). The Public Health England Review (McNeill A 2018) searched peer reviewed literature on e-cigarettes (from January 2015 to 18 August 2017) to determine health effects. Previous reviews concluded that:

Previous studies

'There is **no available evidence** whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima media-thickness and coronary artery calcification) ... and that there was 'limited evidence…that e-cigarette use is associated with…arterial stiffness and autonomic control.'(Stratton, Kwan et al. 2018)

The Public Health England review included the conclusions of other reviews, not just original studies, with one such review claiming that the short-term use of e-cigarettes was associated with low cardiovascular risk among healthy users.

The results from new studies identified in this review were mixed, however, the study with the strongest study design, the randomised cross-over study by Moheimani et al., attributed increased cardiac sympathetic nerve activity to the use of e-cigarettes containing nicotine. The authors attributed the effect to inhaled nicotine. They state the effect should not be considered benign, but related to increased cardiovascular disease.

Heart rate

The US Academies of Sciences review concluded that 'there is **substantial evidence** that heart rate increases after nicotine intake from e-cigarettes.' The Moheimani et al. study confirmed the association between plasma nicotine and heart rate described in previous reviews. The Staudt et al. study did not observe an association between e-cigarette use, with or without nicotine, and heart rate, however, this was a very small study with a number of substantial limitations. The US Academies of Sciences review also highlighted **the different effects of flavourants** on heart rate. Previously, the WHO report suggested that cherry, popcorn and cinnamon flavours were potentially more harmful than others (World Health Organization 2016).

Blood pressure

In regard to blood pressure, the US Academies of Science (Stratton, Kwan et al. 2018) review identified moderate evidence that diastolic blood pressure (DBP) increases after nicotine intake from e-cigarettes and limited evidence that e-cigarette use is associated with a short-term increase in systolic blood pressure (SBP). Of the studies examined here, the cohort study by Polosa et al. found no effect of e-cigarette use on DBP or SBP, however, the sample size of this study was small and confounders were not considered. On the other hand, the randomised cross-over study by Moheimani et al. found plasma nicotine following use of an e-cigarette with nicotine was associated with increased SBP but not DBP or mean BP.

Conclusions

The studies reviewed here were few in number and all had very small sample sizes. The Polosa et al study was the only prospective cohort study considered in this review which also had a very small sample size. Studies with a small sample size have two major limitations which must be considered. Firstly, the power to detect an association is limited and therefore, if no association is observed it may be due to the lack of power of the study rather than the lack of a relationship between e-cigarette use and the health outcome of interest. Secondly, other than the randomised cross-over study, all other studies should control for potential confounders, however, due to the lack of power, these studies were unable to adjust for confounders and this is likely to bias the results.

Overall, due to the few studies and the limitations related to sample size, these studies provide little additional evidence to the relationship between e-cigarette use and cardiovascular outcomes. To assess this relationship adequately, larger randomised controlled trials and prospective cohort studies are required.

2.3 Exposure to carcinogens

This section considers four studies that referred to exposure to carcinogens as a result of e-cigarette usage (Fuller, Acharya et al. 2017, Reidel, Radicioni et al. 2018, Rubinstein, Delucchi et al. 2018, Wei, Goniewicz et al. 2018). All of these studies were cross sectional studies. One of these studies involved adolescent subjects (Rubinstein, Delucchi et al. 2018).

One small (n=23) US cross sectional study sought to determine the risk profile associated with e-cigarette use for **bladder cancer** (Fuller, Acharya et al. 2017). All subjects were former smokers (not smoking for at least 6 months) and 13 currently used e-cigarettes (mean age 39.4 years) whilst 10 were in a control group that did not use e-cigarettes (mean age 30.1 years). Many of the e-cigarette using subjects (9/13) were long term non-smokers (more than 12 months). Subjects in the e-cigarette group mostly vaped more than 28 times per week, with a range of products used. Urine was tested (using liquid chromatography-mass spectrometry, LC-MS) for five known bladder carcinogens: Benz[a]anthracene, Benzo[a]pyrene, 1-hydroxpyrene, o-toluidine and 2-napthylamine (limit of detection 10-100ng/ml).

It was found that the e-cigarette users had significantly higher concentrations of two of the carcinogenic compounds in their urine, o-toluidine (p=0.0013) and 2-naphthylamine (p=0.014), than the control subjects. Mean concentrations of the **two carcinogenic compounds, o-toluidine and 2-naphthylamine, were 2.3 and 1.3-fold higher in the e-cigarette group compared to the non-e-cigarette group**. The other three tested urinary carcinogens and markers of polyaromatic hydrocarbon (PAH) exposure were not detected in both the subject and control groups.

Limitations of this study include the small sample size and the lack of consideration of confounders such as duration of previous conventional cigarette use, packs per day when smoking, and time since last conventional cigarette. In interpreting these results, it is important to note that the level at which aromatic amines (such as naphthylamines and toluidines) initiate the development of bladder cancer is still unknown, and acceptable limits of exposure have not been determined.

The US cross-sectional study by Reidel et al. (Reidel, Radicioni et al. 2018) assessed NNAL levels in the urine samples of 14 current cigarette smokers, 15 current e-cigarette users (who exclusively or predominantly used e-cigarettes in the previous six months; this group consisted of 7 former cigarette smokers, 5 occasional cigarette smokers and 3 never cigarette smokers) and 15 never smokers. E-cigarette users inhaled an average of 218 ± 61 puffs per day. In this study, urine NNAL levels in e-cigarette users were significantly higher than urine NNAL levels in never smokers (mean NNAL=17.22 ± 6.00 pg/ml creatinine vs 0.41 ± 0.22 pg/ml creatinine in e-cigarette users and never smokers respectively; p≤0.001). However, these levels were considerably and significantly less than the levels observed in smokers. NNAL level was not correlated with the number of puffs per day in e-cigarette users.

Another US cross sectional study (Rubinstein, Delucchi et al. 2018) assessed the presence of the metabolites of five **carcinogenic toxicants** linked to e-cigarette use in the urine samples of **adolescents** aged 13-18 years (n=103).

The study sample was divided into three groups:

- e-cigarette only users (n=67),
- dual users of conventional cigarettes and e-cigarettes (n=16), and

- controls who never used e-cigarettes or conventional cigarettes (n=20).

E-cigarette only users who used nicotine in their e-cigarettes reported using these more frequently, with an average use of 15.1 days/month (SD9.2) compared with 7.6 days/month (SD5.6) (p<0.001) for e-cigarette users who did not use nicotine-containing liquids.

The study tested for the presence of five carcinogenic Volatile Organic Compounds (VOCs):

- acrylonitrile (CNEMA),
- acrolein (3-HPMA),
- propylene oxide (2-HPMA),
- acrylamide (AAMA) and
- crotonaldehyde (HMPMA)

as well as biomarkers of nicotine and tobacco-specific nitrosamine.

Metabolites of all five VOCs were significantly higher in the urine samples of e-cigarette only users compared with controls (acrylonitrile: median (IQR)=1.3 (3.2) vs 0 (1.1) ng/mg creatinine in e-cigarette users and controls respectively, p<0.001; acrolein: median (IQR)=254.3 (191.4) vs 192.8 (261.6) ng/mg creatinine respectively, p<0.05; propylene oxide: median (IQR)=28.8 (25) vs 15.2 (14.4) ng/mg creatinine in e-cigarette users and controls respectively, p<0.001; acrylamide: median (IQR)=67.3 (69) vs 34.5 (41.6) ng/mg creatinine respectively, p<0.001; and crotonaldehyde: median (IQR)=148.7 (99) vs 100.4 (129.9) ng/mg creatinine respectively, p<0.05).

These relationships remained after controlling for sex and race/ethnicity. Urine NNAL levels were also significantly higher in e-cigarette only users compared to controls (mean (IQR) 0.3 (0.7) vs 0 (0) pg/ml creatinine in e-cigarette users and controls respectively, p<0.001). The average number of sessions of e-cigarette use per day was also associated with increased levels of CNEMA (r=0.36, p=0.003), however, days of e-cigarette use in the past month was not associated with urinary VOC levels in e-cigarette only users.

There were no differences in levels of the five VOCs based on the type of e-cigarette product used, however, levels of CNEMA and AAMA were higher in those using e-cigarettes containing nicotine. Levels of the three other significant and likely toxic VOCs were just as high in users of non-nicotine products, an important observation given adolescents often initiate e-cigarette use with nicotine free products. Those who reported using fruit flavours in the past month also had higher CNEMA levels than those who did not (p=0.03). Fruit flavours were the most popular choice among the adolescent e-cigarette users in the study.

One large US cross-sectional study (n=1572) (Wei, Goniewicz et al. 2018) investigated whether the use of e-cigarettes increases the body burden of flame retardants in e-cigarette users (n=14), by testing for urinary metabolites of organophosphate flame retardants (OPFRs). Smokeless tobacco product (STP) users (n=15), conventional cigarette users (n=298), cigar users (n=22) and non-users (n=1201) were also examined.

The chemicals diphenyl phosphate (DPhP), bis(1,3-dichloro-2-propyl) phosphate (BDCPP), bis(2-chloroethyl) phosphate (BCEP), and dibutyl phosphate (DBUP) were detected in all e-cigarette users. After adjusting for gender and the interaction between race/ethnicity and education, the adjusted geometric mean (GM) of BCEP, the metabolite of tris(2-chloroethyl) phosphate (TCEP), was **higher in e-cigarette users** than nonusers (0.67µg/ml (95%CI 0.44, 1.04) and 0.37 (95%CI 0.33, 0.42) respectively; p=0.012). The adjusted GM of all other metabolites of OPFRs for e-cigarette users were not statistically different to that of nonusers.

The numbers in the e-cigarette group in this study were very small (n=14), limiting the power to detect associations and the number of confounders and interactions that could be included in the statistical models.

2.3.1   What the new studies add to what is already known about e-cigarettes

Previous studies

The WHO (World Health Organization 2016) has stated that:
- 'The typical use of unadulterated ENDS/ENNDS produces aerosol that ordinarily includes glycols, aldehydes, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbon (PAHs), tobacco-specific nitrosamines (TSNAs), metals, silicate particles and other elements. Dicarbonyls (glyoxal, methylglyoxal, diacetyl) and hydroxycarbonyls (acetol) also are thought to be important compounds in the aerosol. Many of these substances are toxicants that have known health effects resulting in a range of significant pathological changes.'

The US National Academies of Sciences, Engineering and Medicine Review (Stratton, Kwan et al. 2018) concluded that:
- 'There is **no available evidence** whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for comparisons of e-cigarette use compared with combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products.
- There is **substantial evidence** that some chemicals present in e-cigarette aerosols (e.g. formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis. This supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes. Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined.'

The Public Health England review (McNeill A 2018) stated that:
- 'Among e-cigarette users, two studies of biomarker data for acrolein, a potent respiratory irritant, found levels consistent with non-smoking levels.'

Of the four studies considered in this review, one of the studies was also included in the US review (Rubenstein et al.). The other studies cited above are new to this review. The small Fuller et al study found higher levels of two carcinogenic compounds, o-toluidine and 2-naphthylamine, (mean 2.3 and 1.3 fold higher) for the e-cigarette group compared to the non-e-cigarette group, however levels associated with the initiation of cancer are unknown (these carcinogens are not referred to in the US Academies of Sciences review). The Public Health England Review excluded the Reidel et al and Rubenstein et al studies included here. It concluded that 'the cancer potencies of e-cigarettes were largely under 0.5% of the risk of smoking' (McNeill A 2018).

The US review on the impact of e-cigarettes on adolescents and young people states that the full impact of the constituents of e-cigarettes are not fully understood (US Dept of Health and Human Services 2016). Neither of the previous reviews (US Dept of Health and Human Services 2016, McNeill A 2018, Stratton, Kwan et al. 2018) refer to the impact of flame retardants from e-cigarette use. The Wei et al study (Wei, Goniewicz et al. 2018) therefore provides new information, however the size of the e-cigarette group involved in the study was extremely small. In addition, the health impact was not considered. Recent research has shown an association between TCEP and thyroid cancer.[2] Further research is required on the health effects of exposure to these organophosphate flame retardants and other constituents of e-cigarettes.

Conclusions

In summary, the evidence to date suggests that biological samples of e-cigarette users contain metabolites of various known carcinogens and toxic compounds higher than that observed in the biological samples of non-users. Whether these levels are at high enough levels to indicate a higher risk of cancer or other diseases associated with these compounds in long term e-cigarette users is unknown.

2.4 Respiratory system

This section contains the majority of the reviewed studies related to health risks/outcomes. This includes two randomised trials, one prospective cohort study, and five cross sectional studies. Studies in this section considered health risk factors and outcomes for the respiratory system, including respiratory/lung function (Boulay, Henry et al. 2017, Polosa, Cibella et al. 2017, Staudt, Salit et al. 2018) and human airway biology and immune response in the lung (Reidel, Radicioni et al. 2018). Two studies considered the association between e-cigarette use and asthma (Kim, Sim et al. 2017, Schweitzer, Wills et al. 2017), while others considered self-reported bronchitic symptoms (McConnell, Barrington-Trimis et al. 2017) and breathing/coughing (Gucht, Adriaens et al. 2017, Polosa, Cibella et al. 2017).

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[2] Exposure to common flame retardants may raise the risk of papillary thyroid cancer, Science Daily, 2 April 2017, https://www.sciencedaily.com/releases/2017/04/170402111311.htm

2.4.1 Lung function

A prospective cohort study (Polosa, Cibella et al. 2017) (where one researcher had received industry linked funding) assessed **lung function** including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and forced expiratory flow (FEF at 25-75%). In this Italian prospective cohort study (Polosa, Cibella et al. 2017), subjects (total n=21) were recruited from vape shops, and followed for 3.5 years (nine e-cigarette users who had never smoked and 12 controls had never smoked or vaped). Notably, the FEV_1/FVC ratio was lower for all time points for e-cigarette users compared with controls, but the difference was not significant (p=0.09).

The study also performed high resolution computed tomography [HRCT] scans of the lungs to measure parenchymal micronodules, ground-glass opacity or macroscopic emphysema (early signs of chronic obstructive pulmonary disease, COPD), lipoid pneumonia or popcorn lung disease. There were no early signs of bronchiolitis obliterans or early signs of COPD, lipoid pneumonia or popcorn lung disease in any of the eight e-cigarette users undergoing HRCT.

Only six of the nine subjects in the e-cigarette group were vaping nicotine containing e-liquid by the end of the study, and even these were using lower nicotine strength liquid and the other three were using zero nicotine in e-liquid. It should also be noted that the small group of e-cigarette smokers were very young (mean age 26.6 years).

A US randomised cross-over trial (n=30) that considered the effects of an acute (1 hour) vaping session (with a nicotine free and flavour free liquid with 70%PG/30%Gly) on **lung function** in both healthy and **asthmatic** individuals found no differences between groups for spirometry or Forced Oscillation Technique (FOT) tests (Boulay, Henry et al. 2017). The authors recognised the need to study the effects of chronic use.

Another small randomised trial conducted in the US assessed the effects of e-cigarettes on blood pressure, temperature, heart rate, respiratory rate, oxygen saturation, lung function, plasma endothelial microparticle (EMP) levels, and gene expression in the small airway epithelium and alveolar macrophages (Staudt, Salit et al. 2018).

Ten healthy never-smokers with no history of e-cigarette use or use of any other tobacco product completed a range of tests and provided biological samples including a bronchoscopy brushing of the small airway epithelium and a bronchoalveolar lavage. Participants then attended an experimental session one week later during which they inhaled 10 puffs of an e-cigarette, had a 30 minute break, and then inhaled another 10 puffs. Participants were randomised to use either an e-cigarette with nicotine (n=7) or an e-cigarette without nicotine (n=3) during the experimental session. Baseline testing and collection of biological samples was repeated within 2 hours of the second e-cigarette use.

No significant changes in blood pressure, heart rate, lung function or oxygen saturation were observed, however, plasma EMP levels were significantly higher following use of an e-cigarette with nicotine, an indication of endothelial cell damage which has previously been observed in cigarette smokers.

Acute use of an e-cigarette also changed the gene expression profiles in the small airway epithelium and in alveolar macrophages. Use of the e-cigarette with nicotine led to the up-regulation of 19 genes and the down-regulation of 52 genes in the small airway epithelium whilst use of the e-cigarette without nicotine led to the up-regulation of 40 genes and the down-regulation of 25 genes. Examination of the specific genes affected suggest altered activity of the nicotine receptor pathway and the tumour protein p53. Use of the e-cigarette with nicotine also led to the up-regulation of 6 genes and the down-regulation of 21 genes in alveolar macrophages, whilst use of the e-cigarette without nicotine led to the up-regulation of 25 genes and the down-regulation of 36 genes. It was not possible to identify specific pathways affected in alveolar macrophages, however, several of the genes affected are known to play important roles in macrophage physiology and pulmonary health.

This study has a number of limitations that should be considered when interpreting the results. Firstly, the study is small, reducing the power to detect important changes. Secondly, confounders have not been considered and should be considered when the exposure groups are so small that the randomisation cannot control for the relevant confounders. The study assessed the effect of acute use of e-cigarettes, however, it is likely that prolonged use is required to observe changes in health outcome measures such as lung function. There was also no control group in this study. Ideally, all changes observed should have been compared to any changes observed in a control group not exposed to e-cigarette aerosol with or without nicotine.

2.4.2 Composition and integrity of airway mucous

Reidel et al.'s US cross-sectional study examined the **protein composition and integrity of airway mucus** in e-cigarette users compared with traditional cigarette smokers and a non-smoking control group (Reidel, Radicioni et al. 2018). Proteome and mucin concentrations were analysed from induced sputum samples collected from 14 current cigarette smokers, 15 current e-cigarette users (consisting of 7 previous smokers, 5 occasional smokers and 3 never smokers) and 15 never smokers (n=44).

The protein mucus composition of e-cigarette users was found to be different to that of both cigarette smokers and non-smokers. Compared with non-smokers, induced sputum from e-cigarette users contained approximately 81 proteins with significantly altered abundance. This was higher than that of cigarette smokers whose sputum contained approximately 44 proteins with altered abundance compared to non-smokers. The sputum proteome of e-cigarette users showed an upregulation of a protein marker known to be associated with smoking (aldehyde-detoxifying enzyme aldehyde dehydrogenase 3A1, p≤0.05) and an upregulation of proteins involved in the oxidative stress response (thioredoxin, p≤0.001; and gluthione S-transferase, p≤0.05).

There were higher levels of proteins associated with the innate immune response in both e-cigarette users and cigarette smokers compared to non-smokers, however the specific proteins that were higher in these two groups differed. Unlike the sputum of cigarette smokers, higher levels of the mucosal proteins lactotransferrin, trefoil factor 3, deleted in malignant brain tumors 1 (DMBT1) and lysozyme C were not observed in the sputum of e-cigarette users compared to non-smokers. In fact, lower levels of some of these proteins were observed (eg DMBT 1, p≤0.05; lysozyme C, p≤0.01). However, higher levels of other mucosal proteins were observed in the sputum of e-cigarette users compared to non-smokers (neutrophil elastase, p≤0.005; proteinase 3, p≤0.01; azurocidin, p≤0.01; myeloperoxidase, p≤0.01; matrix metalloproteinase, p≤0.05).

The levels of many of these proteins were also significantly higher than that observed in cigarette smokers' sputum. Higher levels of these specific proteins are indicative of neutrophil protein enrichment in e-cigarette users, however, overall neutrophil cell counts were not higher in e-cigarette users compared to non-smokers, suggesting this altered protein profile is not due to a greater number of neutrophils.

Other proteins associated with neutrophil extracellular traps (NETs) were also higher in e-cigarette users (and not higher in cigarette smokers) compared to non-smokers (calprotectin, p≤0.005; coronin-1, p≤0.005; peptidylarginine deiminase 4, p≤0.05), indicating an increase in NET formation in the airways of e-cigarette users. Concentration of mucin MUC5AC and the MUC5AC/MUC5B ratio in sputum, both of which are correlated with COPD progression, were higher in e-cigarette users compared to non-smokers (p=0.05 for both).

2.4.3 Asthma

In a US cross-sectional study (n=6,089) Schweitzer et al. (Schweitzer, Wills et al. 2017) sought to test the hypothesis that e-cigarette use among **adolescents** was associated with **asthma** independently of cigarette smoking. This study used data from the 2015 HYRBS, a survey conducted every two years by the University of Hawaii with students of public middle and high schools (9th-12th grade, mean age 15.2 years) in Hawaii (78% response rate). The study population was highly culturally diverse.

Current e-cigarette use was significantly associated with current asthma vs never having asthma (adjusted OR 1.48, CI 1.24-1.78) and previous asthma vs never having asthma (AOR 1.20, CI 1.00-1.44). This was independent of conventional cigarettes or marijuana use, which were non-significant in the multivariate analysis. There was a significant association of **ever e-cigarette use** with currently having asthma (compared to never) (AOR 1.22, CI 1.01-1.47), and a marginal association for previously having asthma (AOR 1.19, CI 0.99-1.43). E-cigarette use and cigarette smoking were substantially correlated.

The study concludes that the interpretation that e-cigarette use has a contributory role for asthma is plausible, but the issue of temporal ordering needs to be further examined, i.e. the association shown is possibly explained by those with existing asthma switching from smoking to e-cigarettes. The authors state that a reverse-causation argument (i.e. having asthma causes adolescent smokers to use e-cigarettes) is implausible because the base rates of the behaviours are quite different (45% of the population having ever used e-cigarettes whilst cigarette use was 25%). However, these findings should be further explored through prospective studies. Limitations also include the survey category 'ever having asthma' could have represented asthma occurring in distant childhood rather than recent asthma.

Kim et al.'s large cross-sectional study (n=216,056; including n= 211,166 without asthma and 4,890 with asthma) from South Korea considered the association between **asthma** (recent 12 months) and active, passive and e-cigarette smoking in adolescents (Kim, Sim et al. 2017). Subjects were Korean adolescents from 7th to 12th grade (12 - 18 years of age) who participated in the Korea Youth Risk Behaviour web-based Survey in 2011, 2012 and 2013. Current e-cigarette use was defined as any use in the last 30 days. Prevalence of e-cigarette vaping in this population sample was 8%. E-cigarette users were more likely to be both active and passive smokers ($p < 0.001$).

After adjusting for age, physical exercise, sex, obesity, region of residence, economic level, educational level of father and mother, and active and passive smoking, current e-cigarette use was associated with asthma (AOR [95%CI] 1.13 [1.01-1.26], p=0.027). Whilst the study has a large sample size and adjusted for a number of potential confounders, it was cross-sectional only and variables such as family history of asthma and parental smoking, and past smoking history were not accounted for. The relationship between e-cigarette use and asthma may also be explained by smokers with asthma switching to e-cigarettes. Additionally, smoking and asthma status were self-reported which may result in misclassification and introduce bias, and 'dual use' of conventional and e-cigarettes was not accounted for.

2.4.4 Bronchitis

A few studies referred to self-reports of bronchitis symptoms (McConnell, Barrington-Trimis et al. 2017) and breathing/coughing (Gucht, Adriaens et al. 2017, Polosa, Cibella et al. 2017). McConnell et al.'s US population based cross-sectional study (n=2,083, including 502 or 24% who were ever users of e-cigarettes) considered chronic bronchitis symptoms and wheeze for adolescents who were current users (past 30 days) of e-cigarettes (mean age 17.3 years).

After adjusting for key confounders including sociodemographic characteristics, lifetime number of cigarettes smoked and second-hand smoke (SHS) exposure, risk of bronchitis symptoms was higher in those with a history of e-cigarette use (OR 1.71, 95% CI 1.20-2.43). A similar trend was observed for current e-cigarette use which did not reach statistical significance (OR 1.41, 95%CI 0.92-2.17). Assessment of usage patterns also found a trend of increasing risk of bronchitis symptoms with increasing e-cigarette use (OR 1.37, 95% CI 0.79-2.37 for 1-2 days of use, OR 1.64, 95%CI 0.88-3.05 for ≥ 3 days use/past 30 days), however this trend also did not reach significance (p=0.09; OR 1.24, 95% CI 0.78-1.98). After adjusting for confounders, no association was observed between wheeze and e-cigarette use. The major limitations of this study include the use of self-reported data which can introduce misclassification and bias, and the inability to establish a causal relationship due to the cross-sectional study design.

In the industry-funded Polosa et al. Italian cross-sectional study, where subjects (n=21, mean age 29.7 years) were referred to the study from vape shops, subjects were asked to self-report cough, wheezing, shortness of breath and chest tightness symptoms. No coughing, wheezing, shortness of breath and chest tightness were reported in the group who were e-cigarette users and three participants in the control group (which had been selected from hospital staff) reported cough on three occasions. This small study has a high potential for selection and reporting bias.

2.4.5   What the new studies add to what is already known about e-cigarettes

Previous studies

The US Academies of Science Review (Stratton, Kwan et al. 2018) concluded in relation to respiratory diseases that:
- 'There is **no available evidence** whether or not e-cigarettes cause respiratory diseases in humans.
- There is **moderate evidence** for increased cough and wheeze in adolescents who use e-cigarettes and an association with e-cigarette use and an increase in asthma exacerbations.
- There is **limited evidence** of adverse effects of e-cigarette exposure on the respiratory system from animal and in vitro studies.'

Key findings from the Public Health England (McNeill A 2018) review were that:
- There have been some studies with adolescents suggesting respiratory symptoms among e-cigarette experimenters.

Both the US Academies of Science review and the Public Health England reviews included the McConnell et al. (McConnell, Barrington-Trimis et al. 2017) study, whilst the Public Health England Review also included the Schweitzer et al. (Schweitzer, Wills et al. 2017) study.

The remaining studies are new to this review: Thus there are 6 new studies presented here. Two of these 6 studies involved subjects who were recruited from vape shops (Gucht, Adriaens et al. 2017, Polosa, Cibella et al. 2017). Two of the large cross-sectional studies that showed a relationship between asthma and e-cigarettes may simply show a temporal relationship (Kim, Sim et al. 2017, Schweitzer, Wills et al. 2017) rather than a causal relationship. Studies showed no or small effects of short term e-cigarette use on lung function (both increases and decreases on respiratory flow) (Boulay, Henry et al. 2017, Gucht, Adriaens et al. 2017, Staudt, Salit et al. 2018), but sample sizes were small.

The Reidel et al. (Reidel, Radicioni et al. 2018) and Staudt et al. (Staudt, Salit et al. 2018) studies provide evidence that e-cigarette use alters the abundance of proteins in lung tissues and fluids, indicating an increase in oxidative stress, endothelial damage and mucins associated with the progression of COPD; upregulation of neutrophilic immune function; and altered activity of the tumour protein p53, a protein which is important in preventing the development of cigarette-induced lung cancer. Whilst results from both of these studies are promising, each study has substantial limitations including small sample sizes and potential confounding effects.

Conclusions

Further research is needed to establish if e-cigarettes increase the risk of lung conditions and the pathways through which such increased risk may occur. In particular, large, well-designed cohort studies with longer follow-up periods are needed.

2.5 Lymphatic system

In one UK case study (self-reported), (Miler and Hajek 2017) a 26 year old female never-smoker with a history of frequent tonsillitis, recurrent tonsilloliths, sore throat upon waking and coughing/phlegm, became a vaper and after 3 months of e-cigarette use (using 8-20mL e-liquid per day, 0-3mg/mL nicotine, various flavours) experienced a complete resolution of chronic tonsillitis (along with her other symptoms of phlegm, sore throat, etc) and experienced intermittent tonsilloliths. After 8 months tonsillitis had not recurred and her tonsilloliths had markedly improved, and she had not experienced a respiratory infection or cold. This was attributed to the **propylene glycol** in e-cigarettes possibly influencing a microbial strain or the **anti-inflammatory effects of nicotine**. A single case study is anecdotal, useful for the development of hypotheses and in need of verification in a larger study sample.

2.5.1 What the new study adds to what is already known about e-cigarettes

The case study cited above was also referred to in the UK review (McNeill A 2018), which also cited a suggestion that a controlled trial with nicotine free e-cigarettes in non-smoking patients could provide more definitive answers on the potential role of e-cigarettes in reducing current throat infections. It also noted animal studies did not raise concerns about health consequences associated with propylene glycol and glycerine (McNeill A 2018). The US Academies of Science (Stratton, Kwan et al. 2018) review did not consider case studies.

2.6 Oral health

An Italian case-control study (n=90) (Bardellini, Amadori et al. 2018) tested for nine types of oral mucosal lesions (OMLs) in former smokers (n=45) and current e-cigarette users (n=45). For all OMLs, there was no significant difference between the two groups. There were no differences for precancerous OMLs for the two groups; and only one case of squamous cell carcinoma was found on the tongue of a former smoker. The odds ratios for e-cigarette users (when compared to former smokers) were significant for the OMLs **nicotine stomatitis** (OR 6.77, p=0.04), **hairy tongue** (OR 8.11, p=0.02) and **hyperplastic candidiasis** (OR 4.65, p=0.04). However, the number in the groups was small and further studies are required to test OMLs and draw conclusions. It was unclear if the e-cigarette user group were sometimes dual users.

2.6.1 What the new studies add to what is already known about e-cigarettes

Periodontal disease can be measured through intermediate outcomes such as bleeding after probing, plaque index, amount of gingival crevicular fluid, gum recession, bone resorption and tooth loss (Stratton, Kwan et al. 2018). Only the US Academies of Sciences review (Stratton, Kwan et al. 2018) refers to studies which included such measures whilst the UK review does not. The Bardellini et al study is a new study flagging significantly higher levels of some OMLs for e-cigarette users compared to former smokers.

The US Academies of Science review also notes a lack of rigorously designed studies exploring the effects of e-cigarettes on oral health, and no epidemiological studies examining the incidence or progression of periodontal disease. It notes that existing studies suggest that the e-cigarette aerosols can induce gingival inflammation, but that e-cigarette use may be less harmful than tobacco smoking for oral health. It concludes that there is limited evidence suggesting that switching to e-cigarettes will improve periodontal disease or that e-cigarette aerosol can cause oral tissue damage in non-smokers (Stratton, Kwan et al. 2018).

2.7 Dermatitis

One UK case study report (Shim and Kosztyuova 2018) covered two cases of dermatitis (one 50 year old male patient, one 38 year old female patient) caused by nickel in e-cigarette (vaporiser) pens. The male patient presented with hand and facial dermatitis. He had used e-cigarettes for the past six years. He was strongly positive to **nickel** and positive to **mercaptobenzothiazole**. The female patient had a three-year history of pruritic patches on her right palm. Testing showed a positive reaction to nickel.

2.7.1 What the new studies add to what is already known about e-cigarettes

The US Academies of Sciences review notes that allergic dermatitis has previously been associated with propylene glycol (PG) as well as nickel (Stratton, Kwan et al. 2018). The US Academies of Science study does not refer to the allergenic properties of mercaptobenzothiazole – which could also have been linked to the dermatitis in the case study above. The UK review (McNeill A 2018) does not refer to studies on dermatitis associated with e-cigarette use.

2.8 Wound healing

Two case studies reported on the detrimental effects of e-cigarette use upon **wound healing following surgery**. One article (Fracol, Dorfman et al. 2017) presents a US case where wound healing and breast reconstruction failed. The 51-year-old patient had a 1.5 pack/day conventional cigarette smoking history and had ceased smoking several months prior to surgery. Three months prior to surgery for a bilateral mastectomy and immediate tissue expander reconstruction (for a diagnosed right breast cancer) she had started using e-cigarettes (with usage similar to her previous 1.5 pack per day conventional cigarette use). The patient had significant mastectomy skin flap necrosis and breast reconstruction failure.

In another US case (Agochukwu and Liau 2018), a 21 year old male patient used e-cigarettes within 24 hours of free flap (tissue transplantation) surgery. The patient underwent several debridements prior to free flap reconstruction, with the goal of obtaining soft tissue control and coverage prior to tendon reconstruction. Smoking just one e-cigarette within 24 hours of the free flap operation had a significant impact, with the patient having a significant drop in his free flap tissue oximeter readings. Immediately after surgery (free flap reconstruction), the Vioptics reading was in the low 70% range, but less than 24 hours after his surgery, the Vioptics reading had dropped to 19%. On exam, they found the flap to be pale but still with capillary refill and arterial and venous doppler signals. This problem was attributed to the vasoconstrictive effects of nicotine. Nicotine intake was not advised immediately after any surgery.

2.8.1 What the new studies add to what is already known about e-cigarettes

These case studies are potentially significant and have not been referred to in prior comprehensive reviews (McNeill A 2018, Stratton, Kwan et al. 2018). These should be a consideration for harm reduction strategies for surgical patients who use e-cigarettes. Further studies on wound healing and e-cigarette use are likely to be informative.

2.9 Oxidative stress

Moheimani et al. considered oxidative stress and inflammation (Moheimani, Bhetraratana et al. 2017) in **habitual e-cigarette users**. Low-density lipoprotein oxidizability, indicative of susceptibility of apolipoprotein B-containing lipoproteins to oxidation, was **significantly increased in e-cigarette users** (n=12) compared with non-user control participants (n=18) (mean, 3801.0 [415.7] U vs 2413.3 [325.0] U, p=0.01), consistent with increased oxidative stress. High-density lipoprotein antioxidant index was not different between the groups and inflammatory markers were not different between the groups.

In a later study (Moheimani, Bhetraratana et al. 2017), the same group also examined changes in oxidative stress resulting from e-cigarette use in a **short-term** laboratory randomised cross-over study with **non-users of e-cigarettes or tobacco** (included those who had quit for more than one year) (n= 33). There were **no differences** found for changes in any measures of oxidative stress or inflammation for e-cigarette with nicotine and e-cigarette without nicotine users, compared to the sham control.

2.9.1 What the new studies add to what is already known about e-cigarettes

The two small studies reviewed here suggest that short-term e-cigarette exposure does not lead to changes in oxidative stress although it may be associated with habitual e-cigarette use.

2.10 Oral and gut microbiota

A small US cross-sectional study conducted assessed the effect of use of e-cigarettes on the number and diversity of microbial communities in the oral cavity and gut (Stewart, Auchtung et al. 2018). The study involved ten daily e-cigarette users (daily use for at least 6 months), ten tobacco smokers and ten matched controls. There were no differences in age, gender, diet, BMI or race between the three groups, however there were only two females (6.7% of participants) who took part in the study (one e-cigarette user and one control). Diet was also simply categorised as meat eater, vegetarian and vegan with 90% of e-cigarette users and controls being meat eaters.

No differences were found in the bacterial profiles of the fecal samples, buccal swabs or saliva samples of e-cigarette users compared to the control group (p= 0.26, 0.89 and 0.38 for fecal, buccal and saliva samples respectively). Similarly, no differences were observed in the relative abundance of the bacterial genera identified in these samples between the e-cigarette and control groups.

Whilst this study explores an interesting hypothesis, it has a number of significant limitations. Firstly, the small sample size limits the capacity of the study to detect differences between groups. The study has also not considered some important confounders such as socioeconomic status, physical activity and alcohol consumption. Diet, which greatly affects the bacterial communities that exist in the oral cavity and gut, has been crudely controlled for. Large cohort studies are needed to explore the potential relationship between e-cigarette use and the microbiota of the oral cavity and gut appropriately.

2.11 Conclusions

2.11.1 Consistency with previous reviews

This update review largely supports the findings and conclusions of other recent reviews with regard to the health effects of e-cigarette use (McNeill A 2018, Stratton, Kwan et al. 2018). These include:

- The large cross-sectional studies in this review showing a link between asthma and e-cigarette use in adolescents (Kim, Sim et al. 2017, Schweitzer, Wills et al. 2017) may represent temporal ordering (i.e. existing asthma prompting switching to e-cigarettes).

- The review supported findings on exposure to metals and chemical exposure from e-cigarette use regarding aldehydes (Reidel, Radicioni et al. 2018) .

- Exposure to nickel has previously been associated with e-cigarette use (Stratton, Kwan et al. 2018).

- More research is required on the role of e-cigarettes and throat infections.

- The general poor quality (McNeill A 2018), small size or short-term nature of the studies reviewed – more prospective cohort studies and larger studies that are not industry funded are required.

2.11.2 Findings and new areas not previously considered in other reviews

Some new studies in this review have highlighted potential issues of concern in the following areas:

- Wound healing following surgery – while the evidence is only based on case studies, this may have implications for e-cigarette use following surgery.

- Exposure to particular carcinogenic compounds (Fuller, Acharya et al. 2017) and flame retardants from e-cigarette use (Wei, Goniewicz et al. 2018). The implications of raised levels of these chemicals in the body at the levels observed are not well understood.

- Cross sectional studies showed a relationship between e-cigarette use and some types of oral mucosal lesions (OML). More studies on OML and e-cigarette use are required.

- One study suggested that mercaptobenzothiazole was a source of allergic reactions which had not previously been referred to in relation to e-cigarettes.

- Some measures of oxidative stress were increased among habitual e-cigarette users compared to non-users, but not following short term e-cigarette use. Studies in this area were small and results can be considered suggestive only.

2.11.3 Key findings

- A lack of long-term studies means there continues to be no evidence for e-cigarette use to be associated with clinical cardiovascular disease.
- Carcinogenic compounds and carcinogenic metabolites arising from e-cigarette use are demonstrated to be present in e-cigarette users, and in animal studies. However the risk of the development of cancer or other health effects from the levels found is unclear.
- Use of e-cigarettes may impair lung function although the independent effect of e-cigarettes is unclear because of potential confounding by conventional cigarette smoking.
- Case studies, which do not provide strong evidence, have suggested that e-cigarette use interferes with, or delays, wound healing. While these reports are suggestive, this has not yet been examined using appropriately designed studies.

3 Injuries and poisoning

3.1 Introduction

In this section, recent literature on injuries and poisoning resulting from the use of e-cigarettes is reviewed. The section addresses part of the assigned task to 'review all available evidence applicable to the impacts of the use of e-cigarettes, personal vaporisers and nicotine on individual and population health.' A total of 31 papers were reviewed (including two reports that were reviewed based only on the available abstracts):

- 14 case reports
- 8 retrospective case reviews
- 3 case reports (including a literature review)
- 5 letters or commentaries
- 1 cross-sectional study

3.2 Exploding e-cigarettes

The majority of the case reports (nine out of a total of 14) described malfunctioning e-cigarettes where the device exploded or caught fire (Ban, Krishnan et al. 2017, Bauman, Roman et al. 2017, Brooks, Kleinman et al. 2017, Foran, Oak et al. 2017, Norii and Plate 2017, Satteson, Walker et al. 2017, Treitl, Solomon et al. 2017, Ackley, Williams et al. 2018, Chi, Neville et al. 2018).

The cause is stated to be that the lithium ion battery short circuits due to overheating, water exposure, excessive charging, improper charging with incompatible devices, contact with metallic objects or physical battery damage. This so-called 'lithium ion battery runaway' causes an explosion and fire resulting in thermal and chemical burns. Exploding e-cigarettes can also cause projectile injuries where the parts of the device are injected into various parts of the body such as the mouth, mandible, thigh or hand.

The case reports describe the device being in the trousers pocket of the user resulting in burns to the upper legs and lower trunk (Bauman, Roman et al. 2017, Harshman, Vojvodic et al. 2017, Patterson, Beckett et al. 2017, Treitl, Solomon et al. 2017) as well as trauma to the mouth or hands (Satteson, Walker et al. 2017). Five groups of investigators describe facial and arm burns as well as parts of the device being lodged in the mandible and mouth (Anderson, Richie et al. 2017, Ban, Krishnan et al. 2017, Brooks, Kleinman et al. 2017, Foran, Oak et al. 2017, Norii and Plate 2017, Satteson, Walker et al. 2017, Ackley, Williams et al. 2018, Chi, Neville et al. 2018).

Figure 1: Burn to thigh sustained from exploding e-cigarette in pocket; Bauman et al 2017

Foran et al 2017 described a high pressure injection-type injury resulting from the explosion of an electronic cigarette, with injection of e-liquid into the index finger (Foran, Oak et al. 2017).

There were 8 retrospective case review papers (Jiwani, Williams et al. 2017, Ramirez, Ridgway et al. 2017, Rudy and Durmowicz 2017, Serror, Chaouat et al. 2017, Smith, Smith et al. 2017, Toy, Dong et al. 2017, Corey, Chang et al. 2018, Hickey, Goverman et al. 2018). They all described the exploding e-cigarette phenomenon. Four mechanisms were considered responsible for injuries. These could be unique or associated with each other: thermal burns with flames, blast lesions secondary to the explosion, alkali chemical burns and thermal burns without flames (overheating).

Figure 2: Burn to hand sustained from exploding e-cigarette; Hickey et al 2018

Ramirez et al 2017 identified thirty patients with burns resulting from e-cigarettes from three burns centres in the United States from January 2007 to July 2016. Twenty-nine were referred within the most recent 18 months, with the remaining one being referred in the 8 years prior. An explosion was identified by the patient as the precipitating event in 26 of the 30 injuries (87%). Explosion of an isolated battery while it was carried on personal attire was reported in 10 cases. Explosion of a fully assembled e-cigarette was described in 16 cases. In seven of these 16 cases (44%), the explosion occurred while the device was idle and being carried on personal attire. In the other nine cases, the explosion occurred while the device was being operated. No injuries were reported to have occurred while batteries were charging (Ramirez, Ridgway et al. 2017).

Serror et al 2017 describe ten patients that were treated for e-cigarette injuries at one burns centre in Paris, France. In eighty percent of these cases, the e-cigarette exploded while in the pocket (Serror, Chaouat et al. 2017).

Toy et al 2017 (Toy, Dong et al. 2017) reviewed patients from a burns registry in California that admits approximately 400 patients annually. Twenty five patients from this registry had sustained burns associated with e-cigarettes over a 16 month period in 2015-16. Twenty four out of the 25 patients were male and this gender imbalance, consistent with the other reviews, may be due to a preference of men to store e-cigarettes (and other items such as coins and phones) in their trouser pockets.

3.3 E-cigarette liquid ingestion

The other major injury event that is reported is the deliberate ingestion of nicotine containing e-cigarette liquid (Lam, Tang et al. 2017, Morley, Slaughter et al. 2017, Van Der Meer, Pranger et al. 2017, Park and Min 2018).

Morley et al reported the death of a 32 year old male who ingested e-cigarette liquid while under the influence of alcohol (Morley, Slaughter et al. 2017). Park et al 2018 describe two case reports

of attempted suicide by e-cigarette liquid ingestion. Both patients had transient cardiomyopathy but ultimately survived (Park and Min 2018).

Even a few millilitres of nicotine can be lethal therefore nicotine intoxication due to e-liquid ingestion should be considered potentially life-threatening. Generally though, death from e-cigarette liquid ingestion is very rare. More commonly e-cigarette liquid ingestion causes extreme drowsiness, confusion, cardiac arrests and seizures.

3.4 Miscellaneous injuries

Andresen et al 2018 described the case of a man acquiring a chemical burn and throat injury after falling with an e-cigarette in his mouth (Andresen, Lee et al. 2018).

Cant et al 2017 described a necrotic oral ulcer resulting from smoking e-cigarettes apparently as a result of the heating element burning the roof of the mouth (Cant, Collard et al. 2017).

Finally there is a suggestion from Cho et al 2017 that daily e-cigarette use among adolescents may be a risk factor for cracked or broken teeth and tongue and inside-cheek pain (Cho 2017).

3.5 Conclusions

This review of recent case reports and case series indicates that e-cigarettes can explode and cause projectile injuries. While uncommon events, the increase in popularity of e-cigarettes in the US is accompanied by an increase in e-cigarette injury occurrence. Raising awareness about the potential for major injury due to explosions is relevant for e-cigarette users and potential users, and awareness raising amongst medical staff would also be relevant to improve medical care.

Prevention of injuries might be expected to be able to be achieved through improving battery design, battery testing standards and public awareness relating to e-cigarette battery safety. Such safety practices might include advising users to carry devices away from their body in dedicated carrying cases, and without other loose metallic items.

Regulations and continued monitoring of the hazards of e-cigarette use is likely to optimize public safety. Serious injury from explosions and ingestion of harmful e-cigarette liquids can be mitigated with adequate oversight and regulations.

Case reports and case series are useful in reporting rare and atypical events but have limited use as a methodology to provide information on prevalence. This review is consistent with, but doesn't contribute any further insights into, the findings from the US Academies of Science Review and the Public Health England Review. The Public Health England 'Review of e-cigarettes and heated tobacco products' accessed National Poisons Information Service data and data from burn treatment centres to gain better insights into the prevalence and context of injuries from e-cigarettes. Even with access to this information they can only conclude that e-cigarette explosions are 'very rare'. Even so, because of the seriousness of the injuries, it is important to be aware of these incidents and for potential action to minimise future events. There were no Australian case reports in the scientific literature, and the majority of reports of injury from e-cigarettes were from the USA and UK.

Previous studies
The US National Academies of Sciences Review (Stratton, Kwan et al. 2018) concluded that in relation to injuries and poisonings :
- 'There is conclusive evidence that e-cigarette devices can explode and cause burns and projectile injuries. Such risk is significantly increased when batteries are of poor quality, stored improperly or are being modified by users.
- There is conclusive evidence that intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects including but not limited to seizures, anoxic brain injury, vomiting, and lactic acidosis.
- There is conclusive evidence that intentionally or unintentionally drinking or injecting e-liquids can be fatal.'

3.6 Key findings

- The studies reviewed in this section are mainly case studies and case series. However, the injuries incurred can be attributed directly to e-cigarettes.

- E-cigarettes can explode and cause serious projectile and thermal injuries.

- While uncommon events, if e-cigarettes were to increase in popularity without modification, injuries from e-cigarettes could be expected to increase in occurrence.

- Intentional or accidental ingestion of e-fluids can cause serious injury or death.

4 Animal Studies

4.1 Introduction

In this section, recent studies using animal models that are relevant to the health effects of e-cigarettes are reviewed. This section addresses part of the assigned task to 'review all available evidence applicable to the impacts of the use of e-cigarettes, personal vaporisers and nicotine on individual and population health.' From the combined literature searches, 40 reports were identified to be animal studies. Of these, 26 reports were excluded as they were:

- conference abstracts (n=12);
- abstract only (n=8);
- not specific to e-cigarettes (n=4);
- not in live animals (n=5).

Sixteen remaining articles were included.

4.2 Effects on the brain's reward system

Two studies investigated the effects of rodent e-cigarette exposure on the brains reward system.

In the first study, mice exposed to e-cigarette vapour, at doses equivalent to human use, had higher levels of both nicotine and cotinine in the frontal cortex and increased expression of some neurotransmitter transporters in the frontal cortex, striatum and hippocampus. The results indicate that nicotine containing e-cigarettes may upregulate glutamate and therefore are involved in the reward system associated with addiction (Alasmari, Crotty Alexander et al. 2017).

A study by Harris et al. 2018 found that e-cigarette liquids bind with nicotinic acetylcholine receptors, leading to its partial inhibition and possible reduction in the reward system (Harris, Muelken et al. 2018). When intracranial self-stimulation of rats was tested researchers found that rats given IV e-cigarette liquid had the same levels of intracranial self-stimulation as those exposed to pure nicotine (Harris, Muelken et al. 2018). However, this study has a key limitation of not replicating usual intake of e-cigarettes (i.e. IV injection rather than vapour). It is likely that the activation of the brains reward system results from the nicotine present in e-cigarettes, not the other components of e-cigarette liquids (Harris, Muelken et al. 2018).

4.3 Effects during pregnancy

Two studies investigated the effects of e-cigarette vapour and components during the perinatal period, both studies used doses equivalent to human use (Kennedy, Kandalam et al. 2017, Chen, Li et al. 2018).

One study randomised seven week old female mice to room air, nicotine-containing tobacco flavoured e-cigarette vapour (equivalent to 2 tobacco cigarettes twice daily) or nicotine-free tobacco flavoured e-cigarette vapour (Chen, Li et al. 2018). Mothers exposed to e-cigarettes, regardless of nicotine content, had significant lung inflammatory responses (increased pro-inflammatory cytokines IL-1β, IL-6, and TNF-α). The adult male offspring that were exposed in utero had altered homeostatic levels of several pro-inflammatory cytokines with the effect being partially independent of nicotine content (Chen, Li et al. 2018). Thus, different signalling pathways may be altered in mothers and offspring, and epigenetic modifications are likely to contribute in the offspring. The authors state that their findings indicate that exposure to e-cigarettes can lead to immune dysregulation in the lung (Chen, Li et al. 2018).

Kennedy et al. added varying flavours of e-cigarette liquids to petri dishes containing frog embryos in a controlled trial (Kennedy, Kandalam et al. 2017). They found that frog embryos exposed to e-cigarette liquid had craniofacial defects, including median facial clefts and midface hypoplasia, reduced blood supply to the face and muscle defects (Kennedy, Kandalam et al. 2017). They compared craniofacial defects resulting from both nicotine-containing e-cigarette liquids and nicotine-free e-cigarette liquids and found similar craniofacial defects in both (Kennedy, Kandalam et al. 2017). As a result, the authors attributed the craniofacial defects to components found in e-cigarettes other than nicotine (Kennedy, Kandalam et al. 2017).

Thus, results from these studies indicate that maternal e-cigarette exposure during pregnancy, whether nicotine containing or not, is linked to poorer health outcomes in both the mother and the offspring in animals.

4.4 Environmental impacts

Responding to concerns about the environmental impact of e-cigarettes, a study investigated the impact of cigarette and e-cigarette leachates on frog embryos (Parker and Rayburn 2017). In this study, researchers exposed frog embryos to either regular cigarette butt leachate, menthol cigarette butt leachate or e-cigarette leachates to determine the median concentrations for non-observed adverse effects, lowest observed adverse effects, malformations and median lethal concentrations (Parker and Rayburn 2017). The researchers found toxic effects from all three compounds, however e-cigarettes displayed the lowest toxic and teratogenic effects (Parker and Rayburn 2017).

4.5 Lungs and airway function

Five studies used mice (n=3) or rats (n=2) to investigate lung function after exposure to e-cigarette components (Laube, Afshar-Mohajer et al. 2017, Phillips, Titz et al. 2017, Crotty Alexander, Drummond et al. 2018, Lee, Park et al. 2018, Reinikovaite, Rodriguez et al. 2018). Studies exposed mice or rats daily to either e-cigarette vapour or room air, with three studies providing doses equivalent to human usage (Crotty Alexander, Drummond et al. 2018, Lee, Park et al. 2018, Reinikovaite, Rodriguez et al. 2018).

One study found that e-cigarette vapour inhalation increased the levels of circulating inflammatory cytokines in the lungs, including elevated dipeptidyl peptidase-4 (DPPIV) (Crotty Alexander, Drummond et al. 2018). DPPIV is thought to be involved in the development of liver, cardiac and kidney fibrosis (Crotty Alexander, Drummond et al. 2018).

In another study, e-cigarette vapour without nicotine led to stimulation of mucociliary clearance whereas e-cigarette vapour with nicotine slowed mucociliary clearance (Laube, Afshar-Mohajer et al. 2017). Slowed mucociliary clearance may reduce the ability of an animal to protect its airways from pollutants, allergens and pathogens (Laube, Afshar-Mohajer et al. 2017).

Another study exposed mice to e-cigarette vapour and found increased DNA adducts in their lungs and decreased DNA repair proteins compared to room air (Lee, Park et al. 2018). In this study, higher quantities of DNA adducts were found in the lungs compared with the bladder, liver and heart (Lee, Park et al. 2018).

In a study by Phillips and collegues, female rats exposed to nicotine-containing e-cigarette vapour had slightly higher inflammation indicators in the lungs (macrophage and total cell counts) (Phillips, Titz et al. 2017).

The final study found that all of the experimental conditions (e-cigarette vapour, cigarette smoke and subcutaneous nicotine injections) led to emphysematous lung destruction and decreased capillary counts in rats (Reinikovaite, Rodriguez et al. 2018). In this study, capillary counts were significantly lower in the groups exposed to e-cigarette vapour and to cigarette smoke when compared with the group receiving IV nicotine (Reinikovaite, Rodriguez et al. 2018), highlighting the independent deleterious effects of e-cigarette vapour and tobacco smoke on lung health.

Thus, all five studies found that rodents exposed to e-cigarette vapour had worsened lung health in comparison to the control condition of room air only.

4.6 Other organs

4.6.1 Adrenal glands

Adrenal gland weight significantly increased among rats exposed to nicotine-containing e-cigarette vapour, reflecting a possible stress-response to the nicotine (Phillips, Titz et al. 2017). In this study, the dose of e-cigarettes given to rats marginally exceeded the equivalent usual human dose.

4.6.2 Bladder

Mice exposed to e-cigarette vapour, at levels equivalent to human use, had more DNA adducts in their bladder and had lower amounts of DNA repair proteins compared to the control mice (Lee, Park et al. 2018).

4.6.3 Brain

In a study on mice, cigarette and e-cigarette exposure led to downregulation of thrombomodulin (an anti-coagulant), which indicated an increased risk of stroke due to increased coagulation parameters (Kaisar, Villalba et al. 2017). Cigarette and e-cigarette exposure both led to downregulation of Nrf2 expression (nuclear factor erythroid 2-related factor) (Kaisar, Villalba et al. 2017). After both exposures, the brain infarct area increased (after transient middle carotid artery occlusion) and there were worse neurological deficits compared to control mice (Kaisar, Villalba et al. 2017). Thus, the use of e-cigarettes may increase indicators of stroke risk, however studies which provide doses equivalent to human use and studies in humans are required to confirm this.

Furthermore, in this study, measures of oxidative stress and its impact on the blood-brain-barrier were investigated (Kaisar, Villalba et al. 2017). Oxidative stress (assessed using a fluorogenic probe) was induced in both the e-cigarette group and the cigarette group, at a higher level than in the control group. E-cigarettes and cigarettes elicited a similar inflammatory response (downregulated tight junction protein ZO-1, decreased trans-endothelial electrical resistance (both indicating blood-brain-barrier impairment) and upregulated PECAM-1, ICAM-1 and VCAM-1 (indicators of inflammation)) and were equally harmful (Kaisar, Villalba et al. 2017). These results indicate that both e-cigarettes and cigarettes have the ability to induce oxidative stress which can reduce function of the blood-brain-barrier (Kaisar, Villalba et al. 2017).

4.6.4 Heart

E-cigarette vapour exposure, at levels equivalent to human use, was associated with fibrosis of the heart and increased blood pressure in mice (Crotty Alexander, Drummond et al. 2018). Additionally, mice exposed to e-cigarettes, at levels equivalent to human use, had more DNA adducts in their heart and had lower amounts of DNA repair proteins compared to the control (Lee, Park et al. 2018).

4.6.5 Kidneys

Chronic inhalation of e-cigarette vapour in mice, at a dose equivalent to human use, led to renal dysfunction, fibrosis and increased expression of pro-fibrotic factors (Crotty Alexander, Drummond et al. 2018).

4.6.6 Liver

Studies in rats and mice found that exposure to e-cigarette vapour led to increased levels of hepatic fibrosis (at a dose equivalent to human use) (Crotty Alexander, Drummond et al. 2018), reduced serum lipid concentrations (Phillips, Titz et al. 2017) and increased the weight of the liver (Phillips, Titz et al. 2017). In female rats exposed to nicotine-containing e-cigarette vapour, alanine aminotransferase and alkaline phosphatase (liver enzymes) increased in activity (Phillips, Titz et al. 2017). Hepatocyte vacuolation was observed more frequently in the liver of nicotine-exposed rats (Phillips, Titz et al. 2017). However, the doses of e-cigarettes given to rats in this study marginally exceeded the equivalent usual human dose (Phillips, Titz et al. 2017).

4.6.7 Reproductive system

One study in male rats investigated the impact of e-liquids on the epididymis (Rahali, Jrad-Lamine et al. 2018). The researchers gave the rats injections of either sodium chloride (control), sodium chloride mixed with nicotine-containing e-liquid or sodium chloride mixed with nicotine-free e-liquid. The doses were lower than the equivalent human dose and doses were one injection per day, which does not represent the method of exposure in humans. Rats were injected daily for 28 days. After 100 days they were sacrificed and sperm count assessed. E-liquid exposure induced a significant decrease in the epididymal spermatozoa number. The sperm number was 32.3 ± 3.0 million/ml in the nicotine-free e-liquid rats and 38.4 ± 0.9 million/ml in the nicotine-containing e-liquid rats, while the sperm count reached 42.5 ± 2 million/ml in the control rats. Results showed a significant decrease in the percentage of viable cells after nicotine-free e-liquid and nicotine-containing e-liquid exposure in comparison to the control group. Thus, e-cigarettes may also negatively affect reproductive health.

4.7 Serum lipids and glucose concentrations

Rats exposed to nicotine-containing e-cigarettes, at doses marginally exceeding the equivalent human dose, had lower total blood protein concentrations (females only), total blood cholesterol and blood glucose concentrations compared to rats which were not exposed to nicotine (Phillips, Titz et al. 2017).

4.8 Skin flap

Rats exposed to e-cigarette vapour or regular cigarette smoke had higher necrosis in dorsal skin flaps than those exposed to room air (Rau, Reinikovaite et al. 2017). There was no correlation between serum cotinine levels and skin flap necrosis (Rau, Reinikovaite et al. 2017). While this study did not explicitly state that e-cigarette exposures were modelled to imitate human exposure, nicotine and cotinine levels of the rats indicate that levels were consistent with levels seen in human e-cigarette users.

4.9 Toxicology and oxidative stress

Three studies reported on toxicological effects of e-cigarettes.

The first study investigated rats exposed to differing concentrations of e-cigarette vapour with and without nicotine. The researchers did not find any toxicologically relevant effects of e-cigarettes at the concentrations given, which marginally exceeded usual human doses (Phillips, Titz et al. 2017).

The second study, also in rats, did not aim to replicate human e-cigarette exposure (Canistro, Vivarelli et al. 2017). In this study, rats exposed to high levels of e-cigarette vapour had changes in Cytochrome P450 which were related to increased risk of cancer (Canistro, Vivarelli et al. 2017). Rats also had higher plasma levels of reactive oxygen species, reduced antioxidant abilities (measured by ferric reducing antioxidant power, aka FRAP) and more DNA fragmentation than the control group (which was exposed to room air) (Canistro, Vivarelli et al. 2017).

The final study was conducted by Cobb et al. and compared the effects of e-cigarette vapour and cigarette smoke on stress-induced sleep and metallothioneins (MTs) (Cobb, Hall et al. 2018). MTs indicate the presence of reactive oxygen species, induced by toxic substances and include *mtl-1* and *mtl-2*. *C. elegans* larvae (nematodes) were incubated and exposed to cigarette smoke, e-cigarette vapour or fresh air in varying quantities (15, 30 or 45 puffs). Exposure to cigarette smoke resulted in dose-dependent increases in stress-induced sleep in the nematodes, whereas e-cigarette vapour and the control did not. Cigarette smoke, but not e-cigarette vapour, induced *mtl-1* expression. No condition induced *mtl-2* expression. This indicates increased reactive oxygen species presence after exposure to cigarette smoke but not e-cigarettes. Thus, this study found that e-cigarettes had a minimal toxic impact on the nematodes, whereas cigarettes did.

These three studies indicate that while e-cigarettes may increase oxidative stress, they likely have lower levels than cigarette smoke and do not elicit toxic responses.

4.10 Infection

One study investigated the effect of e-cigarette vapour on infection by exposing mice to e-cigarette vapour after nasopharyngeal pneumococcal colonisation (Miyashita, Suri et al. 2018). The nicotine-free e-cigarette vapour did not increase nasopharyngeal pneumococcal colony forming units (CFU) or nasal epithelial platelet activating factor receptor (PAFR) expression at four days post intranasal instillation of bacteria, but the nicotine-containing e-cigarette vapour did (Miyashita, Suri et al. 2018). Vulnerability to invasive pneumococcal disease is associated with exposure to tobacco smoke.

4.11 Conclusions

Recent studies indicate that e-cigarette vapour can cause significant damage to frog embryos, rats and mice. Adverse outcomes include increased release of pro-inflammatory cytokines, emphysematous lung destruction, renal, hepatic and heart fibrosis among rodents exposed to e-cigarettes vapours or IV e-cigarette liquids compared with those exposed to room air. E-cigarette vapour exposure also had significant effects on offspring of exposed pregnant mice and frog embryos including increased release of pro-inflammatory cytokines, sleep disturbances and craniofacial defects.

4.12 Key findings

- Recent studies indicate that e-cigarette vapour can cause significant damage to frog embryos, rats and mice.

- Adverse outcomes include increased release of pro-inflammatory cytokines, emphysematous lung destruction, renal, hepatic and heart fibrosis among rodents exposed to e-cigarettes vapours or intravenous e-cigarette liquids compared with those exposed to room air.

- E-cigarette vapour exposure also had significant effects on offspring of exposed pregnant mice and frog embryos including increased release of pro-inflammatory cytokines, sleep disturbances and craniofacial defects.

5 In Vitro Studies

5.1 Introduction

This section reviews in vitro studies relevant to the health effects of e-cigarettes. In vitro studies refer to studies of isolated tissue or samples – excluding studies of living humans or animals. This section addresses part of the assigned task to 'review all available evidence applicable to the impacts of the use of e-cigarettes, personal vaporisers and nicotine on individual and population health.'

Fifty-five studies were classified as *in vitro* after title and abstract review of the combined literature search results. Twenty-seven studies were excluded at full-text review due to being a

- conference abstract (n=14),
- not classified as in vitro (n=7),
- letter to the editor or review (n=2),
- not studying e-cigarettes (n=3)
- or not being within the date range of 2017-18 (n=1).

Thus, 28 studies are included in the following summary of findings.

The in vitro studies reviewed included studies investigating toxicology, lung function, oxidative stress, inflammatory and infectious response, gene alterations and disease risk.

5.2 Toxicology

Many studies aimed to investigate viability of cells in vitro after exposure to e-cigarette liquids or vapours. Cell viability describes the number of living or dead cells, while toxicity describes the ability of a substance to kill a certain percentage of cells (usually 70-80%). Studies investigating toxicology used human lung cells. Control conditions were fresh air, no exposure, exposure to cigarette smoke or exposure to cigarette extracts.

Studies which compared cells exposed to e-cigarette vapour or liquids to cells exposed to air did not find consistent results. In two studies, exposure of lung epithelial cells to e-cigarette liquids, vapour or condensate, with or without nicotine, did not impact on lung epithelial cell viability or fibroblast cell viability or cytotoxicity (Gerloff, Sundar et al. 2017, Solleti, Bhattacharya et al. 2017). However, in another study, cell viability significantly decreased in the plasmid and bacteria cells exposed to e-cigarette liquid compared with the room air control (Bharadwaj, Mitchell et al. 2017). The dose of e-cigarettes play a key role in determining cytotoxicity, with higher doses showing higher toxicity (Breheny, Adamson et al. 2017, Clapp, Pawlak et al. 2017, Muthumalage, Prinz et al. 2017, Bishop, Haswell et al. 2018, Otreba, Kosmider et al. 2018). One study tested this by altering the voltage of the e-cigarettes in the study (Otreba, Kosmider et al. 2018). The researchers found that as voltage increased, cell viability of the human lung carcinoma cells decreased.

Three studies which investigated the toxic effects of e-cigarette vapour in the lungs, found that e-cigarette vapour had less toxic effects than cigarette smoke (Antherieu, Garat et al. 2017, Breheny, Oke et al. 2017, Leslie, Vasanthi Bathrinarayanan et al. 2017). More specifically, e-cigarette vapour did not elicit any significant cytotoxic effects on bronchial epithelial cells while cigarette smoke reduced cell viability (Antherieu, Garat et al. 2017). Similarly, aqueous extracts of e-cigarette vapour were not toxic for fibroblast cells (even when tested undiluted), but aqueous extracts of cigarette smoke led to toxicity at concentrations >15% (Breheny, Oke et al. 2017). While e-cigarette extracts also decreased cell viability, the amount of reduction varied for different cell types (bronchial epithelial, fibroblast and macrophage cells) (Leslie, Vasanthi Bathrinarayanan et al. 2017).

Another study found that cell viability was higher in human lung carcinoma cells after exposure to e-cigarette vapour compared with cigarette smoke (Otreba, Kosmider et al. 2018). However, other studies have found that e-cigarettes elicited similar toxic responses to cigarettes. Barber et al. found that endothelial cell viability was decreased after exposure to both e-cigarette vapour extract and tobacco smoke extract (Barber, Ghebrehiwet et al. 2017).

In a similar study in epithelial airway cells, undiluted e-cigarette vapour (with and without cinnamaldehyde flavouring) and cigarette smoke all led to dose-dependent cytotoxicity, however concentrations were significantly higher than normal human consumption (Bishop, Haswell et al. 2018). Additionally, these studies did not expose cells to e-cigarettes or cigarettes in a way which reflects human use. This includes exposure for a longer duration than a normal vaping or smoking session, exposing cells to extracts or concentrations of e-cigarettes and cigarettes which are higher than that of commercial products. This is highlighted in a study which investigated the cytotoxicity of 32 different e-cigarette flavours (liquid and vapour) and three components of e-cigarettes (vegetable glycerine, pure nicotine liquid and propylene glycol) and found that cytotoxicity of human pulmonary fibroblasts, lung epithelial cells and human embryonic stem cells of the e-cigarettes was not consistent between the vapour and liquid forms (Behar, Wang et al. 2017).

Thus, the study completed by Moses and colleagues provides useful information on cytotoxicity at exposures which reflect normal human use (Moses, Wang et al. 2017). In this study they found that cigarette smoke showed cytotoxicity but there was no significant cytotoxicity of menthol or tobacco flavoured e-cigarette vapours (only two flavours tested) with or without nicotine in human bronchial epithelial cells (Moses, Wang et al. 2017). Thus, while e-cigarettes can elicit a cytotoxic response, they may not be as toxic as traditional cigarettes.

5.2.1 Toxicity of e-cigarette components and flavours

It is likely that the toxicological response of cells to e-cigarette vapour is dependent on its constituents as different brands and flavours of e-cigarettes contain different chemicals. One study investigated different brands and flavours of e-cigarettes and found 91% of glycerin-based fluids were cytotoxic to endothelial cells when vaporised (Barber, Ghebrehiwet et al. 2017). However, it is unlikely that cytotoxicity is the result of just one component of e-cigarette vapour. Chemicals found to be cytotoxic or reduce cell viability in lung cells, include nicotine and flavouring components (menthol, Sini-cide, strawberry, cherry, Pentanedione, Cinnamaldehyde, O-vanillin, acetoin, diacetyl, maltol, coumarin, Banana Pudding, Kola, Hot Cinnamon Candies and Menthol Tobacco) (Bengalli, Ferri et al. 2017, Leslie, Vasanthi Bathrinarayanan et al. 2017, Muthumalage, Prinz et al. 2017, Ween, Whittall et al. 2017, Otreba, Kosmider et al. 2018).

Another study investigated nicotine-containing versus nicotine-free e-cigarette liquids on gingival fibroblast cells and found that nicotine-containing cells elicited significant toxicity (Sancilio, Gallorini et al. 2017). The authors of this paper suggested that nicotine-free liquids were able to counteract toxicity by activation of the lysosome compartment of cells (Sancilio, Gallorini et al. 2017). Conversely, some studies found that cytotoxicity was not induced by nicotine in e-cigarette vapour (Rowell, Reeber et al. 2017, Ween, Whittall et al. 2017) and another found that it did not lead to cytotoxicity but did reduce cell viability (Leslie, Vasanthi Bathrinarayanan et al. 2017). Additionally, strawberry, cherry, diacetyl, maltol, and coumarin flavours not only reduced cell-viability but also led to cytotoxicity in some cell-types (bronchial epithelial cells and pleural cell tissue) (Leslie, Vasanthi Bathrinarayanan et al. 2017, Muthumalage, Prinz et al. 2017). Finally, one study compared different e-cigarette brands and found that results varied depending on the brand (Leslie, Vasanthi Bathrinarayanan et al. 2017). Thus, e-cigarette vapours cannot be assumed to all have the same toxicity.

5.3 Oxidative stress

Four studies investigated oxidative stress or production of reactive oxygen species (ROS) in cells *in vitro* after exposure to e-cigarette liquids or vapour.

In a study by Antherieu et. al, acute (8-48 minutes) e-cigarette vapour and regular cigarette smoke exposure both led to similar acute levels of oxidative stress in bronchial epithelial cells (as measured by elevated intracellular glutathione and glutathione disulphide) (Antherieu, Garat et al. 2017).

Exposure to e-cigarette liquid led to an oxidative stress response in lung epithelial cells (Solleti, Bhattacharya et al. 2017). E-cigarette liquid or vapour, with or without nicotine, led to increased expression of four indicators of oxidative stress (glutamate-cysteine ligase (GCLC), NAD(P)H Quinone dehydrogenase 1 (NQO1), heme oxygenase 1 (HO1) and glutathione peroxidase (GPX2)) (Solleti, Bhattacharya et al. 2017), whereas cigarette smoke exposure only led to increased expression of three indicators of oxidative stress (GCLC, GPX2 and NQO1) in lung epithelial cells (Solleti, Bhattacharya et al. 2017). Nicotine-containing e-cigarette vapour elicited the highest oxidative response out of all tested substances (Solleti, Bhattacharya et al. 2017).

In a study investigating ROS (H_2O_2) in different e-cigarette flavouring chemicals, all flavours elicited extremely low levels of H_2O_2 in human pleural tissue, indicating limited oxidative stress (Muthumalage, Prinz et al. 2017). However, mixing flavours together (which replicates vaping different flavours using one device) and flavoured e-cigarette vapours led to elevated ROS (Muthumalage, Prinz et al. 2017).

The final study aimed to determine the impact of e-cigarettes on infection following oxidative stress. In this study, alveolar epithelial cells, bronchial epithelial cells, and nasal epithelial cells were exposed to pure nicotine or to e-cigarette vapour extracts with and without nicotine. All cells were incubated with N-acetylcysteine to induce oxidative stress and were then penetrated with *Streptococcus pneumoniae*. Researchers found that both nicotine-containing and nicotine-free e-cigarette vapours led to increased pneumococcal cell penetration and increased PAFR expression, indicating increased susceptibility to pneumococcal infection (Miyashita, Suri et al. 2018).

In summary, two out of four studies found that e-cigarettes elicited more oxidative stress than traditional cigarettes and all studies found increased oxidative stress following e-cigarette exposure. This may indicate an increased health risk for e-cigarette users, above that for cigarette smokers.

5.4 Inflammatory and infectious response

Inflammatory and/or infectious response resulting from e-cigarette vapour, liquids and flavour extract exposure was investigated in lung cells in six studies (Antherieu, Garat et al. 2017, Bengalli, Ferri et al. 2017, Clapp, Pawlak et al. 2017, Gerloff, Sundar et al. 2017, Muthumalage, Prinz et al. 2017, Ween, Whittall et al. 2017, Crotty Alexander, Drummond et al. 2018). Measurements of inflammatory and/or infectious response were identified by increased secretion of pro-inflammatory cytokines, measuring phagocytosis, neutrophil extracellular trap formation and natural killer cells.

5.4.1 Pro-inflammatory cytokines

The most commonly investigated pro-inflammatory cytokine was IL-8. Interestingly, depending on the study IL-8 either increased (Bengalli, Ferri et al. 2017, Clapp, Pawlak et al. 2017, Ween, Whittall et al. 2017, Crotty Alexander, Drummond et al. 2018), decreased (Clapp, Pawlak et al. 2017) or did not change significantly (Antherieu, Garat et al. 2017) following human lung cell or macrophage exposure to e-cigarette liquid or vapour. Cigarette smoke was also found to increase IL-8 in bronchial epithelial cells (Antherieu, Garat et al. 2017), indicating a similar detrimental effect from both e-cigarettes and cigarettes on inflammatory response.

Results of studies varied depending on the cell exposure model used and different flavours of e-cigarettes (Bengalli, Ferri et al. 2017, Clapp, Pawlak et al. 2017). For example, when epithelial alveolar cells and lung microvascular endothelial cells were exposed to e-cigarette vapour in a cell monoculture model e-cigarette exposure led to increased IL-8 secretion, whereas when the cells were trialled using an alveolar blood barrier model, there was no increase in IL-8 (Bengalli, Ferri et al. 2017). The impact of different flavours of e-cigarettes on IL-8 secretion was investigated in more detail in other studies.

In a study investigating lung adenocarcinoma cells, nicotine-containing cinnamon flavoured e-cigarette vapour increased IL-8 but IL-8 did not increase after exposure to other flavours or the cinnamon flavour without nicotine (Bengalli, Ferri et al. 2017). Three more studies investigated more e-cigarette flavours. The first investigated seven e-cigarette liquid flavours on neutrophils. The researchers found that five e-cigarette liquid flavours (Menthol Tobacco, Hot Cinnamon Candies, Kola, Banana Pudding and Banana) led to increased IL-8 secretion among neutrophils, one flavour did not increase IL-8 (Solid Menthol) and the results from the last flavour were likely inaccurate due to cytotoxicity (Sini-cide) (Clapp, Pawlak et al. 2017).

Another study found that acetoin, diacetyl, maltol and ortho-vanillin (flavouring chemicals) all led to release of IL-8 in Beas2B cells, HFL-1 cells, lung epithelial cells and fibroblasts (Gerloff, Sundar et al. 2017). However, two flavours (cinnamaldehyde and coumarin) suppressed IL-8 in Beas2B and HFL-1 cells and there was no effect on H292 cells (Gerloff, Sundar et al. 2017). The final study investigated both the vaporised flavoured e-cigarettes and the flavour extracts in two different pleural cell types. In the first pleural cell type (U937), diacetyl, 2, 3-pentanedione, o-vanillin, maltol and coumarin all increased IL-8 secretion. However acetoin decreased IL-8 in a dose-dependent manner. A small concentration of cinnamaldehyde ($10\mu M$) increased IL-8 secretion, but at a high concentration ($1000\mu M$) IL-8 decreased likely due to cytotoxicity (Muthumalage, Prinz et al. 2017). In the second cell type (MM6), IL-8 secretion increased after acetoin, cinnamaldehyde and vanillin exposure while diacetyl and coumarin did not increase IL-8 significantly (Muthumalage, Prinz et al. 2017).

Finally, the same study also investigated the vaporised flavours on pleural cells and found that while the flavours Cinnamon Roll, Mystery Mix, Cafe Latte and mixed flavours (combining all of the flavours, to replicate use of e-cigarettes where the same device is used for different flavours) increased IL-8, Mega Melons, Grape Vape, Pineapple Coconut, American Tobacco and Very Berry decreased IL-8. The remaining two flavours (Fruit Swirl and Strawberry Zing) did not influence IL-8 levels as they did not differ from the control (Muthumalage, Prinz et al. 2017). The authors of one study hypothesised that some differences in effects were due to the synergistic action between flavour molecules and nicotine, as nicotine alone did not lead to a pro-inflammatory response (Bengalli, Ferri et al. 2017).

Three studies investigated other inflammatory cytokines. While one study found that exposure to e-cigarette vapours led to increased IL-6 in bronchial epithelial cells (Antherieu, Garat et al. 2017), another found that the inflammatory response was dependent on the e-cigarette liquids flavour (Clapp, Pawlak et al. 2017).

In the second study, investigating alveolar macrophages, Kola e-liquid exposure led to increased IL-6 secretion but Sini-cide led to suppressed IL-6 secretion (Clapp, Pawlak et al. 2017). Cigarette smoke led to a similar elevation of IL-6 in bronchial epithelial cells as e-cigarette vapour (Antherieu, Garat et al. 2017).

Another study investigated THP-1 macrophages and found that after exposure to cigarette smoke extract, nicotine and two out of three e-cigarette flavours, IL-1β, MIP-1α, MIP-1β and TNFα all decreased (Ween, Whittall et al. 2017). After exposure to all e-cigarettes, cigarette smoke extract, nicotine IL-6, MCP-1 decreased (Ween, Whittall et al. 2017). Proplyene glycol also decreased IL-1β, MIP-1α, TNFα (Ween, Whittall et al. 2017).

These studies show that e-cigarette flavours have different effects on inflammatory response. This highlights the difficulty of generalisation of the impact of e-cigarettes on specific inflammatory response.

5.4.2 Phagocytosis

Phagocytosis is the process by which cells ingest bacteria or other material. In one in vitro study, exposure to apple-flavoured e-cigarette liquids (with and without nicotine) and cigarette smoke extracts led to decreased phagocytosis by THP-1 macrophages (Ween, Whittall et al. 2017). Additionally, flavoured e-cigarette liquids and nicotine reduced expression of a phagocytosis receptor (Ween, Whittall et al. 2017).

Another study investigated the impact of different e-cigarette flavours on alveolar macrophages, neutrophils and natural killer (NK) cells (Clapp, Pawlak et al. 2017). Out of seven e-cigarette flavours, only kola and sini-cide led to significant phagocytosis suppression compared with propylene glycol/ vegetable glycerin controls in alveolar macrophages, which may be due to their cinnamaldehyde component (Clapp, Pawlak et al. 2017). In neutrophil cells, the propylene glycol/ vegetable glycerin and five of the seven experimental flavours reduced phagocytosis in a dose-dependent manner (Clapp, Pawlak et al. 2017). Thus, e-cigarettes have the potential to reduce phagocytosis and therefore limit the body's ability to respond to infection.

5.4.3 Infections

Neutrophil extracellular traps (NET) are generated by neutrophils to help control microbial infections. One study examined NET formation and natural killer (NK) cells in neutrophils after exposure to a liquid e-cigarette base (propylene glycol/ vegetable glycerin) and liquid flavoured e-cigarettes. In this study, propylene glycol/ vegetable glycerin (e-cigarette liquid base) did not induce NET formation in neutrophils, while Hot Cinnamon Candies suppressed NET formation and Kola increased NET formation (Clapp, Pawlak et al. 2017). Sini-cide was cytotoxic which meant NET formation could not be studied (Clapp, Pawlak et al. 2017). NK cells killing efficiency was reduced after alveolar cells were exposed to cinnamon-flavoured e-liquids (Clapp, Pawlak et al. 2017). Once again, different flavoured e-cigarettes elicited different responses.

5.5 Gene alterations

5.5.1 Damage

While e-cigarette vapour extracts led to DNA damage (Bharadwaj, Mitchell et al. 2017, Ganapathy, Manyanga et al. 2017), cigarette smoke extracts were more damaging to DNA found in oral and lung epithelial cells (Ganapathy, Manyanga et al. 2017). A reduction in proteins associated with DNA damage removal was also found in some cells exposed to e-cigarettes and all cells exposed to cigarette smoke (Ganapathy, Manyanga et al. 2017).

5.5.2 Mutation

There was no increase in mutation frequency (supF) after human plasmid cells were exposed to e-cigarette vapour extracts but there was a significant increase in supF mutation frequency after cells were exposed to the positive control (UV-irradiation) (Tommasi, Bates et al. 2017). Additionally, exposure to tobacco carcinogens (benzoαpyrene and 4-aminobiphenyl), but not e-cigarette vapour extracts, led to increased CII mutant frequency, indicating mutation in mouse fibroblasts (Tommasi, Bates et al. 2017). This study indicates that the three e-cigarette extracts tested did not lead to mutations, however further testing with more types of e-cigarette liquids on different cell-types is warranted.

5.5.3 RNA Expression

Expression of many RNA and microRNA differed after e-cigarette exposure. In one study, 578 microRNA from lung epithelial cells were expressed differently after e-cigarette liquid exposure (Solleti, Bhattacharya et al. 2017). In another study, 493 genes had different expressions after exposure to menthol versus tobacco flavoured e-cigarettes (Moses, Wang et al. 2017). Despite this, a few studies found that fewer genes in bronchial epithelial BEAS-2B cells were up- or down-regulated by e-cigarette vapour than cigarette smoke (Antherieu, Garat et al. 2017, Haswell, Baxter et al. 2017).

A more comprehensive study identified both the gene effected and the effect on the cell, at exposures replicating human exposures (Moses, Wang et al. 2017). In this study, bronchial epithelial cells were exposed to fresh air (control), menthol and tobacco flavoured e-cigarette vapour with and without nicotine, or cigarette smoke.

Gene expression analysis revealed that expression was downregulated after exposure to e-cigarettes or cigarettes in genes related to cilium assembly and movement. Genes which were upregulated by exposure to e-cigarettes or cigarettes were involved in apoptosis, xenobiotic stress, oxidative stress and DNA damage. Genes expressed more by e-cigarettes than cigarettes were related to cell cycle regulation and cell division (nuclear division, cytokinesis). Exposure to menthol e-cigarettes was associated with increased DNA expression related to cell adhesion and protein polymerisation. Tobacco-flavoured e-cigarettes were associated with increased expression of genes associated with cell cycle and superoxide response. Nicotine-containing e-cigarettes led to alteration in 162 genes, including upregulation of genes associated with ROS, epithelium differentiation and cytochrome P450 pathway and downregulation of genes associated with response to inorganic substances.

Researchers also identified that e-cigarettes were able to downregulate the structural cilia dynein gene DNAH10 and ciliated cell marker FOXJ1 (previously identified as a key reason that cigarettes interfere with ciliated cells). This indicates that the pathway by which e-cigarettes reduce cilia function is the same pathway found when cigarettes reduce cilia function. Both e-cigarette and cigarettes activated genes associated with the cytochrome P450 pathway, which is associated with xenobiotic stress and oxidative stress, these were even more enhanced by e-cigarettes with nicotine.

5.6 Lung function

Studies investigated the impact of e-cigarettes on cilia function, mucous production and transport, barrier function and lung surfactant.

5.6.1 Cilia function

Two studies compared cilia function in airway epithelial cells after exposure to cigarette smoke or e-cigarette vapour. One found that cigarette smoke elicited a greater reduction in mucous production and cilia bearing than e-cigarette vapour (Aufderheide and Emura 2017). The other found that both e-cigarette vapour and cigarette smoke led to reduced ciliary motility and ciliary beat frequency in epithelial airway cells (Carson, Zhou et al. 2017). A study comparing cilia beat frequency in airway epithelial cells after exposure to room air or e-cigarette vapour found no difference between groups (Haswell, Baxter et al. 2017). Differences between results may be due to brand of e-cigarette used, duration of exposure (eight days versus one hour versus three minutes), flavour (tobacco flavour versus no flavour), nicotine content (ranged from 0-24mg/mL) or differences in cells from different donors.

5.6.2 Mucous production and transport

Mucous secretions were reduced after bronchial epithelial cells were exposed to both nicotine-free unflavoured e-cigarette vapour and cigarette smoke (Aufderheide and Emura 2017). Both e-cigarette and tobacco smoke led to increased epithelial airway cell secretions, however tobacco smoke elicited a greater response than tobacco flavoured, nicotine-containing e-cigarette vapour (Carson, Zhou et al. 2017). Differences may be due to differences in flavour, nicotine content and/ or length of exposure (8 days versus approximately 3 minutes).

Excised bullfrog palates exposed to e-cigarettes showed a modest inhibitory effect on mucous transport velocity compared with an air exposure (Palazzolo, Nelson et al. 2017). However, exposure to cigarette smoke completely inhibited mucous transport velocity during exposure and 24hr after exposure (Palazzolo, Nelson et al. 2017). While visual assessment of the palates showed no effect of cigarette or e-cigarette exposure on submucosal architecture (collagen was unaffected), smoke-exposed palates appeared to be thinner due to epithelial disruption (Palazzolo, Nelson et al. 2017). Thus, cigarette smoke appears to have a more detrimental effect on mucosal production and transport than e-cigarettes (Carson, Zhou et al. 2017, Laube, Afshar-Mohajer et al. 2017, Palazzolo, Nelson et al. 2017, Reinikovaite, Rodriguez et al. 2018).

5.6.3 Lung epithelial barrier function

After exposure to infectious pseudomonas aeruginosa and then e-cigarettes, bronchial epithelial cells had changes in tight junction proteins which indicated reduced lung barrier function (Crotty Alexander, Drummond et al. 2018). Loss of barrier function could lead to increased passage of external antigens and chemicals into the lungs and blood. This finding is supported by another study which found that epithelial cells exposed to nicotine and some e-cigarette flavours (diacetyl, coumarin, acetoin, maltol, cinnamaldehyde) led to rapid loss of epithelial barrier function (Gerloff, Sundar et al. 2017). However, in this study other e-cigarette flavours did not lead to loss of epithelial barrier function (pentanedione and ortho-vanillin) (Gerloff, Sundar et al. 2017). Thus, the impact of e-cigarettes on barrier function appears to differ between e-cigarette fluids. Finally, another study found that e-cigarette vapour exposure led to decreased trans-epithelial electric resistance, compared with the air control, indicating a loss of barrier integrity, however the levels were still within a functional range (Haswell, Baxter et al. 2017).

Pulmonary surfactant is a thin layer of fluid, secreted by alveolar cells to reduce surface tension and prevent alveolar collapse (Przybyla, Wright et al. 2017). In a study on lung surfactant from calves, e-cigarette vapour did not affect surfactant interfacial properties regardless of dose or flavouring (Przybyla, Wright et al. 2017). However, cigarette smoke exposure led to reduced maximum surface pressure (Przybyla, Wright et al. 2017). Upon further investigation, nicotine, acetaldehyde, and isoprene did not significantly alter interfacial properties, however tar (from cigarette smoke) led to a high disruption of lung surfactant (Przybyla, Wright et al. 2017). Both e-cigarette vapour and cigarette smoke led to changes in surfactant microstructure, which led to an increase in the area of lipid multilayers (Przybyla, Wright et al. 2017). These results are supported by a study which simulated pulmonary surfactant and found that while both e-cigarette vapour and cigarette smoke led to impaired surfactant performance, the effects from cigarette smoke were worse than e-cigarette vapour (Davies, Birkett et al. 2017).

5.7 Risk of disease

A study investigating the impact of e-cigarette and tobacco extracts on umbilical vein cells found that some indicators of cardiovascular disease (CVD) development (C1q, C5b-9, gC1qR and CD35) increased after exposure to e-cigarette extract, but other indicators (C3b and C4d) did not increase (Barber, Ghebrehiwet et al. 2017). Pure nicotine exposure also led to enhanced expression of gC1qR, an indicator of CVD development (Barber, Ghebrehiwet et al. 2017). Another study reported the effects of e-cigarette vapour extracts and cigarette smoke extracts on endothelial cell migration after scratch-wound injury(Taylor, Jaunky et al. 2017). Endothelial migration is involved in vascular repair mechanisms and is an indicator of endothelial dysfunction, a marker of CVD development. In this study, cigarettes led to dose-dependent inhibition of endothelial migration, however e-cigarettes did not influence endothelial migration at any dose. Thus, CVD risk increased after exposure cigarette smoke extracts but not e-cigarette vapour extracts. However, endothelial migration is only one indicator of CVD.

Another study found that exposure of oral cavity cells (gingival cells) to e-cigarette vapour altered cell morphology, increased cell damage (indicated by increased lactate dehydrogenase) increased apoptotic and necrotic cells (Rouabhia, Park et al. 2017), indicating increased risk of oral diseases.

A study investigated the tumour promoter activity (promotors of tumour growth) of aqueous extracts of both e-cigarettes and cigarettes (Breheny, Oke et al. 2017). After exposure to cigarette extracts there were significant increases in tumour promoter activity and cell growth, however increases after e-cigarette extract exposure were not significant (Breheny, Oke et al. 2017). Increasing tumour promoter activity does not increase risk of initial tumour formation, but may be relevant to an increased risk of tumour growth following initiation.

5.8 Conclusions

In summary, in vitro studies on e-cigarette vapour, liquid and extracts strongly indicated potential health risks including cell death, increased oxidative stress, reduced lung function, changes in inflammatory response, altered gene expression and increase of cellular risk factors for cardiovascular disease.

A key limitation of the studies was that most did not state the extent to which the e-cigarette or cigarette related exposure was reflective of regular human use of e-cigarettes or cigarettes, and the extent to which e-cigarette extracts, liquids or vapour might be expected to be similar. The great variation among e-cigarette components may explain some of the inconsistency in findings and limit the capacity to generalise the in vitro findings.

5.9 Key findings

- In vitro studies on e-cigarette vapour, liquid and extracts strongly indicated potential health risks including cell death, increased oxidative stress, reduced lung function, changes in inflammatory response, altered gene expression and increase of cellular risk factors for cardiovascular disease.

- There is a lack of clarity about the direct implications of the in vitro findings for human health.

6 Modelling studies

6.1 Results of modelling studies

In a US study (Logue, Sleiman et al. 2017), a model was used to consider the health impacts associated with indoor exposure to vaping e-cigarettes (for e-cigarette users and bystanders). Recently reported emission rates of potentially harmful compounds were used to assess intake and predict health impacts for vapers and bystanders exposed passively. Data was gathered for three different vaping scenarios:

1) frequent short sessions, 25 daily session of 10 puffs each;
2) intermediate 'typical' conditions, with 10 daily sessions of 25 puffs each;
3) infrequent long sessions, with only five daily sessions of 50 puffs each.

In experiments, two vaporisers were used, an eGO CE 4 single coil vaporiser and a dual coil device, the Kangertech Aerotank Mini. Three different e-liquids were used (with switching between these not having a major effect on emissions). Two indoor settings were explored: a residential setting where a nonuser lives with a user, and a bar setting that allows vaping indoors.

The integrated health damage from passive vaping was derived by calculating disability adjusted life years (DALYs) lost due to exposure to second hand vapour.

Acrolein was considered to be the dominant contributor to aggregate harm (75%) with formaldehyde contributing 21%, and much smaller contributions from other compounds (glycidol, acetaldehyde and benzene). Acrolein levels were close to the 1 h Californian OEHHA (Office of Environmental Health Hazard Assessment) REL (Reference Exposure Level) and formaldehyde levels exceeded the 8 h REL. DALYs for the various device/voltage combinations were lower than, or comparable, to those estimated for exposures to second hand and third hand tobacco smoke.

The main toxic burden of e-cigarettes is said to be likely to be associated with thermal decomposition by products of the main e-fluid constituents (propylene glycol and glycerin). Some of the same by products also originate from the decomposition of flavourings. The study was a preliminary evaluation for a subset of compounds detected in the vapour of e-cigarettes.

The authors acknowledge that the estimations of DALYs attributed to exposure to the compounds investigated are preliminary due to incomplete epidemiological and toxicological data. Their reason for expressing results in terms of DALYs was to have a common metric for indoor exposure to a range of compounds. This modelling study does not attempt to estimate the indoor exposure experienced by a population, does not total the health impact and does not account for competing risks such as a decrease in exposure to tobacco smoke.

An Italian study (Scungio, Stabile et al. 2018) used the Excess Lifetime Cancer Risk model to evaluate the potential carcinogenic effect of the sub-micron and super-micron particles in e-cigarette aerosols considering the typical vaping habits of male and female Italian vapers. They concluded that the surface area concentrations in e-cigarette aerosols were lower than that in conventional cigarette smoke and that the excess lifetime cancer risk for e-cigarette aerosols was five orders of magnitude lower than that for conventional cigarette smoke.

6.2 Key findings

The validity of modelling of health impact is dependent on the assumptions made and the complete understanding of health risks. Both modelling studies suggest that the specific health risks examined from e-cigarette aerosols are substantially lower than that from cigarette smoke.

7 Tables

Table 1: Human health outcomes studies – randomised trials

Study	Design	Duration	Population	Groups/comparisons	Funding
Boulay et al. 2017	Randomised crossover, placebo controlled trial.	1 week (experimental and placebo group took place 1 week apart). Just a 1 hr smoking session as the intervention.	Healthy subjects (between 20 and 37 years) and asthmatic volunteers (between 21 and 40 years).	No control group. Control condition (placebo). Both healthy (n=20) and asthmatic volunteers (n=10) spent time in both the placebo and experimental groups. All volunteers were non-smokers and non e-cig users.	NR (not reported)
Krishnan-Sarin et al. 2017	Randomised crossover trial.	Pilot: 1 session (1 day). Main study: 3 laboratory sessions separated by 48 hours (total trial length = 9 days), approximately 1 and a half weeks.	Pilot study: 10 e-cigarette users. Main study: 60 e-cigarette users. Pilot study: 7/10 male, main study 29/60 male. Young sample: 18.1 mean age in pilot, 18.8 mean age in main study.	Control group = 10 for pilot study and 21 for main study.	National Institute of Health grants and the FDA Center for Tobacco Products (CTP).
Moheimani et al. 2017	Randomised crossover trial.	12 weeks (three sessions separated by a 4-week washout period).	33 participants underwent experimental sessions (13 male) and sham control. Mean age, 23.6 years.	In random order, each participant underwent the following three exposure sessions, each session separated by a 4-week washout: (1) e-cigarette with nicotine; (2) e-cigarette without nicotine (same flavouring and solvent as the 'with nicotine' exposure); and (3) sham control consisting of puffing on a device without e-liquid.	Supported by Tobacco-Related Disease Research Program (TRDRP) and 25IR-0024 (Middlekauff), American Heart Association, Western States Affiliate, Grant-in-Aid, 15GRNT22930022 (Middlekauff), the National Institute of Environmental Health Sciences, National Institutes of Health, R56 ES016959-06 (Araujo), Training Grant in Molecular Toxicology T32ES015457 (Bhetraratana), Irma and Norman Switzer Dean's Leadership in Health and Science Scholarship (Moheimani), and the UCLA Clinical and Translational Science Institute (CTSI) grant number UL1TR000124.
Staudt et al. 2018	Randomised trial.	1 week (baseline measures and experimental session took place 1 week apart). Experimental session – 2x10 puffs of e-cigarette 30 minutes apart.	10 never smokers or e-cigarette users were randomised to use an e-cigarette with nicotine (n=7) or without nicotine (n=3) in the experimental session	Each participant completed a range of testing at baseline. Testing was repeated post experimental session. Changes from baseline were assessed and compared between the nicotine and non-nicotine groups.	Research reported in this publication was supported by the National Institute of Health (NIH) and the Food and Drug Administration (FDA).

Table 2: Human health outcomes studies – prospective cohort studies

Study	Design	Duration	Population	Groups/comparisons	Funding
Lechner et al. 2017	Prospective cohort study.	12 months.	Data was collected from 3383 (at baseline/first wave), 6-months = 3293 (97%) and 12-months = 3282 (96.6%). 2460 adolescents completed measures used within the current analyses for all three waves. Female: 53.4% Ethnically diverse Baseline mean age of 14.1 years.	Compared e-cigarette and cigarette use at each wave, past use, and frequency of use.	National Institutes of Health Grants.
Polosa et al. 2017	Prospective cohort study.	3.5 years.	9 daily e-cigarette users (for >3 months) who have never smoked. Control group of 12 never smokers. 11 Males, 5 Females in EC group at baseline and 10 males, 5 female non-smoking controls at baseline. 9 EC users (6 male) and 12 controls (8 male) in analysis. Mean age 29.7 years.	Control group of never smokers.	Catania University Grant. One of the researchers had received lecture fees from a number of European electronic cigarette industry and trade associations (including FIVAPE in France and FIESEL in Italy) that were linked to vaper advocacy no profit organisations.
Walele et al. 2018	Prospective cohort study.	2 years.	A closed system electronic vapour product (EVP) was used by former smokers of conventional cigarettes (CCs) for 24 months in a real life setting. 209 started. 206 used the product once, 102 (48.8%) went on to use the product for 24 months. 110 were compliant - used EVP for 80% of study days. Both male (115, 55%) and female (94, 45%). Completers: 57 male, 45 female. Aged between 21 and 65 years.	No control group. Compared results of all subjects with EVP compliant subjects (n=110) and completers (n=102).	Fontem Ventures B.V. Imperial Brands Group plc is the parent company of Fontem Ventures B.V., the manufacturer of the EVP used in this study.

Table 3: Human health outcomes studies – case control studies

Study	Design	Duration	Population	Groups/comparisons	Funding
Bardellini et al. 2017	Case-control.	Examined patients with a 2 year period.	Examined former smokers and EC consumers who were outpatients of the dental clinic of the University of Brescia within a 2 year period (Jan 2015 to Dec 2016) consecutively enrolled patients, to detect possible oral lesions. 90 patients, n=45 former smokers and n=45 e-cig users. Mean age 47 years. Male former smokers n=22 Male e-cigarette users n=41. Female former smokers = 23, female e-cigarette users n=4.	Compared former smokers and current EC users.	NR.

Table 4: Human health outcomes studies – cross-sectional studies

Study	Design	Duration	Population	Groups/comparisons	Funding
Boas et al. 2017	Cross-sectional analytic.	Short-term. NR.	Habitual tobacco cigarette smokers or habitual e-cigarette users (not dual users) who had used tobacco cigarettes or e-cigarettes, respectively, most days for a minimum of 1 year, in who plasma cotinine levels were elevated. 31 patients enrolled, 3 excluded. 9 healthy nonuser controls, 9 e-cigarette users, 9 tobacco cigarette smokers. M=20, F= 7. Non user control M=6 F=3, e-cigarette users, M=7, F=2, Tobacco cig smoker M=7, F=2. Aged 21-45 years old.	Considered activation of the splenocardiac axis (increased metabolic activity of the hematopoietic and vascular tissues) across the 3 groups (e-cig users, tobacco users, non-users).	Tobacco-Related Disease Research Program; American Heart Association, Western States Affiliate, Grant in Aid; the National Institute of Environmental Health Sciences, National Institutes of Health; Training Grant in Molecular Toxicology; Irma and Normal Switzer Dean's Leadership and Science Scholarship and UCLA Clinical and Translational Science Institute.
Fuller et al. 2017	Cross-sectional analytic.	Short-term. NR.	13 e-cig users and 10 non e-cig users and non smokers. All subjects were former smokers (non smoking for at least 6 months). 69.2% Male for e-cigarette users. 50% for controls. Mean age of 39.4 years for e-cig users. Mean age of 30.1 for controls.	Considered bladder cancer risk profile across e-cigarette users, and non e-cigarette users and non smokers.	NR. Abstract only.
Gucht et al. 2017	Cross-sectional.	Short-term. NR.	Convenience sample of a medium sized dedicated web shop. All customers who made an online purchase in the time window 18 Dec 15 to 12 Jan 16 were referred to the questionnaire and asked to complete on a voluntary basis. N=203, 57.1% (116) male. Average age 46 years.	No comparison group.	Not stated, but the authors states that they are advocates for e-cigarette based THR.
Kim et al. 2017	Cross-sectional analytic.	Short-term. NR.	Korean adolescents from 7th through 12th grade (i.e. 12 - 18 years of age), performed at schools. Cross-sectional study of Korea Youth Risk Behavior Web-based Survey in 2011, 2012, 2013. N=216,056 (211,166 without asthma and 4,890 with asthma)	Compared active smoking, passive smoking and e-cigarette use. Active smoking categorised into 4 groups (0 days, 1-5 days, 6-19 days, and > or = 20 days/month). Passive smoking categorised into 4 groups (0 days, 1-2 days, 3-4 days, and > or = 5 days/week). Current e-cigarette use (yes or no in last 30 days). Considered asthma symptoms (self-reported).	National Research Foundation (NRF) of Korea grant (NRF-and a research grant funded by Hallym University Sacred Heart Hospital and Korea Ministry of Environment (MOE), "The Environmental Health Action Program".

Study	Design	Duration	Population	Groups/comparisons	Funding
McConnell et al. 2017	Cross-sectional analytic.	Short-term. NR.	2086 participants of Southern California Children's Health Study who provided information on e-cigarette use and either wheeze or bronchitic symptoms. Analysis was based on subjects with complete information on e-cig use, including 1,922 subjects also not missing information and not reporting don't know regarding bronchitic symptoms and 2083 subjects not missing wheeze information. 2083 participants included in the analysis. 502 (24%) had ever used e-cigarettes, 301 (14.4%) were past and 201 (9.6%) (adolescent) participants of the survey were current users of e-cigarettes. Female 49.6%, Male 50.4% Adolescents completing 11th and 12th grade in 2014. Mean age of the sample was 17.3 years.	Compared past and current users of e-cigarettes with self-reported wheeze and bronchitic symptoms.	National Institute of Health grants.
Moheimani et al. 2017	Cross-sectional analytic.	Short-term. NR	42 participants, 23 self-identified habitual e-cigarette users and 19 self-identified non tobacco cigarette, non e-cigarette user controls. 2 of the 23 e-cigarette users were initially eliminated, and a further 5 (of 21) were eliminated when indicators of cigarette use were found (results of 16 e-cig users analysed). 1 of the controls also eliminated when it was found that they had exposure to tobacco cigarette (18 controls analysed). 35% Female. Mean age 27.6 years.	16 e-cigarette users and 18 controls compared on imbalance of cardiac autonomic tone and oxidative stress and inflammation.	Tobacco-Related Disease Research Program, American Heart Association, National Institute of Environmental Health Sciences, National Institutes of Health, Training Grant in Molecular Toxicology, Irma and Normal Switzer Dean's Leadership in Health and Science Scholarship, University of California LA Clinical and Translational Science Institute Grant.
Reidel et al. 2017	Cross-sectional.	Short-term. NR.	Collected sputum samples from 14 current tobacco cigarette smokers, 15 current e-cigarette users and 15 never smokers. Mean age and gender not recorded.	Compared e-cig users with tobacco smokers and never smokers. E-cig use, average number of puffs inhaled per day was 280 (had been predominantly exclusive users for 6 months, but 12/15 had previously smoked cigarettes. 5/15 occasionally smoked cigarettes). Conventional cigarette users, average number smoked per day was 11.	National Institutes of Health and the Family Smoking Prevention and Tobacco Control Act.
Rubinstein et al. 2018	Cross-sectional.	Short-term. NR.	67 e-cigarette only users and 16 dual users. There were 20 age matched controls who did not use e-cigarettes or cigarettes. Male: 49 e-cigarette only (73%), 12 dual users (80%), 7 controls (35%). Aged 13-18 years.	Compared e-cig only users with dual users and age-matched controls. E-cigarette users only reported using their e-cigarettes a mean of 12.8 days/mon (SD 8.9) compared with 25.5 days (SD6.6) for dual users (<0.001). E-cigarette only users who used	National Institutes of Health.

Study	Design	Duration	Population	Groups/comparisons	Funding
				nicotine in their e-cigarettes reported using their e-cigarettes more frequently with an average use of 15.1 days/month (SD9.2) compared with 7.6 days/month (SD5.6) (p<0.001).	
Schweitzer et al. 2017	Cross-sectional.	Short-term. NR.	Data was analysed from a 2015 study of adolescents in Hawaii. This is the 2015 HYRBS, a survey conducted every 2 years by the University of Hawaii with students of public middle and high schools (9th-12th grade). 33 of 43 schools were randomly selected to participate, using a 3 stage sample stratified by racial/ethnic concentration and metropolitan statistical area status to produce a representative sample of students in grades 9-12. Response rate was 78%. 2% American Indian or Alaska Native, 3% Black/African American, 29% Filipino, 39% Native Hawaiian or Other Pacific Islander, 16% Japanese or Other Asian, 11% Caucasian. N=6089. Female 50%. Mean age 15.2 years.	Cigarette and e-cigarette smoking status was compared along with current and previous asthma.	National Cancer Institute. Division of Intramural Research, National Institute on Minority Health and Health Disparities.
Stewart et al 2018	Cross-sectional.	Short-term. NR.	10 daily e-cigarette users, 10 tobacco smokers and 10 controls. 2 female (6.7%); 1 e-cigarette user and 1 control. 1 e-cigarette user reported smoking 1 tobacco cigarette/week. All others reported no tobacco cigarette use.	Bacterial profiles of fecal, buccal and saliva samples from e-cigarette users, tobacco smokers and controls were compared.	National Cancer Institute; Veteran Health Administration; McNair Medical Institute.
Wei et al. 2018	Cross-sectional analytic.	Short-term. NR.	Participants of the National Health and Nutrition Examination Surveys (NHANES) from 2013 to 2014. N=1572. Male non user 534/1201, Male cigarette user, 170/298, male cigar user 18/22, male e-cigarette user 8/14, male user of smokeless tobacco products 15/15. Mean age NR.	Compared groups such as non-users (if not using tobacco or nicotine products within 5 days prior to the NHANES examination), exclusive e-cigarette users, exclusive cigarette smokers, exclusive cigar smokers and exclusive users of smokeless tobacco products (if using such products within the five days prior to examination).	NR. The NHANES is a study conducted by the National Center for Health Statistics (NCHS) and the US Centers for Disease Control and Prevention (CDC). One researcher reported receiving a research grant from Pfizer and being a member of an advisory board to Johnson & Johnson.

Table 5: Human health outcomes studies – case studies

Study	Design	Duration	Population	Groups/comparisons	Funding
Agochukwu et al. 2018	Case report.	Patient was able to be discharged after 5 days with a healing flap.	1 male, 21 years old.	NA (Not applicable)	NR
Flower et al. 2017.	Case report.	3 month follow-up.	1 male, 33 years old.	NA	NR
Fracol et al. 2017	Case report.	NR.	1 female, 51 years old.	NA	NR
Itoh et al. 2017	Case report.	4 week follow-up.	1 male, 46 years old.	NA	NR
Khan et al. 2018	Case report.	NR.	1 female, 40 years old.	NA	NR
Miler et al. 2017	Case report.	8 month follow-up.	1 female, 26 years old.	NA	NR
Shim et al. 2018	Case reports.	3 month follow-up.	1 female, 28 years old. 1 male, 50 years old.	NA	NR
Sturek et al. 2017	Case report.	1 month follow-up.	1 female, 56 years old.	NA	NR. Abstract only.

Table 6: Human health outcomes studies – modelling studies

Study	Design	Duration	Population	Groups/comparisons	Funding
Levy et al. 2018	Modelling Study.	N/A	N/A	Uses a model to consider potential health outcomes/deaths averted if cigarette smokers switched to vaping e-cigarettes (compares a status quo scenario with a substitution model where vaping replaces cigarettes over a 10 year period). Modelling for e-cigarette users that never smoked, e-cigarette users among former smokers, former e-cig users and current and former smokers who have not yet switched to e-cigarette use.	National Institute on Drug Abuse, Cancer Intervention and Surveillance Modelling Network of the Division of Cancer Control and Population Sciences, National Cancer Institute.
Logue et al. 2017	Modelling Study.	N/A	N/A	Uses a model to consider health impact associated with exposure to vaping (users and bystanders). Six scenarios considered. Investigated 3 different vaping scenarios: Frequent short sessions, 25 daily session of 10 puffs each. Intermediate 'typical' conditions, with 10 daily sessions of 25 puffs each and Infrequent long sessions, with only 5 daily sessions of 50 puffs each. Used two vaporizers, an eGO CE 4 single coil vaporizer and a dual-coil device, the Kangertech Aerotank Mini. Used 3 different e-liquids: Apollo Classic Tobacco, Drip Mojito Mix and Drip Bubblicious. Two indoor settings considered were a residential setting where a nonuser lives with a user and a bar setting that allows vaping indoors.	University of California Tobacco-Related Disease Research Program. CONECET. National Institute on Drug Abuse.

Table 7: Human health outcome studies - injury study data

Study Reference	Study objective or purpose	Country of case	Year (of event)	Description of event	Subject Age (years)	Subject Gender (M/F)	Caused by	Author's Conclusion	Any other information from study report
Ackley E et al 2017	Case study.	USA	NA	ENDS device exploded just as the boy was about to take a puff resulting in burned thumb with sensory loss, decreased motor control and heavy bleeding.	17	M	Explosion of ENDS device due to the lithium ion battery that powers the device short circuits.	Although uncommon, the potential for major injury due to explosions may be a compelling talking point with teens.	The lithium ion battery short circuits due to overheating, water exposure, excessive charging, improper charging with incompatible devices, contact with metallic objects or physical battery damage. Known as 'thermal runaway"
Anderson et al 2017	Letter.	UK		Burns to arms and face due to exploding ENDS.	30	F	Exploding ENDS	As e-cigarette use increases so will injuries.	
Andresen et al 2018	Case report.	USA (Iowa City)	NA	Chemical burn and throat injury after falling with e-cigarette in mouth.	NA	M	Falling while e-cigarette in mouth	Unrecognised and unpublished danger associated with e-cigarette use.	
Arnaout et al 2017	Letter.	UK		Discussion of best ways to treat burns.				From our experience of 12 cases a conservative approach in treating these burns is advocated unless the burns are full thickness and require skin grafting. We would still advise first aid with copious amount of running cold water if access to mineral oil is not readily available.	
Arnaout et al 2017	The Southwest UK Burns Network experience with e-cigarette explosions and review of literature.	UK	Oct 2015 - July 2016	Case 1 - e-cigarette placed on charger when it shot across the room and exploded, igniting the carpet causing burns when attempting to put it out.	22	M	Exploding ENDS	Use mineral oil to treat burns not water. Recommend restrictions to import of e-cigarettes to ensure standards met. Consumer guidance needed re storage and charging of e-cigarettes. Query allowing e-cigarettes in carry-on luggage on aircraft.	Injuries often preceded with 'battery in the pocket' -damp environment may have sufficient moisture to start a chemical reaction with battery and presence of metal objects can produce a short circuit which can overheat the battery leading to an explosion.
				Case 2 - e-cigarette in pocket when it exploded causing burns to thigh and scrotum and hand when trying to put it out.	22	M	Exploding ENDS		

Study Reference	Study objective or purpose	Country of case	Year (of event)	Description of event	Subject Age (years)	Subject Gender (M/F)	Caused by	Author's Conclusion	Any other information from study report
				Case 3 - had lithium-ion battery in pocket with coins when battery starts heating up then bursts in to flames.	49	M	Exploding ENDS		
Ban C et al Sept 2017 ABSTRACT ONLY	Case report.	USA	NR	ENDS device exploded after changing the battery causing first degree burns to the abdomen, fracturing right thumb, and embedding a portion of the electronic cigarette into the maxilla.	53	M	Exploding ENDS	Given the recent rise in popularity of electronic cigarettes, combined with the volatile nature of lithium batteries, it stands to reason that maxillofacial blast injuries from electronic cigarettes will increase in frequency.	
Bauman et al 2017	Case report.	USA	NR	Case 1 - lithium ion battery runaway caused an explosion of ENDS in pants pocket resulting in extensive thigh burn.	58	M	Exploding ENDS		Lithium batteries can become flawed from three different mechanisms: thermal damage, mechanical damage or electrical damage.
				Case 2 - he disassembled his e-cigarette and changed out the used battery, putting the device in his right anterior pants pocket, which also contained his car keys and some spare change. These metallic items likely caused a short in the unshielded battery leading to thermal runaway and the resulting flame burn.	20	M	Flaming ENDS		
				Case 3 - pants caught fire, pocket had e-cigarette when it became very hot.	37	M	Fire from ENDS in pocket		
Brooks et al June 2016	Case report.	USA	NR	The patient had been smoking for about an hour after an overnight recharge of its lithium-ion battery. The patient recalled that immediately after he had replenished the e-cigarette with the e-liquid, an explosion had occurred and propelled the mouthpiece into his mouth. The opposite end of the device, referred to as the 'button', projected outwardly with such force to ricochet against the nearby wall, ceiling and floor, leaving burn residue.	18	M	Explosion of ENDS	Greater strides should be undertaken to increase public awareness of the dangers of e-cigarettes and institute educational programs to deter their practice, particularly targeting the at-risk younger generation.	Multiple reports of e-cigarette-related explosions resulting in head and neck injuries have been publicized over the past several years, with the preponderance of cases having been reported in the news media and on Internet websites. Although the accuracy of most of these cases has not been vetted in peer review journals,

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									several observations of e-cigarette usage and injuries can be summarized. Interestingly, over 90% of the reported individuals were male, which is in contrast to the slight gender difference with e-cigarette users overall (male— 14.2% versus female—11.2%).
Cant et al 2017	Letter.	UK	NR	Necrotic oral ulcer resulting from smoking ENDS.	72	M	Use of ENDS	Potential hazards and safety concerns associated with the e-cigarette requires further research.	
Chi et al 2018	Case report.	USA	?	Patient had ENDS in his mouth when it exploded, the patient's left mandibular central incisor apparently was avulsed. He had just charged the battery.	20	M	Explosion of ENDS	This case illustrates the potential for significant orofacial trauma from e-cigarette explosion. Although some studies and authorities have supported the use of e-cigarettes for tobacco cessation or harm reduction, recent reports of e-cigarette explosions raise important safety concerns.	More studies are needed to assess e-cigarette safety. Device regulation as well as user education may help to prevent such incidents in the future.
Cho et al 2017	Cross-sectional study to assess the relationship between e-cigarette use and oral health.	Korea	NR					The results suggest that daily e-cigarette use among adolescents may be a risk factor for cracked or broken teeth and tongue and/or inside-cheek pain.	
Corey et al 2016	Review - a short report on burn injuries emergency departments in 2016.	USA	2016	In 2016, 26 ENDS battery-related burn cases were captured by NEISS, which translates to a national estimate of 1007 (95%CI: 357–1657) injuries presenting in US EDs. Most of the burns were thermal burns (80.4%) and occurred to the upper leg/lower trunk (77.3%). Examination of the case narrative field indicated that at least 20 of the burn injuries occurred while ENDS batteries were in the user's pocket.			Exploding ENDS	The nature and circumstances of the injuries suggest these incidents were unintentional and would potentially be prevented through battery design requirements, battery testing standards and public education related to ENDS battery safety.	A product code specific to ENDS could be informative for future surveillance activities.
Foran et al 2017	Case report.	USA	NR	High pressure injection-type injury resulting from the explosion of an	30	M	Exploding ENDS	The use of electronic cigarettes has risen sharply in the past decade, and reports of	

Study Reference	Study objective or purpose	Country of case	Year (of event)	Description of event	Subject Age (years)	Subject Gender (M/F)	Caused by	Author's Conclusion	Any other information from study report
				electronic cigarette, with injection of e-liquid into the index finger.				battery-related explosions are on the rise. Because of the handheld nature of these instruments, future high-pressure injection injuries are possible.	
Harshman et al 2017	Case report and literature review.	Canada	NR	ENDS in pocket and battery ignited.	31	M	Exploding ENDS	Lit review indicated 50% of exploding ENDS injuries require surgery. Most frequent site of injury is lower extremity and hands. Injuries becoming more frequent and e-cigarette use increases in popularity.	This case series and literature review highlight the need for improved regulation of e-cigarette devices and advocate for clear warnings on product labels, to make e-cigarette users aware of the risks of battery explosion.
				ENDS in pocket and battery ignited; battery case was embedded in thigh.	36	M	Exploding ENDS		
Hickey et al Feb 2018	Retrospective review of all patients admitted to the Massachusetts General Hospital Burn Center.	USA	January 2015 to April 2017	E-cigarette burns occurred in males 93% (13/14) of the time. Thermal and blast injuries associated with e-cigarette device failure tend to cause small TBSA burns that are deep 2nd and 3rd degree wounds. The most common location for e-cigarette device storage among males was the front pants pocket.			Malfunctioning/exploding ENDS	E-cigarette device users should be made aware of the dangers associated with e-cigarette use and advised to carry e-cigarette devices away from their body in dedicated carrying cases without loose metallic items.	
Jiwani et al Feb 2017	Retrospective review of 10 patients at a single burns centre over a 2 year period.	USA	2014-2016	The cohort was comprised mainly of young adults who sustained mixed partial and full thickness thermal burn injuries. Nine of the 10 injuries were the result of thermal injury with the remaining one a combination of thermal and blast injury.			Malfunctioning/exploding ENDS	In many documented scenarios, a malfunctioning or over-heated battery is the cause. The study data support the need for increased awareness among healthcare providers and the general public of the potential harms of e-cigarette use, modification, storage, and charging.	The investigators recommend development of a standardized incident reporting protocol for injuries associated with e-cigarettes so they can better characterize the problem at hand.
Lam et al 2017	Case report.	China	NR	Toxicity resulting from ingestion of e-cigarette fluid.	24	M	Within 30min of ingestion, the case became somnolent, confused, and agitated, with palpitation and vomiting.	In the context of acute poisoning, the presence of unexplained tachyarrhythmia, confusion, and a negative recreational drug screen should prompt clinicians to consider synthetic cannabinoid toxicity as a differential diagnosis.	

Study Reference	Study objective or purpose	Country of case	Year (of event)	Description of event	Subject Age (years)	Subject Gender (M/F)	Caused by	Author's Conclusion	Any other information from study report
Loewenstein et al 2017	Commentary re FDA regulations.	USA	NR					The proposed FDA regulations of the e-cigarette devices are insufficient to protect users from the real and present hazards of poor device workmanship and potential to reach supra-high temperatures.	
Morley et al 2017	Case report.	England	NR	Individual ingested nicotine-containing e-liquid while under the influence of alcohol.	32	M	Ingesting e-liquid	Death secondary to e-liquid ingestion is still very rare, but has the potential for causing deaths due to the easy access of such liquids to the general public. Such toxicity should be considered in individuals who present in the early phases with symptoms of stimulant toxicity, but also in the latter phase where there may be autonomic depressive effects.	
Norii et al 2017	Case report.	USA	NR	The e-cigarette exploded during use, sending the mouthpiece through the pharynx and into the first cervical vertebra and resulting in fractures of the first and second vertebrae.	27	M	Exploding ENDS	This case report is the first case of a cervical spine injury due to the explosion of an e-cigarette.	As the use of e-cigarettes continue to increase, it is likely that injuries associated with them will also increase.
Park et al 2018	Case report.	Korea	NR	Attempted suicide by nicotine intoxication	27 17	M F	Ingesting e-liquid	Ingestion of e-liquid led to seizures, myocardial dysfunctions, and cardiac arrests but not death	Ingestion of EC liquid can be one of the emerging methods for suicide, especially in young adults and adolescents.
Patterson et al 2017	2 case reports and literature review.	USA	NR	Case 1 - burn to thigh and penis after e-cigarette exploded in pocket	46	M	Exploding ENDS	Establishing a regulatory standard is paramount, for the safety of not only electronic cigarette users, but also rescue personnel who put their lives on the line responding to these incidents. Ideas that may further be investigated include charging the device correctly; charging the device in a safe area that will not result in a fire if it explodes; not carrying the device in one's pocket; and carrying the device in a container that will protect against a burn if the device ignites.	Broadly, the mechanism for burns associated with e-cigarette devices can be classified into two categories: direct from the device (types 1–3, 5a) and indirect (types 4 and 5b) from the fire caused by the device. Direct burns can be further categorized into three distinct patterns (types 1–3) and direct inhalation injury (type 5a).
				Case 2 - burn to face, lip laceration, and corneal abrasion from an e-cigarette that exploded in his face while using the device	41	M			

Study Reference	Study objective or purpose	Country of case	Year (of event)	Description of event	Subject Age (years)	Subject Gender (M/F)	Caused by	Author's Conclusion	Any other information from study report
Ramirez et al 2017	A retrospective study was performed to review all cases of burns related to e-cigarettes referred to three burn centers in California.	USA	Jan 2007 - July 2016	Referral records to three burn centers from January 2007 to July 2016 were searched to identify patients with injuries caused by e-cigarettes.			Exploding ENDS	Thirty patients with burns resulting from e-cigarettes were identified. Twenty-nine were referred within the most recent 18 months. Only one was referred in the preceding 8 years. An explosion was identified by the patient as the inciting event in 26 of the 30 injuries (87%). Explosion of an isolated battery while it was carried on personal attire was reported in 10 cases. Explosion of a fully assembled e-cigarette was described in 16 cases. In seven of these 16 cases, the explosion occurred while the device was idle and carried on personal attire. In the other nine cases, the explosion occurred while the device was being operated. No injury occurred while batteries were charging.	The thighs, hands, and genitalia were the most common sites of injury. Twenty-six patients required hospital admission and nine required surgery. Serious burn injuries from e-cigarettes have recently occurred with greatly increased frequency. The increase in injuries appears out of proportion to the increased popularity of e-cigarettes. The most common pattern of injury is explosion when either the idle device or its batteries are carried on personal attire.
Rudy et al 2016	Retrospective study to identify the number and nature of ENDS incidents.	USA	2009 - 2015	Center for Tobacco Products (CTP) scientists searched for event reports among five US federal agencies, scientific literature and media outlets.				100 reference sources identified 92 overheating, fire and explosion events in the USA, of which 45 (49%) injured 47 people, and 67 (73%) involved property damage beyond the product.	More comprehensive reporting could assist future analyses and may help to identify root causes and contributors to the overheating, fire and explosion events.
Satesson et al 2017	Case report.	USA	NA	Sustaining extensive thermal and blast injuries to his hand when the device exploded while he was holding it.	35	M	Exploding ENDS	With increasing numbers of such injuries, hand surgeons must be aware of the blast mechanism involved so as to avoid missing deep soft tissue injury or disruption of deep structures, as demonstrated in this case.	
Serror K, Chaouat M, De Runz A et al et al 2017	Letter.	France	NA	Thermal burn to thigh with the resistor - no explosion or flames; no burns to trousers or damage to e-cigarette.	NA	M	malfunctioning ENDS	Care needs to be taken with regulations of e-cigarettes as they become more popular	
Serror K, Chaouat M, Legrand MM et al 2017	Retrospective review of our institutional burn database.	France	June 2016 - July 2017	10 patients treated for burns.			Exploding ENDS (80% of the time the ENDS was in the pocket)	It is considered that a classification based on the mechanisms of the burns will have a direct impact on the management of the patients and will help specialist and non-specialists to deal with these injuries. The four mechanisms that can be responsible for injuries can be	An international multi-centre prospective study to increase the number of patients included in the series studying injuries

Study Reference	Study objective or purpose	Country of case	Year (of event)	Description of event	Subject Age (years)	Subject Gender (M/F)	Caused by	Author's Conclusion	Any other information from study report
								unique or associated: thermal burns with flames (Type A), blast lesions secondary to the explosion (Type B), alkali chemical burns (Type C) and thermal burns without flames (overheating) (Type D).	related to the use of e-cigarettes may be useful.
Smith et al 2017	Case series review.	USA	Dec 2015-Oct2016	10 adults treated.	20-49	All men	Exploding ENDS.	This small case series revealed serious injuries with significant and long-term implications for the victims of e-cigarette explosions.	A serious, and most impactful limitation is the lack of consensus on the safety of e-cigarettes and the implications of long-term use.
Toy et al 2017	Retrospective review focused on patients from the Arrowhead Regional Medical Center (ARMC) burn registry.	USA	Nov 2015 - March 2017	25 adults treated.	Ave age 34	All men	Exploding ENDS (72% of the time the ENDS was in the pocket).	With ENDS use on the rise, the primary objectives of regulatory agencies and public health organizations may include wider dissemination of education on ENDS safety hazards and improvement of device safety, as well as to develop standardized guidelines for the treatment of the potentially devastating injuries that may result from ENDS malfunction.	
Treitl et al 2017	Case reports.	USA		Case 1 - ENDS exploded in pocket.	mid-20s	M	Exploding ENDS - spontaneous combustion of lithium-ion batteries used for e-cigarettes.	In presenting these cases, the goal is to provide education to health care providers, e-cigarette manufacturers, and the community on the proper use and storage of lithium-ion batteries, to prevent such burns.	Potential risk associated with thermal runaway (Figure 4). We also recommend that e-cigarette manufacturers include a fire warning on e-cigarette label.
				Case 2 - ENDS exploded in pocket.	mid-30s	M			
				Case 3 - ENDS exploded in pocket.	mid-40s	M			
Van de Meer et al 2017 ABSTRACT ONLY	Case report.	Netherlands		Deliberate ingestion of e-cigarette liquid.	42	M		Intentional ingestion can lead to toxic levels of nicotine which are associated with cardiac arrhythmias or arrest. Because even a few millilitres can be lethal, nicotine intoxication due to e-liquid ingestion should be considered potentially life-threatening.	
Vardavas et al 2017	Retrospective analysis of exposure to e-liquids as reported to poison centres within the 22 EUMC.	European Union Member states	2012 - March 2015	277 incidents were reported. Unintentional exposure was the most frequently cited type of exposure (71.3%), while e-cigarette refill vials were responsible for the majority of the reported incidents (87.3%). Two-thirds of all exposures (67.5%) occurred as ingestion of e-liquids, which was more frequent among children (≤ 5 years, 6 –18				This study highlighted parameters related to e-cigarette exposure incidents in 10 EU MS, indicating that consideration should be given to the design features which may mitigate risks, thereby protecting users, non-users and especially children.	This is the first study to report exposure incidents attributable to e-cigarettes.

Study Reference	Study objective or purpose	Country of case	Year (of event)	Description of event	Subject		Caused by	Author's Conclusion	Any other information from study report
					Age (years)	Gender (M/F)			
				years) compared to adults (87.0% vs. 59.3% vs. 57.6%, p<0.001 respectively), exposure via the respiratory (5.4% vs. 22.2% vs. 22.2%, p<0.001) were more frequent among paediatric patients while ocular routes (2.2% vs. 3.7% vs. 11.4%, p=0.021) were more frequent among adults.					

Table 8: Data from animal studies

Study reference	Study objectives	Study Population Species	Gender (% male)	Duration	Exposures Control	Experimental	Dose equivalent to humans?	Further notes on study protocol	Outcome	Author Conclusion statement
Alasmari 2017	To determine the effect of chronic exposure to EC vapour containing nicotine on GLT-1, xCT, and GLAST expression in FC, STR, and HIP in mice.	Mice (outbred)	0	1 hr/d for 6 months	Put in restraints, breathed room air.	Put in restraints, breathed EC vapour (24mg/mL nicotine).	Yes (as shown by cotinine levels).	Mice were sacrificed and brain tissue harvested to detect changes in expression of a-7 nAChR, GLT-1, xCT, GLAST and nicotine and cotinine present.	EC group had increased expression of a-7 nAChR in the FC and STR but not in the HIP, reduced expression of GLT-1 in the STR but not in the FC or HIP. xCT expression was decreased in the EC group in the STR and HIP but not in the FC. The EC group had higher nicotine and cotinine levels. GLAST expression did not differ between groups for all three brain regions.	"These data demonstrated that nicotine exposure alters glial glutamate transporters as well as nicotinic receptors, which might be key proteins in the development of nicotine dependence."
Canistro 2017	To determine if ECs cause in vivo toxicological effects which could contribute to cancer.	Rats (Sprague Dawley)	100	17 puffs every 20 mins, 5d/wk, 4 wks	No exposure to EC substances.	EC vapour containing 18mg/mL.	No.	Mice were sacrificed and organs investigated.	Cytochrome P450 changes: increased CYP1A1/2, CYP2B1/2 and CYP3A in EC group only, which is related to increased cancer risk. Only the EC group had increased ROS. Ferric reducing antioxidant power (FRAP) reduced in the lungs of the EC group. Fragmented DNA was more extensive in EC group.	"Our results demonstrate that exposure to e-cigarettes could endanger human health, particularly among younger more vulnerable consumers."
Chen 2018	To develop a mouse model of maternal e-vapour exposure and investigate the impact on the growth and lung inflammation in both offspring and mothers.	Mice (Balb/c)	Mothers: 0% Offspring: 100%	2x 15mins/d for 6 wks before mating until pups weaned.	Exposed to room air.	Exposed to nicotine-containing EC vapour OR nicotine free EC vapour.	Yes (as shown by cotinine levels).	N/A	Effects on mothers: Weight gain did not differ between nicotine-EC & control, but nicotine-free EC group had 1/3 of the control weight gain. Liver weight did not differ. Retroperitoneal fat mass was lower and TNF-α and ErK1/2 were upregulated in EC groups compared with control. IL-1β increased in nicotine-containing EC group in comparison to the other conditions. IL-6 increased and JNK was upregulated in the nicotine-free EC group but not in the others. p38, p65 and NF-kB did differ between groups. Effects on off-spring: Results for body weight differed over the time period. Cotinine levels were highest among the nicotine-exposed group. No significant differences were found between groups for ephrine B2 mRNA expression or IL-6. PDGF mRNA was upregulated, IL-1β was supressed, p38 increased and TNF-α was increased in the EC groups. JNK protein, p-p38 and p-Erk1/2 increased in the nicotine-containing EC group compared with the control.	"In this study, we found that EC exposure during pregnancy adversely affected maternal and offspring lung health. As this occurred with both nicotine-free and nicotine-containing e-vapour, the effects are likely due to by-products of vapour rather than nicotine."

Study reference	Study objectives	Study Population Species	Gender (% male)	Duration	Exposures Control	Experimental	Dose equivalent to humans?	Further notes on study protocol	Outcome	Author Conclusion statement
									p-JNK protein increased in the nicotine-free EC group compared with the nicotine group. Global methylation and inflammatory cytokine expression increased in both EC groups. In the nicotine-free EC group, IL-5, IL-13 and TNF-α increased. No changes were observed for IL-α, IL-1β or IL-6 for any group.	
Cobb 2018	"To gauge the safety level of e-cigarettes as a 'harm reduction' alternative to conventional cigarettes." Compared heavy metal exposure (via metallothioneins (MT)) and ROS exposure in e-cigarettes and tobacco smoke.	L4 larvae from C. elegans (nematode)	N/A	NR	Exposed to 30 puffs of air.	Exposed to 15, 30 or 45 puffs of e-cigarette vapour or cigarette smoke.	NR	Used a pharyngeal pumping assay to determine if the nematodes had undergone stress-induced sleep. Also conducted RNA isolation and RT-PCR.	Movement post-cigarette exposure was reduced but not after e-cigarette vapour or the control. Exposure to cigarette smoke resulted in dose-dependent increases in stress-induced sleep in the nematodes, e-cigarette vapour and the control did not. Cigarette smoke induced mtl-1 expression, e-cigarette vapour did not. No condition induced mtl-2 expression. This indicates increased ROS presence after exposure to cigarette smoke but not e-cigarettes.	"The data demonstrate that e-cigarettes do not induce a stress response and that no MT expression was found, suggesting little to no ROS present after exposure... These data, along with previous studies, suggest that e-cigarettes, although not completely harmless, may be a safer alternative to conventional cigarettes."
Crotty Alexander 2018	To determine if exposure to EC vapour components alters barrier function of airway epithelium, inflammatory release and organ injury.	Mice (C57BL/6 and CD-1)	0	5 d/wk, for 3-6 months	Put in restraints, breathed room air.	Put in restraints, breathed EC vapour.	Yes (study designed to imitate human use)	GFR and cardiac function assessed one week prior to sacrifice. All other measures assessed after sacrifice.	EC-exposed group had: Increased levels of circulating inflammatory cytokines in the lungs, including DPPIV. Elevated cotinine. Renal dysfunction, fibrosis and increased expression of pro-fibrotic factors. Fibrosis of the heart and increased blood pressure. Higher levels of hepatic fibrosis.	"These data demonstrate that chronic inhalation of EV may lead to increased inflammation, organ damage, and cardiorenal and hepatic disease."
Harris 2018	To assess the ICSS response from nicotine and ECs, as well as binding affinity of nicotine and EC liquids at nAChRs.	Rats (Holtzman)	100	Duration varied	Nicotine, administered IV	Janty or NicVape nicotine-containing EC liquid OR Janty OR NicVape nicotine-free EC liquid, IV administered.	NR	Rats had electrodes implanted into the medial forebrain bundle and were trained to respond to electrical brain stimulation.	Nicotine-containing liquids led to similar reductions of ICSS thresholds. Nicotine-free EC liquids did not affect ICSS. However, all EC liquids bound with nAChRs, leading to its partial inhibition.	"These findings suggest that non-nicotine constituents in these EC liquids do not contribute to their reinforcement-enhancing effects. However, they may attenuate nicotine's acute aversive/ anhedonic and/or toxic effects, which may moderate the abuse liability and/or toxicity of ECs."

Study reference	Study objectives	Study Population Species	Gender (% male)	Duration	Exposures Control	Experimental	Dose equivalent to humans?	Further notes on study protocol	Outcome	Author Conclusion statement
Kaisar 2017	To investigate EC vaping and blood-brain barrier (BBB) integrity and vascular inflammation and the influence of Metformin on these processes.	Mice	100	6x/d, 7d/wk, 2wks	Oxygenated air	CIG smoke OR EC vapour.	NR	Mice administered with MF (Metformin) or saline solution. After 2 wks mice were sacrificed and samples analysed.	Oxidative stress induced by both EC group and CIG group were higher than the control. ECs and CIGs elicited a similar inflammatory response (downregulated tight junction protein ZO-1, decreased trans-endothelial electrical resistance (both indicate blood-brain-barrier impairment) and upregulated PECAM-1 , ICAM-1 and VCAM-1 (indicators of inflammation)) and were equally harmful. CIG and EC exposure led to downregulation of thrombomodulin (anti-coagulant), which indicated an increased risk of stroke. Also led to downregulation of Nrf2 expression. After both exposures, the brain infarct area increased and there was worse neurological deficits compared to control mice.	"...we provide evidence that likewise to TS, chronic EC (e-Cig) vaping can be prodromal to the loss of blood-brain barrier (BBB) integrity and vascular inflammation as well as act as a promoting factor for the onset of stroke and worsening of post-ischemic brain injury."
Kennedy 2017	To test the effects of several aerosolized EC liquids in an in vivo craniofacial model and a mammalian neural crest cell line.	Frog embryos	N/A	Depended on growth of embryo.	Embryos arrayed on a culture/petri dishes with EC liquids. EC liquids: 'lab grade' liquid created at the lab (varied in concentration) and 6 flavoured EC products). Craniofacial tissue was inspected.		Yes (designed to have equivalent nicotine levels to humans).	N/A	EC exposure led to craniofacial and other defects including median facial clefts, midface hypoplasia, cranial cartilage, muscle defects, a reduction in facial blood supply and reduced expression of markers for vascular and cartilage differentiation. Nicotine was not the main factor in inducing craniofacial defects, but exacerbated EC components. Liquids produced slightly different deleterious effects.	"Our work is the first to show that EC use could pose a potential hazard to the developing embryo and cause craniofacial birth defects. This emphasizes the need for more testing and regulation of this new popular product."
Laube 2017	To determine the effect of acute & chronic exposure to EC emissions on lung mucociliary clearance.	Mice (C57BL/6)	100	20min/d for 1 wk (acute) or for 3 wks (chronic)	No exposure to EC substances.	Either 0% nicotine/ propylene glycol OR 2.4% nicotine/ propylene glycol	No (puff duration exceeded equivalent human use).	Measured mucociliary clearance 6 hours after exposure.	Differences in mucociliary clearance were not significant for acute exposures. Chronic exposure to propylene glycol (nicotine-free ECs) stimulated mucociliary clearance, while nicotine exposure reduced clearance. Serum cotinine levels were higher among the nicotine group compared to the other groups.	"In this murine model, a chronic, daily, 20min-exposure to nicotine/ propylene glycol, but not an acute exposure, slowed mucociliary clearance, compared to exposure to propylene glycol alone and led to systemic absorption of nicotine."
Lee 2018	To determine whether ECs can induce DNA damage in different mouse organs and whether ECs can affect DNA-repair activity.	Mice, human tissue.	100	3hr/d, 5d/wk, 12 wks	Not described.	10mg/mL nicotine in a propylene glycol/ vegetable glycerine mixture.	Yes (dose and duration equivalent to light EC smoking for 10 years).	Mice were sacrificed after exposure and lungs, liver, bladder and heart were examined.	Mice exposed to ECs had more DNA adducts in their lungs, bladder and heart. Increased quantities of DNA adducts were found in the lungs compared with the other tissues. Mice exposed to ECs had lower amounts of DNA repair proteins compared to the control.	"These results indicate that nicotine nitrosation occurs in vivo in mice and that EC smoke is carcinogenic to the murine lung and bladder and harmful to the murine heart. It is therefore possible that EC smoke may contribute to lung

Study reference	Study objectives	Study Population Species	Gender (% male)	Duration	Exposures Control	Experimental	Dose equivalent to humans?	Further notes on study protocol	Outcome	Author Conclusion statement
										and bladder cancer, as well as heart disease, in humans."
Miyashita 2018	To determine if EC vapour increases pneumococcal adhesion to airway cells.	Mice (and human and in vitro).	0	2x/d, 8d	DPBS control extract	EC vapour ±nicotine	On day 4 mice were exposed to	Measured nasopharyngeal pneumococcal colonisation 4d after.	The nicotine-free EC did not increase nasopharyngeal pneumococcal CFU or nasal epithelial PAFR expression at 4 days post intranasal instillation of bacteria, but the nicotine-containing EC did.	"This study suggests that EC vapour has the potential to increase susceptibility to pneumococcal infection."
Parker 2017	To investigate developmental toxicities of CIG butt leachates and EC leachate on frog embryos (environmental impacts of ECs).	Frog embryos.	N/A	96hr	Exposed to regular CIG butt/ menthol CIG butt or electronic CIG leachate, using FETAX (frog embryo teratogenesis assay- Xenopus).		N/A	Measured median lethal concentration, malformation, non-observed adverse effect concentration, and lowest observed adverse effect concentration.	The lowest median lethal concentration was determined for EC exposure at 17.9 CIG butts/L. Regular CIG butts had the highest median lethal concentration, malformation and ECs had the lowest. ECs also had the lowest non-observed adverse effect concentration and lowest observed adverse effect concentration.	Regular CIG butt leachate is the most toxic compound, while menthol CIG butt leachate has the higher teratogenicity. EC leachate has the lowest toxic and teratogenic effects on embryos but there were still noticeable effects.
Phillips 2017	To determine toxicity of EC liquids, nicotine, propylene glycol, and vegetable glycerin in mixtures.	Rats (Sprague-Dawley, outbred).	Both male and female.	6hr/d, 5d/wk, 13 wks	Nose-only exposed to filtered fresh air.	Nose-only exposed to one of three concentrations of propylene glycol/ vegetable glycerin mixtures, with and without nicotine.	No (doses marginally exceeded equivalent human use).	After 13 wks mice were sacrificed and organs analysed.	The total amount of the recovered nicotine metabolites in urine samples collected over 24 h (both during and after the exposure) was similar among all nicotine-exposed groups, indicating a similar uptake by the rats. Rats exposed to nicotine had higher food intakes & females had significantly higher body weights. Female rats exposed to nicotine had slightly higher inflammation in the lungs (macrophage and total cell counts). Nicotine-exposed rats had lower: total protein concentrations (females only), total cholesterol, glucose concentrations and higher liver weights. In female rats exposed to nicotine, alanine aminotransferase and alkaline phosphatase (liver enzymes) increased in activity. Hepatocyte vacuolation was observed more frequently in the liver of nicotine-exposed rats. Adrenal gland weight significantly increased among nicotine-exposed rats, reflecting a	"Altogether, under the conditions of this 90-day SD rat study, several nicotine related responses have been observed but taking in to account the overall weight of evidence no adverse effects were observed for propylene glycol/ vegetable glycerin /nicotine up to 438/544/6.7 mg/kg/day, since the vast majority of the effects observed are considered to be adaptive changes caused by the nicotine levels and they have been shown to be reversible on cessation of treatment."

Study reference	Study objectives	Study Population		Duration	Exposures		Dose equivalent to humans?	Further notes on study protocol	Outcome	Author Conclusion statement
		Species	Gender (% male)		Control	Experimental				
									possible stress-response to the nicotine. No toxicologically relevant effects were observed.	
Rahali 2018	To evaluate the impact of e-liquid with or without nicotine on the epididymis of rats.	Rats	100	28 days	Given injection of NaCl in [9g/L].	NaCl with e-liquid containing nicotine or a nicotine-free e-liquid at 0.5mg/kg body weight/day	No- dose was lower/ day but entire dose was given at once.	Rats sacrifice at 4 wks. Sperm count and eosine-nigrosine staining was conducted to estimate viability of sperm cells.	E-liquid exposure induced a significant decrease in the epididymal spermatozoa number (Table 1). Sperm number was 32.3 ± 3.0 million/ml in the nicotine-free e-liquid rats and 38.4 ± 0.9 million/ml in the nicotine-containing e-liquid rats, and the sperm count reached 42.5 ± 2 million/ml in the control rats. Results showed a significant decrease in the percentage of viability for nicotine-free e-liquid and nicotine-containing e-liquid rats in comparison to the control group.	E-liquid exposure led to decreased epididymal spermatozoa count (32.3 ± 3.0 million/ml in the e-liquid nicotine-free condition, 38.4 ± 0.9 million/ml in the nicotine-containing E-liquid, 42.5 ± 2 million/ml in the control). There were also fewer viable cells in the e-liquid conditions compared with the control. Testosterone levels in the e-liquid-exposed rats was also lower, while inflammatory and oxidative states were higher.
Rau 2017	To examine the toxic microcirculatory effects ECs may have in comparison with tobacco CIGs.	Rats	NR	5 wks	Exposure to room air.	Tobacco smoke OR medium nicotine content (1.2%-12mg/mL) EC vapour OR high nicotine content (2.4%-24mg/mL) EC vapour.	NR, however dose is likely equivalent as indicated by cotinine and nicotine plasma levels.	Skin flaps were assessed at 4 and 5 wks. After 5 wks rats were euthanized and nicotine, cotinine, flap tissues were analysed.	Skin flap survival was significantly reduced and immunoreactivity for hypoxia was increased among the EC and tobacco groups when compared with the control group. Serum nicotine and cotinine was higher among rats exposed to CIG smoker when compared with EC-exposed rats. Both were higher than the control group exposed to room air. There was no correlation between cotinine levels and gross necrosis.	Nicotine exposure, regardless of whether it is from ECs or tobacco CIGs, led to skin flap necrosis and hypoxia. Thus, ECs have similar skin-flap toxicity as tobacco CIGs.

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Study reference	Study objectives	Study Population		Duration	Exposures			Dose equivalent to humans?	Further notes on study protocol	Outcome	Author Conclusion statement
		Species	Gender (% male)		Control	Experimental					
Reinikovaite 2018	To examine whether long-term exposure to EC vapour or nicotine produce the same effect on the lung structure and vasculature as tobacco smoke.	Rats (Sprague-Dawley).	NR	2x2hr sessions/d for 6 wks.	Exposure to room air.	IV nicotine injections (25ng/mL) comparable to vapour produced in EC machines for habitual smokers OR EC vapour (12mg/mL nicotine) OR CIG smoke.		Yes (designed to replicate EC use in humans).	At the end of the exposure, rats were sacrificed and the mean alveolar airspace enlargement was measured.	EC vapour, IV nicotine and traditional CIG smoke all led to significant emphysematous lung destruction compared with the control (room air). The capillary count was decreased in IV nicotine, CIG and EC vapour compared with the control. EC and CIG smoke both had lower capillary counts in comparison to nicotine alone. Serum nicotine and cotinine were higher among CIG smoke than EC vapour.	"Our results clearly demonstrate that ECs are as damaging to pulmonary structures as traditional tobacco CIGs. The emphysematous changes seen in CIG smoke exposed rat lungs are also abundantly apparent in EC- and in nicotine-treated rat lungs."

d: day; CIG: traditional tobacco cigarette EC: e-cigarette; FC: Frontal cortex; HIP: hippocampus; Hr: hour; ICSS: intracranial self-stimulation; NR: not reported; STR: striatum

Table 9: Data from in vitro studies

Study reference	Study objectives	Species	Control exposure	Experimental exposure	Cells	Further notes on study protocol	Outcome(s)	Conclusion(s)
Antherieu 2017	To investigate the toxicity of e-vapours in human bronchial epithelial BEAS-2B cells in comparison to CIG smoke.	Human	CIG smoke.	EC vapours (6 different vapours used).	Bronchial epithelial BEAS-2B cells.	Determined cytotoxicity, glutathione contents, secreted mediators of inflammation, RNA and DNA analysis.	No significant cytotoxic effects on BEAS-2B cells were found for any of the ECs at any time point. CIG smoke caused intracellular ATP changes with 48 minute exposures and also reduced cell viability after 96 min exposures. Acute EC or regular CIG exposures led to oxidative stress (elevated intracellular GSH and GSSG), however there was no alterations 3h after exposures. IL-6 secretion (inflammatory marker) was elevated after EC use and CIG smoke. However, CIG smoke also led to increased IL-8. Fewer genes were up- or down-regulated by EC exposure compared with CIG smoke.	"These results strongly suggest a lower toxicity of e-vapours compared to CIG smoke in the BEAS-2B cell line and constitute a baseline for further experimental studies with a larger spectrum of e-liquids and e-cigarette models."
Aufderheide 2017	To study whether ECs exert toxicologic effects equivalent to those exerted by conventional CIGs in a similar cell model.	Human	Clean air.	50 EC puffs/d OR 4 CIGs/d	Bronchial epithelial NHBE cells from male with non-small cell lung cancer.	Conducted histological sampling and immunohistochemical staining.	CIG smoke-exposed cells had a reduction in mucous production and cilia bearing. This was also observed among EC exposed cells but to a lesser extent. Exposure to EC vapour or CIG smoke had a reduction in mucous-secreting cells and their activity. No changes to p63 cells (tumour promotion protein) was found.	"In summary, the EC vapour induced qualitative and quantitative morphological alterations comparable with those observed with conventional CIG smoke thus pointing to a serious risk by this vapour."
Barber 2017	To explore the effects of EC extract exposure on endothelial cell complement activation as a marker for enhanced vascular inflammation.	Human	Extracts from CIGs.	Extracts from ECs.	Endothelial cells from umbilical veins.	Endothelial cell inflammatory processes, viability, density and metabolic activity were observed.	Endothelial cell viability decreased after exposure to tobacco products, EC products but not nicotine. Endothelial cell density reduced after exposure to tobacco smoke, EC vapour, EC extracts and pure nicotine. Endothelial cell metabolic activity significantly reduced after exposure to tobacco smoke extracts and most EC vapour extracts but not pure nicotine. C1q and C5b-9 deposits, but not C3b and C4d (indicators of development of CVDs) were enhanced in the tobacco smoke and EC exposed cells. Enhanced expression of gC1qR (receptor for C1q) was found after EC vapour, tobacco smoke or pure nicotine exposure. CD35 (regulates C3b and C4b) was enhanced in all smoke and vapour conditions.	"…results were independent of nicotine and the exposure to e-vapour was just as harmful as tobacco smoke extracts. Thus, the exposure to fine particulate matter and not toxic combustion gases or nicotine may be the most critical for regulating CVD progression."
Behar 2017	To compare the cytotoxicity of EC refill fluids/solvents and their corresponding vapours using in vitro cultured cells.	Human	32 flavours & 3 components of EC liquids.	32 flavours & 3 components of EC fluids, vaporised.	Pulmonary fibroblasts, lung epithelial cells (A549) and human embryonic stem cells.	Tested cytotoxicity of flavours/ components of EC liquids and EC vapours on all three cell types.	Embryonic stem cells were more sensitive than lung cells. 7/35 (20%) of fluids and its vapour were non-cytotoxic, 19/35 (54%) of both the fluid and vapour were cytotoxic, 1/35 (3%) had a cytotoxic fluid but not vapour and 8/35 (23%) had a cytotoxic vapour but not fluid. 10/11 glycerine-based fluids were cytotoxic when vaporised (91%). Researchers also noted that the creamy/ buttery flavours were the most cytotoxic.	"Our data show that various flavours/ brands of EC refill fluids and their vapours are cytotoxic and demonstrate the need for further evaluation of EC products to better understand their potential health effects."
Bengalli 2017	To test the effects of condensed vapours from three main e-liquid categories	Human	2 vaporised EC bases (PG, VG, water), ± nicotine	5 EC flavours (1 cinnamon, 2 tobacco, 2 menthol), ± nicotine, vaporised	Epithelial alveolar cells, lung microvascular	Tested cytotoxicity and cytokine release in two different cell models (cells monoculture & ABB model).	Cells monoculture model: Both the base and tobacco-flavoured ECs did not lead to cytotoxic or pro-inflammatory responses, regardless of the nicotine content. However, cell death increased among nicotine-containing cinnamon and menthol EC liquids, but not nicotine-free variants. Exposure to Menthol 2 + nicotine led to cell-death in 90% of cells. Cinnamon + nicotine ECs led to release of pro-inflammatory	Nicotine-containing EC liquids may produce cytotoxic effects because of synergistic action between the flavour and nicotine molecules.

Study reference	Study objectives	Species	Control exposure	Experimental exposure	Cells	Further notes on study protocol	Outcome(s)	Conclusion(s)
	(tobacco, mint, and cinnamon as food-related flavour), with (18 mg/mL) or without nicotine.				endothelial cells.		cytokines (1L-8 & MCP-1) in epithelial cells. This was not observed in other flavour variants, however in Menthol 2 exposures, the cytotoxic response was so strong that the cells were unable to secrete inflammatory signals. ABB model: Cinnamon and Menthol 2 were found to be cytotoxic. No increases in IL-8 or MCP-1 was found in any flavour.	
Bharadwaj 2017	To discriminate the deleterious effects of EC refills (e-juice) and soluble e-juice vapour (SEA) by employing stress-specific bioluminescent recombinant bacterial cells (RBCs) as whole-cell biosensors.	Plasmids and Bacteria (E. coli).	No exposure to ECs.	Liquid and vapour ECs.	Plasmids & recombinant bacteria cells.	Assessed cell viability and DNA fragmentation (via an alkaline gel electrophoresis assay).	Bioluminescent signals were dose-dependently inhibited by exposure to e-liquids, reflecting an ability for e-liquids to inhibit growth. Suggested mechanism of growth inhibition was inhibition or blocking of the DNA repair mechanism, likely the copA gene cassette which is essential for heavy metal ion pumps. Cell viability significantly decreased in the EC exposed cells compared with the ctrl. After vaporising e-liquids, bioluminescent signals were no longer inhibited at high doses. Maximum doses of e-liquids led to significant DNA fragmentation, with lower doses showing partial fragmentation.	"Despite their state of matter, the e-juice and its vapours induce cytotoxicity and alter normal cellular functions, respectively that raises concerns on use of ECs as alternative to CIG."
Bishop 2018	To explore EC cytotoxicity using undiluted vapour techniques.	Human	CIG smoke	Vaporised undiluted EC ± cinnamaldehyde.	Epithelial airway cells.	Assessed cytotoxic responses.	Both undiluted EC vapour and CIG smoke led to full cytotoxicity dose response. 50% toxicity was observed at 2.1min and 30mins of CIG and EC exposure, respectively. After adding 0.025% cinnamaldehyde, there was an 80% loss of cell viability. Cytotoxicity of cinnamaldehyde was dose-dependent.	"This study demonstrates that undiluted vapour testing represents a tangible step forward in the assessment of EC vapours in vitro."
Breheny 2017	To compare the relative biological effects of new categories of tobacco and nicotine products with CIGs.	Mice	Aqueous extracts of CIG (3R4F).	Aqueous extracts of ECs (18mg/mL nicotine).	Fibroblast cells.	Measured nicotine levels, toxicology and promoter activity.	Nicotine levels in the cells after exposure to CIGs were about twice those of ECs. Toxicology of the aqueous extracts was assessed in CIGs and ECs. In ECs no toxicity was found up to 100% aqueous extracts, however complete loss of cell viability was identified at >15% aqueous extracts of CIGs. CIG concentrations of 2.5% also impacted toxicity. After exposure to CIGs at 6, 12, 24, 48 & 60ug/mL the number of 'transformed colonies' increased, i.e. there was increased tumour promoter activity/ cell growth. Increases in the EC group were not significant.	"These data add to growing evidence suggesting that ECs may provide a safer alternative to CIGs."
Carson 2017	To measure ciliary function and secretions, as well as cellular and exogenous NO concentrations subsequent to a single exposure to tobacco smoke (TS) or EC vapour (EV) on cultured	Human	No EC or tobacco exposure.	EC vapour, Tobacco smoke.	Epithelial airway cells (nasal).	Measured cilia beat frequency, secretions, cellular and exogenous NO concentrations. Matched cells to compare cells from the same origin.	Ciliary motility was reduced after 1 minute of exposure to either tobacco smoke or EC smoke but not in the ctrl. Tobacco smoke exposure led to hypersecretions as indicated by matting and coalescence of cilia. While EC exposure also led to increased secretions, the effect was not as strong as tobacco smoke. Ciliary beat frequency decreased in both experimental conditions (decline of 40% after tobacco smoke, 33% after EC smoke) but recovered again in the hr post-exposure (15% recovery tobacco smoke, 19% EC).	"This study demonstrates a similar pattern of epithelial response to acute tobacco smoke or EC vapour exposure."

	human airway epithelium.							
Clapp 2017	To investigate the effects of seven flavoured nicotine free e-liquids on primary human alveolar macrophages, neutrophils, and NK cells.	Human	PG/VG	7 flavours of EC liquids at concentrations of 0.25, 0.5 & 1%.	Alveolar macrophages, neutrophils, and NK cells.	Neutrophils and NK cells were isolated from blood samples. Alveolar macrophages were isolated from brochoalveolar lavage fluid from a brochoscopy. Assessed effects on neutrophils, NK cells and alveolar macrophages.	Alveolar macrophages: Only kola (at 1% concentration) and sini-cide (0.25, 0.5 & 1% concentrations) led to significant phagocytosis suppression compared with PG/VG ctrls. 1% Kola e-liquid exposure led to increased IL-6 secretion but 0.5% Sini-cide led to suppressed IL-6 and IL-8 (IL-8 supressed in all concentrations) secretion. Neutrophils: The ctrl and 5 experimental flavours reduced neutrophil phagocytosis in a dose-dependent manner. Toxicity was observed at 1% Kola and 0.5 & 1% Sini-cide flavours. All flavours except Solid Menthol and Sini-cide led to increased IL-8 secretion. Sini-cide likely did not increase IL-8 due to cytotoxicity. NET: PG/VG did not induce NET formation. Hot Cinnamon Candies suppressed NET formation, Kola increased NET formation, while Sini-cide was cytotoxic which meant NET formation could not be studied. NK cells: Killing of target cells was reduced after exposure to cinnamon-flavoured e-liquids. Cinnamaldehyde: Reduced phagocytosis in alveolar macrophages and neutrophils and reduced killing efficiency in NK cells.	"These findings add to the concern that flavoured e-liquids may broadly contain potentially hazardous chemicals and illustrate the need to investigate the respiratory effects of common flavourings used in the manufacture of e-liquids."
Crotty Alexander 2018	To investigate the effect of ECs on permeability of epithelial surfaces and inflammation.	Human	Air	EC vapour	Bronchial epithelial cells.	Cells were exposed to infectious Pseudomonas aeruginosa. Inflammatory response and tight junction proteins were investigated.	After exposure to infection, EC-exposed airway epithelium secreted higher IL-8 than the ctrl, indicating increased inflammation following infection. EC exposure led to changes in tight junction proteins and thus may reduce barrier function in the lungs. This could lead to increased passage of external antigens and chemicals into the lungs and blood.	"These data demonstrate that chronic inhalation of EV may lead to increased inflammation…"
Davies 2017	To evaluate the influence CIG/EC vapour has on model surfactant films located within a simulated pulmonary environment using a lung bio simulator.			CIG and EC vapour.	Simulated pulmonary surfactant.	Much of the paper described the lung bio simulator which was developed by this group.	"On exposure to smoke vapour, Langmuir isotherms exhibited condensed character and a significant reduction in maximum surface pressure was noted in all cases. Langmuir isocycles, reflective of the human breathing cycle, demonstrated condensed character on smoke vapour delivery. A reduction in the maximum surface pressure was clear only in the case of CIG vapour application. The components of CIG vapour can cause oxidative damage to pulmonary surfactant and impair recycling. Neutral nicotine molecules can weaken the structure of the monolayer and cause destabilisation. A protective effect was evident in the case of repeated surfactant compression – relaxation cycles (i.e. the ability to reduce the surface tension term was impaired less), demonstrating a likely innate biological defensive mechanism of the lung."	"EC vapour appeared to have a reduced impact on surfactant performance, which may hold value in harm reduction over the longer term." "exposure to CIG/EC vapour does modify the structure-function activity of simulated pulmonary surfactant monolayers under physiologically relevant conditions. "
Ganapathy 2017	To determine the genotoxicity and the mechanisms induced by EC vapour extracts on human oral	Human	Unexposed cells	CIG smoke extracts, 5 EC vapour extracts ± nicotine.	Epithelial cells: oral squamous cell carcinomas &	Measured DNA damage, cell viability, ROS, total antioxidant capacity, mRNA & protein expression.	In all cell types, ECs induced dose-dependent DNA damage, irrespective of the nicotine content. However, damage was less than that induced by CIG smoke extracts. ECs led to oxidative damage (as shown by 8-oxo-dG, a mutagenic oxidative DNA lesions). Oxidative damage was higher after long-term exposure to ECs than CIG smoke. Antioxidant capacity decreased and reactive oxygen species increased	"Exposure to EC vapour extracts suppressed the cellular antioxidant defences and led to significant DNA damage."

Study reference	Study objectives	Species	Control exposure	Experimental exposure	Cells	Further notes on study protocol	Outcome(s)	Conclusion(s)
	and lung epithelial cells.			Replicated human user.	premalignant dysplastic oral mucosal keratinocyte cells.		after EC exposure, at a similar level to CIG smoke. A reduction in proteins associated with DNA damage removal was also found in some cells exposed to ECs and all cells exposed to CIG smoke.	
Gerloff 2017	To evaluate the release of the pro-inflammatory cytokine IL-8 and epithelial barrier function in response to different e-cigarette flavouring chemicals.	Human	TNF-α cells	EC flavourings, ± nicotine (0-24mg/mL)	Bronchial epithelial cells (Beas2B), human mucoepidermoid carcinoma epithelial cells (H292), and human lung fibroblasts (HFL-1).	Assessed components and emissions of each flavour and exposed the flavour-component of the EC them to cells. Assessed inflammation.	Identified that ECs contain: cinnamaldehyde, vanillin, ethyl maltol, benzaldehyde, pyrazine and menthol. Beas2B and HFL-1 cells: Acetoin, diacetyl, maltol and ortho-vanillin all led to release of IL-8 at 1mM concentration. However, two out of seven flavouring chemicals suppressed IL-8. There was no effect on H292 cells. Lung epithelial cells and fibroblasts: acetoin (100μM and 1mM), diacetyl (100μM and 1mM), ortho-vanillin (1mM), and maltol (10μM and 1mM) all led to release of IL-8. Cell viability and cytotoxicity did not occur. Epithelial barrier function: Nicotine, diacetyl, coumarin, acetoin, maltol and cinnamaldehyde led to loss of barrier function, whereas pentanedione and ortho-vanillin did not.	"Our findings suggest that some of the e-cigarette liquids/vapours containing flavouring chemicals can cause significant loss of epithelial barrier function and pro-inflammatory response in lung cells."
Haswell 2017	To assess the transcriptional response of a primary 3D airway model acutely exposed to EC vapour and CIG (3R4F) smoke.	Human	Room air	Blended tobacco flavoured EC vapour OR CIG smoke	Airway epithelial cells.	Determined nicotine concentrations, isolated RNA, conducted RNA sequencing and determined gene expression.	There was no difference in nicotine delivery between the CIG and EC. There was no difference in cilia beat frequency in the air ctrl and EC group. EC exposure led to decreased trans-epithelial electric resistance, compared with the air ctrl, but the levels were still within a functional range. MUC5AC decreased after EC exposure compared with the ctrl (interpret with caution). Cytotoxicity and FOXJ1 was not affected. CIG smoke elicited a greater RNA differentiation response than ECs. 24 and 48hrs after EC exposure, 3 RNAs were differentially expressed. 20 RNAs were the same for both ECs. 11 RNAs overlapped after CIG and EC exposure. CIG smoke elicited the largest changes in RNA folding.	"Based on equivalent or higher nicotine delivery, an acute exposure to EC vapour had a reduced impact on gene expression compared to 3R4F smoke exposure in vitro."
Leslie 2017	To evaluate the acute cytotoxicity of EC vapour extract (ECE) on airway-related cells in vitro.	Human	No exposure	CIG smoke extract, EC extracts (15 flavours & the PG & glycerine extracts).	Bronchial epithelial (BEAS-2B, IB3-1 and C38), fibroblast (Wi-38) and macrophage (J774 and THP-1) cell lines.	Assessed cell viability.	CIG smoke extract led to a dose-dependent decrease in cell viability (BEAS-2B, IB3-1 and C38) and cytotoxicity of the C38 cell line. EC extracts decreased cell viability, but the amount of reduction varied for different cell types. Nicotine-containing EC exposure led to a reduction in cell-viability but it was not dose-dependent and it was not cytotoxic. Strawberry-flavoured EC extracts were the most toxic found (cytotoxic for BEAS-2B, IB3-1 and C38). Cherry-flavoured EC extracts were cytotoxic for BEAS-2B and C38. Tobacco-flavoured EC extracts were cytotoxic for BEAS-2B. Strawberry flavour was tested with THP-1 & Wi-38; cell viability was not affected by concentration and cytotoxicity did not occur. Results varied depending on the brand.	"...several flavours proved cytotoxic, with variation between different brands and cell lines. These data indicate that not all ECs are the same and that use of a particular flavour or brand may have differing effects."
Miyashita 2017	To determine if EC vapour increases pneumococcal	Human	Pure nicotine	5% EC extract ± nicotine	Alveolar epithelial cells, bronchial	Used an in vitro adhesion assay to determine	Both nicotine-containing and nicotine-free EC vapours led to increased pneumococcal cell penetration, increased PAFR expression.	This study suggests that EC vapour has the potential to increase susceptibility to pneumococcal infection.

Study reference	Study objectives	Species	Control exposure	Experimental exposure	Cells	Further notes on study protocol	Outcome(s)	Conclusion(s)
	adhesion to airway cells.				epithelial cells, nasal epithelial cells.	pneumococcal adhesion.		
Moses 2017	To determine the molecular impact of EC vapour exposure in human bronchial epithelial cells (HBECs).	Human	Fresh air	Flavoured EC vapour (menthol, tobacco) ±nicotine OR CIG smoke. Matched to human exposure.	Bronchial epithelial cells.	Conducted cytotoxicity assays, gene-expression analysis and measured reactive oxygen species. Study also investigated in vivo effects in human participants.	At exposures which reflect normal human use, CIG smoke showed cytotoxicity but there was no significant cytotoxicity of menthol or tobacco flavoured ECs with or without nicotine. Gene expression analysis revealed that genes which had downregulated expression after exposure to ECs or CIGs related to cilium assembly and movement. Genes which were upregulated by exposure to ECs or CIGs were involved in apoptosis, xenobiotic stress, oxidative stress and DNA damage. Genes expressed more by ECs than CIGs were related to cell cycle regulation and cell division (nuclear division, cytokinesis). 493 genes had different expressions after exposure to menthol vs tobacco flavoured ECs. The menthol EC was associated with increased DNA expression related to cell adhesion and protein polymerisation. Tobacco-flavoured EC was associated with increased expression of genes associated with cell cycle and superoxide response. Nicotine-containing ECs led to alteration in 162 genes, including upregulation of genes associated with ROS, epithelium differentiation and cytochrome P450 pathway and downregulation of genes associated with response to inorganic substances. ECs downregulated the structural cilia dynein gene DNAH10 and ciliated cell marker FOXJ1 (previously identified as a key reason that CIGs interfere with ciliated cells). Both EC and CIGs enriched genes associated with the cytochrome P450 pathway, xenobiotic stress and oxidative stress, these were even more enhanced by ECs with nicotine. In vitro exposures reflected in vivo exposures in human participants.	"Our data suggest that EC vapour can induce gene-expression changes in bronchial airway epithelium in vitro, some of which are shared with CIG smoke. These changes were generally less pronounced than the effects of CIG exposure and were more pronounced in EC products containing nicotine than those without nicotine."
Muthumalage 2017	To assess the immuno-toxicological and the oxidative stress effects by EC flavouring chemicals on two types of human monocytic cell lines, Mono Mac 6 (MM6) and U937.	Human	PG	Vaporised flavoured EC and their flavouring, at different doses (10-1,000µM).	Monocytic cell types (MM6 and U937) from pleural tissue.	Assessed cell viability, inflammatory cytokine release and cytotoxicity.	% of cells viable in U937 cells: Pentanedione: 62%; Cinnamaldehyde 100µM 65%, 500µM 15%, 1000µM 2%; O-vanillin: 12-19%, mixing flavours: 59%. Cetoin, diacetyl, maltol, and coumarin did not affect cell viability. Cell viability of MM6 cells: above 70% for acetoin, diacetyl, pentanedione, maltol, vanillin, and coumarin; cinnamaldehyde: 100µM 61%, 1000µM 32%. Cytotoxicity: Mystery Mix (menthol flavour) was the only flavour to elicit significant cytotoxicity. ROS: All flavours of ECs had extremely low levels of H_2O_2, a ROS. Mixing flavours together elevated H_2O_2. IL-8 in U937 cells: IL-8 increased after exposure to diacetyl, 2, 3-pentanedione, o-vanillin, maltol and coumarin. IL-8 decreased after acetoin. 10µM of cinnamaldehyde increased IL-8 but 1000µM decreased (likely because of cytotoxicity). IL-8 in MM6 cells: IL-8 increased after acetoin, cinnamaldehyde & vanillin. Diacetyl, coumarin did not increase IL-8 significantly. IL-8 increased after exposure to Cinnamon Roll, Mystery Mix, Cafe	"Our data suggest that the flavourings used in e-juices can trigger an inflammatory response in monocytes, mediated by ROS production, providing insights into potential pulmonary toxicity and tissue damage in EC users."

Study reference	Study objectives	Species	Control exposure	Experimental exposure	Cells	Further notes on study protocol	Outcome(s)	Conclusion(s)
							Latte and Mixed flavours. IL-8 decreased after Mega Melons, Grape Vape, Pineapple Coconut, American Tobacco and Very Berry. Fruit Swirl and Strawberry Zing IL-8 levels did not differ from the ctrl.	
Otreba 2018	To examine the toxicity of vapour from e-cigarette liquids and components of e-cigarettes (GC, PG and GC/PG) compared with cigarette smoke as well as battery output voltage on A549 cells.	Human	Cigarette smoke extract	Vapour from e-cigarette liquids and components of e-cigarettes (GC, PG and GC/PG). Used different voltages of e-cigarettes (3.2, 4.0, 4.8)	Human lung carcinoma cells A549	Used a cell viability assay.	E-cigarettes had lower cytotoxicity levels than cigarettes. Increasing the voltage of the e-cigarette had further reductions in cell viability. Cell viability also decreased with increasing concentrations of propylene glycol, glycerol, glycerol/ propylene glycol and nicotine. Cell viability after exposure to cigarette smoke was lower than after exposure to e-cigarette vapour.	"Our results not only confirm less cytotoxicity of e-liquid aerosol than cigarette smoke, but also demonstrate that solutions used in e-liquids and, for the first time, battery output voltage have a significant impact on cytotoxicity of e-cigarette vapour. Thus, the results of this study are very important for the current and future legal regulations on e-cigarettes."
Palazzolo 2017	To test the effect of EC-generated vapour and smoke on mucous transport velocity using the frog palate paradigm.	Frog	Air	CIG smoke or EC vapour.	Excised bullfrog palates.	Measured mucous transport velocity.	When compared to a ctrl of air, ECs showed a modest inhibitory effect on mucous transport velocity. CIG smoke completely inhibited mucous transport velocity during exposure and 24hr after exposure. Images of the palates showed no effect of CIG or EC exposure on submucosal architecture (collagen was unaffected). However, vapour deposition was evident after the EC exposure but not smoke or ctrl. Smoke-exposed palates appeared to be thinner due to epithelial disruption.	"These results indicate that EC-generated vapour has only a modest effect on mucociliary clearance of bullfrog palates and vapour sedimentation accounts for epithelial thickening."
Pryzbyla 2017	To examine the potential adverse effects of EC vapour and conventional CIG smoke on lung surfactant interfacial properties	Cow	CIG smoke	Unflavoured, berry and mint-flavoured ECs.	Lung surfactant from calf.	Vapour was bubbled to create an e-liquid.	EC vapour did not affect surfactant interfacial properties regardless of dose or flavouring. However, CIG smoke-exposure led to reduced maximum surface pressure. Both EC vapour and CIG smoke led to changes in surfactant microstructure, which led to an increase in the area of lipid multilayers. Nicotine, acetaldehyde, and isoprene did not significantly alter interfacial properties. Tar was the component from CIG smoke which disrupted the surfactant function the most.	"While both EC vapour and conventional CIG smoke affect surfactant lateral structure, only CIG smoke disrupts surfactant interfacial properties. The surfactant inhibitory compound in conventional CIGs is tar."
Rouabhia 2017	To investigate the effect of EC vapour on human gingival epithelial cells.	Human	Absence of vapour	EC vapour + nicotine(Smooth Canadian Tobacco flavour)	Gingival epithelial cells	Measured LDH activity, apoptosis/ necrosis.	Cell morphology: the ctrl the cells were clustered, cuboidal, with a small nucleus and cytoplasm. EC vapour cells were larger, elongated & had lower cell density. LDH activity increased significantly after EC vapour exposure, indicating cell damage. Ctrl cells had a higher percentage of viable cells (81.6±4.9) than the EC exposed cells, especially after cells were exposed to the vapour three times (67.9±7.2). Both apoptotic cells and necrotic cells increased after exposures to ECs. EC exposure led to increased caspase-3 protein (involved in apoptosis) production.	"The effects of EC vapour on gingival epithelial cells may compromise epithelial tissue, resulting in periodontal disease development and potentiating inflammation resulting from the tissue damage."
Rowell 2017	To conduct a screen that would test whether different flavoured	Human	Cigar-flavoured EC ± nicotine	13 flavoured EC liquids and vapours with 12mg/ ml	Lung epithelial cell line (CALU3).	Determined MTT metabolism of liquids and vapours, cell viability, cytotoxicity, changes	Viable cells and cell proliferation decreased in a dose-dependent manner after EC exposure, irrespective of nicotine content. Banana pudding, Kola, Hot Cinnamon Candies and Menthol Tobacco all had larger decreases in cell proliferation and viable cells compared with the PG/VG solution. Researchers found increased Ca^{2+} but attributed	"These data revealed that beyond nicotine and PG/VG, the 13 flavoured e-liquids have diverse chemical constituents. Since all of the flavours exhibited some degree

Study reference	Study objectives	Species	Control exposure	Experimental exposure	Cells	Further notes on study protocol	Outcome(s)	Conclusion(s)
	e-liquids exhibited different toxicant profiles.			nicotine and a PG/VG liquid		in Calcium signalling, RNA extraction and cDNA synthesis. Identified chemical constituents via mass spectrometry.	this to cytotoxicity rather than nAChRs mediation. MTT absorbance decreased in a dose-dependent manner with increasing nicotine concentration, however this also occurred at very low concentrations of nicotine, so may have been caused by increasing the concentration of PG/VG solution. Kola, Hot Cinnamon Candies, Menthol tobacco & Banana pudding were more toxic (reduced cell density and viability) than PG/VG or the cigar-flavoured ECs ± nicotine, but they did not increase LDH. Hot cinnamon candies and menthol tobacco showed higher levels of cytotoxicity than Banana pudding, kola, peanut butter cookies and PG/VG solution. Results were supported in the vapour model. Constituents: Hot cinnamon candies and menthol tobacco shared 8 constituents, with 9 and 11 unique constituents. Banana pudding and kola had 3 shared constituents and 14, 15 unique constituents. All four flavours shared 3 constituents.	of toxicity and a diverse array of chemical constituents with little inhalation toxicity available, we conclude that flavoured e-liquids should be extensively tested on a case-by-case basis to determine the potential for toxicity in the lung and elsewhere."
Sancilio 2017	To examine the ultrastructure, collagen production, and lysosome compartment changes in human gingival fibroblasts exposed to EC fluids.	Human	Untreated human gingival fibroblasts	Diluted EC fluid with or without nicotine (at 1mg/mL)	Gingival fibroblasts	Lactate dehydrogenase assay (LDH), electronic microscopy analysis, collagen I production, flow cytometry lysosome compartment evaluation, and western blotting light chain 3 (microtubule-associated protein 1A/1B-LC3) expression were performed.	Nicotine exposure led to increased large vacuoles in the cytoplasm, empty vacuoles, mitochondria which were indistinguishable, large, disassembled RERs and "a heavily-dilated reticulum disposed at the periphery". However without nicotine, cells appeared the same as without any liquids at all. Reduced collagen expression and release in nicotine-treated cells but not in those exposed to nicotine-free fluid. "Nicotine-containing fluids exert a considerable toxicity as attested by transmission electron microscopy, lactate dehydrogenase assay, and collagen reduced release, whereas nicotine-free fluid treated cells seem to be able to counteract cytotoxicity by activation of the lysosome compartment."	"EC fluids (with and without nicotine) trigger molecular and morphologic responses in oral fibroblasts, raising concerns about their role in the pathogenesis of oral diseases." "ECs fluids, especially those containing nicotine, exert cytotoxicity on human gingival fibroblasts and consequently play a role in the pathogenesis of oral diseases, such as periodontitis."
Solleti 2017	To study the global effects of EC on the micro RNA (miRNA) transcriptome in human lung epithelial cells.	Human	No exposure	EC liquids, vapours and condensate ± nicotine OR CIG smoke condensate.	Lung epithelial cells.	Isolated RNA and conducted microRNA sequencing.	Exposure of any EC experimental condition did not induce cell death. EC liquid exposure led to oxidative stress response. EC liquid or vapour ± nicotine increased expression of four genes. CIG smoke increased expression of three genes. Nicotine-containing EC vapour elicited the highest oxidative response. 578 microRNA were expressed differently after EC liquid exposure. After EC liquid exposure, MIR26A-2-3P, MIR126-5P, MIR140-5P, MIR29A-5P, MIR374A-3P and MIR147B all had increased expression. MIR126-5P expression increased after CIG smoke exposure but it was not significant.	"These data demonstrated that e-cigarette exposure has profound effects upon gene expression in human lung epithelial cells, some of which are epigenetically programmed at the level of miRNA regulation."
Taylor 2017	To compare the effects of two commercial EC	Human	CIG aqueous extract.	'Blended tobacco' flavoured EC	Endothelial cells, from	Used a 'scratch wound' assay to determine	CIGs led to dose-dependent endothelial migration (with complete inhibition at doses >20%). EC did not influence endothelial migration at any dose (up to 100% - equivalent to 30% for CIG extract).	"Our data demonstrate that ECs do not induce the inhibition of endothelial cell migration in vitro

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Study reference	Study objectives	Species	Control exposure	Experimental exposure	Cells	Further notes on study protocol	Outcome(s)	Conclusion(s)
	products (Vype ePen & Vype eStick) and a scientific reference CIG (3R4F) on endothelial migration in vitro.			vapour extracts + nicotine.	umbilical vein.	endothelial cell migration.		when compared to 3R4F [The scientific CIG reference]."
Tommasi 2017	To investigate whether e-cig vapour induces mutation in mouse or human cells.	Mouse or human cells.	Dimethylsulfoxide, tobacco carcinogens (mouse ctrl), UV-irradiated plasmid (human ctrl).	Three EC vapour extracts dissolved in dimethylsulfoxide.	Fibroblasts (mice), pSP189 plasmid (humans).	Determined the induction of mutagenesis in a reporter gene (cII transgene) in mice cells. Screened for induced mutations in the supF gene in human cells.	Tested cytotoxicity after mouse fibroblasts were exposed to varying concentrations of EC extracts and found no significant differences with ctrl. Exposure to tobacco carcinogens (benzoαpyrene and 4-aminobiphenyl led to increased CII mutant frequency, indicating mutation. ECs did not increase mutation frequency (supF) in human cells but exposure to UV-irradiation did.	"Our data indicate that e-cigarette vapour extracts from the selected brands and at concentrations tested in this study have limited mutagenicity in both mouse and human cells in vitro."
Ween 2017	To compare the effect EC of components; e-liquid flavours, nicotine, VG, and PG on phagocytosis, proinflammatory cytokine secretion, and phagocytic recognition molecule expression using differentiated THP-1 macrophages.	Human	CIG smoke extract.	Three apple-flavoured ECs ± nicotine, nicotine + PG, PG, VG, PG/VG.	THP-1 macrophages (derived from leukaemia patients).	Assessed phagocytosis, pro-inflammatory cytokine secretion, and phagocytic recognition molecule expression.	None of the EC components tested elicited toxicity responses. Apple-flavoured EC (with and without nicotine) exposure and exposure to CIG smoke extracts led to decreased phagocytosis. PG, VG and PG/VG did not elicit a significant change in phagocytosis. EC vapour and pure nicotine reduced expression of the phagocytosis receptor, but PG, VG & PG/VG did not. EC exposure, CIG smoke extract exposure and exposure to pure nicotine led to increased IL-8 secretion. PG, VG, PG/VG did not increase. After exposure to CIG smoke extract, nicotine and 2 out of 3 ECs IL-1β, MIP-1α, MIP-1β and TNFα all decreased. After exposure to all ECs, CIG smoke extract, nicotine IL-6, MCP-1 decreased. PG also decreased IL-1β, MIP-1α, TNFα. IP-10 only decreased after CIG extract exposure. IFNγ, IL-10, and IL12p70 did not change after any exposure.	"We conclude that ECs can cause macrophage phagocytic dysfunction, expression of phagocytic recognition receptors and cytokine secretion pathways."

CIG: traditional tobacco cigarette;Cq1: complement component 1q; C3b; part of complement component 3; C4d: part of complement component 4; C5b-q: complement membrane attack complex; d: day; EC: e-cigarette; FOXJ1: Forkhead box protein J1 gene; GSH: glutathione; GSSG: glutathione disulphide; hr: hour; IL-6: Interleukin 6; IL-8: Interleukin 8; LDH: lactate dehydrogenase; MUC5AC: Mucin 5AC; nAChR: nicotinic acetylcholine receptors; NK: natural killer; PG: propylene glycol (e-cigarette liquid constituent); ROS: reactive oxygen species; VG: vegetable glycerine (e-cigarette liquid constituent).

PART 2: Impact of e-cigarettes and personal vaporisers on smoking tobacco

Executive summary

Gateway Effect

The 'gateway effect' refers to use of e-cigarettes being a facilitator of the initiation of other harmful behaviours. It is possible that e-cigarette use and conventional cigarette use have common antecedents, or that e-cigarette use is a direct determinant of conventional cigarette use (i.e. is causative). Other pathways, and a mixture of pathways are also possible.

- Evidence for a strong positive relationship between use of e-cigarettes and later cigarette smoking amongst youth continues to accumulate. The evidence is consistent in observational studies and across different countries.
- A plausible biological pathway from use of e-cigarettes to conventional cigarette smoking operates through developing addiction to nicotine. Use of e-cigarettes with higher concentrations of nicotine is observed to have a stronger association to later conventional cigarette use.
- A positive association is observed between initiation of conventional smoking following use of non-nicotine e-cigarettes (however much weaker than the association with nicotine containing e-cigarettes). This highlights the possibility of other causal mechanisms besides the development of nicotine addiction.
- There is insufficient evidence to draw any conclusion about whether the use of e-cigarettes results in the use of other substances such as marijuana.
- Almost all investigations of 'gateway effect' focus on youths.

Smoking cessation

- Observational studies indicate that e-cigarettes are subjectively a preferred smoking cessation method in some, but not all, populations.
- There is good evidence from clinical trials that e-cigarettes may reduce withdrawal symptoms in smokers after a short period of cigarette abstinence. Conditions in the trials have limited application with most trials being short term.
- There is currently no evidence that quit rates for smoking have decreased as a result of e-cigarette use. Long-term cessation was not measured in trials.
- Results from randomised controlled trials indicate that nicotine-containing e-cigarettes are more effective at reducing the amount of conventional smoking than nicotine-free e-cigarettes or no e-cigarettes.
- There is limited evidence comparing the effectiveness of e-cigarettes for smoking cessation with other smoking cessation methods.

8 E-cigarette use as a gateway to cigarette use and use of other substances among youth

8.1 Introduction

This section considers studies investigating the use of e-cigarettes as a possible gateway to the use of conventional cigarettes and other tobacco products, illicit drugs and the misuse of other harmful substances. This section addresses part of the assigned task to 'review all available evidence applicable to the use of e-cigarettes, personal vaporisers and nicotine on rates of smoking.' The purpose of this report is to update the evidence reviewed in the previous, recently published comprehensive reports produced by the US National Academy of Sciences and Public Health England (McNeill, Brose et al. 2018, Stratton, Kwan et al. 2018). Therefore, only studies published recently and not considered in these reports will be reviewed and the results will be compared to the overall findings of these previous reviews.

This section contains two parts. The first assesses the evidence for e-cigarette use as a risk factor for the initiation of conventional cigarette smoking, the second reviews the evidence for e-cigarette use as a risk factor for subsequent use of illicit drugs and other harmful substances. Some studies may be referred to in both sections where relevant.

8.2 E-cigarette use and use of conventional cigarettes

The search of the literature is outlined in Part 1: Health Impact of e-cigarettes and personal vaporisers. A review of the titles found in the literature search identified 52 potential publications on the use of e-cigarettes as a possible gateway to the use of conventional cigarettes and other substances. Of these, 22 were excluded from this section of the review (seven were not a report on an original study; four were not a gateway study; 11 were included in the recent US or UK reports (McNeill, Brose et al. 2018, Stratton, Kwan et al. 2018) or in a meta-analysis included in these reports.

Of the remaining 30 studies, 17 examined the relationship between e-cigarette use and conventional cigarette use, seven investigated the relationship between e-cigarette use and the use of illicit drugs and other harmful substances, and six assessed both.

Of the 23 studies exploring the relationship between e-cigarette use and conventional cigarette use, eight studies were longitudinal cohort studies and 15 were cross-sectional study designs.

8.2.1 Cohort studies

The cohort study design is a more suitable study design to establish that e-cigarette use can lead to the initiation of conventional cigarettes as these studies can confirm that initiation of e-cigarette use occurred prior to the initiation of conventional cigarette use, satisfying one of the key factors required to establish that e-cigarette use causes cigarette use – temporality (i.e. that the proposed cause occurs before the proposed effect).

All of the eight cohort studies we reviewed found that e-cigarette use was associated with later initiation and/or regular use of conventional cigarettes in teenagers and young adults (Kinnunen, Minkkinen et al. 2017, Lozano, Barrientos-Gutierrez et al. 2017, Pearce, Best et al. 2017, Treur, Rozema et al. 2017, Chaffee, Watkins et al. 2018, East, Hitchman et al. 2018, Morgenstern, Nies et al. 2018, Penzes, Foley et al. 2018). These studies were conducted in different populations across different countries, further confirming the robustness of the relationship.

One such study, conducted by East and colleagues, involved a cohort of 923 youth in Great Britain (age range 11-18 years) who had never smoked conventional cigarettes, followed over five months. At baseline, only 21 of these never smokers had used e-cigarettes (East, Hitchman et al. 2018). This study found ever e-cigarette use and escalation of e-cigarette use over the follow up period was associated with initiating conventional smoking (OR: 11.89; 95%CI: 3.56-39.72 and OR: 7.89; 95%CI: 3.06-20.38, respectively), after adjusting for age, gender, school performance, problem behaviour, monthly alcohol use, smoking susceptibility, friends smoking and e-cigarette use, parental smoking and e-cigarette use, sibling smoking and e-cigarette use, and perceptions of public approval of smoking and e-cigarette use. A direct causal effect of ever e-cigarette use on smoking initiation at follow up (OR: 1.34; 95%CI: 1.05-1.72) was also observed in a causal inference analysis.

Lozano and colleagues conducted a large, good quality study of 4,695 middle school students in Mexico who were followed over 20 months (Lozano, Barrientos-Gutierrez et al. 2017). At baseline, all participants had not tried conventional cigarettes and 5% had tried e-cigarettes. After adjusting for confounders, this study found ever e-cigarette use was associated with having tried conventional cigarettes at follow up (OR: 1.40; 95%CI: 1.22-1.60). A similar trend was observed for past 30-day conventional cigarette use at follow up which did not reach statistical significance (OR: 1.43; 95%CI: 0.94-2.16). The confounders that were considered in this study were sex, age, parent socio-economic status (SES), sensation seeking, friends smoking, parental smoking, siblings smoking, ever tried alcohol, binge drinking (drinking >3 alcoholic drinks in the past 30 days) and exposure to internet tobacco advertising. This study also excluded those who had reported having tried cocaine or marijuana at baseline. The response rate was reasonable (84%), however, the retention rate at follow up was low (63%), which may have introduced bias.

In another cohort of 2,100 students (aged 11-17 years) recruited from 19 randomly selected schools in the Netherlands, Treur and colleagues assessed the use of e-cigarettes with and without nicotine and cigarette smoking six months later (Treur, Rozema et al. 2017). Prevalence of ever use of e-cigarettes with nicotine and e-cigarettes without nicotine in never cigarette smokers at baseline was 13.7% and 29.4% respectively. After adjusting for confounders, ever use of e-cigarettes with nicotine and e-cigarettes without nicotine predicted cigarette smoking six months later (OR: 11.90; 95%CI: 3.36-42.11 and OR: 5.36; 95%CI: 2.73, 10.52 respectively). These associations were strongest in adolescents with a low baseline risk of smoking. This study adjusted for age, sex, educational attainment and propensity to smoke which was comprised of three factors – personality (anxiety sensitivity, hopelessness, sensation seeking and impulsivity), susceptibility to peer pressure and smoking intentions.

Morganstern and colleagues conducted another study in a cohort of 2,186 10th grade students in Lower Saxony and Schleswig-Holstein, Germany (Morgenstern, Nies et al. 2018). All students who were included in the analysis had never smoked conventional cigarettes at baseline, however, 14.3% had tried e-cigarettes. After adjusting for confounders including demographics, personality traits (sensation-seeking, impulsivity, anxiety, hopelessness, extraversion, agreeableness, conscientiousness, neuroticism, openness) and use of alcohol, cannabis and other illicit drugs, the authors found having tried e-cigarettes at baseline was associated with a greater risk of experimentation with conventional cigarettes six months later (RR=2.18; 95%CI: 1.65-2.83). This association was also found to be stronger among adolescents with low sensation-seeking scores and without any binge-drinking experience.

Although this study reported very good response and retention rates (84.5% and 92.7% respectively), attrition analysis found differences in e-cigarette use and other key variables (e.g. sensation seeking, impulsivity, hopelessness, use of cannabis and other illicit drugs) between those who were followed up and those who were not. Therefore, selection bias is likely to have affected the estimated risk ratios. The extent of this effect is unknown. The follow up period is also short and may not have captured the full effect of e-cigarette use on subsequent cigarette experimentation.

Kinnunen and colleagues conducted a study of 1,988 school students aged 16 to 18 years in Helsinki, Finland (Kinnunen, Minkkinen et al. 2017). In this study, the relationship between use of e-cigarettes with and without nicotine in never cigarette smokers and daily cigarette smoking two years later was examined. At baseline, 103 participants had tried e-cigarettes with nicotine, 65 had tried e-cigarettes without nicotine and 1,820 had not tried e-cigarettes. There was an association between the use of e-cigarettes with and without nicotine and daily smoking at follow up with 8.7% and 1.5% reporting daily smoking two years later compared to 0.8% of those who had not tried e-cigarettes at baseline. These results should be considered carefully, however as the proportion of participants in the exposed groups are small, no confounders have been reported, and a full-peer reviewed article of the results is yet to be published.

Another study was performed by Pearce and colleagues in a cohort of 2,998 students from four high schools in Scotland (Pearce, Best et al. 2017). All students included in the analysis had never smoked a conventional cigarette at baseline. This study found that those who had tried an e-cigarette were 2.53 times (95% CI 1.71 to 3.75) more likely to have smoked a conventional cigarette at the one-year follow up compared to those who had never used an e-cigarette. They also observed a higher odds of smoking initiation following use of e-cigarettes in those who were not susceptible to smoking and those who had no friends who smoked at baseline. These results should be interpreted with caution, however, as a full, peer-reviewed article of this study is yet to be published.

Penzes and colleagues followed a cohort of 1,369 ninth grade students from 16 high schools in Tirgu Mures, Romania for a period of six months (Penzes, Foley et al. 2018). Although 35.8% had tried e-cigarettes at baseline, most of these had also tried conventional cigarettes or a waterpipe with only 36 participants having only tried e-cigarettes at baseline. Using a cross-lagged causal model, this study found that having tried e-cigarettes at baseline predicted trying conventional cigarettes (OR: 3.57; 95%CI: 1.96–6.49) and waterpipe (OR =1.51, CI95%: 1.07–2.14) at follow-up. This study is a secondary analysis of data obtained during a randomised controlled trial investigating the effectiveness of a web-based multimedia program to prevent the initiation of smoking among adolescents.

Although allocation into the intervention or control group was controlled for, there may be residual confounding. There were also many key confounders that were not considered in this analysis. Therefore, the results are likely affected by these confounders and the true relationship between e-cigarette use and future conventional smoking in this sample remains unknown. Differences in grades, smoking behaviours and having friends who smoke were also observed between those who took part in the follow up and those were lost to follow up, which would likely also introduce bias.

Another study, conducted by Chaffee and colleagues, had a slightly different study design (Chaffee, Watkins et al. 2018). This study assessed whether use of e-cigarettes was associated with established smoking (defined as smoking a total of 100 cigarettes in their lifetime), smoking in the past 30 days and current established smoking (i.e. both established and past 30 day smoking) within one year in a cohort of 1,295 US adolescents aged 12-17 years who had previously tried conventional cigarettes at baseline (Chaffee, Watkins et al. 2018).

This study found that ever e-cigarette use at baseline was associated with current established smoking at follow up (OR: 1.80; 95%CI: 1.04-3.12), with a similar trend observed for established smoking (OR: 1.57; 95%CI: 0.99-2.49) and past 30-day smoking (OR: 1.32; 95%CI: 0.99-1.76). When e-cigarette use was defined as never use, former use (non-past 30 day use) and current use (past 30-day use), former e-cigarette use at baseline was associated with current established smoking at follow-up (OR: 1.85; 95%CI: 1.02-3.36) and current e-cigarette use at baseline was associated with past 30-day smoking at follow up (OR: 1.64; 95%CI: 1.12-2.41).

In these analyses, the authors adjusted for demographic factors (gender, age, race/ethnicity), parent education, urban residence, ever alcohol use, tobacco advertisement receptivity (brand recall from favourite advertisement), sensation seeking, exposure to cigarette warning labels, time of year of interview, and ever use of any other tobacco product. Unfortunately with this study design, the sequence of initiation of conventional cigarettes and e-cigarettes cannot be deduced. Therefore, temporality, a requirement for establishing a causal relationship, cannot be satisfied.

There are a number of limitations in the above studies that need to be considered when interpreting the results.

- Firstly, the regular use of e-cigarettes and cigarettes is usually measured by asking about past 30-day use of these products which is then converted into a binary variable – any use and no use. However, any use in the past 30 days may not be a good indicator of regular use.

- Most studies also have a follow up period of 6-12 months which may not be long enough to observe the full effect of e-cigarette use on cigarette smoking, particularly regular cigarette smoking which is the main concern regarding e-cigarette use in youth.

- A few studies have small numbers of participants who had used e-cigarettes at baseline which limits the ability of these studies to observe an association, adjust for all the confounders and provide an accurate estimate of the odds ratio (indicated by wide confidence intervals).

- Some studies have adjusted for intention to smoke which is not a true confounder of the relationship but a mediator through which other confounders would operate. This would result in over-adjustment and would likely affect the estimate of the odds ratio (i.e. act to inappropriately adjust in the direction of no relationship).

- Lastly, most studies do not report response and retention rates and/or do not compare participants who participated in the follow-up and those who did not. Differences between these two groups can be a source of selection bias which would affect the estimated odds ratios.

8.2.2 Cross-sectional studies

There were 15 cross-sectional studies examining the relationship between e-cigarette use and conventional cigarette smoking all of which have observed a positive association (Choi, Grana et al. 2017, de Lacy, Fletcher et al. 2017, Hammond, Reid et al. 2017, Hines, Fiala et al. 2017, Kinouani, Pereira et al. 2017, Lanza, Russell et al. 2017, Milicic and Leatherdale 2017, Park, Lee et al. 2017, Ramji, Arnetz et al. 2017, Temple, Shorey et al. 2017, Farsalinos, Siakas et al. 2018, Lanza and Teeter 2018, Parikh and Bhattacharyya 2018, Pepper, Farrelly et al. 2018). However, most of these studies have not adjusted for key confounders of this relationship that were adjusted for in the cohort studies. For example, sensation seeking personality, stress or anxiety, and having friends or family who smoke.

Only six studies considered confounders other than basic demographics. One such study, conducted by Lanza and colleagues, examined the association between ever e-cigarette use and ever, current (≥5 times in last 30 days) and former (ever ≥5 times in 30 days) cigarette smoking in a sample of 452 college students in California, USA (mean (SD) age 21.26 (2.57) years) (Lanza, Russell et al. 2017). After adjusting for confounders including demographics, percentage of friends that have used e-cigarettes, and perceiving e-cigarettes to be healthier than cigarettes, associations were observed between e-cigarette use and all smoking variables with those that had smoked a cigarette, were a current smoker and were a former smoker being more likely to have ever used e-cigarettes (adjusted ORs (p-values) were 8.39 (p<0.001), 4.59 (p<0.05) and 8.90 (p<0.01) respectively).

In a South Korean study of 6,307 current adolescent smokers, Park and colleagues found that, after adjusting for confounders, former and current e-cigarette use was associated with daily smoking and a higher number of cigarettes smoked per day (Park, Lee et al. 2017). The confounders that were considered in this study included demographics, perceived stress, and parent and peer smoking.

Farsalinos and colleagues conducted a study in a representative sample of adults living in the Attica prefecture, Greece (n=4058). After adjusting for confounders including basic demographics, socioeconomic status variables, and perceived harmfulness of e-cigarettes, the authors observed strong associations between ever and current e-cigarette use and cigarette smoking status (current smokers: ever e-cigarette use OR=33.38 (95%CI: 25.20-44.21) and current e-cigarette use OR=30.82 (95%CI: 10.21-93.01); former smokers: ever e-cigarette use OR=9.05 (95%CI: 6.81-12.04) and current e-cigarette use OR=69.33 (95%CI: 23.12-207.90); all p-values <0.0001) (Farsalinos, Siakas et al. 2018). It should be noted, however, that the study sample included adults of all age groups and it is likely that initiation of cigarette smoking occurred prior to initiation of e-cigarette use for many participants, particularly those in older age groups.

Pepper and colleagues examined the relationship between type of e-cigarette usually used (with or without nicotine) and current cigarette smoking in a sample of US adolescents aged 15-17 years (n=896 for multivariable analysis). Participants were recruited through advertisements on online social media platforms (Facebook and Instragram). The study found current cigarette smokers were less likely to usually use e-cigarettes without nicotine than non-smokers (OR=0.20; 95% CI 0.14, 0.30). Similar results were also observed for users of cigars/cigarillos and other tobacco products. The confounders considered in this study included demographics, past 30 day use of other tobacco products, e-cigarette use characteristics (frequency of use, device type, owning an e-cigarette, social context of use), perceived health risks and prevalence of e-cigarette use, and knowledge about nicotine and vapour from e-cigarettes. The sampling method for this study may have introduced selection bias which may affect the estimated odds ratios.

Another study conducted by Ramji and colleagues in a sample of 1,006 Swedish adolescents found an association between waterpipe use and e-cigarette use (OR: 3.26; 95%CI: 2.12-4.99) (Ramji, Arnetz et al. 2017). This analysis controlled for school performance, stress, mental energy (a proxy measure for depression and anxiety), sleep quality, exercise in leisure time, gambling, and the use of cigarettes, snus, alcohol and narcotics.

Another US study with a slightly different study design assessed the association between the use of electronic nicotine delivery systems (ENDs) and acceptability of adult cigarette smoking and susceptibility to cigarette smoking in a sample of 68,928 middle and high school students in Florida (Choi, Grana et al. 2017). In a mediation analysis, Choi and colleagues found ENDs use was indirectly associated with susceptibility to cigarette smoking among never smokers through peer acceptance of adult cigarette smoking. This study adjusted for demographics, exposure to cigarette marketing and living with a smoker.

8.2.3 Does the use of e-cigarettes cause cigarette smoking?

To establish a causal relationship all the evidence must be examined together and considered against the Bradford-Hill criteria for causation. Firstly, the studies are reasonably heterogeneous, studying populations of youth from various countries. As the results observed are all consistent across these studies, this suggests a positive relationship between use of e-cigarettes and later cigarette smoking. This is further confirmed in a systematic review and meta-analysis of nine cohort studies performed by Soneji and colleagues which found consistent and strong evidence that e-cigarette use is associated with an increased odds of cigarette smoking among youth (Soneji, Barrington-Trimis et al. 2017). This study observed a pooled odds ratio for cigarette smoking initiation of 3.62 (95%CI 2.42-5.41) in ever e-cigarette users (compared to never e-cigarette users) and a pooled odds ratio for past 30-day cigarette smoking of 4.28 (95%CI 2.52-7.27) in past 30-day e-cigarette users (compared to non-users) at baseline.

The cohort studies discussed in detail in this report have not been included in this meta-analysis, however, the results are consistent with that of the meta-analysis with odds ratios for cigarette smoking initiation ranging from 1.40 to 11.90 in ever vs never e-cigarette users at baseline. These results also indicate a reasonably strong effect, providing more confidence in a true causal relationship which cannot be explained by residual confounding.

There are a number of cohort studies examining the relationship between use of e-cigarettes and later cigarette smoking which establish the necessary time sequence of events for causation – that e-cigarette use occurs prior to conventional smoking in these adolescents and young adults. Therefore, the criteria of temporality, which is the only essential criteria to establish causality, is satisfied. Lastly, there are a few cohort studies which have compared the effect of e-cigarettes with and without nicotine on later cigarette smoking. The two such studies discussed above have both found a greater odds of cigarette smoking at follow up with the use of e-cigarettes containing nicotine at baseline.

Another study conducted by Goldenson and colleagues found a dose-response effect of nicotine concentration in the e-cigarette used and frequent smoking six months later (Goldenson, Leventhal et al. 2017). This study involved a cohort of 181 tenth grade students in Los Angeles, California, all of whom had used e-cigarettes in the past 30 days. E-cigarette concentration was defined as none (0mg/ml), low (1-5mg/ml), medium (6-17mg/ml), and high (≥18mg/ml). This study observed an increase in the odds of frequent smoking (smoking on ≥3 of the past 30 days vs no smoking) of 2.26 (95%CI 1.28-3.98) for each successive increase in nicotine concentration category. These studies together suggest that nicotine addiction from use of e-cigarettes may be a biological pathway leading to later cigarette smoking.

8.2.4 Conclusion

In summary, the above evidence suggests that e-cigarette use, particularly e-cigarettes with nicotine, is likely to be causative for later cigarette smoking in adolescents and young adults. Given the known adverse health effects of cigarette smoking, the 'gateway' path to initiation of cigarette use has substantial relevance.

8.2.5 Key findings

- Evidence for a strong positive relationship between use of e-cigarettes and later cigarette smoking amongst youth continues to accumulate. The evidence is consistent in observational studies and across different countries.

- A plausible biological pathway from use of e-cigarettes to conventional cigarette smoking operates through developing addiction to nicotine. Use of e-cigarettes with higher concentrations of nicotine is observed to have a stronger association to later conventional cigarette use.

- A positive association is observed between initiation of conventional smoking following use of non-nicotine e-cigarettes (however much weaker than the association with nicotine containing e-cigarettes). This highlights the possibility of other causal mechanisms besides the development of nicotine addiction.

8.3 E-cigarette use and use of other substances

Of the 13 studies exploring the relationship between e-cigarette use and use of other substances, two studies were longitudinal cohort studies and 11 were cross-sectional studies.

8.3.1 Cohort Studies

There have only been two cohort studies looking at e-cigarette use and progression to the use of other substances, in this case marijuana. One study was conducted by Lozano and colleagues in a large cohort of 5,672 middle school students in Mexico (Lozano, Barrientos-Gutierrez et al. 2017). At baseline, none of the students included in the analysis had used cocaine or marijuana, 7% had tried e-cigarettes and 17% had tried conventional cigarettes. This study found e-cigarette use at baseline was not independently associated with marijuana use at the 20-month follow-up (OR: 1.42; 95%CI: 0.84 – 2.37), however, e-cigarette use was associated with conventional cigarette use at follow up (reported in section 9.2.1 above) and conventional cigarette use and use of both e-cigarettes and conventional cigarettes were associated with marijuana use at follow up (OR: 2.05; 95%CI: 1.53-2.75, and OR: 2.67; 95%CI: 1.78-4.02, respectively). These results suggest e-cigarette use is associated with progression to conventional cigarettes and conventional cigarette use is associated with progression to marijuana and perhaps a longer follow up period was required to observe an association between e-cigarette use and marijuana use at follow up.

The other study, conducted by Dai and colleagues, followed a large, nationally representative, US cohort of 10,364 adolescents aged 12-17 years over a period of one year (Dai, Catley et al. 2018). All participants included in the analysis reported never having used marijuana at baseline and 5.1% reported ever using e-cigarettes. After adjusting for confounders, baseline e-cigarette users were more likely to report marijuana use in the past 12 months at follow up (OR: 1.9; 95%CI: 1.4-2.5) but were not more likely to report heavy use of marijuana (OR: 1.3; 95%CI: 0.8-2.1). These associations were modified by age group. There was a stronger association between baseline e-cigarette use and past 12 month marijuana use in the younger 12-14 years age group (OR: 2.7; 95%CI: 1.7-4.3) than the older 15-17 years age group (OR: 1.6; 95%CI: 1.2-2.3). Baseline e-cigarette use was also associated with heavy marijuana use at follow up in young adolescents only (OR: 2.5; 95%CI: 1.2, 5.3). The confounders that were considered in this study include demographics, school performance, sensation seeking personality and ever use of alcohol, cigarettes, prescription medication (for non-medical purposes) and illicit drugs. These results may be affected by residual confounding from unmeasured variables such as other personality traits and social influences (i.e. having friends and/or family members who smoke marijuana). The initial response rate was also low at 54% which may have introduced bias.

8.3.2 Cross-sectional studies

Of the eight cross-sectional studies examining the association between use of e-cigarettes and the use of other substances, only three have adjusted for confounders other than basic demographics (i.e. age, gender, race and socio-economic measures). Of these studies, one has examined the association between alcohol use and e-cigarette use, one has examined the association between e-cigarette use and vaping cannabis and one has assessed the association between use of e-cigarettes and alcohol use and lifetime use of drugs or butane gas.

Lanza and colleagues performed one such study, examining the association between ever e-cigarette use and early alcohol initiation (≤ 14 years), ever binge drinking, recent binge drinking (last month) and recently getting drunk (past month) in a sample of 452 college students in California, USA (Lozano, Barrientos-Gutierrez et al. 2017). Binge drinking was defined as drinking four or more alcoholic drinks in one sitting for females, five or more for males. After adjusting for confounders including demographics, percentage of friends that have used e-cigarettes, and perceiving e-cigarettes to be healthier than cigarettes, this study found that those who had ever engaged in binge drinking had a higher likelihood of having ever used e-cigarettes (OR: 2.53, p<0.001). A similar trend was also observed in those who had been drunk in the past month (OR: 2.00, p=0.061).

In another study of 6,307 Korean adolescent smokers, Park and colleagues found that, after adjusting for confounders, current e-cigarette use were associated with recent at-risk drinking (past 30 days) and lifetime use of drugs or butane gas, daily smoking and a higher number of cigarettes smoked per day (Park, Lee et al. 2017). This study adjusted for demographics, perceived stress, cigarette smoking and parent and peer smoking.

Morean and colleagues assessed vaping cannabis in 552 adult e-cigarette users in the USA (mean (SD) age: 34.07 (9.65) years (Morean, Lipshie et al. 2017). This study observed an association between lifetime and past month cannabis vaporisation and initiating e-cigarette use at an early age. It also found frequency of vaping cannabis was associated with heavier e-cigarette use. This study adjusted for legal status of cannabis, cannabis vaping beliefs and impulsivity. However, there are likely to be other key confounders of the relationship between e-cigarette use and cannabis vaping and therefore, the results observed are potentially biased.

8.3.3   Conclusion

Most of the studies examining the relationship between e-cigarette use and the use of other substances are cross-sectional studies. These studies can establish an association, but causal inference is prone to error. The quality of these studies is also generally poor. With only two cohort studies investigating this relationship, the evidence at this stage is inadequate to determine whether use of e-cigarettes causes the use of other substances. One of the existing cohort studies suggests that if e-cigarette use is related to the progression to marijuana use, it is likely to occur through cigarette smoking. Further studies are needed to appropriately assess this theory.

8.3.4   Key findings

- There is insufficient evidence to draw any conclusion about whether the use of e-cigarettes results in the use of other substances such as marijuana.

- Almost all investigations of the 'gateway effect' focus on youths.

9 Use of e-cigarettes for smoking cessation

9.1   Introduction

This section considers recent studies that investigate the use of e-cigarettes to support cessation of smoking conventional tobacco products. It addresses part of the assigned task to 'review all available evidence applicable to the use of e-cigarettes, personal vaporisers and nicotine on rates of smoking.'

After title and abstract review, 119 studies assessing the use of e-cigarettes for smoking cessation were identified. Seventy studies were excluded due to:

- review, letter, editorial or framework report (n=30);
- not addressing smoking cessation (n=18);
- not written in English (n=5);
- published before 2017 (n=5);
- qualitative studies (n=5);
- unavailable full-text (n=4);
- or no data on e-cigarettes (n=3).

The remaining studies (n=51) were:

- cross-sectional (n=27);
- longitudinal (n=11);
- uncontrolled trials (n=3);
- randomised controlled trials (n=10).

9.2   Preference for e-cigarettes as a smoking cessation tool

Ten cross-sectional studies assessed smokers preferred smoking cessation tools or reasons for using e-cigarettes.

9.2.1 Cross-sectional studies

Reasons that e-cigarettes are used

In two studies, vapers ranked reasons for using e-cigarettes, and smoking cessation was the most common reason (Gucht, Adriaens et al. 2017, Sussan, Shahzad et al. 2017). The first study was an online survey of 203 Dutch and Flemish online vape shop customers, who had a mean age of 46 years (SD 12.5) and were 42.9% female (Gucht, Adriaens et al. 2017). In this survey, 99% of participants had ever smoked and 16.7% were current smokers. 93.6% of the participants were 'regular vapers' and 73% of surveyed participants were 'mainly using e-cigarettes to quit smoking' (95% CI, 0.67, 0.79). Other reasons for e-cigarette use included 'because it is healthier than smoking' (57.4%), 'because of financial reasons' (27.7%), 'to decrease tobacco cigarette consumption' (16.9%), 'because smoking is prohibited in several contexts' (15.9%), and 'out of curiosity' (14.4%) (Gucht, Adriaens et al. 2017). However, the poor response rate (16%) and recruitment method limits the applicability of these findings to all e-cigarette users from the Netherlands.

The second survey recruited 320 online and in-store US vape shop customers, who were never (6%), former (74%) or current smokers (20%). All were current e-cigarette users (Sussan, Shahzad et al. 2017). Response rate was not reported for this study. If the response rate was low, this may have introduced bias (selection bias). Participants were predominantly under 35 years (58%) and male (78%), and found that the most common reason for using e-cigarettes was as a quit smoking aid (42% of former smokers and 39% of current smokers). Other reasons for e-cigarette use included the belief that e-cigarettes were healthier than tobacco cigarettes (38% of former smokers, 33% of current smokers) or that e-cigarettes were cheaper than cigarettes and enjoyable (≤13%). Those who had never smoked primarily used e-cigarettes for enjoyment (68%), however this data only represents 19 people (6% of the survey) (Sussan, Shahzad et al. 2017). While the most common reason for e-cigarette use was smoking cessation, 58% of users were using e-cigarettes for another reason, thus it is likely that consumers do not view e-cigarettes solely as a smoking cessation tool.

Similarly in a Spanish survey, participants were most likely to use e-cigarettes in order to reduce their cigarette consumption (Bunch, Fu et al. 2018). Researchers hired trained sensors (people trained to recruit participants for studies of uncommon products) to recruit e-cigarette users in all neighbourhoods of Barcelona, Spain. They identified individuals using or carrying an e-cigarette in public and approached them to participate in the survey. All participants were current e-cigarette users at the moment of the interview, but may have been infrequent users. There was a 90.3% response rate, with 63.5% female participants and 49.8% aged between 25-44 years. The analyses adjusted for sociodemographic variables and found that the most common reasons for e-cigarette use were: to reduce tobacco smoking (48%, n=288), smoking cessation (39.2%, n=235), and to use e-cigarettes in places where tobacco smoking was prohibited (10.2%, n=61). Older people were more likely to use e-cigarettes for smoking cessation (≥65, OR=13.8, 95% CI 2.62 to 72.41), while younger participants (OR=4.36, 95% CI 1.99 to 9.57) and women (OR=1.87, 95% CI 1.02 to 3.43) were more likely to use e-cigarettes for places where smoking is prohibited. Data from this study should be interpreted with caution as it was not representative data and may have included infrequent or once-off e-cigarette users.

Data suggests that reasons for e-cigarette use differs among young adults. A secondary analysis of a sub-set of the PATH (Population Assessment of Tobacco and Health) study 2013-15, a US nationally representative study, assessed the reasons for e-cigarette use among young adult vapers (18-34 years) (Chen 2018). There were 844 participants, the majority (58.5%) of whom were aged between 25-34 years and were 62.1% male. Response rate was not reported, and the data was assessed at one time point (2014-15). The subjects were shown 13 common reasons for using e-cigarettes and asked if they endorsed that reason. The highest level of endorsement was for "e-cigarettes might be less harmful to people around me than cigarettes" (85.4%), followed by "e-cigarettes can be used where smoking cigarettes is not allowed" (82.2%), and "e-cigarettes come in flavors I like" (80.2%). This indicates that health and convenience were key reasons for e-cigarette use among young adult vapers, where a high percentage (73.4%) said that they use e-cigarettes as a way to cut down smoking.

A study from China in 2015 provides insight on motivation to use e-cigarettes among Chinese adolescents. In this study, 2,042 Chinese adolescents (15-18 years, 16.45% female) were recruited using an app (response rate NR) (Wang, Zhang et al. 2018). They completed a short survey on smoking, e-cigarettes and demographics on the app. Unlike the other studies, the most common reason for using e-cigarettes was not to quit smoking. In this study the most common reasons for using e-cigarettes was "to avoid the harm of cigarettes" (44.63%), followed by "to avoid the second-hand harm of smoking to others" (26.30%), because "they were curious of e-cigarettes" (25.56%) or "they expected e-cigarettes to help quit smoking" (24.26%). Less frequently cited reasons included because they "thought it was fashionable to do so", "e-cigarettes were cheaper than conventional cigarettes" or "were handy wherever a smoking ban is applied". Thus, while use of e-cigarettes for smoking cessation was not the most commonly cited reason for using e-cigarettes, the most common reasons all related to health. It is important to note that this study did not use a representative sampling method and that the population was highly niche (Chinese adolescents).

Preference for e-cigarettes compared with other smoking cessation methods

A Canadian survey recruited 180 cigarette smokers through pharmacies (31% response rate), 63% of whom were aged 26-55 years and approximately half were male (51.1%) (Phung, Luo et al. 2017). A high percentage of this sample (81%) had used smoking cessation products with the intention to quit, and 60% had attempted to quit within the last year. Previous use of e-cigarettes was reported by 9.2% of smokers and current use by 14.7%. E-cigarettes was the preferred smoking cessation method for 97.2% of the sample who had tried them. Nicotine gum was the most widely used smoking cessation method (33% for previous use, 16% for current use) (Phung, Luo et al. 2017).

The 2013-14 Population Assessment of Tobacco and Health (PATH) survey, a representative US population-based survey of 16,321 current (70%) and former (30%) smokers also studied popular quit methods (Rodu and Plurphanswat 2017). Response rate, gender and age were not reported in this study. Of the total sample, 28% had tried and 5% had successfully quit smoking. Current and former smokers were more likely to have used e-cigarettes to attempt to quit smoking (n=587) than nicotine replacement therapies (n=338) or prescription drugs (n=106). However, the most common method for attempting to quit smoking was 'unaided' (2013 n=1797, 2014 n=1831), followed by help from friends and family (n=676). Thus, while data indicates that e-cigarettes are used, smokers in this study preferred other quit methods.

Another secondary analysis was conducted using data from the 2014 and 2015 PASSI surveys, nationally representative population surveys conducted in Italy (Gorini, Ferrante et al. 2017). 6,112 smokers were included in the study, aged 18-69 years (see table 12 for details) and the population was 56.1% male. Response rates for these studies were relatively high (2014: 83%, 2015: 82%). Quit attempts were measured and quit methods analysed. The researchers found that the most common quit methods used by Italians in 2014-15 were no aid (86%) and e-cigarettes only (11%). The remaining 3% were largely undefined but included smoking cessation programs. These findings indicate that while e-cigarettes were the second most preferred smoking cessation method, a much larger number of participants preferred using no aid.

One study conducted a cross-sectional secondary analysis of a longitudinal US community postal survey of 15,943 current adult smokers, aged >18 (36.9% aged 35-54 years) and who were 51.3% male. This analysis included only smokers who had attempted to quit smoking in the past three months. Participants reported all methods used to attempt to quit smoking over the previous three months (Caraballo, Shafer et al. 2017). Initial response rates were not reported, however 50.2% completed the follow-up surveys. Overall 74.7% of the adult current smokers had used multiple quit methods in their most recent attempt. The most reported smoking cessation methods were giving up cigarettes all at once (65.3%) and gradually cutting back on cigarettes (62.0%), followed by substituting some cigarettes with e-cigarettes (35.5%), nicotine patches and gum (25.4%), abruptly switching to e-cigarettes (24.7%), changing to mild cigarettes (20.4%), getting help from a doctor or other health professional (15.2%) or using medication (12.2%) (Caraballo, Shafer et al. 2017). Thus, while e-cigarettes were identified as a smoking cessation method, they were not the most preferred.

In contrast to the above surveys, other cross-sectional studies indicated low preference for e-cigarettes as a smoking cessation tool. In a survey of 421 Southeast Queensland Aboriginals, recruited from Aboriginal & Torres Strait Islander Community Health Service urban dental clinics, nearly half (47%) currently smoked daily of whom 4% currently used e-cigarettes (Cockburn, Gartner et al. 2018). Interestingly, none of the former smokers (19%) were currently using e-cigarettes. This survey had a high rate of missing data (24-42% for preference data) however, for current smokers, e-cigarettes were one of the least preferable quit options with abrupt cessation, cutting down, free nicotine replacement therapy and prescription medication being more preferred. This indicates that while some population groups are interested in e-cigarettes, others are not. This may be reflected in substance use – the Aboriginal sample had a high prevalence of smoking, and a low prevalence of e-cigarette use (only 2% overall). Additionally, for this sample, a high proportion of smokers (>50%) were not interested in paid nicotine replacement therapy, Quit line, one-on-one support, group support or community support as smoking cessation interventions. It is possible that participants in this survey were not interested in smoking cessation.

9.2.2 Conclusions

Data from five cross-sectional studies suggest that the main reason that adults use e-cigarettes is to quit smoking, while young adults use them as a healthier alternative to tobacco cigarettes. This area is lacking Australian data. Qualitative studies would provide a deeper understanding into the motivation for using e-cigarettes. Studies indicate that e-cigarettes are a preferred smoking cessation method among some, but not all, populations. There has only been one recent study conducted in Australia in a small sample of South East Queensland Aboriginals which suggested that e-cigarettes are not a popular smoking cessation tool in this population group. Preference of e-cigarettes as a smoking cessation tool among the general Australian population remains unknown.

9.2.3 Key findings

- Among adults, the most common reason for using e-cigarettes was to quit or reduce smoking.

- Among young adults, the most common reason for using e-cigarettes is because they are a 'healthier alternative'.

- Assuming that they would be successful in quitting smoking, smokers preferred to quit using e-cigarettes instead of other established cessation methods. However, if they could, most smokers would still prefer to quit unaided.

- In a survey of Southeast Queensland Aboriginals, e-cigarettes were one of the least preferable smoking cessation methods.

- Further Australian data is needed on preferred smoking cessation methods and reasons for using e-cigarettes.

9.3 Association between e-cigarette use and motivation to quit or quit attempts

One trial without a control group, one longitudinal study and two cross-sectional studies investigated motivation to quit smoking among e-cigarette users and non-users.

9.3.1 Uncontrolled trials

Motivation to quit was measured in a trial without a control group where participants were provided e-cigarettes (Rohsenow, Tidey et al. 2018). In this US trial 18 smokers (10+ cigarettes/day for past six months) were recruited from community flyers. Participants were predominantly female (61%), with a mean age of 45.1(±7.8) years. Participants were non-treatment seeking and were given e-cigarettes and told to use them instead of smoking for 10 weeks. This led to reduced cigarette consumption and increased motivation to quit (measured using the contemplation ladder scale) after 10 weeks (Rohsenow, Tidey et al. 2018). Whether this could lead to smoking cessation over a longer period of time is unclear. Findings from this study are limited due to the short duration and small number of participants.

9.3.2 Longitudinal studies

One study recruited Military Veteran smokers undergoing psychiatric services from the Department of Veterans Affairs (VA) Connecticut Healthcare System by word of mouth (Valentine, Hefner et al. 2017). Fifty participants were recruited, all did not have an intention to immediately stop smoking, were predominantly male (93%) and had a mean age of 56.9 (±8.0) years. The researchers provided participants with e-cigarettes to test whether it would influence the veterans motivation to quit. They found that 90% of the participants were still using e-cigarettes after four weeks and had a higher motivation to quit at the end of the study than at baseline. Three out of 50 participants (6%) reported complete cessation of smoking which was confirmed using a carbon monoxide breath test (Valentine, Hefner et al. 2017). However this is a very unique population group and findings may not be applicable to the wider population.

9.3.3 Cross-sectional studies

The Action on Smoking Health (ASH) Smoke free Great Britain surveys included 12,157 currently smoking adults who completed online surveys on smoking status, e-cigarette use and motivation to quit smoking (response rate, age and gender not reported) (Simonavicius, McNeill et al. 2017). In this study, e-cigarette users who were also conventional cigarette users had a higher motivation to quit smoking than cigarette-only users (measured on the 'motivation to stop' scale). Dual users of cigarettes and e-cigarettes were more likely to use e-cigarettes as a smoking reduction aid than past e-cigarette users. In addition, current dual users reported a higher motivation to stop smoking than past users, never users and past e-cigarette triers (Simonavicius, McNeill et al. 2017). This indicates a correlation between e-cigarette use and motivation to quit. However, motivation to quit may have led to e-cigarette use, rather than e-cigarette use leading to motivation to quit.

Results from a South Korean survey conducted by Sung et al. contradict the findings from Simonavicius et al. 2017 (Sung 2017). This study was a secondary analysis of the Korean National Health and Nutrition Examination Survey (KNHANES), a nationally representative study. This analysis included 2965 current adult smokers who were predominantly male (85.5%) and aged >19 years (see Table 12 for more details). Response rate was not reported. The study found a negative relationship between intention to quit smoking and e-cigarette use. Additionally, e-cigarette users reported fewer quit attempts than non-e-cigarette users. Differences between results of this study and Simonovicius et al.'s study may be due to the use of different motivation questions. The Motivation to Stop scale, used in the study by Siminovicius et al., is a validated measurement of likelihood of attempting to quit smoking (Kotz, Brown et al. 2013). It is unclear if the question used in KNHANES is validated, and the questions included different time frames; KNHANES asked participants if they were going to stop smoking in the next six months and the Great Britain study asked if they were going to stop within one to three months. Different outcomes may also have been due to cultural or demographic differences.

9.3.4 Conclusions

The above studies indicate that there may be an association between e-cigarette use and motivate smokers to quit. However, these studies mostly investigated opinions and motivation which may not represent quit attempts or successful smoking cessation. Additionally, some studies only included current vapers, which may not capture smokers who had tried e-cigarettes and found them to be an unsatisfactory cessation method. Finally, there are limited studies and study designs are unable to establish cause and effect. Randomised controlled trials would provide higher quality evidence for this area.

9.3.5 Key findings

- Studies indicate that there may be an association for smokers between e-cigarette use and increased motivation to quit.

- It is likely that people who use e-cigarettes are already interested in quitting smoking, therefore have higher quit motivations than non-users.

- Randomised controlled trials are needed to determine if using e-cigarettes increases motivation to quit smoking.

9.4   Use of e-cigarettes for reducing withdrawal symptoms

Six randomised controlled trials (RCTs), one non-randomised trial and one cross-sectional study investigated the use of e-cigarettes to reduce withdrawal symptoms from tobacco cigarettes.

9.4.1   Randomised controlled trials

In these randomised controlled trials, participants (all adult smokers) were asked to abstain from smoking for 3 to 24 hours and had their cravings and withdrawal symptoms assessed before and after using e-cigarettes with and without nicotine, or a control (tobacco cigarette, no smoking/ vaping).

The first RCT was a US-based double-blind, cross-over design with participants recruited from the community using online advertisements (Harvanko, Martin et al. 2017). There were nine participants, all were adult smokers without an interest in smoking cessation, three were female (33%) and mean age was not reported. In this trial, participants were instructed to abstain from smoking for 24 hours (verified by carbon monoxide testing) and were then randomised to be given 10 puffs of either a tobacco cigarette, or a 0 mg/mL, 8 mg/mL or 16 mg/mL nicotine e-cigarette. While use of the tobacco cigarette led to a reduction in the responses to 'desire or craving to smoke', 'desire for a cigarette right now' and 'I am going to smoke as soon as possible', e-cigarette use did not (Harvanko, Martin et al. 2017).

Results from the RCT conducted by Harvanko et al. conflict with the results of a second study by Perkins et al (Perkins, Karelitz et al. 2017). In this parallel RCT, 28 US smokers with no intention of quitting smoking in the next six months and who had not previously used e-cigarettes were recruited via public notices. Participants were predominantly female (57.1%) and had a mean age of 26.5(±6.6) years. Participants underwent overnight cigarette deprivation, verified by carbon monoxide testing. They were then randomised to receive a 0mg/mL e-cigarette, a 36mg/mL e-cigarette or no device and waited for two hours. Withdrawal symptoms were measured before and after exposures. Researchers identified a larger reduction in withdrawal symptoms after use of an e-cigarette with nicotine (36 mg/mL) than after use of a nicotine-free e-cigarette or when given nothing (Perkins, Karelitz et al. 2017).

Findings from the Perkins et al. study are supported by the results of a cross-over, double-blind RCT conducted by Hiler et al. (Hiler, Breland et al. 2017). Smokers were recruited in Virginia, USA via advertisements (details not provided) and word of mouth. The sample was predominantly male (70%) with a mean age of 30.6(±9.1) years. Participants were divided into two groups; regular e-cigarette users (n=31) and naïve e-cigarette users (had not previously used e-cigarettes) (n=30). Participants were then randomised to receive 10 puffs of e-cigarettes with either 0, 8, 18 or 36mg/mL nicotine after >12 hour e-cigarette and cigarette abstinence. All participants had reductions in cigarette cravings and urges, however reductions were larger in the group of participants who regularly used e-cigarettes. In the higher nicotine conditions, there were larger reductions in reported cigarette cravings and urges as well as self-reported feelings of depression and sweat (Hiler, Breland et al. 2017).

An RCT conducted by Van Heel et al. was a parallel design and the researchers did not report whether it was blinded (Van Heel, Van Gucht et al. 2017). A total of 81 participants were recruited through flyers and online advertisements in Leuven, Belgium. 45.7% were female and participants had an average age of 29.8(±13.2) years. This study required participants to abstain from smoking for 12 hours (verified by carbon monoxide test). Then participants were randomised into sixteen groups with the variables; 0% or 3.6% nicotine-containing e-cigarette, 'bad apple' or 'tobacco regular' flavours, with or without a blindfold and with or without a vaping stand.

While tobacco cravings reduced after the use of any e-cigarette, the reduction was largest after using the nicotine-containing e-cigarette, but only after hand-to-mouth cues were removed (i.e. participants vaped from a vaping stand) (Van Heel, Van Gucht et al. 2017). This suggests that the movements associated with smoking also are involved in alleviating withdrawal symptoms. Thus e-cigarettes may reduce smoking withdrawal symptoms by providing both nicotine and the familiar habit of hand-to-mouth movements. However, results must be interpreted with caution as group sizes were very small (n≈5).

In a short term (nine day) US randomised cross-over study (Krishnan-Sarin, Green et al. 2017), conducted with young people (n=60, mean age 18.8 years) who were e-cigarette users, the independent effects of menthol and nicotine on stimulant effects, nicotine withdrawal, taste and coolness were tested.

Participants were randomised to a single nicotine concentration (0mg/ml, 6mg/ml or 12mg/ml) and received all three menthol concentrations (0%, 0.5% and 3.5%) during separate sessions in random order. Each session consisted of three fixed puffing bouts of 10 puffs, with a 10 minute break between puffing bouts. Participants completed a modified version of the Drug Effects Questionnaire to measure stimulant effects and nicotine withdrawal after each fixed puffing bout.

The study did not observe any effect of nicotine or menthol on stimulant effects or nicotine withdrawal. It did observe a significant **effect of time on nicotine withdrawal** ($F_{(3, 170)}=19.54$, $p<0.0001$); post hoc comparisons showed that withdrawal symptoms improved from baseline to puffing periods 1 to 3 (e.g. baseline 17.19 ± 1.45, puffing period 3: 11.71 ± 1.32, p <0.0001). These results suggest that the behaviour of using e-cigarettes may reduce withdrawal symptoms regardless of the nicotine concentration used.

The final RCT investigated the effects of nicotine and expected nicotine content of e-cigarettes on craving reduction (Palmer and Brandon 2018). 130 current or ex-smokers were recruited, predominantly from local vape shops, and were asked to abstain from nicotine for three hours before the experiment (confirmed with a carbon monoxide test). The included participants were 38% female and had a mean age of 36.40(±13.79) years. Participants were randomised to either receive a nicotine-containing or non-nicotine e-cigarette and told that the e-cigarette either did or did not contain nicotine, i.e. there were four conditions; in two conditions the participants were told the incorrect information about nicotine content. The study was double-blind. Researchers collected craving information using the Questionnaire of Smoking Urges-Brief before and after a ten minute vaping session.

Among smokers, while there was no main effect of drug (nicotine vs non-nicotine), participants told that their e-cigarette contained nicotine had larger craving to smoke reductions regardless of nicotine content. Craving to vape was only reduced in the group told to expect nicotine who actually received a nicotine-containing e-cigarette. These results provide further insight into the use of e-cigarettes to reduce cigarette craving and suggest that nicotine-free e-cigarettes may be just as effective as nicotine-containing e-cigarettes for craving reduction and thus smoking cessation. This is of particular importance due to concerns about the safety of nicotine products.

These results should be interpreted with caution due to the biased study population (e-cigarettes were already accepted by this population) and the limited applicability to real-life smoking cessation (consumers would know the nicotine content of the product they are purchasing). Additionally, the duration of smoking and vaping abstinence was very short (three hours), which likely does not reflect cravings of a smoker attempting to quit permanently. Nonetheless, this study provides interesting new information on smoking cessation using nicotine-free e-cigarettes.

9.4.2 Parallel group trial

A German parallel trial recruited participants from the community using flyers and via internet advertisements (Ruther, Hagedorn et al. 2018). Participants were included if they were adult male smokers (n=11; mean age 26.2±6.9 years) or e-cigarette users (n=9; mean age 28.5±8.9 years). These men abstained from smoking or vaping for >12 hours, verified by a carbon monoxide test, and were then provided with either a tobacco cigarette (tobacco group) or randomised to be given a tank model e-cigarette or a cigalike (e-cigarette group). A significant reduction in cravings was observed after e-cigarette users vaped tank-model e-cigarettes and smokers used tobacco cigarettes, but not after e-cigarette users vaped cigalikes (Ruther, Hagedorn et al. 2018). This suggests that the type of e-cigarette or familiarity with the device may also influence cravings as all of the e-cigarette users included in the study were regular tank-model e-cigarette users.

9.4.3 Cross-sectional studies

One study investigated smoking cessation and e-cigarette use in IBD patients (Serpen, Gutierrez et al. 2017). The researchers conducted a small survey of 27 adult smokers with IBD (67.5% response rate), using combined collection methods of a retrospective database and medical record audit and a phone questionnaire. Age and gender was not reported, however there was no significant difference between the e-cigarette users and smokers. E-cigarette use was associated with reduced cravings for regular cigarettes in 21/27 participants (Serpen, Gutierrez et al. 2017). There was limited information on this study as it is only available as a conference abstract and findings cannot be applied to the broader population due to the disease state and limited information.

9.4.4 Conclusions

Results from these studies suggest that e-cigarettes may reduce withdrawal symptoms in smokers and e-cigarette users after a short period of cigarette abstinence and thus may encourage smoking cessation. However, cigarettes appear to be more effective at reducing withdrawal symptoms than e-cigarettes, and e-cigarettes with higher nicotine doses appear to be more effective than low or nicotine-free devices. Interestingly, the knowledge that an e-cigarette contains nicotine may be sufficient to reduce withdrawals, as suggested in the study by Palmer et al. where participants had reductions in withdrawals after being told their e-cigarette contained nicotine, regardless of actual nicotine content. Further studies are required to confirm all findings, particularly the effect of nicotine, including low nicotine delivery doses. It is unclear from these studies whether e-cigarettes would continue to alleviate withdrawal symptoms following continued, long-term abstinence from nicotine.

9.4.5 Key findings

- E-cigarettes can reduce smoking withdrawal symptoms.

- Cigarettes are more effective at reducing smoking withdrawal symptoms than e-cigarettes.

- E-cigarettes containing nicotine reduce smoking withdrawal symptoms more than e-cigarettes without nicotine.

- Reducing smoking withdrawal symptoms is complicated with many factors involved. E-cigarettes may reduce withdrawal symptoms because of the familiar hand-to-mouth actions, nicotine content and knowledge that the e-cigarette contains nicotine.

- Further studies are required to determine if e-cigarettes continue to help with withdrawal symptoms when smokers have stopped smoking for longer than one day.

9.5 Association between e-cigarette use and smoking quit attempts

One randomised controlled trial, one trial without a control group and four cross-sectional studies assessed the association between e-cigarette use and quit attempts.

9.5.1 Randomised controlled trials

In a randomised controlled trial, 17 smokers (12 completers) who were intending to quit, were recruited from public notices for a cross-over trial (Perkins, Karelitz et al. 2017). Blinding was not reported by the authors. Participants were 58% male with a mean age of 29.4(±11.3) years. Participants were randomised to treatment order and received either a nicotine-containing (mg/mL nicotine) or nicotine-free e-cigarette device for three days. While withdrawal and cravings were reduced in the nicotine vs placebo group, ability to temporarily quit smoking did not differ between groups (2.9 ± 0.3 vs. 2.3 ± 0.3 days, $t(82)=1.6$, ns.) (Perkins, Karelitz et al. 2017).

9.5.2 Non-randomised trial

One trial recruited 74 smokers and 74 dual e-cigarette and cigarette smokers through Facebook ads and point-of-purchase convenience stores in Wisconsin, USA. Participants were 49.3% female; age and recruitment rate was not reported. Smokers were divided into e-cigarette users and non-users and were asked to attempt three days of smoking cessation. Dual users were more able to achieve 100% smoking abstinence for three days than non-users (97.1% vs. 81.2%) (Jorenby, Smith et al. 2017). The selection method and limited description of the participants limit the applicability of these findings to other e-cigarette users and cigarette smokers.

9.5.3 Cross-sectional studies

Cross-sectional studies also measured quit attempts in non-e-cigarette and e-cigarette users. In the US, an online survey recruited 1528 current smokers through a national commercial consumer panel (O'Connor, Rees et al. 2017). Participants were aged ≥14 years (38.6% aged 26-35 years) and over half were male (57%). The study examined the association between self-stigma, discrimination and quit attempts. In addition to the main findings that self-stigma was associated with increased intent to quit, the study also found that daily and some-day e-cigarette users were more likely have made at least three quit attempts in the previous year and to intend to quit in the next month. However, quit attempts do not necessarily reflect long-term smoking cessation. In addition, the association between e-cigarettes and quit attempts was not the primary outcome of this study, therefore results should be interpreted with caution.

The 2012-13 and 2013-14 US National Adult Tobacco Surveys also collected cessation method data. This survey included 20,270 past-year adult smokers (i.e. current and former smokers) (median age 41, IQR: 29-54; 42.5% female), with response rates of 44.9% (2012-13) and 36.1% (213-14) (Anic, Holder-Hayes et al. 2018). Results were adjusted to be nationally representative. Results found that there was a larger proportion of recent quitters who used e-cigarettes than smokeless tobacco. This data indicates that smokers are using e-cigarettes as a smoking cessation method. However, quit attempts may not reflect life-long quit success. Additionally, this study reported that 10.4% (2012-13) and 14.8% (2013-14) of smokers with unsuccessful quit attempts were using e-cigarettes compared with 9.1% (2012-13) and 15.8% (2013-14) of recent quitters. This indicates that e-cigarettes may only occasionally be associated with successful smoking cessation. Causation cannot be inferred due to the study design.

Data from the 2014 National Health Interview Survey, a nationally representative sample of the USA, was also analysed to determine if there is an association between e-cigarette use and quit attempts (Stokes, Collins et al. 2018). The researchers analysing the data included participants who had been diagnosed with cardiovascular disease. Age was not reported but participants were 53.2% female. They found that there was increased odds of ever (OR=1.70; 95% CI, 1.25, 2.30) and current (OR=1.97; 95% CI, 1.32, 2.95) e-cigarette use among smokers who had attempted to quit in the past year.

Results from the above studies are supported by a school and college-based survey from the US (Camenga, Kong et al. 2017). This study surveyed 4,969 students who were established smokers, with a mean age of 18.3 years and who were 49.3% male. Response rates ranged from 87.1% to 94.1% for college and school students. After adjusting for confounders including race, e-cigarette frequency and e-cigarette flavours, 41.8% of the young adult smokers surveyed had used e-cigarettes to quit. However, the results also found no association between e-cigarette use to quit smoking and current smoking status. This key finding suggests that while e-cigarettes may be used with the intention of smoking cessation, they may not be effective.

9.5.4   Conclusions

The randomised controlled trial found that using an e-cigarette did not increase the participants' ability to quit smoking temporarily. However, the non-randomised trial found an association with e-cigarette use and ability to quit smoking for three days. Additionally, the four cross-sectional studies found an association between quit attempts and e-cigarette use. However, cause and effect cannot be concluded from cross-sectional studies. The e-cigarette users may have possessed other traits which made them more likely to attempt to quit smoking, e.g. higher motivation to quit. Overall, there is insufficient evidence to form a conclusion. In particular, more randomised controlled trials are needed. Additionally, quit attempts may not reflect the ability to quit smoking permanently.

9.5.5 Key findings

- There is insufficient evidence from recent studies to draw a conclusion on whether the use of e-cigarettes can lead to an increased number of quit attempts.

- More randomised controlled trials are required.

- Number of quit attempts may not reflect successful smoking cessation.

- While cross-sectional studies indicate a relationship between quit attempts and e-cigarette use, the association may be due to motivation (i.e. smokers who are motivated to quit smoking may attempt to quit smoking and may also try e-cigarettes).

9.6 Smoking cessation rates

Four randomised controlled trials, one uncontrolled trial, ten longitudinal studies and ten cross-sectional surveys, and included smoking cessation as a study factor, outcome or trial endpoint.

9.6.1 Randomised control trials

Randomised controlled trials (RCTs) provide insight into the use of e-cigarettes for smoking cessation. There were four RCTs which provided smokers with nicotine-free or nicotine-containing e-cigarettes and measured quit attempts and quit status.

A double-blind, parallel 24 week RCT from the USA included 40 participants (20 in each group), 52.5% of whom were female, with a mean age of 53 (±10.1) years (Baldassarri, Bernstein et al. 2018). The main aim of the study was to determine the feasibility of adding e-cigarettes to an outpatient tobacco treatment centre. Participants were randomised to receive either a nicotine-containing e-cigarette (24 mg/mL nicotine) or a nicotine-free e-cigarette. They were then encouraged to use e-cigarettes instead of cigarettes and, if possible, abstain from both. There was no difference in quit status at 24 weeks in participants given a nicotine-free or nicotine-containing e-cigarette. 15% of participants were abstinent at 24 weeks and half of these were still using the e-cigarette (Baldassarri, Bernstein et al. 2018).

A 21 day parallel pilot study randomised participants to receive either a 16 mg/mL, a 24 mg/mL nicotine e-cigarette or no e-cigarette (Carpenter, Heckman et al. 2017). 41 participants were recruited from the local community (south eastern U.S. urban area) using various media outlets (details not provided). Participants were 60% female and mean age was not reported. There was at least a 50% reduction in smoking by 5% in the no-e-cigarette group, by 30% in the 16 mg/mL nicotine group and by 35% in the 24 mg/mL nicotine group. Thus results indicated a reduction in cigarette smoking dependent on e-cigarette nicotine dose. The researchers concluded that the study indicated a strong interest in the uptake of e-cigarettes and trends towards cessation (Carpenter, Heckman et al. 2017). However, while participants reduced cigarette consumption, it is unclear if this would translate to complete smoking cessation over a longer duration. Additionally, the study did not compare e-cigarette use with other smoking cessation treatments.

An RCT based in both Christchurch (n=22) and Wellington (n=13), New Zealand, recruited participants from the community and via internet ads (Tucker, Laugesen et al. 2017). 40 participants were recruited and 35 completed the trial. 26.7% were female and the mean age was 26.8(±10.6) years. The RCT was a cross-over design with four, two-week periods. Participants were randomised to treatment order and received either a 0, 6, 12 or 18 mg/mL nicotine e-cigarette. They were instructed to use the e-cigarette ad libitum, in attempt to substitute the e-cigarette for the regular cigarette. Daily use of both cigarettes and e-cigarettes was reported using SMS messages. Mean cigarettes per day decreased from baseline (9.69 ± 5.07) to end of the study (6.09 ± 4.18). There was a 37% reduction in cigarettes per day when any e-cigarette was available ($t(62)=2.75$, $p=0.008$). There was a significant effect of nicotine concentration ($f(3, 59.8)=2.95$, $p=0.04$), such that participants used the e-cigarettes more frequently when using the higher nicotine e-cigarettes (Tucker, Laugesen et al. 2017).

An Italian study with 170 smokers randomised participants into three groups; e-cigarettes with nicotine (8mg/mL), e-cigarettes without nicotine or no e-cigarette (Masiero, Lucchiari et al. 2018). The study design was double-blind and parallel. All participants received telephone counselling every four weeks throughout the 12 week study. Participants attempted cessation from weeks 2-12 of the study. Participants in the e-cigarette group were instructed to use <1mL of e-cigarette liquid per day. Mean age of participants was 62.8±4.6 years and 37% were female. Seventy participants were randomised into each condition, but only 170 completed the trial (study did not report the number of completers per condition but noted it was similar in each group). The e-cigarette groups had higher successful cessation rates than the control group (25.4% (n=34) of nicotine-containing e-cigarette group; 23.4% (n=13) of nicotine-free e-cigarette group and 10.3% (n=6) of control group).

Thus, in this trial use of e-cigarettes led to smoking cessation in a larger percentage of participants compared with no e-cigarette use. However, this comparison does not provide insight into whether e-cigarettes are more effective at achieving smoking cessation than other smoking cessation methods (e.g. nicotine patches, intensive counselling). A key difference in this study was that all participants were highly motivated to stop smoking (self-reported on a motivational questionnaire). This differs to other studies which included smokers with low motivation to quit. Thus, this study may have more relevance to the population of smokers wishing to quit smoking using e-cigarettes.

9.6.2   Uncontrolled trials

A trial without a control group recruited 40 smokers who were interested in e-cigarettes but not necessarily smoking cessation, via flyers, internet and newspapers. They provided the smokers with free e-cigarettes. The participants were predominantly male (73%) and had a mean age of 30.1(±8.8) years. After two weeks 40% reported smoking cessation and at four weeks, 15% reported cessation (Pulvers, Emami et al. 2018). A longer follow-up period would have provided evidence as to whether this was a sustainable behaviour.

9.6.3   Longitudinal Studies

Four longitudinal studies support the use of e-cigarettes for smoking cessation. The first was a 12 month study which recruited 3,868 current (23%) and former (77%) smokers through a tobacco cessation website (Etter 2017). All participants used e-cigarettes, with a median vaping duration of 5 months. The former smokers were predominantly recent quitters, with a median quit duration of 3 months at baseline. 58% of participants were male, with a mean age of 41 years (standard deviation not reported). Over the 12 months of data collection, 9% of former cigarette users relapsed, while 28% of daily smokers stopped smoking. Those that stopped vaping (1.4%) tended to relapse to smoking (Etter 2017).

One longitudinal study recruited 118 New Zealand current vapers via online vaper and smoking cessation networks (Truman, Glover et al. 2018). The survey participants were predominantly older (55% >60 years) and male (70%). In this survey, 79% of participants reported that they had used vaping to help them cease smoking. While only two participants (1.7%) ceased smoking during the study, 73% had once been smokers and now exclusively vaped. However, it is unclear if vaping was the main smoking cessation technique used or if it was used alongside other smoking cessation tools. The sample of participants was biased to select committed vapers due to the recruitment method, and the study excluded two participants who had stopped vaping because they did not find it a good substitute to smoking. Thus this study was likely to capture participants who had strong positive beliefs about e-cigarettes and not capture smokers who may have tried e-cigarettes but found them not useful for smoking cessation. Therefore findings may be misleading due to the participants included and likely do not reflect vaping or smoking populations. Additionally, generalisability is limited as the sample size was small (118), predominantly male (70%) and older (55%). Critically, this study only surveyed current e-cigarette users (recruited online through vaper and smoking cessation networks).

Data from the 2013-15 US PATH (Population Assessment of Tobacco) Study also supports the use of e-cigarettes as a smoking cessation tool (Berry, Reynolds et al. 2018). 5,124 participants were recruited to create a nationally representative sample. 45% were female and mean age was not reported (see table 13 and 14). This secondary analysis included data from Wave 1 (2013-14) and Wave 2 (2014-15). Data was analysed after adjusting for covariates of age, sex, race/ethnicity, household income, education and region. Results indicated that participants who were cigarette smokers at Wave 1 who began using e-cigarettes by Wave 2 were 7.88 times more likely to have cessed smoking for at least 30 days at Wave 2 (95% CI, CI 4.45 – 13.95). Additionally, those who did not achieve cessation were 5.70 times more likely to have reduced cigarette consumption if they were using e-cigarettes at Wave 2 (95% CI, 4.45 – 13.95). This data indicates that e-cigarettes may be an effective smoking cessation tool, however they did not consider other smoking cessation tools and e-cigarette use may simply be an indicator of quit motivation.

Seven longitudinal studies found results which contradict a positive association between e-cigarette use and smoking cessation. One study had a relatively small sample size and was not nationally representative (Curry, Nemeth et al. 2017). This study followed-up participants from a randomised smoking cessation trial. The trial randomly assigned Ohio counties to 10 weeks of either face-to-face counselling or the Ohio Tobacco Quitline. They tracked smoking habits, e-cigarettes use and had a main outcome of smoking cessation at 12 months. A secondary analysis of this data was conducted to determine the association between e-cigarette use and smoking cessation among these smokers who were attempting to quit. Participants in the secondary analysis were predominantly female (76.7%) and 53.5% were aged between 25-54 years.

Four times as many non-e-cigarettes users were abstinent at 12 months than e-cigarette users (19.0% vs. 4.7%, p=.021). They also grouped participants according to when they had used e-cigarettes. Results indicated that 16.7% of base-line e-cigarette users had abstained from e-cigarettes at 12 months. 19.3% of never-users at baseline and post-treatment had abstained at 12 months and e-cigarette users at both baseline and post-treatment had an abstinence rate of 6.7% (Curry, Nemeth et al. 2017). Results from this study should be interpreted with caution because e-cigarette use was not a primary measurement.

One longitudinal study recruited 408 young adults (mean age 20.5±1.8 years, 57% male) from a Californian community (details not provided), who were either regular cigarette smokers or non-smokers and who had regular internet access (Brikmanis, Petersen et al. 2017). Participants completed online surveys at baseline, 3, 6 and 9 months to track their cigarette and e-cigarette use. 85% of participants had completed >92.1% of surveys and were included in analysis. Results found that e-cigarettes were used to supplement current tobacco smoking, rather than to quit smoking. Additionally, intent to quit smoking was unrelated to e-cigarette frequency (Brikmanis, Petersen et al. 2017).

A public health initiative in Hong Kong collected data throughout a contest to quit smoking, called *Quit to Win,* where participants were provided with incentives and social support to promote abstinence from cigarettes (Yong-da Wu, Wang et al. 2018). Participants were adult (≥18 years) Cantonese-speaking Hong Kong residents who were regular smokers and were not involved in other smoking cessation programs. Survey data was collected regularly (1 week, 1, 2, 3, 6 months) throughout the six month study and included data on e-cigarette use, smoking behaviours, quit attempts and sociodemographic status. Quit status was further biochemically validated in 70.5% of participants using a salivary cotinine test.

The results found that ever using an e-cigarette did not predict self-reported (AOR 0.99, 95% CI 0.57–1.73) or biochemically validated quitting (AOR 1.22, 95% CI 0.64–2.34), any cessation attempt (AOR 0.74, 95% CI 0.48–1.14), or smoking reduction (AOR 0.89, 95% CI 0.54–1.47). Additionally, e-cigarette use during the first 3 months did not predict quitting (AOR 1.02, 95% CI 0.22–4.71). It is important to note that 'e-cigarette use' was defined as any e-cigarette use, including 1 puff. Therefore this data does not reflect regular e-cigarette use or use of e-cigarettes as a cessation method. Additionally, e-cigarettes were likely nicotine-free due to regulations in Hong Kong and Hong Kong has very high smoking rates thus it may not reflect Australian use and cessation rates.

Another study used data from an evaluation of an online internet smoking cessation campaign. 2,057 smokers were recruited and weighted to represent the total population of France (Pasquereau, Guignard et al. 2017). 45.9% were female and age ranged from 15-85 years (see table 13 and 14). Initial response rates were not reported, however attrition at 6 months was 31.4%. While e-cigarette users were more likely to reduce their cigarette consumption (aOR= 2.6, 95%CI= 1.8-3.8) and to have made a seven-day quit attempt (aOR= 1.8, CI= 1.2–2.6) than tobacco-only smokers, cessation rates at six months did not differ (12.5 versus 9.5%, p=0.18, aOR=1.2, CI= 0.8–1.9) (Pasquereau, Guignard et al. 2017).

Data from Rigotti et al's study provides information on a niche but relevant sample of recently hospitalised smokers who wanted to quit smoking. This group of participants may have had higher quit motivations due to recent health issues (including conditions related to smoking) (Rigotti, Chang et al. 2018). 1,357 smokers were recruited to a randomised controlled trial where they either received approved tobacco medication and five telephone calls or a recommendation to contact a free quit line. Data was also collected on e-cigarette use and thus was able to be analysed in this secondary analysis. The genders and age of the study participants were not reported. There was a 75% follow-up rate at six months (participants lost to follow-up were younger and were less likely to have been admitted due to a smoking-related disease). The researchers used propensity score matching to compare e-cigarette use and smoking cessation.

It was found that those who used e-cigarettes within the first three months were less likely to be biochemically abstinent at six months than those not using e-cigarettes (10.1% vs. 26.6%; risk difference, -16.5% [95% CI, -23.3% to -9.6%]). While e-cigarette use included any use, rather than regular use, this study adds important information to data about e-cigarettes and smoking cessation among this unique group of motivated and unwell smokers.

In a four year study following 586 youth smokers, frequency of e-cigarette use was not associated with reductions in future smoking (Selya, Dierker et al. 2017). This study recruited 9th and 10th graders through Chicago schools (US) and followed them for eight years. 35% of invited students participated in the study and retention at 8 years was 79.7% (n=1007), including both smokers and non-smokers. 86.9% were female and the mean age at eight years was 23.6 years. Participants included in this analysis reported smoking at least once during the eight-year study. E-cigarette use was analysed in last four years of the study (waves 5-8; years that e-cigarette data was collected). This study compared various quit methods (seeking support from a cessation group, Internet, or phone resource, using medications or herbal supplements or using nicotine replacement products) and only found nicotine replacement products to be effective and only in highly nicotine-dependent smokers. Despite this finding, among those who used e-cigarettes with the intention of quitting smoking, e-cigarette use was not associated with reductions in future smoking (Selya, Dierker et al. 2017).

Frequency of e-cigarette use is a key variable in smoking cessation outcomes. 2,760 smokers seeking cessation treatment were recruited for a seven-month study through quit lines in the US. Response rates were reported according to the three states involved; 58.3% for Minnesota, 49.3% for Oklahoma, and 48.3% for Florida. Participants were 57.9% female and >18 years (age reported in table 13 and 14). Analyses controlled for age, gender, level of education, tobacco type, advice from a health professional, a combined state-program variable, and stop-smoking medication use post-enrolment. Any past 30-day e-cigarette use was associated with lower quit rates than no e-cigarette use (AOR=0.63; p=0.001). When compared with non-use, infrequent (AOR=0.35; CI=0.20–0.59) and intermediate (AOR=0.50; CI=0.32–0.80) past 30-day e-cigarette use was associated with lower rates of tobacco abstinence. However, daily e-cigarette users when compared with non-users was not associated with quit status (AOR=1.16; p=0.453) (Subialka Nowariak, Lien et al. 2018). In summary, daily e-cigarette users and non-users had similar quit successes, but infrequent e-cigarette users had poorer smoking cessation rates.

9.6.4 Cross-sectional Studies

The first cross-sectional study was a secondary analysis of the National Health Interview Survey, a nationally representative survey, and investigated patterns of e-cigarette use and smoking cessation (Giovenco and Delnevo 2018). This study analysed data from 15,532 former (24%) and current (76%) smokers, 52.6% of whom were male and 36.1% were aged between 45-64 years. Response rate was not reported. In this study, 52.2% of daily e-cigarette users had quit smoking and, after covariate adjustment (gender, age, race/ethnicity, education, census region, health insurance status, and serious psychological distress), they were more than three times more likely to have quit conventional smoking than those who never used e-cigarettes. However, some-day e-cigarette use was associated with a lower likelihood of having quit smoking (Giovenco and Delnevo 2018). This study did not consider other quit methods, thus it is unclear if smoking cessation is more strongly related to e-cigarette use than other types of smoking cessation tools.

In the survey of IBD smokers (study described section 10.4.3) who also used e-cigarettes, 17/27 participants (~60%) reported smoking cessation (Serpen, Gutierrez et al. 2017). Additionally, in a vape-shop survey of 203 Dutch or Flemish adults (study described in section 10.2.1), 74% of the surveyed customers reported they had successfully quit smoking and now used e-cigarettes, while only 20% were continuing to smoke (Sussan, Shahzad et al. 2017). These two studies indicate a possible positive relationship between e-cigarette use and smoking cessation. However, their results cannot be generalised to broader cigarette smokers due to their highly specific population groups. In particular, studies focusing specifically on e-cigarette users will not capture those who have tried e-cigarettes and found them unhelpful as a smoking cessation method.

Zhu et al. conducted a secondary analysis of the US Current Population Survey-Tobacco Use Supplement, collected in the US census in 2001-02, 2003, 2006-07, 2010-11 and 2014-15 (Zhu, Zhuang et al. 2017). Each survey contained between 23,270 and 163,920 participants. Gender was approximately equal (55.4% female) and aged >18 years (see table 12 for details). They found that more e-cigarette users attempted smoking cessation than non-users (65.1% v 40.1%) and that they were more likely to successfully quit (8.2% v 4.8%, change= 3.5%, CI: 2.5% to 4.5%) (Zhu, Zhuang et al. 2017). However, this study did not investigate other smoking cessation methods. Thus people who were already motivated to quit smoking may have been more likely to use e-cigarettes. The researchers also did not investigate whether e-cigarette users used other quit methods. Thus, quit success could have resulted from use of other smoking cessation methods. Additionally, assessing quit success among current e-cigarette users only may be misleading as it does not capture smokers who have previously attempted smoking cessation using e-cigarettes but were unsuccessful.

While these studies indicate an association between e-cigarette use and having quit smoking, this evidence is generally limited by small study samples, lack of comparison with other smoking cessation tools and insufficient covariate adjustment. Seven cross-sectional studies had results which do not support a positive association between e-cigarette use and smoking cessation.

While Zhu et al. found a positive association between e-cigarette use and quit success, Levy et al. found mixed results depending on the frequency of e-cigarette use (Levy, Yuan et al. 2017). Levy et al. conducted a secondary analysis of the 2014-15 Tobacco Use Supplement-Current Population Survey from the US census. This included 21,226 smokers, 49.8% were male and participants were largely aged 45-64 years (42.2%). The response rate was not reported. Smokers who used e-cigarettes were more likely to report quit attempts than non-users. Researchers analysed quit successes of all smokers who had attempted to quit at least once in the past year, categorised by e-cigarette use (regular (≥five times per week), ever or never users). The researchers found that smokers who had ever used e-cigarettes reported fewer quit successes than non-users and regular users. However, regular e-cigarette users were more likely to have abstained from smoking compared with never or ever users (Levy, Yuan et al. 2017).

Another secondary analysis was conducted using data from the 2014-15 PASSI survey, details of this study are included in section 10.2.1 (Gorini, Ferrante et al. 2017). This study analysed the success of different quit methods among smokers who had attempted to quit smoking in the past year. Of those using e-cigarettes, 8% reported smoking abstinence, which was statistically the same as the 9% who successfully quit without aid. Those using established quit methods (smoking cessation programs, medications, other unspecified methods) had a 15% success rate. Thus this study indicates that e-cigarettes were less effective for smoking cessation than established quit methods.

In a study of young adults, previously described in section 10.5.3, use of e-cigarettes to quit smoking was not associated with current smoking status (Camenga, Kong et al. 2017). In a survey of Chinese adolescents outlined in section 10.2.1 results found that among currently smoking adolescents who 36.02% had attempted to quit using e-cigarettes, 12% had attempted using a patch and 52% used other methods (Wang, Zhang et al. 2018). However, among the 192 former smokers or those who had successfully quit, 17.19% used patches, 13.54% used e-cigarettes, and 69.72% used other methods to help quit. This suggests that the success from patches and other quit attempts was higher than success from e-cigarettes. However, due to the study design cause and effect cannot be established. It is important to note that this study did not use a representative sampling method and that the population was Chinese adolescents, thus results cannot be generalised to Australian adults.

A study conducted by Ekanem et al. analysed data collected in the Arkansas Behavioural Risk Factor Surveillance System (Ekanem, Cardenas et al. 2017). This study included 1083 current (75%) or past smokers who had quit within last 5 years (25%). The population was older; over 46.1% of the population was >65 years old and predominantly female (63.7%). Response rate was not reported. Participants were recruited through a random-digit dial system. 80.3% of e-cigarette users had continued to smoke tobacco cigarettes. E-cigarette use was associated with significantly reduced likelihood of smoking cessation (OR= 0.53, 95%CI= 0.34-0.83).

An online survey was conducted on 798 smokers in 2015 in Japan (Hirano, Tabuchi et al. 2017). Participants were 72.7% male, age ranged from 20-69 years (see table 12). Participants were recruited through a commercial research provider. In this study, after adjusting for covariates (gender, age, health-related factors and other quitting methods), e-cigarette use was negatively associated with smoking cessation (OR= 0.632; 95%CI= 0.414-0.964). However, smoking cessation therapy (including prescription medications) was significantly associated with smoking cessation (OR=1.885; 95%CI=1.018-3.492) (Hirano, Tabuchi et al. 2017). While the study was a representative sample, there was a very low response rate (8.5%), limiting applicability to the general population.

Two nationally representative cross-sectional surveys found associations between e-cigarette use and reduced rates of tobacco smoking cessation (El-Khoury Lesueur, Bolze et al. 2018, Kulik, Lisha et al. 2018). The first was a secondary analysis of the 2016 DePICT (Description des Perceptions, Images, et Comportements liés au Tabagisme) survey, a nationally representative survey conducted in France. The researchers recruited 2,110 smokers through randomly generated telephone numbers and had a 67% response rate. Age and gender were not reported. They determined key factors associated with successful smoking cessation; smoking>19 cigarettes per day, no lifetime use of e-cigarettes (OR=6.05, 95% CI, 462–7.92), no lifetime use of nicotine replacement products, no exposure to environmental tobacco, and no cannabis use (El-Khoury Lesueur, Bolze et al. 2018).

The second was a secondary analysis of nationally representative surveys of European countries (including UK), using data from the 2014 Eurobarometer survey. This survey included 12,608 current (54.4%) and former (45.6%) smokers. A multistage probability sample was conducted and participants were interviewed in their homes. Participants had a mean age of 49.9(±16.8) years and 55.6% were male. The response rate was not reported. Both unadjusted and adjusted models of the data revealed that daily, occasional or experimental use of nicotine-containing e-cigarettes was associated with lower odds of being a former, rather than current, smoker (adjusted models: daily use OR=0.52, 95% CI=0.36, 0.73; occasional use OR=0.33, 95% CI=0.23, 0.47; and experimentation OR=0.32, 95% CI=0.25, 0.41). This was in comparison to participants who had never used e-cigarettes. When analysed using just the Great Britain data, results were similar (Kulik, Lisha et al. 2018).

9.6.5 Conclusions

The majority of observational studies did not support a positive association between e-cigarette use and smoking cessation, when compared with non-users of e-cigarettes. Uncontrolled trials indicated a possible relationship between e-cigarette use and ability to cease smoking for short durations (three days to four weeks). However, long-term cessation was not measured in these studies. Results from randomised controlled trials indicated that nicotine-containing e-cigarettes were more effective at reducing amount of smoking and withdrawal symptoms compared to nicotine-free e-cigarettes or no e-cigarettes. However, randomised controlled trials did not find significant associations between e-cigarette use and smoking cessation. They were also limited by duration; with the reviewed trials lasting no longer than 24 weeks. This means that long-term smoking cessation could not be measured. Critically, trials did not compare e-cigarettes with other smoking cessation methods. Thus, conclusions cannot be made about the effectiveness of e-cigarettes when compared with other smoking cessation methods.

9.6.6 Key findings

- E-cigarettes can help people to quit smoking for a short period of time (up to 24 weeks).

- Nicotine-containing e-cigarettes are more effective at helping to quit smoking than nicotine-free e-cigarettes.

- It is unclear whether e-cigarettes are able to help people quit smoking permanently.

- It is not known whether e-cigarettes are as effective as other smoking cessation methods (e.g. nicotine patches, counselling).

- Long-term randomised controlled trials need to be conducted which compare e-cigarettes to other smoking cessation methods.

9.7 What the new studies add to what is already known about e-cigarettes

Studies summarised in this report generally support the findings from the US Academies of Science report:

Conclusion 17-1. *Overall, there is **limited evidence** that e-cigarettes may be effective aids to promote smoking cessation.*

Conclusion 17-2. *There is **moderate evidence** from randomized controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation.*

Conclusion 17-3. *There is **insufficient evidence** from randomized controlled trials about the effectiveness of e-cigarettes as cessation aids compared with no treatment or to Food and Drug Administration–approved smoking cessation treatments.*

Conclusion 17-4. *While the overall evidence from observational trials is mixed, there is **moderate evidence** from observational studies that more frequent use of e-cigarettes is associated with increased likelihood of cessation.*

In particular, the new studies outlined in this report provide further evidence for conclusion 17-2. While the above report found limited evidence for smoking cessation, the most recent evidence suggests that the association between e-cigarette use and smoking cessation may even be negative (i.e. e-cigarette use is counterproductive for smoking cessation). However, more evidence is needed before a conclusion can be made.

The Public Health England e-cigarette review found the following key findings:

1. *E-cigarette use, alone or in combination with licensed medication and behavioural support from a Stop Smoking Service, appear to be helpful in the short term. However, fewer smokers use an e-cigarette as part of a quit attempt with a Stop Smoking Service compared with licensed medication.*

2. *We identified 14 systematic reviews of e-cigarettes for smoking cessation and /or reduction published since our last report, seven of which included a meta-analysis. The authors of the systematic reviews arrived at the same conclusion that further randomised controlled trials of e-cigarettes are needed. However, the reviews that included a meta-analysis produced*

different results; two found a positive effect on cessation for e-cigarette use, four found an inconclusive effect for cessation and one found a negative effect.

There are insufficient studies to contribute to further evidence for statement 1. Mixed findings from the reviews (statement 2) is also highlighted in the reviewed studies, however more observational studies were found which had negative effects for smoking cessation than positive effects.

As suggested by the two previous reports, further randomised controlled trials are required to determine the effectiveness of e-cigarettes as a smoking cessation tool compared to other methods.

10   Tables

Table 10: E-cigarette use and conventional smoking studies

Study	Design	Duration	Population	Comparisons	Funding
Chaffee et al 2018	Cohort	1 year	US adolescents aged 12-17 years who had tried smoking but had not yet smoked 100 cigarettes at baseline (N=1,295)	Exposures: e-cigarette use (ever/never; never/non-past 30-day use/ past 30-day use). Outcomes: established smoking (≥100 cigarettes), past 30-day smoking, current established smoking (≥100 cigarettes and past 30-day smoking).	US National Cancer Institute, the US Food and Drug Administration Center for Tobacco Products, the National Institute on Drug Abuse and National Institutes of Health (NIH).
East et al 2018	Cohort	~5 months	Young never smokers aged 11-18 years in Great Britain (N=923)	Exposures: ever e-cigarette use; escalation of e-cigarette use. Outcomes: smoking initiation.	Cancer Research UK; UK Public Health Research Consortium
Kinnunen et al 2017	Cohort	2 years	School students in Helsinki, Finland aged 16 at baseline (N=3,474)	Exposure: e-cigarette use (never tried/ non-nicotine e-cigarettes/ nicotine e-cigarettes). Outcome: daily cigarette smoking.	Not reported
Lozano et al 2017	Cohort	20 months	Middle school students in 3 largest cities in Mexico (N=4,695)	Exposure: e-cigarette use (ever/never). Outcomes: cigarette smoking (ever/never; past 30-day use (any/none)).	Fogarty International Center; National Cancer Institute of the US National Institute of Health
Morganstern et al 2018	Cohort	6 months	10th grade students in Lower Saxony and Schleswig-Holstein, Germany, who have never smoked (N=2,186)	Exposure: e-cigarette use (ever/never). Outcome: smoking initiation.	Federal Center for Health Education on behalf of the Federal Ministry for Health
Pearce et al 2017	Cohort	1 year	High school students in Scotland who have never smoked (N=2,998)	Exposure: e-cigarette use (ever/never). Outcome: smoking initiation.	Not reported
Penzes et al 2018	Cohort	6 months	9th grade students in Tirgu Mures, Romania (N=1,369)	Exposure: e-cigarette use (ever/never). Outcome: smoking initiation.	Fogarty International Center; National Cancer Institute of the National Institutes of Health
Treur et al 2017	Cohort	6 months	School students aged 11-17 years in the Netherlands who have never smoked (N=2,100)	Exposures: ever and past month use of e-cigarettes with nicotine and without nicotine. Outcomes: conventional smoking (ever/never); smoking status (never/former/current).	European Research Council; Netherlands Organisation for Health Research and Development; the National Institute for Public Health and the Environment
Choi et al 2017	Cross-sectional	N/A	Middle and high school students in Florida (N=68,928)	Exposures: ENDs use (ever/never; past 30-day use/non-past 30-day use/never). Outcomes: Peer and community acceptability of adult cigarette smoking; susceptibility to cigarette smoking.	National Cancer Institute; National Institute on Minority Health and Health Disparities Division of Intramural Research

Study	Design	Duration	Population	Comparisons	Funding
De Lacy et al 2017	Cross-sectional	N/A	Students aged 11-16 years in network schools in Wales (N=32,479)	Exposure: e-cigarette use (regular (≥once/week), occasional (<once/week), never). Outcome: smoking status; used first (e-cigarette or cigarette) in those who have tried both.	Health and Care Research Wales via the National Centre for Health and Well-being Research; DECIPHer, a UKCRC Public Health Research Centre of Excellence; the British Heart Foundation; Cancer Research UK; Economic and Social Research Council; Medical Research Council; the Welsh Government; the Wellcome Trust, under the auspices of the UK Clinical Research Collaboration
Farsalinos et al 2018	Cross-sectional	N/A	Representative sample of adults living in Attica prefecture, Greece (N=4,058)	Exposure: e-cigarette use (ever/never; past 30-day use (yes/no)). Outcome: smoking status (never, former, current).	Not reported
Hammond et al 2017	Cross-sectional	N/A	Grades 9-12 secondary school students in Ontario and Alberta, Canada (N=44,163)	Exposure: past 30-day use of e-cigarettes (yes/no). Outcome: smoking (never tried, not susceptible/never tried, susceptible/puffer/experimental smoker/former smoker/current occasional smoker/current daily smoker).	Canada institutes of health research (CIHR)
Hines et al 2017	Cross-sectional	N/A	8th and 11th grade students in Oregon, USA (N=29,674)	Exposure: introductory tobacco product used. Outcome: ever and current tobacco product use (used in the past 30 days).	Not reported
Kinouani et al 2017	Cross-sectional	N/A	Higher education students in France (mean age: 21 years) (N=2,720)	Exposure: e-cigarette use (current user/former user (tried but not currently using)/never tried). Outcome: cigarette smoking (current/former/never).	French National Research Agency; Institut National du Cancer
Lanza et al 2017	Cross-sectional	N/A	US school students aged 11-19 years (N=21,798)	Exposure: use of e-cigarettes in the past 30 days (Yes/No). Outcome: cigarette smoking in the past 30 days (yes/No).	National Institute on Drug Abuse; the National Cancer Institute
Lanza et al 2018	Cross-sectional	N/A	Undergraduate students at California State University, USA (N=452)	Exposure: e-cigarette use (ever/never). Outcomes: early cigarette initiation (≤14 years), smoked a cigarette (ever/never), current smoker (≥5 times in last 30 days), former smoker (ever ≥ 5 times in 30 days).	National Institute of General Medical Sciences of the National Institutes of Health
Milicic et al 2017	Cross-sectional	N/A	Grades 9-12 secondary school students in Ontario and Alberta, Canada (N=39,897)	Exposure: e-cigarette use in the past 30 days (Yes/No). Outcome: smoking status (current/former/non-smoker based on ever smoked 100 cigarettes and any use in the past 30 days).	Canadian Institutes of Health Research (CIHR) Institute of Nutrition, Metabolism and Diabetes (INMD); Canadian Institutes of Health Research (CIHR) Institute of Population and Public Health
Parikh et al 2018	Cross-sectional	N/A	Adults in the USA (mean age 47.1 years) (N=162,048)	Exposure: e-cigarette use (non-user/occasional user/daily user). Outcome: conventional cigarette use (non-smoker/occasional smoker/daily smoker).	Not reported

Study	Design	Duration	Population	Comparisons	Funding
Park et al 2017	Cross-sectional	N/A	Korean adolescents who smoked on at least one day in the past 30 days (N=6,307)	Exposures: cigarette smoking - past 30 day use, daily use, cigarettes/day. Outcome: e-cigarette use (non-use/former use/current use).	Not reported
Pepper et al 2018	Cross-sectional	N/A	US adolescents aged 15-17 years who are using e-cigarettes were recruited from Facebook and Instagram (N=1,589. Analysis included 896 participants with complete data)	Exposure: Use of cigarettes in the past 30 days (any/none) Outcome: Usual type of e-cigarette used (with nicotine/without nicotine).	Strategic Investment Funds from RTI International (an independent nonprofit research institute)
Ramji et al 2017	Cross-sectional	N/A	Adolescent high-school students aged 16–19 years in Umea, Sweden (N=1,006)	Exposure: ever use of cigarettes, e-cigarettes, snus, alcohol, narcotics. Outcome: ever water pipe use.	The Public Health Agency of Sweden
Temple et al 2017	Cross-sectional	N/A	Sample recruited from public high schools in southeast Texas, USA as part of a longitudinal study. Data from wave 6 of study. Age range: 18-23 years. (N=662)	Exposure: past year use of e-cigarettes (Yes/No). Outcome: past year use of cigarettes (Yes/No).	Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), Methesda, MD, and the National Institute of Justice (NIJ), Washington, DC.

Table 11: E-cigarette use and the use of other substances studies

Study	Design	Duration	Population	Comparisons	Funding
Dai et al 2018	Cohort	1 year	Nationally representative sample of US adolescents aged 12-17 years who have never used marijuana (N=10,364)	Exposure: e-cigarette use (ever vs never; number of e-cigarettes and/or cartridges used in life (categorical ranging from 0 (no use) to 7 (100 or more)). Outcome: marijuana use in the past 12 months (ever/never); heavy marijuana use (weekly or more).	Not reported
Lozano et al 2017	Cohort	20 months	Middle school students in 3 largest cities in Mexico (N=4,695)	Exposure: e-cigarette use (ever/never). Outcome: marijuana use in the past 12 months.	Fogarty International Center; National Cancer Institute of the US National Institute of Health
Azagba et al 2018	Cross-sectional	N/A	Grades 6-12 school students in Canada (N=23,429)	Exposures: e-cigarette use, cigarette use or dual use in the past 30 days (any vs none). Outcome: frequency of past 30-day cannabis use (none, once or twice, 1-2 times/week, 3-6 times/week, every day)	Not reported
Curran et al 2018	Cross-sectional	N/A	US school students in grades 9-12 (N=15,624)	Exposures: past 30-day e-cigarette use (any/none); past 30-day use of conventional cigarettes (any/none); past 30-day use of other tobacco products (any/none). Outcomes: Alcohol use (ever/never; past 30 day use (any/none)); marijuana use (ever/never; past 30 day use (any/none)); lifetime use of other drugs (cocaine; glue; aerosols/paints; injected illegal drugs; heroin, methamphetamines, or ecstasy; or steroids without a doctor's prescription) (ever/never); prescription drug misuse (ever/never).	Mr Thad Burk's position was funded by grants from the Department of Health and Human Services, US Centers for Disease Control and Prevention. No other funding disclosed.
Kristjansson et al 2017	Cross-sectional	N/A	Grades 6-8 middle school students in West Virginia, USA (N=6,547)	Exposure: smoking status (Never, ever e-cigarette only, ever cigarette only, ever use both). Outcome: ever chewing tobacco; ever alcohol (more than just a few sips); ever been drunk; ever sniffing (glue,sprays, paints); ever prescription drugs without prescription; ever synthetic marijuana; ever bath salts; ever marijuana; ever hallucinogenic drugs (all Yes/No).	Sisters Health Foundation in Parkersburg, West Virginia; Substance Abuse and Mental Health Services Administration
Lanza et al 2018	Cross-sectional	N/A	Undergraduate students at California State University, USA (N=452)	Exposure: e-cigarette use (ever/never). Outcomes: Early alcohol initiation (≤14 years), ever binge drinking (≥ 4 drinks in one sitting for females, 5 for males (yes/no)), binge drinking in the last month (yes/no), Drunk in the past month (yes/no).	National Institute of General Medical Sciences of the National Institutes of Health
Milicic et al 2017	Cross-sectional	N/A	Grades 9-12 secondary school students in Ontario and Alberta, Canada (N=39,897)	Exposure: e-cigarette use in the past 30 days (Yes/No). Outcomes: binge drinking (non-binge drinker (none), ocassional binge drinker (<1/month), monthly binge drinker (1-3 times/month), weekly binge drinker (1-7 times/week); marijuana use (never, non-current (< 1/month), current (1/month or more).	Canadian Institutes of Health Research (CIHR) Institute of Nutrition, Metabolism and Diabetes (INMD); Canadian Institutes of Health Research (CIHR) Institute of Population and Public Health
Morean et al 2017	Cross-sectional	N/A	Adult e-cigarette users in the USA (N=552)	Exposures: age of e-cigarette onset, e-cigarette use frequency. Outcomes: lifetime cannabis vaporization, past-month cannabis vaporization, cannabis vaping frequency.	Not reported
Parikh et al 2018	Cross-sectional	N/A	Adults in the USA (mean age 47.1 years) (N=162,048)	Exposure: e-cigarette use (non-user/occasional user/daily user). Outcome: alcohol use (non-drinker, occasional drinker, light drinker, moderate/heavy drinker).	Not reported

Study	Design	Duration	Population	Comparisons	Funding
Park et al 2017	Cross-sectional	N/A	Korean adolescents who smoked on at least one day in the past 30 days (N=6,307)	Exposures: at risk drinking in the past 30 days (yes/no), lifetime use of drugs or butane gas (yes/no). Outcome: e-cigarette use (non-use/former use/current use).	Not reported
Richter et al 2017	Cross-sectional	N/A	8th, 10th and 12th grade students in the USA (N=28,536 8th and 10th graders; N=13,015 12th graders)	Exposure: past 30-day use of combustible cigarettes only, e-cigarettes only, other nicotine products only, or multiple nicotine products. Outcome: current use of alcohol, marijuana, other illicit drugs (hallucinogens, LSD, heroin, cocaine), the misuse of controlled prescription drugs (narcotics, stimulants, sedatives, tranquilizers), poly substance use (≥ 2 substances used in the past 30 days vs ≤ 1 substance used).	No funding received
Temple et al 2017	Cross-sectional	N/A	Sample recruited from public high schools in southeast Texas, USA as part of a longitudinal study. Data from wave 6 of study. Age range: 18-23 years. (N=662)	Exposure: past year use of e-cigarettes (Yes/No). Outcome: past year use of alcohol (more than just a few sips), marijuana, hard drugs (cocaine, amphetamines, inhalants, hallucinogens, ecstasy, misuse of over-the-counter cold or cough medication, misuse of prescription medication) (all Yes/No).	Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), Methesda, MD, and the National Institute of Justice (NIJ), Washington, DC.
Wong et al 2018	Cross-sectional	N/A	Representative sample of adolescents aged 12-17 in California, USA (N=1,806)	Exposure: e-cigarette use (ever/never). Outcome: alcohol use (more than just a few sips; ever/never).	Not reported

Table 12: Cross-sectional smoking cessation studies

Study reference	Study objectives	Survey name	Country/ location	Year data collected	Participants (n)	Age (years) M±SD	% female	Recruitment method	Response rate (%)	Findings	Conclusion
Anic 2018	Estimated the prevalence of e-cigarette and smokeless tobacco use and switching among current and recent former adult cigarette smokers.	National Adult Tobacco Survey	USA	2012–2013 & 2013–2014	2012–2013: 8,891 2013–2014: 11,379)	2012-13: 41 (IQR: 29.0-53.2) 2013-2014: 41.4 (IQR: 29.6-53.7)	42.5	Nationally representative, random-digit dialled telephone survey. Participants were aged ≥18 yrs and were some or every day cigarette smokers.	44.9% and 36.1%	More recent quitters completely switched to e-cigarettes in the past year (15.3% in 2012–2013, 25.7% in 2013–2014) than to smokeless tobacco (4.6% in 2012–2013, 4.5% in 2013–2014).	Current e-cigarette use was most prevalent among unsuccessful quitters and recent quitters, who were substantially more likely to report complete switching to e-cigarettes than smokeless tobacco.
Bunch 2018	This study seeks to describe current e-cigarette users' patterns of use including primary motivation for use, dual use, use with nicotine and principal flavour used, according to individuals' sociodemographic characteristics and conventional tobacco consumption in Barcelona, Spain.	Own data	Barcelona, Spain	2015	600	25-44: 49.8%	63.50%	Trained sensors (people trained to recruit participants for studies of uncommon products) recruited e-cigarette users in all neighbourhoods of the city of Barcelona. They identified individuals using or carrying an e-cigarette in public. All participants were current e-cigarette users at the moment of the interview, independent of whether they used it daily or occasionally.	90.3	The most prevalent motivation for using e-cigarettes was to reduce tobacco smoking (48%, n=288), followed by quitting smoking (39.2%, n=235), and to use e-cigarettes in places where tobacco smoking was prohibited (10.2%, n=61). People younger than 25 years old (OR=4.36, 95% CI 1.99 to 9.57) and women (OR=1.87, 95% CI 1.02 to 3.43) were more likely to state their main motivation for use as to use e-cigarettes where cigarettes were prohibited, while older people were more likely to use them to quit smoking tobacco (≥65, OR=13.8, 95% CI 2.62 to 72.41).	Younger users of e-cigarettes and non-smokers are more likely to use flavours other than tobacco and to use e-cigarettes mainly for recreational purposes.
Camenga 2017	This exploratory study examines the prevalence and predictors of current and former smokers' use of e-cigarettes for smoking cessation among a sample of adolescent and young adult established smokers.	Own survey	USA	2013-14	Middle school: 1166 High school: 3614 College: 625 [189]	18.3±2.8	50.7	Through schools. Only included participants who were established smokers.	87.1-94.1%	Overall, 41.8% of the sample reported that they "have used an e-cigarette to quit smoking." In adjusted models, older age, White race, higher e-cigarette frequency, and preference for using a combination of e-cigarette flavours predicted increased odds of having used e-cigarettes to quit smoking (p<0.05). Using e-cigarettes to quit smoking was not associated with current or former cigarette smoking status.	Adolescents and young adults who report more frequent e-cigarette use and preference for using flavor combinations are more likely to use e-cigarettes for smoking cessation.

Study reference	Study objectives	Survey name	Country/ location	Year data collected	Participants (n)	Age (years) M±SD	% female	Recruitment method	Response rate (%)	Findings	Conclusion
Chen 2018	This study seeks to understand which e-cigarette flavours-sweet and fruity or tobacco and menthol/mint-are more likely to be associated with smoking reduction and cessation among young adults.	PATH study (Population Assessment of Tobacco and Health), a nationally representative random sample.	USA	2013-14, 2014-15	4645	42.9	"18-24: 39.1%	Included young adults (ages 18-34) smokers who had smoked at least 100 cigarettes at wave 1 and had complete data for analysis.	NR	The top three endorsed reasons for using e-cigarettes among current users were that e-cigarettes (1) "might be less harmful to people around me than cigarettes" (85.4%), (2) "can be used where smoking cigarettes is not allowed" (82.2%), and (3) "come in flavours I like" (80.2%).	The positive association between past-year smoking reduction and cessation and current NTM flavoured e-cigarette use may be explained by young adults' escalated e-cigarette use with NTM flavours.
Cockburn 2018	This study measured tobacco and e-cigarette use, knowledge of smoking related health effects, motivations to quit and interest in cessation aids in Indigenous Australians.	Own survey	Southeast Queensland, Australia	2014-15	421 [390]	Median: 37, IQR: 21	59.3	Clients of Aboriginal & Torres Strait Islander Community Health Service dental clinics in Southeast Queensland (n=421) completed a brief written questionnaire while in the waiting room.	92.5	For current smokers, previously used quit methods were abrupt cessation (42%), nicotine replacement therapies (NRT; 25%), prescription medications (23%), e-cigarettes (9%, n=17) and other methods (3%). Current smokers were most interested in cutting down (85%), abrupt cessation (75%) and free NRT (72%).	Our study found there was interest in accessing smoking cessation aids among the clients of this community-controlled health clinic, particularly if provided free of charge.
Ekanem 2017	To determine the prevalence of ENDS use, the impact of ENDS use on smoking cessation, and beliefs about ENDS use in Arkansas.	Arkansas Behavioural Risk Factor Surveillance System.	Arkansas, USA	2014	1083	Total study (n=4465): 18-24: 3% 25-34: 6.6% 35-44: 8.4% 45-54: 13.7% 55-64: 22.1% ≥65: 46.1%	63.7	Random-digital-dial health survey. Included participants who were current smoking or had quit in the last 5 years.	NR	Of the current smokers or those who had quit smoking within the past 5 years, 515 (54.1%) had used ENDS. Of the 515 ENDS users, 404 (80.3%) had continued smoking. ENDS use was significantly associated with reduced odds of quitting smoking (weighted OR= 0.53; 95% CI, 0.34-0.83).	Most smokers who indicated smoking in the past 5 years and who tried ENDS did not stop smoking. ENDS use was inversely associated with smoking cessation.
El-Khoury 2018	We examine the role of tobacco use characteristics, other substance-related factors, as well as socio-demographic characteristics in relation to successful and unsuccessful smoking cessation.	DePICT (Description des Perceptions, Images, et Comportements liés au Tabagisme)	France	2016	2110	NR	NR	Randomly generated telephone lists.	~67%	...substance use factors associated with a higher likelihood of successful smoking cessation, as compared with no attempt to quit smoking, included characteristics of tobacco and other substance use: smoking> 19 cigarettes per day, no lifetime use of e-cigarettes (OR=6.05, 95% CI, 462–7.92), no lifetime use of nicotine replacement products,	Our data also suggest that e-cigarette use is associated with unsuccessful rather than successful smoking cessation, which should be verified in additional, longitudinal, studies.

Study reference	Study objectives	Survey name	Country/ location	Year data collected	Participants (n)	Age (years) M±SD	% female	Recruitment method	Response rate (%)	Findings	Conclusion
										no exposure to environmental tobacco, and no cannabis use.	
Filipidis 2018	To identify changes in use of smoking cessation assistance in the European Union (EU) and factors associated with use of cessation assistance.	Eurobaro meter 2012, 2017	Europe	2012, 2017	2012: 9921 2017: 9489	>15 years	NR	Multistage probability sample of European countries.	NR	Researchers adjusted for socio-demographic characteristics. The use of any self-reported smoking cessation assistance decreased in the EU between 2012 and 2017.	The use of established aids such as pharmacotherapy have become less popular, while e-cigarettes as a potential cessation or switching method has grown between 2012 and 2017.
Giovenco 2018	To describe patterns of e-cigarette use between smokers who have quit and those who are currently smoking, and examine e-cigarette use as an independent correlate of population smoking cessation after controlling for other factors known to predict quitting.	NHIS	USA	2014-2015	15532	18-24: 11.8% 25-34: 22.8% 35-44: 19.2% 45-64: 36.1% 65+: 10.2%	46.40%	Complex, multistage probability design.	NR	The prevalence of being quit was significantly higher among daily e-cigarette users compared to those who had never used e-cigarettes [52.2% vs. 28.2%, aPR: 3.15 (2.66, 3.73)]... Relationships held even after accounting for making a quit attempt and use of other tobacco products. Notably, over half of daily e-cigarette users (52.2%) quit smoking in the last 5 years, a higher prevalence than any other demographic or behavioural subgroup. Across all four sample restrictions, daily e-cigarette use was consistently the strongest independent correlate of smoking cessation.	Among those with a recent history of smoking, daily e-cigarette use was the strongest correlate of being quit at the time of the survey, suggesting that some smokers may have quit with frequent e-cigarette use or are using the products regularly to prevent smoking relapse.
Gorini 2017	This study explored e-cigarette use as an aid to quit smoking and compared abstinence rates for different quitting methods.	PASSI	Italy	2014-2015	6112	18-34: 36% 35-49: 35% 50-69: 29%	43.9	Randomly sampled residents with an available telephone number and capable of being interviewed. Stratified to represent population. Included adults who smoked and made at least one quit attempt in the previous 12 months.	83% 2014; 82% 2015	11% used e-cigarettes only, 86% no aid, 3% other quitting methods. Smoking abstinence was reported among 9% of those using no aid; 8% of e-cigarette users; 15% of those using other methods. No significant differences in abstinence were observed for e-cigarette users compared with those reporting no aid (adjusted Prevalence Ratio [aPR]=0.81; 95%Confidence Interval (CI) =0.58–1.14). Changing the reference group to e-cigarette users, those using other quitting methods were significantly	One out often smokers who attempted to quit in 2014–2015 in Italy used e-cigarettes. E-cigarettes users were as likely to report abstinence as those using no aid, but were less likely to report abstinence than users of established quitting methods.

Study reference	Study objectives	Survey name	Country/ location	Year data collected	Participants (n)	Age (years) M±SD	% female	Recruitment method	Response rate (%)	Findings	Conclusion
										more likely to report abstinence than e-cigarette users (aPR=1.76; 95%CI=1.07–2.88).	
Gucht 2017	This study aimed to provide an answer to the question: What is the typical profile of the (Dutch or Flemish) online vape shop customer?	Own survey	Netherland online store (European customers)	Dec 2015-Jan 2016	203	46±12.5	42.9	All customers who made a purchase through an online vape shop over 1 month were contacted to be involved in an online survey.	16	Almost everyone (99%, 95% CI 0.96, 1.00) smoked before they started vaping. A great majority agreed that unlike with other smoking-cessation aids, they could quit smoking (81%, 95% CI 0.79, 0.90) due to vaping. Vapers indicated that they were/are mainly using e-cigarettes to quit smoking (73.3%, 95% CI 0.67, 0.79), because it is healthier than smoking (57.4%), because of financial reasons (27.7%), to decrease their tobacco cigarette consumption (16.9%), because smoking is prohibited in several contexts (15.9%), and out of curiosity (14.4%).	Findings are similar to those obtained in other vape shop studies, but also to the results of convenience samples of less-well-defined populations.
Hirano 2017	We conducted an online survey to collect information on tobacco use, difficulties in smoking cessation, socio-demographic factors, and health-related factors in Japan.	Own survey	Japan	2015	798	20-29: 12.4% 30-39: 22.2% 40-49: 23.8 50-59: 22.7 60-69: 18.9%	33.3	Via a commercial research provider to ensure a representative sample. Conducted survey online.	8.5	E-cigarette use was negatively associated with smoking cessation (odds ratio (OR)=0.632; 95% confidence interval (CI)=0.414–0.964) after adjusting for gender, age, health-related factors, and other quitting methods. Conversely, smoking cessation therapy (i.e. varenicline) was significantly associated with smoking cessation (OR=1.885; 95% CI=1.018–3.492).	For effective smoking cessation, e-cigarette use appears to have low efficacy among smokers in Japan.
Kulik 2018	In 2016–2017, the relationship between e-cigarette use and having stopped smoking among ever (current and former) smokers was assessed in the European Union and Great Britain by itself.	Eurobaro meter survey	European Union and Great Britain	2014	12608	49.9±16.8	44.4	Multistage probability sample, weighted. Home-based interviews. Analysed data from current or former smokers.	NR	In unadjusted models, daily use (OR=0.42, 95% CI=0.31, 0.56); occasional use (OR=0.25, 95% CI=0.18, 0.35); and experimentation (OR=0.24, 95% CI=0.19, 0.30) of nicotine e-cigarettes were associated with lower odds of being a former smoker compared with having never used nicotine-containing e-cigarettes. Comparable results were found	These results suggest that e-cigarettes are associated with inhibiting rather than assisting in smoking cessation. On the population level, the net effect of the entry of e-cigarettes into the European Union (and Great Britain) is associated with depressed smoking

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Study reference	Study objectives	Survey name	Country/ location	Year data collected	Participants (n)	Age (years) M±SD	% female	Recruitment method	Response rate (%)	Findings	Conclusion
										in adjusted models. Results were similar in Great Britain alone.	cessation of conventional cigarettes.
Levy 2017	This study examines the role of e-cigarettes in quit attempts and 3-month cigarette abstinence using a large, recent nationally representative US sample.	Tobacco Use Supplement-Current Population Survey (TUS-CPS)	USA	2014-15	21226	18-21: 2.4% 22-25: 6.1% 26-29: 7.4% 30-34: 10.7% 35-44: 18.9% 45-64: 42.2% 65+: 12.5%	50.2	A probability sample employs stratified clusters of households drawn from an initial sampling frame that covers the civilian, non-institutionalized population.	NR	Having made a quit attempt was more likely among smokers using e-cigarettes than non-users. Among those making at least one quit attempt, quit success was lower among ever users, but higher among those with at least 5 days use of e-cigarettes in the last month. A negative relationship was obtained between quit success and e-cigarette ever use, but a positive relationship was observed with current e-cigarette use measures. Moreover, the AOR of quit success was 59% higher with 5+ days use and 181% higher with 20+ days use.	Both quit attempts and quit success were positively associated with increased frequency of e-cigarette use. Frequency of e-cigarette use was important in gauging the nature of these relationships.
O'Connor 2017	This study examined correlates of smoking self- and felt-stigma and discrimination, among current smokers.	Own survey	USA	2015	1528	14-17: 5.4% 18-25: 4.2% 26-35: 38.6% 36-45: 22.5% 46-55: 16.5% 56+: 12.8%	43	Recruited through a national commercial consumer panel. Web-based survey.	NR	Self-stigma was significantly associated with higher intent to quit in the next 6 months and in the next 30 days, relative to no intention to quit, as well as having made 1 or 2 quit attempts in the past year or 3 or more quit attempts and associated with daily e-cigarette use (OR D 1.73, p<0.05). Felt-stigma was positively associated with intent to quit in the next 30, having made 3 or more quit attempts in the past year, and both daily (OR D 2.05,	Smokers who reported greater feelings of stigmatization about their smoking were more likely to report having made recent quit attempts, report a stronger intention quit smoking in the future, and report use of e-cigarettes, suggesting that feelings of self- and felt-stigmatization are related to greater motivation to stop smoking.

Study reference	Study objectives	Survey name	Country/ location	Year data collected	Participants (n)	Age (years) M±SD	% female	Recruitment method	Response rate (%)	Findings	Conclusion
										p<0.05) and some-day (OR D 1.30, p<0.05) e-cigarette use.	
Phung 2017	This study examined the use of smoking cessation agents, including nicotine replacement products and prescription medications, in a sample of smokers in the city of Winnipeg.	Own survey	Winnapeg, Canada	2015	180	26-55: 63%	48.9	Approached with paper-based survey in a pharmacy.	30.7	The product most commonly used by current smokers was nicotine gum (16.3%). Use of electronic cigarettes was reported by 14.7% of users, nicotine patches by 10.8% and varenicline by 7.6%; none of the participants reported use of bupropion or nicotine inhalers. While 25.6% of all responders felt that none of the smoking cessation methods were effective, electronic cigarettes were rated as the preferred method (97.2%) by those who had tried them.	Smokers wanting to quit undergo many attempts. Pharmacists should assume a key role in reaching out to smokers.
Rodu 2017	This report describes the quit methods used in the past 12 months by current and former smokers in the baseline Population Assessment of Tobacco and Health (PATH) Study during 2013–2014.	Population Assessment of Tobacco and Health (PATH) Study	USA	2013-14	16321	NR	NR	Representative population sample as per PATH protocol. Interviews of non-institutionalised American's.	NR	Unaided quit attempts were the most common; the number was almost as high as all single methods combined (n=1797 and n=1831 respectively). The most frequently used single method was help from friends and family (n=676) followed by e-cigarettes (n=587). Use of e-cigarettes was the only method with higher odds of users being a former smoker than unaided attempts (OR=1.42, 95% CI 1.12–1.81). Current use of e-cigarettes among current (34%) and former (54%) smokers was significantly higher than current	In 2013–2014 e-cigarettes were used by American adult smokers as quit-smoking aids more frequently than NRT products or prescription drugs.

Study reference	Study objectives	Survey name	Country/ location	Year data collected	Participants (n)	Age (years) M±SD	% female	Recruitment method	Response rate (%)	Findings	Conclusion
										use of nicotine replacement therapy (NRT).	
Serpen 2017 (conference abstract only)	To analyse the associated behaviour and patterns of e-cigarette usage among patients with IBD.	Own survey	USA	NR	27	NR	NR	Used a retrospective database of smoking behaviours in an IBD population. Phone questionnaire and medical record audit.	67.5	Current e-cigarette users, however were less likely to be current smokers (0% versus 50%, p=0.0261). Current e-cigarette users tended to use e-cigarettes for a longer duration of time (34 versus 6 mo, p=0.0355) with fewer times per day (6 versus 12.5) and a lower nicotine content (3 versus 11 mg/mL). Use of e-cigarettes was found to reduce cravings for regular cigarettes in 21 of 27 people but sustained smoking cessation was only seen in 17 of the 27.	E-cigarette users experienced a lessened craving for regular cigarettes while using e-cigarettes but did not experience significance in sustained smoking remission.
Simonaviciu s 2017	The aim was to assess factors associated with ongoing e-cigarette use and discontinuation among smokers.	ASH Smokefre e GB surveys	Great Britain	2016	12157	NR	NR	Online survey of smokers in UK.	NR	Current dual users were more motivated to stop smoking than past users (AOR=1.95, 95% CI: 1.10-3.46); never users' or past triers' motivation did not differ from past users'. Dual users were less dependent on cigarettes (AOR=0.54, 95% CI: 0.35–0.86) and more likely to use e-cigarettes as an aid to reduce smoking (AOR=2.40, 95% CI: 1.59–3.64) and to deal with smoking restrictions (AOR=2.03, 95% CI: 1.22–3.38) than past users.	Among smokers, ongoing use of e-cigarettes is associated with reasons for reducing smoking and dealing with smoking restrictions, heightened motivation to stop smoking, and lower dependence on smoking.
Stokes 2018	We examined e-cigarette use in adults aged 18 to 89 years with a history of CVD, using data from the 2014	NHIS 2014	USA	2014	4966	NR	53.2	Nationally representative sample. Participants included in this survey were diagnosed with CVD.	NR	There was increased odds of ever (OR=1.70 (95% CI, 1.25, 2.30)) and current (OR=1.97; 95% CI, 1.32, 2.95)) e-cigarette use among smokers who had attempted to quit in the past year.	Individuals with CVD who recently quit smoking or reported a recent quit attempt were significantly more likely to use e-cigarettes than current

Study reference	Study objectives	Survey name	Country/ location	Year data collected	Participants (n)	Age (years) M±SD	% female	Recruitment method	Response rate (%)	Findings	Conclusion
	National Health Interview Survey										smokers and those who did not report a quit attempt.
Sung 2018	The objective of this study was to identify the relationship between e-cigarette use and smoking cessation among South Korean adult smokers.	Korea National Health and Nutrition Examinati on Survey	South Korea	2013-15	2965	19-29: 14.1% 30-39: 21.7% 40-49: 23.0% 50-59: 19.4% 60-64: 7.4% ≥65: 14.2%	14.5	Nationally representative sample of Koreans.	NR	Adult smokers who had not used e-cigarettes were more likely to attempt to quit smoking than those who had used e-cigarettes in the pre-matching (OR=1.58; 95% CI=1.18-2.12) and post-matching (OR=1.62; 95% CI=1.08-2.44) samples.	This study suggests that e-cigarette use among South Korean adult smokers was not related to smoking cessation.
Sussan 2017	The goal of our current study was to investigate behaviours, perceptions, and motivations underlying the use of ECs in adults.	Own survey	USA	2014-15	320	18-24: 18% 25-34: 40% ≥35: 42%	22	Through online recruitment or in vape shops in Baltimore.	NR	For former and current smokers, the primary motivation for EC use was assistance to quit smoking, and nearly half indicated that they plan to reduce their nicotine concentration and eventually quit using ECs.	These responses provide insight into the underlying thoughts and behaviours of smoking and non-smoking EC users and also suggest that never smoking EC users are an emerging demographic with different motivations and perceptions than those of current and former smokers.
Wong 2018	This study focuses on the adolescent group in China and examines their perception and use of e-cigarettes and the association with smoking abstinence.	Own survey	China	2015	2042	ages 15-18	16.45	Recruited participants through mobile app to answer survey.	NR	Chinese adolescents picked up e-cigarettes because they wanted to avoid the harm of cigarettes (44.63%), or to avoid the second hand harm of smoking to others (26.30%), or they expected e-cigarettes to help quit smoking (24.26%). Meanwhile, a significant portion of the respondents used e-cigarettes because they thought it was fashionable to do so (15.37%) or simply because they were curious of e-cigarettes (25.56%). Among the 192 former smokers or those who had successfully quit, 17.19% used patches, 13.54% used e-cigarettes, and 69.72%	E-cigarettes are widely known and quite popular among Chinese adolescents. However, the association between e-cigarette use and smoking cessation deserves further examination until a clearer picture is revealed.

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Study reference	Study objectives	Survey name	Country/ location	Year data collected	Participants (n)	Age (years) M±SD	% female	Recruitment method	Response rate (%)	Findings	Conclusion
										used other methods to help quit.	
Zhu 2017	To examine whether the increase in use of electronic cigarettes in the USA, which became noticeable around 2010 and increased dramatically by 2014, was associated with a change in overall smoking cessation rate at the population level.	US Current Population Survey-Tobacco Use Supplement	USA	2001-02, 2003, 2006-07, 2010-11, 2014-15	Ranged between 23270 - 163 920 depending on survey and question analysed	18-24: 6.6% 25-44: 32.8% 45-64: 36.8% ≥65: 23.8%	55.4	Via Census	64.0%, 63.6%, 62.0%, 61.2%, and 54.2% for 2001-02, 2003, 2006-07, 2010-11, and 2014-15, respectively.	E-cigarette users were more likely than non-users to attempt to quit smoking, 65.1% v 40.1% (change=25.0%, 95% confidence interval 23.2% to 26.9%), and more likely to succeed in quitting, 8.2% v 4.8% (3.5%, 2.5% to 4.5%). Recent quitters had the highest ever use rate, 49.3%, compared with current smokers (38.2%) and never smokers: 2%	The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level.

Table 13: Longitudinal smoking cessation studies: characteristics

Study reference	Study objectives	Selection method	Inclusion criteria	Year of data collection	Participants (n)	Female (%)	Age M±SD
			Study Population				
Berry 2018	To investigate the associations between e-cigarette initiation and cigarette cessation/ reduction in the USA.	Used data from the PATH study (Population Assessment of Tobacco and Health), a nationally representative random sample.	The current analysis was restricted to adults 25 years and older who were current established tobacco cigarette smokers but not current e-cigarette users at wave 1.	2013-14, 2014-15	5124	45	25-34: 28.1% 35-44: 22.7% 45-54: 23.2% 55-64: 18.1% 65-74: 6.5% ≥75: 1.5%
Brikmanis 2017	To investigate perceptions of e-cigarettes, cigarette smoking intentions, and their associations with e-cigarette use over time.	Recruited from community.	Monthly cigarette smoking for 6 months, never having smoked daily for one month or more, California residency and own a smartphone or have regular internet access.	2015-16	408	43	20.5 ±1.8
Caraballo 2017	To quantify the prevalence of 10 quit methods commonly used by adult cigarette smokers.	Probability sample of residential mailing addresses, covering approximately 95% of all US households.	Current smoker.	2014-16	15943	48.7	35-54: 36.9%
Curry 2017	To describe the association between use of e-cigarettes before and after cessation treatment and tobacco abstinence at 12 months.	Appalachian smokers enrolled in a community-based tobacco dependence treatment trial.	Age≥ 18, daily use of combustible tobacco, resident of a participating county, no contraindication to NRT, if female, non-pregnant, willing to participate in study protocol, and provision of written informed consent.	2012-13	217	76.7	25-54: 53.5%
Etter 2017	We assessed change in vaping and smoking behaviours over 12 months in regular vapers.	Posted a questionnaire on website: Stop-Tabac.ch	>18yrs, used e-cigarettes.	2012-16	3868	42	41±NR
Pasquereau 2017	To assess whether regular use of e-cigarettes while smoking is associated with subsequent smoking cessation.	Recruited from internet in order to assess success of internet campaign. Weighted responses to reflect population.	NR	2014-15	2057	45.9	15-24: 18.1% 25-34: 23.8% 35-49: 34.8% 50-85: 23.4%
Pulvers 2018	To better understand the risk–benefit ratio of ECs, more information is needed about net nicotine consumption and toxicant exposure of cigarette smokers switching to ECs.	Using flyers, internet postings, and newspaper advertisements seeking smokers with a statement that "free electronic cigarettes and $100 would be provided for qualified smokers' participation in a research study."	Interested in switching to ECs but not necessarily quitting smoking.	2015	40	27	30.08±8.82
Rigotti 2018	To determine whether e-cigarette use after hospital discharge is associated with subsequent tobacco abstinence among smokers who plan to quit and are advised to use evidence-based treatment.	Secondary analysis of data from a clinical trial. Recruited hospitalised cigarette smokers. Clinical trial randomised participants to receive FDA approved tobacco medication and 5 telephone calls OR recommended them to contact a free quitline.	Hospitalized adult cigarette smokers who planned to stop smoking.	2012-15	1357	50.5	E-cigarette users: 49±12 E-cigarette non-users: 52 ±12

		Study Population					
Study reference	Study objectives	Selection method	Inclusion criteria	Year of data collection	Participants (n)	Female (%)	Age M±SD
Selya 2017	We examined whether e-cigarette use predicted future conventional smoking behaviour among youth who reported using e-cigarettes to help them quit smoking.	Through schools in the Chicago area.	9th and 10th graders, qualifying as novice smokers (smoked <100 cigarettes/lifetime) and light smokers (smoked >100 cigarettes/lifetime and smoked within the past 30 days, but smoked ≤5 cigarettes/day), as well as random samples of non-smokers, were invited to participate (N=3654).	NR	1263	86.90	23.6
Subialka Nowariak 2018	This study looks at the relationship between e-cigarette use frequency and abstinence among a sample of treatment-seeking tobacco users.	Through quit lines.	NR	2013-14	2760	57.9	18-24: 7.8% 25-34: 18.5% 35-44: 17.1% 45-54: 24.6% 55-64: 21.7% 65+: 10.2%
Truman 2018	This paper reports the results of an electronic survey of vapers in New Zealand, a country where the sale and supply of e-liquids containing nicotine is illegal, although vapers can legally access e-liquids from overseas.	Online recruitment using vaper and smoking cessation networks.	NR	2016	118	30	<20: 2% 20–30: 40% 31–40: 28% 41–50: 21% 51–60: 37% >60: 55%
Valentine 2017	To examine impact of e-cigarette use on combustible tobacco use as well as on the readiness to quit smoking and changes in nicotine dependence in a multi-morbid population.	Recruited from within the Department of Veterans Affairs (VA) Connecticut Healthcare System by word of mouth.	Military Veteran Smokers receiving psychiatric services, without intention to immediately stop smoking (30 days), smoking history of ≥5 cigarettes/d. Exclusion: untreated medical or psychiatric and/or substance use disorders as determined by a review of the veteran's electronic medical record, current use of nicotine replacement or other cessation pharmacotherapies, and use of e-cigarettes or smokeless tobacco products for more than 2 of the past 30 days.	NR	50	7	56.9±8.0
Yong 2018	To investigate the effects of ever use of electronic cigarettes (ECs), many of which lack nicotine, on abstinence from convention cigarettes among Hong Kong adult smokers.	Used data from the Quit to Win contest, a competition with incentives and social support to promote abstinence from cigarettes.	Smokers who were residents of Hong Kong, aged 18 or above, able to communicate in Cantonese, and not involved in other smoking cessation programs were recruited. Excluded light smokers.	2014-15	956	18.2	28 - 55

Table 14: Longitudinal smoking cessation studies: outcomes

Study reference	Survey description	Outcome	Follow-up (months)	Country/ region	Conclusion statement
Berry 2018	Data was collected on age, sex, race/ethnicity, household income, education, region, cigarette use, e-cigarette use, quit attempts, successful quit attempts.	Between waves 1 and 2, 6.9% of cigarette smokers who were not current e-cigarette users transitioned to former smokers. After adjusting for covariates, cigarette smokers who initiated e-cigarette use between waves and reported they used e-cigarettes daily at wave 2 had 7.88 (95% CI 4.45 to 13.95) times the odds of 30-day cigarette cessation compared with non-users of e-cigarettes at wave 2. Cigarette smokers who began using e-cigarettes every day and did not achieve cessation had 5.70 (95% CI 3.47 to 9.35) times the odds of reducing their average daily cigarette use by at least 50% between waves 1 and 2 compared with e-cigarette non-users.	12	USA	Daily e-cigarette initiators were more likely to have quit smoking cigarettes or reduced use compared with non-users. However, less frequent e-cigarette use was not associated with cigarette cessation/reduction.
Brikmanis 2017	Participants reported e-cigarette use over the past 14 days at baseline, and for the past 9 days at 3, 6, and 9 months.	Intent to quit smoking cigarettes and intent to maintain smoking were unrelated to e-cigarette frequency. The remaining cigarette intent items, including intent to maintain or increase over the next year (d =0.06, z =1.02, p=0.307), intent to quit over the next month (d=-0.07, z =-1.25, p=.210), and intent to quit over the next year (d=-0.09, z=-1.41, p=.158) were in the expected direction but not significant.	9	USA	Findings suggest e-cigarettes may be more often used to supplement cigarette smoking. Including e-cigarettes under smoking restrictions and educating young adults about potential long-term consequences may help prevent and reduce e-cigarette use.
Caraballo 2017	Assessed smoking cessation attempts, methods and smoking habits.	Overall, 74.7% of adult current cigarette smokers used multiple quit methods during their most recent quit attempt (Table 1). Giving up cigarettes all at once (65.3%) and gradually cutting back on cigarettes (62.0%) were the most commonly used methods to try to quit, followed by substituting some cigarettes with e-cigarettes (35.3%), using a nicotine patch or gum (25.4%), switching completely from cigarettes to e-cigarettes (24.7%), and switching from "regular" cigarettes to "mild" cigarettes (20.4%). Quit methods used less often were getting help from a doctor or other health professional (15.2%), using smoking cessation medications approved by the US Food and Drug Administration (FDA) (12.2%), and getting help from a website (7.1%) or a telephone quitline (5.4%).	24	USA	Giving up cigarettes all at once (65.3%) and reducing the number of cigarettes smoked (62.0%) were the most prevalent methods. Substituting some cigarettes with e-cigarettes was used by a greater percentage of smokers than the nicotine patch, nicotine gum, or other cessation aids approved by the US Food and Drug Administration.
Curry 2017	Six counties each were randomly assigned to one of two treatment conditions: face-to-face counselling or referral to the Ohio Tobacco Quitline. Both treatment conditions included standardized cognitive-behavioural counselling and free NRT (daily 21 mg patch for 8 weeks) as recommended by the US Public Health Service. While the aim of the trial was to assess treatment methods, none of the main treatment methods were e-cigarettes.	Four times as many participants who reported no use of e-cigarettes post-treatment were tobacco abstinent at 12 months, as compared to those who used post-treatment (19.0% vs. 4.7%, p=0.021). This difference corresponded to an odds ratio of 0.21 comparing those who used post-treatment to those who did not use post treatment (95% CI: 0.048, 0.906). As compared to baseline and posttreatment never users (referent), participants who reported baseline use but no post-treatment use had lower odds of 12-month abstinence (OR=0.834; 95% CI 0.265, 2.629). Those who reported use at baseline and post-treatment, as well those who used e-cigarettes at post-treatment only, had lower odds of 12-month abstinence compared to never e-cigarette users (OR=0.298; 95% CI 0.038, 2.359 and OR=0.155; 95% CI 0.020, 1.184, respectively).	12	USA	Among adult Appalachian smokers enrolled in community-based tobacco cessation treatment, use of e-cigarettes post-treatment was associated with lower abstinence rates at 12 months.
Etter 2017	Assessed: e-cigarettes use; reasons to vape; perceived difficulty to stop vaping; addiction to e-cigarette; strength and frequency of urges to vape; Smoking	In exclusive vapers (ex-smokers), nicotine concentration in e-liquids decreased over time (from 12 to 9 mg/mL), but puffs/day remained stable (200 puffs/day). After 12 months, 9% of 687 former smokers relapsed to smoking and 28% of 64 daily smokers (dual users) stopped smoking. After 12 months, when participants stopped vaping, they tended to relapse to smoking (+18% daily	12	Switzerland	After 12 months, enjoyment and relapse prevention were the most important reasons to vape. Rates of relapse to smoking were low in former smokers and quit rates were high in

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Study reference	Survey description	Outcome	Follow-up (months)	Country/ region	Conclusion statement
	behaviour; Tobacco withdrawal symptoms and body weight.	smokers among those who stopped vaping versus -2% in permanent vapers, p<0.001). When ex-smokers relapsed to smoking, they tended to stop vaping.			current smokers. Stopping vaping was associated with relapsing to smoking.
Pasquereau 2017	The three outcomes assessed at 6 months were: a minimum 50% reduction in the number of cigarettes smoked per day, quit attempts of at least 7 days and smoking cessation of at least 7 days at the time of follow-up.	Baseline dual users were more likely than baseline exclusive tobacco smokers to have halved cigarette consumption [25.9 versus 11.2%, p<0.001, adjusted odds ratio (aOR)=2.6, confidence interval (CI)=1.8– 3.8]. Dual users at baseline were also more likely to have made a quit attempt of at least 7 days (22.8 versus 10.9%, p<0.001, aOR=1.8, CI=1.2–2.6). No significant difference was found for 7-day cessation rates at 6 months (12.5 versus 9.5%, p=0.18, aOR=1.2, CI=0.8–1.9).	6	France	Among people who smoke, those also using an e-cigarette regularly are more likely to try to quit smoking and reduce their cigarette consumption during the next 6 months. It remains unclear whether regular e-cigarette users are also more likely to stop smoking.
Pulvers 2018	4-week observational study and provided an e-Go C non-variable battery and refillable atomizers and choice of eight flavours in 12 or 24 mg nicotine dosage. Measurement of urinary cotinine (metabolite of nicotine), 4-(methylnitrosamino)-1-(3pyridyl)-1-butanol (NNAL; a pulmonary carcinogen), and eight volatile organic compounds (VOCs) that are toxic tobacco smoke constituents was conducted at baseline and week 4.	All participants with follow-up data (92.5%) reported using the study EC. Of the 40 smokers, 16 reported no cigarettes at week 2 (40%) and six continued to report no cigarettes at week 4 (15%). Change in nicotine intake over the 4 weeks was non-significant (p=0.90). Carbon monoxide (p<0.001), NNAL (p<0.01) and metabolites of benzene (p<0.01) and acrylonitrile (p=0.001) were significantly decreased in the study sample. Smokers switching exclusively to ECs for at least half of the study period demonstrated significant reductions in metabolites of ethylene oxide (p=0.03) and acrylamide (p<0.01).	1	San Diego, USA	Smokers using ECs over 4 weeks maintained cotinine levels and experienced significant reductions in carbon monoxide, NNAL, and two out of eight measured VOC metabolites. Those who switched exclusively to ECs for at least half of the study period significantly reduced two additional VOCs.
Rigotti 2018	Data collected: demographic factors (age, sex, race/ethnicity, and education), health insurance status, nicotine dependence (number of cigarettes per day and time to first cigarette after awakening [19]), prior use of tobacco cessation treatment, perceived importance of and confidence in quitting (5point Likert scales), post discharge intention to quit (plan to remain abstinent vs. plan to try to remain abstinent), presence of another smoker at home, screening for alcohol abuse (Alcohol Use Disorders Identification Test), illicit drug use in the past 30 days, and depression and anxiety symptoms (Patient Health Questionnaire-4 [PHQ-4]). Also collected saliva sample for cotinine test and CO testing if using nicotine replacement therapies or e-cigarettes.	75% follow-up rate. Used propensity score matching to compare e-cigarette use and smoking cessation. Found that those who used e-cigarette within the first 3 months were less likely to be biochemically abstinent at 6 months than those not using e-cigarettes (10.1% vs. 26.6%; risk difference, -16.5% [95% CI, -23.3% to -9.6%]).	1, 3, 6	USA	During 3 months after hospital discharge, more than a quarter of smokers attempting to quit used e-cigarettes, mostly to aid cessation, but few used them regularly. This pattern of use was associated with less tobacco abstinence at 6 months than among smokers who did not use e-cigarettes.
Selya 2017	Surveyed over 4 years. Nicotine dependence was measured using a version of the Nicotine Dependence Syndrome Scale (NDSS)31which was adopted for use in adolescent smoker. Quit attempts were self-reported as a binary (yes/no) variable at each wave.	For those who used e-cigarettes in a cessation attempt, the frequency of e-cigarette use was not associated with reductions in future conventional smoking frequency.To compare the use of e-cigarettes as a quit aid with other methods of quitting, follow-up VCMs were run examining the nicotine dependence varying effects of (1) seeking support from a cessation group, Internet, or phone resource; (2) using a prescription (Zyban or Chantix), (3) using an herbal strategy; and (4) using nicotine replacement products (all reported at the 5-year follow-up wave) on future smoking frequency (data not shown). Of these methods, only nicotine replacement products were significantly associated with later reductions in smoking frequency (by up to 11	48	Chicago, USA	These findings offer possible support that e-cigarettes may act as a smoking reduction method among highly nicotine-dependent young adult cigarette smokers. However, the opposite was found in non-dependent smokers, suggesting that e-cigarette use should be discouraged among novice tobacco users. Additionally, although a substantial proportion of young adults used e-cigarettes to help them quit smoking, these self-initiated quit attempts with e-cigarettes were

Study reference	Survey description	Outcome	Follow-up (months)	Country/ region	Conclusion statement
		fewer days smoked out of the past month) and only among those with the highest levels of nicotine dependence (NDSS>3.7).			not associated with future smoking reduction or cessation.
Subialka Nowariak 2018	Seven-month follow-up survey data from N= 2760 treatment-seeking tobacco users who utilized statewide tobacco quitlines in three states were used to assess the relationship between 30-day point prevalence abstinence and e-cigarette use frequency at follow-up. E-cigarette use was examined in two ways. First, we looked at any use in the past 30 days versus no use. Additionally, past 30-day e-cigarette use frequency was categorized into four groups: 0 days, 1–5 days – infrequent, 6–29 days – intermediate, 30 days – daily. Logistic regression models were constructed predicting 30-day point prevalence tobacco abstinence.	Any past 30-day e-cigarette use at follow-up had a lower quit rate than those who did not use e-cigarettes in the past 30 days (AOR=0.63; p= 0.001). The AOR was similar to the unadjusted OR (OR=0.64, p<0.001). Further adjustment (infrequent vs intermediate e-cigarette use) daily e-cigarette use (AOR=1.16; p=0.453) compared to no e-cigarette use was not associated with quit status. Both infrequent (AOR=0.35; CI=0.20–0.59) and intermediate (AOR=0.50; CI=0.32–0.80) past 30-day e-cigarette use were associated with lower rates of tobacco abstinence versus no past 30-day use. However, daily e-cigarette users (AOR=1.16; CI=0.71–1.70) had similar 30-day abstinence when compared to non-users. Controlled for: age, gender, level of education, tobacco type, advice from a health professional, a combined state-program variable, and stop-smoking medication use post-enrolment.	7	USA	Results from this study of treatment-seekers support findings from studies of general population tobacco users that suggest frequency of e-cigarette use is an important moderating variable in the relationship between e-cigarette use and tobacco cessation.
Truman 2018	Conducted surveys online, with follow-up surveys at 1 and 2 months.	The majority of participants (159, 73%) were smokers when they started vaping, and now only vaped. One had subsequently stopped vaping. All considered that their vaping and their stopping smoking were related. The majority (79%) said that they had used vaping to help them stop smoking. Twenty (12%) reported that they had not intended to stop smoking when they started to vape. The remainder had used vaping to avoid relapse to smoking.51 vaping participants (23%) reported some smoking during the course of these surveys indicating that they were both vaping and smoking. Two of these came from the ex-smoker group. Of these 51, 34 (67%) only smoked occasionally (less than once a day).	1 or 2 (varied)	New Zealand	Vaping had resulted in effective smoking cessation for the majority of participants.
Valentine 2017	Participants were provided with a study e-cigarette they could use ad libitum along with other tobacco products and were encouraged to attend weekly laboratory visits and a one-month follow-up visit.	Mean e-cigarette use was 5.7 days per week and only 9% of participants used the e-cigarette for fewer than 4 days per week. Significant reductions in breath CO (9.3 ppm to 7.3 ppm, p<0.02) and CPD (from 16.6 to 5.7, p<0.001) were observed across study weeks, and no serious adverse events were reported. Three participants (10% of completers) reported smoking cessation that was corroborated biochemically.	1	USA	E-cigarettes are acceptable to smokers with psychiatric comorbidities, as indicated by sustained and frequent e-cigarette use by 90% of participants, and may promote reduction and/or cessation of combustible cigarette use. E-cigarettes appear to be a viable harm reduction modality in smokers with psychiatric comorbidities.

Study reference	Survey description	Outcome	Follow-up (months)	Country/ region	Conclusion statement
Yong 2018	Data collected on e-cigarette use, smoking behaviours, quit attempts and sociodemographic status. Also measured quit status using a salivary cotinine test.	Ever e-cigarette use at baseline did not predict self-reported PPA (AOR 0.99, 95% CI 0.57–1.73), biochemically validated quitting (AOR 1.22, 95% CI 0.64–2.34), cessation attempt (AOR 0.74, 95% CI 0.48–1.14), or smoking reduction (AOR 0.89, 95% CI 0.54–1.47). E-cigarette use during the first 3 months did not predict quitting (AOR 1.02, 95% CI 0.22–4.71). Ever e-cigarette users who achieved abstinence at the 6-month follow-up had a low level of nicotine dependence and were readier to quit at baseline than those who had ever used e-cigarette but remained smoking, suggesting that ever e-cigarette use may have little effect on abstinence from conventional cigarette.	6		Hong Kong	We found that ever use of EC, many of which were nicotine-free products, did not predict abstinence from conventional cigarettes among smokers who participated in the QTW contest in Hong Kong and was also not associated with indicators of future successful quitting.

Table 15: Smoking cessation trials: characteristics

Study reference	Study objectives	Country	Study Design				Study population					Inclusion/ Exclusion criteria
			Design type	Duration (wks)	Blinding type	Sampling method	Sample size (enrolled [completers])			Female n(%)	Age Mean (SD)	
							Total	Experimental	Control			
Baldassarri 2018	To establish the feasibility of adding an EC to outpatient tobacco treatment as part of a standard care regimen.	USA	Parallel	24	Double	Recruited from the Yale-New Haven Hospital outpatient pulmonary and primary care clinics, Tobacco Treatment Service, and through referrals from medical providers in the Yale-New Haven Health system.	40 [40]	20 [20]	20 [20]	21 (52.5)	53 (10.1)	Inclusion criteria: Age 18 years or older; Smoking 1 or more tobacco cigarettes per day; Willing to quit smoking. Exclusion criteria: Unstable psychiatric or medical conditions requiring hospitalization within the past 4 months; Acute coronary syndromes or stroke within the past 30 days; History of allergic reactions to adhesives; Women who were pregnant, nursing, or not practicing effective contraception; Current use of an EC for the purpose of stopping tobacco cigarette smoking.
Carpenter 2017	Our general aim was to approximate the real-world scenario in which smokers are exposed to e-cigarette and decide on their own if and how they will use them.	USA	Parallel	21days, then 16 wk f/up	N	Recruited from the local community (south eastern U.S. urban area; approximately 30% non-white) using various media outlets.	68[50]	G1 (16mg nicotine): 25[19] G2 (24mg nicotine): 21[15]	22[16]	41 (60)	NR	(1) age 18+, (ii) current smoker of 5 cigarettes per day (CPD) for 1 year, (iii) no recent history of cardiovascular distress (heart attack in past 3 months, arrhythmia, uncontrolled hypertension), (iv) neither pregnant nor breastfeeding (verified), (v) absence of any major current psychiatric impairment, (vi) current, active use of email, (vii) at least some concern for health effects of smoking (>none at all on a Likert scale), and (viii) not used any ENDS product in the past 6 months, and (ix) never purchased an ENDS product.
Harvanko 2017	To examine the behavioural effects of controlled puffs from a CC (participant's own brand) and EC producing aerosol from commercial solutions containing 0, 8, or 16mg/ml of nicotine following 24 h of smoking deprivation.	USA	Cross-over	NR	Double	Participants were recruited from the community using online advertisements.	9[8]	9[8]	9[8]	3 (33)	NR	Inclusion criteria were smoking an average of 10 or more non-menthol tobacco cigarettes per day for at least one year, breath carbon monoxide (CO) levels of 10 ppmor higher during screening, and not being a regular EC user (defined as daily use of an EC for the past seven days). Individuals were excluded if they expressed interest or engagement in smoking cessation treatment.
Hiler 2017	To determine if liquid nicotine concentration and user experience directly influences outcomes such as plasma nicotine delivery, HR, puff topography, and user subjective effects.	USA	Cross-over	NR	Double	Advertisement and word of mouth	86[64]	31	33	19 (30)	30.6 (9.1)	Eligible: healthy, aged 18-55y. Control: eligible if used e-cigarette for ≥3 months and currently using ≤5 conventional tobacco cigarettes daily, OR using ≥10 tobacco cigarettes/d and <5 e-cigarette uses ever, carbon monoxide sample ≤10 ppm. Exclusion: history of chronic disease or psychiatric condition, regular use of a prescription medication, marijuana use >10d and alcohol use >25 days in the past 30 days, any illicit

Study reference	Study objectives	Country	Study Design				Study population					Inclusion/ Exclusion criteria
			Design type	Duration (wks)	Blinding type	Sampling method	Sample size (enrolled [completers])			Female n(%)	Age Mean (SD)	
							Total	Experimental	Control			
												drug use in the past 30 days and a positive pregnancy test.
Jorenby 2017	To evaluate how experienced dual users used cigarettes and e-cigarettes in real-world use and under different levels of cigarette availability.	USA	Parallel	3.7 (27d)	None	Via point-of-purchase displays at convenience stores in southern Wisconsin and the Milwaukee metropolitan area and through a context-sensitive Facebook ad seeking both smokers and dual users.	148	74	74	73 (49.3)	NR	>18 years; able to read and write English; smoking ≥ 5 cigarettes/d for ≥six months; not currently using any smoking cessation medication; planning to remain in the area for the study duration; no history of psychosis or bipolar disorder; not planning to quit tobacco use in the next 30 days; willing to follow study procedures; and if female, not be pregnant or nursing and willing to use acceptable methods of birth control during the study. Smoke Only group: not have used a single type of alternate tobacco products (e.g., e-cigarettes, snus, or chewing tobacco) >five times in life and not have used alternate tobacco products in the past six months. Dual Use group: used e-cigarettes at least three times/wk for the past three months.
Masiero 2018	To assess the efficacy of the use of e-cigarettes in a tobacco cessation program with a group of chronic smokers voluntarily involved in long-term lung cancer screening.	Italy	Parallel	12	Double	Recruited from long-term cancer screening program for smokers (COSMOS II (Continuous Observation of SMOking Subjects)).	210 [170]	[70]	[70] [70]	78 (37)	62.8 (4.6)	Having smoked at least 10 cigarettes a day for the past 10 years; High motivation to stop smoking; not enrolled in another smoking cessation programme. Exclusion: Severe cardiovascular and respiratory diseases; Use of psychotropic medication; Current or past history of alcohol abuse; Any use of NRTs or e-cigarettes.
Palmer 2018	The primary goal of the present study was to investigate the effects of nicotine and expectancies on cravings to smoke and cravings to vape.	USA	Parallel	1 day	Double	Predominantly from vape shops.	130 [128]	NR	NR	49 (38)	36.4 (13.8)	(1) >18 years old; (2) current e-cigarette users (daily nicotine solution use for >30 days); (3) history of cigarette smoking (>100 lifetime cigarettes; >1 cigarette/day for >30 days); (4) no current e-cigarette cessation attempt; and (5) not currently pregnant, attempting to get pregnant, or nursing.
Perkins 2017 a (study 1)	To compare withdrawal relief effects of nicotine versus placebo e-cigarettes versus no e-cigarette, each after overnight abstinence.	USA	Parallel	3 d	Unclear, at least single blind.	Public notices	28	NR	NR	16 (57.1)	26.5 (6.6)	>18y, smoking history of ≥10 cigarettes/d for >1 year, nicotine dependent (as per Diagnostic and statistical manual of mental disorders (4th ed.)), and no interest in quitting in the next 6 months but also e-cigarette use ≤ once/week.
Perkins 2017 b (study 2)	To explore effects found in study 1 during separate 4-day periods of ad libitum	USA	Cross-over (with 1	2x 4d periods	Unclear, at least single blind.	Public notices	17[12]	17[12]	17[12]	5 (41.7)	29.4 (11.3)	Intention to quit tobacco permanently within next 2 months, >18y, smoking history of ≥10 cigarettes/d for >1 year, nicotine dependent

Study reference	Study objectives	Country	Study Design				Study population					Inclusion/ Exclusion criteria
			Design type	Duration (wks)	Blinding type	Sampling method	Sample size (enrolled [completers])			Female n(%)	Age Mean (SD)	
							Total	Experimental	Control			
	nicotine versus placebo e-cigarette exposure after ≥24 hr abstinence in those who were preparing to quit soon.		wk washout period)									(as per Diagnostic and statistical manual of mental disorders (4th ed.)), taking medications for serious psychological disorders and e-cigarette use ≤ once/week.
Rohsenow 2018	To investigate the effects of asking smokers to switch to e-cigarettes for 6 weeks on smoking, exhaled carbon monoxide (CO) concentration, dependence, and motivation to quit smoking.	USA	Uncontrolled trial	6 wks	Uncontrolled trial.	From community using flyer ads.	18	N/A	N/A	61	45.1±7.8	Smoker, considering cessation, breath alcohol<0.02 g% and negative urine drug screen (other than marijuana) on day of informed consent and baseline assessment; 18–65 years old; report reliable birth control, menopause or past hysterectomy. Exclusion criteria: currently quitting smoking, used cessation products, non-cigarette tobacco or e-cigarettes in the past 30 days, daily use of marijuana, weekly use of marijuana mixed with tobacco, any other illicit drugs in the past 30 days; medications that could reduce smoking, medical contraindications for inhaled nicotine, unstable medical or psychiatric conditions.
Ruther 2018	We monitored blood nicotine levels and smoking urges during the acute phase in volunteers using disposable cigalikes and a tank model e-cigarette and compared them with blood nicotine levels in subjects using a tobacco cigarette.	Germany	Parallel	4 wks	Not blinded, not randomised.	Flyers and internet.	20 [20]	9 [9]	11 [11]	0	Experimental: 28.5 (8.9) Control: 26.2 (6.9)	Healthy male, >18 yrs, routine user of e-cigarettes (e-cigarette group) or smoker for >3 years (cigarette group).

Study reference	Study objectives	Country	Study Design				Study population					Inclusion/ Exclusion criteria
			Design type	Duration (wks)	Blinding type	Sampling method	Sample size (enrolled [completers])			Female n(%)	Age Mean (SD)	
							Total	Experimental	Control			
Tucker 2017	We aimed to: (1) compare self-reported smoking behaviour and e-cigarette use over a period of 2 weeks for the four different nicotine levels; (2) compare subjective effects ratings of e-cigarettes after a 2-week period across nicotine levels; and (3) test if the model from Tucker et al., which predicted simulated demand based on subjective effects, could predict actual e-cigarette use.	New Zealand	Cross-over	4x 2week periods	Unclear, at least single blind	Recruited by community and internet advertisement in two New Zealand cities [Christchurch n=22; Wellington n=13]	40 [35]	40 [35]	40 [35]	12 (26.7)	26.76 (10.6)	Smoked ≥1 cigarette/d and not be: pregnant or breastfeeding, currently using nicotine replacement products or smoking cessation medication, and suffering from any acute or chronic respiratory, cardiovascular, hepatic, or renal disease.
Van Heel 2017	This study examined the impact of four variables pertaining to the use of e-cigarettes (e-cigs) on cravings for tobacco cigarettes and for e-cigarettes after an overnight abstinence period.	Leuven, Belgium	Parallel	2	NR	Recruited through flyers and online advertisements in local community.	81	NR	NR	37 (45.7)	29.8 (13.2)	Smoking ~10 cigarettes/d over past 3 yrs, no experience with vaping, and, in women, not pregnant or breastfeeding. Exclusion: not currently attempting to quit smoking, nor to have the intention to quit smoking in the near future; diabetes, severe allergies, asthma, other airway disorders, psychiatric problems, chemical dependence other than nicotine, high blood pressure or other cardiovascular diseases.

Table 16: Smoking cessation trials: outcomes

Study reference	Control intervention	Experimental intervention	Smoking Outcomes		Effect measure (i.e. quantitative result of trial)	Conclusion statement
			Methods for measuring smoking outcome	Results for smoking outcome		
Balassarri 2018	Both groups given nicotine patches. Control given nicotine-containing e-cigarettes, experimental given nicotine-free e-cigarettes. Encouraged to use e-cigarettes instead of cigarettes. Encouraged to abstain from use of either e-cigarette or cigarettes if possible.		Use of cigarettes and e-cigarettes measured by survey.	No differences in reported cigarette use or abstinence between groups. 15% of all participants were abstinent by the end of the study.	Non-smoker at 24 weeks: overall 17.5% (95%CI: 0.056-1.971), p=0.41	In conclusion, the addition of a 2nd generation EC to outpatient tobacco treatment among tobacco smokers was feasible. Fifteen percent of the subjects were abstinent from tobacco at week 24. Among those who quit smoking, half were still using the EC.
Carpenter 2017	No e-cigarette.	E-cigarette provided to participants. 2 groups: 16mg nicotine or 24mg nicotine. Used ad libitum.	Participants were emailed surveys semi-randomly 3x/d to determine how much they had used the e-cigarette and how many cigarettes they had smoked.	32% of 16mg nicotine group used the e-cigarette daily, vs 60% of the 24mg nicotine group vs 13% of the control. Ave cigarettes smoked per day: 8.4 for 16mg group (30.2% reduction), 5.3 for 24mg group (45.1% reduction), 11.2 for cigarette group (0.7% increase).	30% (16 mg nicotine), 35% (24 mg nicotine), and 5% (control) of participants had reduced their smoking by at least 50% since baseline. At the end of the entire study, respective rates of 50% reduction were 16% versus 47% versus 19% (overall p=0.09).	The results of this small pilot study suggest strong interest and uptake of ENDS among smokers, with favourable perception comparable with that of conventional cigarettes, and trends toward positive changes in cessation-related behaviour.
Harvanko 2017	After 24h of smoking deprivation (verified with breath CO analysis), participants were given 10 puffs of a tobacco cigarette.	After 24h of smoking deprivation (verified with breath CO analysis), participants were given 10 puffs of an e-cigarette with either 0mg, 8mg, or 16mg nicotine.	Withdrawal symptoms (measured on Minnesota Nicotine Withdrawal Scale), smoking urges (Questionnaire of Smoking Urges-Brief), Visual Analog Scale-Smoking Effects and Visual Analog Scale Post smoking to assess smoking or e-cigarette use effects. Also measured cognition.	Cigarette use led to reduction in 'desire or craving to smoke', 'desire for a cigarette right now', 'I am going to smoke as soon as possible.' E-cigarette use did not.	The mixed model for change in total trials on the DSST from before to after cigarette or e-cigarette use during deprivation sessions indicated a significant effect of drug (F[3, 21]=3.18, p=0.045).	No significant reductions in smoking urges were indicated following use of the EC at any nicotine concentration.
Hiler 2017	Experienced e-cigarette users. Abstained from e-cigarette or cigarette for >12hrs (as proven by CO test). Then given 10 puffs of an e-cigarette with 0, 8, 18 or 36mg/mL nicotine (experiment	Naive e-cigarette users. Abstained from e-cigarette or cigarette for >12hrs (as proven by CO test). Then given 10 puffs of an e-cigarette with 0, 8, 18 or 36mg/mL nicotine (experiment	Intention to smoke and anticipation of relief from withdrawal symptoms measured via the modified Hughes-Hatsukami Withdrawal Scale, the Direct Effects of Nicotine Scale, the Direct Effects of e-cigarettes -use Scale, and the 10-item Tiffany-Drobes Questionnaire of Smoking Urges (QSU) Brief.	Results for 'craving', 'depression', 'drowsy', 'sweaty' and 'urge' had larger reductions in higher nicotine conditions. Reductions were significantly larger among e-cigarette experienced individuals compared with e-cigarette naive individuals.		E-cigarettes use also suppressed nicotine/tobacco abstinence symptoms in both groups; the magnitude of abstinence symptom suppression depended on liquid nicotine concentration and user experience.

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Study reference	Control intervention	Experimental intervention	Methods for measuring smoking outcome	Results for smoking outcome	Effect measure (i.e. quantitative result of trial)	Conclusion statement
	conducted 4 times).	conducted 4 times).				
Jorenby 2017	Used only traditional cigarettes. Had 1 week of ad libitum use, then asked to reduce tobacco cigarettes by 75%, then another 1 wk of ad libitum use. Then 3 days of cessation.	Used traditional cigarettes and e-cigarettes. Had 1 week of ad libitum use, then asked to reduce tobacco cigarettes by 75%, then another 1 wk of ad libitum use. Then 3 days of cessation.	Used smartphone app to record product use, craving, and withdrawal symptoms 3 times/d.	Dual users were more able than cigarette-only smokers to achieve brief abstinence from smoking. Women dual users had reduced cravings resulting from smoking reduction and abstinence.	Dual users did not smoke fewer cigarettes than smoke-only participants during ad lib periods, but quadrupled their use of e-cigarettes during smoking reduction periods. Dual users were significantly more likely to maintain 100% reduction (97.1% vs. 81.2%). Amongst women, dual use was associated with higher nicotine levels and withdrawal suppression.	Among a group of experienced dual users, e-cigarettes helped maintain smoking reduction and reduced some withdrawal symptoms, although both withdrawal symptoms and nicotine levels varied as a function of gender.
Masiero 2018	Placebo: Provided with an e-cigarette kit with 0mg/mL nicotine. Told not to use more than 1mL of the e-cigarette liquid/d. Used with cig's for 1 week. Then attempted smoking cessation for 11 wks. Phone counselling every 4 wks. Control: phone counselling every 4 wks.	Provided with an e-cigarette kit with 8mg/mL nicotine. Told not to use more than 1mL of the e-cigarette liquid/d. Used with cig's for 1 week. Then attempted smoking abstinence for 11 weeks. Received telephone counselling every 4 wks.	Measured motivational questionnaire (motivation to quit).	Across study arms, 20% of participants (N=34) stopped smoking at month 3. The percentage was significantly higher in the nicotine (N=15; 25.4%) and nicotine-free (N=13; 23.4%) e-cigarette groups than in the control group (N=6; 10.34%) ($\chi2(2)$=4.899, p=.044). Lower consumption of cigarettes in e-cigarette groups, lowest in nicotine-containing e-cigarette group (but not always statistically significant).		Our findings support the efficacy and safety of e-cigarettes in a short-term period. E-cigarettes use led to a higher cessation rate. Furthermore, although all participants reported a significant reduction of daily cigarette consumption compared to the baseline, the use of e-cigarettes (including those without nicotine) allowed smokers to achieve better results.
Palmer 2018	Participants were told to abstain from e-cigarettes or cigarettes before 3 hours before testing (compliance checked with CO test). Then given either a nicotine-free or a nicotine-containing e-cigarette and told it was either nicotine-free or nicotine-containing (4 conditions; true positive, false positive, true negative, false negative). Allowed 10 puffs over 10 minutes.		Completed craving measures before and after e-cigarette administration.	While there was no main effect of drug (nicotine vs non-nicotine), the 'instructional set' did elicit a significant effect on craving reduction for smoking. I.e. participants told that their e-cigarette contained nicotine had larger craving reductions for smoking regardless of the actual nicotine content. Craving to vape was only reduced in the group told to expect nicotine who actually received a nicotine-containing e-cigarette.	Among current smokers (n=52), the main effect of instructional set was observed on change in craving to smoke as measured by the QSU, $F(1, 44)$=4.21, p=.046, n2= 0.09. Greater craving reduction was found among those told they received nicotine (M=7.92, SD=6.59) than among those told they did not	The results of the present study suggest that nicotine delivery may not be necessary for the acute management of cravings to smoke via vaping. Thus, the possibility of further harm-reduction through the elimination or reduction of nicotine content without sacrificing e-cigarettes' potential efficacy for smoking cessation is promising.

Study reference	Control intervention	Experimental intervention	Smoking Outcomes		Effect measure (i.e. quantitative result of trial)	Conclusion statement
			Methods for measuring smoking outcome	Results for smoking outcome		
					receive nicotine (M=4.25, SD=5.31).	
Perkins 2017 a (study 1)	After overnight smoking deprivation (verified with breath CO analysis), participants had measurements taken and waited 2hrs.	After overnight smoking deprivation (verified with breath CO analysis), participants were given 10 puffs of an e-cigarette containing 0mg/ml nicotine OR 36mg/ml nicotine.	Measured withdrawal before and after e-cigarette use using the Minnesota Nicotine Withdrawal Scale.	Decline in withdrawal was greater in the e-cigarette + nicotine group than the nicotine-free e-cigarette (t(27= 2.17, p<0.005, d=0.41). There was no significant difference between nicotine-free e-cigarette and no e-cigarette (t(27)= 1.50, p=0.14, d=0.28).	A significant main effect of e-cigarette condition on withdrawal was found (F(2, 54)=6.92, p<0.005, np² =.20).	In sum, compared with placebo e-cigarettes, nicotine e-cigarettes can relieve smoking abstinence symptoms, perhaps in a manner similar to Food and Drug Administration–approved nicotine replacement therapy products, although much more research with larger samples is needed.
Perkins 2017 b (study 2)	Given nicotine-containing e-cigarette to use while attempting to abstain from smoking.	Given nicotine-free e-cigarette to use while attempting to abstain from smoking.	Measured withdrawal and cravings. Measured number of days without cigarettes.	Withdrawal and craving were reduced because of nicotine versus placebo e-cigarette use (both p<.05). Number of days quit did not differ between groups and neither did ad libitum e-cigarette use.	There was no difference in number of quit days between e-cigarette + nicotine vs nicotine-free e-cigarette (2.9 ± 0.3 vs. 2.3 ± 0.3), t(82)=1.6, ns.	
Rohsenow 2018	Non-treatment seeking daily smokers (n=18) were given free e-cigarettes and instructed to use them instead of smoking cigarettes for 6 weeks.		Smokers were assessed at baseline, weekly for 6 weeks, and at 8 and 10 weeks for cigarettes/day, e-cigarette use, CO, cigarette dependence, and Contemplation Ladder.	Cigarette dependence scores were a third lower at Weeks 6 (p<0.002) and 10 (p<0.001) than at baseline. Contemplation Ladder scores were higher at Weeks 6 and 10 (p's<0.001) than at baseline. All these statistical effect sizes were large. At Week 6, number of reasons not to use e-cigarettes increased (p<0.011).	At Week 6, cigarettes/day were reduced by two-thirds and CO by 45% from baseline (p's<0.001), with reductions maintained at Week 10 (p's<0.005).	Results show preliminary evidence for beneficial effects of short-term switching to e-cigarettes by non-treatment seeking smokers in terms of reduced smoke toxicant exposure and cigarette dependence, and increased motivation to quit, all maintained at least 4 weeks after free e-cigarettes were no longer provided.
Ruther 2018	Abstained from nicotine for >12hrs (confirmed with CO test) then given tobacco cigarette.	Abstained from nicotine for >12hrs (confirmed with CO test) then given either a tank model e-cigarette	Questionnaire on Smoking Urges.	Smoking urges decreased significantly in the tobacco group and the tank model e-cigarette group.	NR	Withdrawal and craving for smoking decreased with the TM by the same amount as with the TC, even though less nicotine was delivered to the blood and considerably fewer side effects occurred.

Study reference	Control intervention	Experimental intervention	Methods for measuring smoking outcome	Results for smoking outcome	Effect measure (i.e. quantitative result of trial)	Conclusion statement
		or a cigalike e-cigarette				
Tucker 2017	Given e-cigarette with 0mg nicotine to use ad libitum, in attempt to substitute it for the regular cigarette, as much as possible.	Given e-cigarette with 6, 12, 18mg nicotine to use ad libitum, in attempt to substitute it for the regular cigarette, as much as possible.	Reported daily cigarette and e-cigarette use using SMS text messages.	Mean cigarettes per day decreased from 9.69 (SD=5.07) at baseline to 6.09 (SD=4.18) when e-cigarettes were available [$t(62)=2.751$, $p=0.008$, $d=0.77$]; a 37% reduction. The mixed model analysis confirmed a significant effect of e-cigarette nicotine [$F(3, 59.846)=2.952$, $p=0.040$] on cigarettes smoked per day	As per smoking outcome results	Availability of e-cigarettes reduced cigarette smoking behavior regardless of nicotine content, and e-cigarette use was greater with nicotine-containing cartridges.
Van Heel 2017	12h of smoking abstinence, then a 5 minute lab-based vaping session using 0% nicotine, 'bad apple' or 'tobacco regular' flavoured e-cigarettes with or without a blindfold, either holding the e-cigarette or vaping using a stand.	12h of smoking abstinence, then a 5 minute lab-based vaping session using 3.6% nicotine, 'bad apple' or 'tobacco regular' flavoured e-cigarettes with or without a blindfold, either holding the e-cigarette or vaping using a stand.	Measured cravings for tobacco cigarette and e-cigarette, perceptions of e-cigarettes.	A mixed-effects model clearly showed the importance of nicotine in craving reduction. However, also non-nicotine factors, in particular the sensorimotor component, were shown to contribute to craving reduction. Handling cues interacted with the level (presence/absence) of nicotine: it was only when the standard hand-to-mouth action cues were omitted that the craving reducing effects of nicotine were observed. E-cigarette cravings: In the nicotine group, we observed a reduction of 5.57 TCQ points ($p<0.01$), and, in the no-nicotine group, we observed a decline of 1.68 TCQ points that was non-significant. Tobacco cravings: reduced after e-cigarette use, reduced more after nicotine use.	Across Nicotine Level conditions, there was an overall effect of Measurement Moment ($p<0.01$), implying a craving reduction for tobacco cigarettes of 5.51 points on the TCQ scale ($p<0.01$). In addition, there was an interaction between Nicotine Level and Measurement Moment for tobacco cigarette craving ($p<0.01$). In the nicotine group, we observed a reduction of 7.75 TCQ points ($p<0.01$), and, in the no-nicotine group, we observed a decline of 3.34 TCQ points ($p<0.01$).	Our findings indicate that nicotine is an important variable in craving reduction. However, we also observed reliable craving reduction when the e-cigarette contained no nicotine, be it to a lesser degree than with nicotine. For one thing, this clearly demonstrates that the non-nicotine CSs that are present when using an e-cigarette do contribute to craving reduction.

PART 3: Impact on health of e-cigarettes and personal vaporisers in countries where they have been allowed

Executive summary

A country-level impact of e-cigarettes would be suggested by a change in the trend in a health index (such as a mortality rate, or disease rate) from the trend that was present prior to the uptake of e-cigarettes, and that wasn't explicable for other reasons.

The difficulty in demonstrating this is that the prevalence of use of e-cigarettes is low in all countries, diseases often have long latent periods (periods during which they are developing), and are often due to multiple factors combined.

A country such as the US has a history of use of e-cigarettes of more than 10 years, and a good national health surveillance system. It also has a high global market share of e-cigarette use (estimated at 56% by 2015 (World Health Organization 2016)). It is therefore relevant to examine time trends of health indices for this country. There is no apparent change in the decreasing trend of age-adjusted Chronic Obstructive Pulmonary Disease deaths over the period of 2000-2014, and no change in the trend for no change in the prevalence of age-adjusted hypertension from 1999-2016.

In examining the trend for cigarette smoking, the long-term decrease in prevalence of current smoking continues over 2005-2016 except that the prevalence was not different in 2015 (15.1%) and 2016 (15.6%). It is too early to describe this as a change in trend, however a plateau in the smoking trend would be an adverse indicator for population health. Consistent with the trend towards less current smokers, the Quit ratio (the ratio of former smokers to ever smokers) is slowly increasing over 2005-2016. There is not a break in trend to indicate an effect of e-cigarettes in any of the four age groups shown although the low prevalence of e-cigarettes use would not be expected to have a marked impact.

Health impact can also be assessed by modelling population data, however in all models it is necessary to make simplifications and assumptions in the absence of evidence. Population models of the health harms and benefits of e-cigarettes have been constructed for the United States, and one result is that the question of whether e-cigarettes cause initiation of conventional smoking in young people who otherwise wouldn't smoke becomes very important, as does the question of whether e-cigarettes are an effective method for smokers to stop smoking.

If the answer to both questions is affirmative, then the magnitude of the effects is critical to determine whether e-cigarettes have a net population health benefit or health harm. None of the population models incorporated possible harms coming from e-cigarettes in non-smokers (other than transitioning to tobacco smoking) probably because understanding of the magnitude of such harms is not yet conclusive.

There is no conclusive evidence of a positive or negative health impact of e-cigarettes on a population. Modelling of different scenarios is hampered by lack of knowledge of the impact of e-cigarettes, such that there cannot yet be agreement about the direction of any health impact.

11   National health impacts

11.1   Introduction

This section addresses the assigned task to 'assess the impacts on health of allowing the use of e-cigarettes and personal vaporisers in countries where they have been permitted'.

An impact of e-cigarettes on health at a national level can be conceptualised to occur by e-cigarettes causing direct harm or benefit to health by their use, or by use of e-cigarettes having an indirect effect through modification of other behaviours, for example, by reducing tobacco smoking. The most obvious country to examine in relation to an impact on health is the United States of America because it has had a relatively long history of popularised e-cigarette use (although still only just over a single decade which is short for exposures that might be expected to impact on rates of chronic disease), and has a relatively good monitoring system for population health parameters.

It is relevant to note that with a behaviour such as tobacco smoking, changes in the national smoking rate have a delayed effect on health indices such as disease and mortality rates even though it is well-accepted that smoking tobacco causes the disease and the deaths. This occurs because there is a lag time between exposure and manifestation of disease, and the risk of disease increases with cumulative exposure. For cigarette smoking, the pattern of mortality for a population increasing their smoking rate followed by reducing their smoking rate is shown in Figure 3 (Lopez AD 1994). This pattern shows an increasing rate of smoking for adults (to a lower peak for women and lagging behind men) followed by a very substantial decrease in the smoking prevalence rate in both groups. However the percentage of deaths due to cigarette smoking in men continues to rise for the next 30 years following the peak of smoking prevalence – for the first three decades of the cigarette smoking prevalence falling, the percentage of deaths due to smoking continues to increase.

Figure 3: Four stages of the tobacco epidemic

Source: Lopez et al 1994

| Byrne S, Brindal E, Williams G, Anastasiou KM, Tonkin A, Battams S and Riley MD (2018), E-cigarettes, smoking and health. A Literature Review Update. CSIRO, Australia.
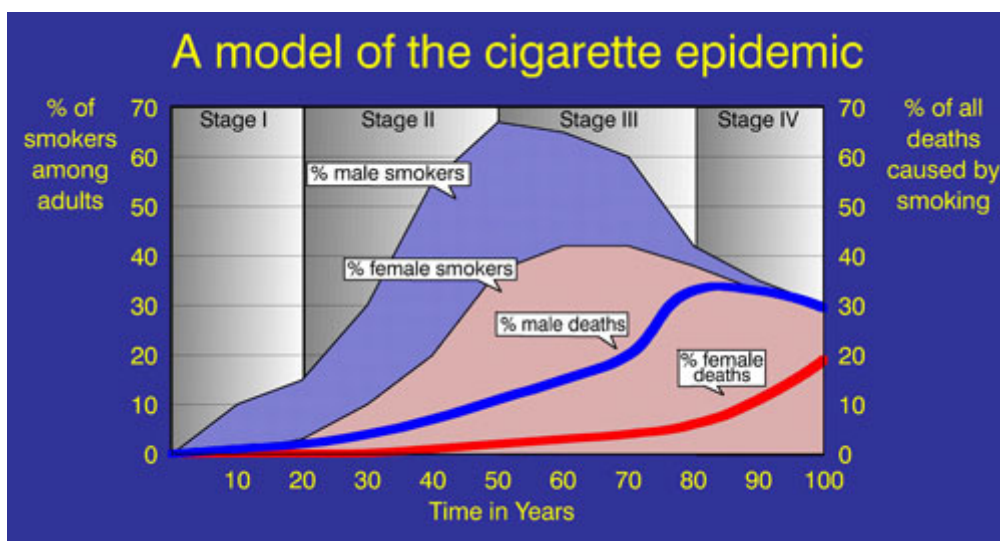
Countries such as Canada, New Zealand, the United States, Australia and the United Kingdom fit into Stage Four of this model.

11.2   Trends for rates of disease potentially relevant to e-cigarette use

Direct benefit on health from e-cigarettes has not been proposed and direct harmful impact on health is proposed to be much lower than from conventional tobacco smoking. The prevalence of current e-cigarette use in the United States is relatively low (estimated to be 3.7% for US adults in 2014) (Schoenborn and Gindi 2015) although the percentage who had ever tried an e-cigarettes is higher (12.6%). Therefore there is substantial difficulty in demonstrating a direct impact on health due to increased use of e-cigarettes. For example, the trend in the rate of Chronic Obstructive Pulmonary Disease (COPD) related deaths in US adults aged 25 years and over has decreased over the time period 2000-2014 (Ni and Xu 2016) (Figure 4). The reason for the decrease has been attributed to the decrease in smoking prevalence rate over the same period – part of a long term trend for decrease from 1965 (Courtney 2015) due to multiple tobacco control strategies. The increase in use of e-cigarettes occurs in the latter half of this figure (from 2006 onwards), and no marked interruption to the trend is seen.

Figure 4: Crude and age-adjusted rates for COPD-related deaths for adults aged 25 and over, by sex: United States, 2000–2014
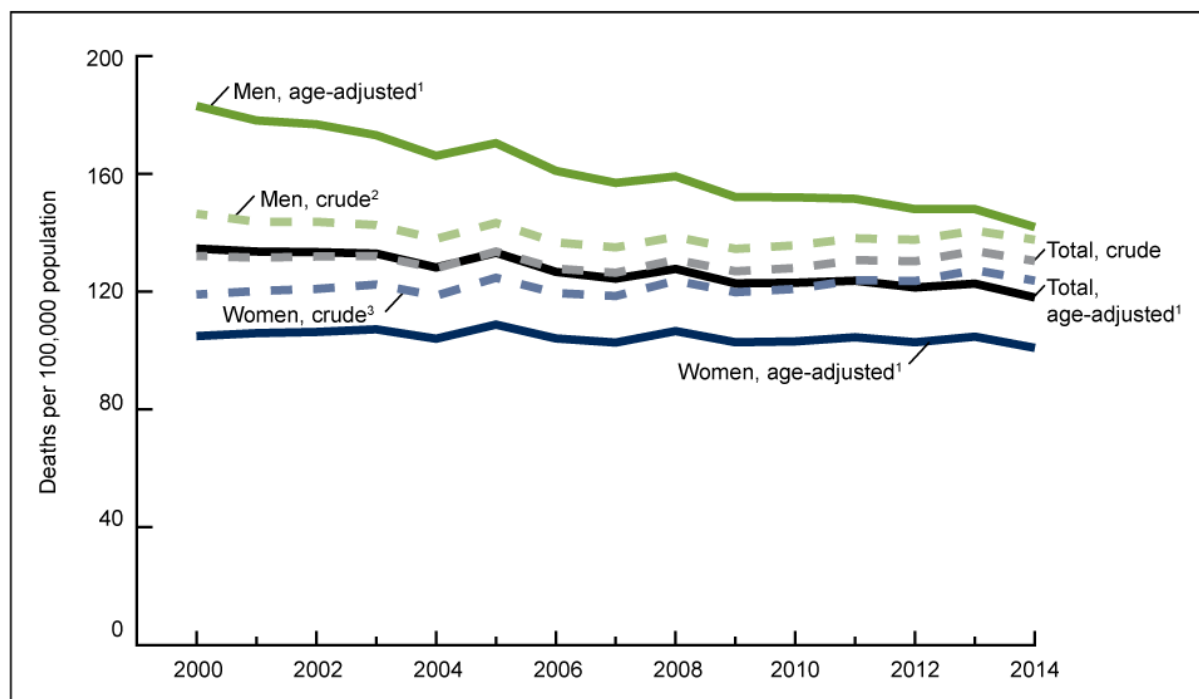
[1]Statistically significant decrease in age-adjusted COPD-related death rate from 2000 through 2014 ($p < 0.05$).
[2]Statistically significant decrease in crude COPD-related death rate from 2000 through 2009 ($p < 0.05$).
[3]Statistically significant increase in crude COPD-related death rate from 2000 through 2014 ($p < 0.05$).

Source: (Ni and Xu 2016)

For high blood pressure, Figure 5 shows the rate of diagnosed hypertension within the adult population of the US over the period 1999-2016. Hypertension is defined as taking medication for hypertension, or systolic blood pressure greater than or equal to 140mmHg, or diastolic blood pressure greater than or equal to 90 mmHg. Controlled hypertension refers to those who are using medication who have blood pressure in the normal range. From the figure it can be seen that prevalence of hypertension does not change over the period of the surveys included.

Figure 5: Age-adjusted trends in hypertension and controlled hypertension among adults aged 18 and over: United States, 1999–2016
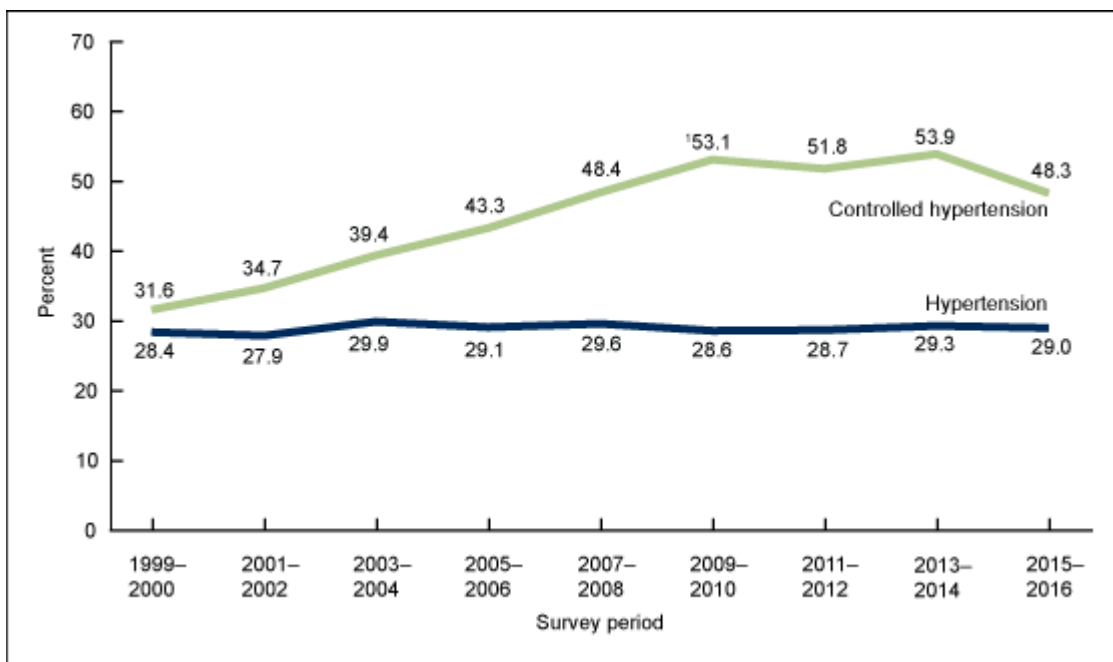
Source: (Fryar, Ostchega et al. 2017)

This highlights the difficulty of assessing impact on health of one factor used by a small percentage of the population for diseases and conditions that are multifactorial.

Therefore, while the analysis is not exhaustive, the direct impact of e-cigarettes on health in a country where e-cigarettes are used are used are not detectable. This is not surprising in view of the low prevalence of current use across the population, and the lag time of disease development for many conditions.

11.3   Potential impact of e-cigarettes on conventional cigarette smoking

A plausible pathway for e-cigarettes to impact on health is by changing the prevalence of conventional tobacco smoking.

The prevalence of current conventional cigarette smoking amongst US adults has decreased from 20.9% in 2005 to 15.5% in 2016 (Jamal, Phillips et al. 2018). This represents a change from 45.1 million people in 2005 to 37.8 million in 2016. However the prevalence for current smoking did not change from 2015 (15.1%) to 2016. The prevalence of current smokers varies by many demographic factors being higher in men than women, lower for people over 65 years of age, higher for people living below the poverty line, higher for people identifying as Gay/Lesbian/Bisexual, lower for people with higher educational attainment and much higher (35.8%) for people assessed as being in serious psychological distress.

The quit ratio has been increasing over the period 2005 to 2016 (Figure 6) although it may have also flattened for 2015 and 2016. The quit ratio is the percentage of former smokers amongst ever smokers, and therefore an increasing quit ratio is consistent with a decreasing prevalence of current smokers. The authors of this report (Jamal, Phillips et al. 2018) suggest that one reason for the flattening of the trend may be increased nicotine dependence from the concurrent use of other products. The prevalence of ever use, or current use, of e-cigarettes among US adults is higher for younger age groups, however the trend of the quit ratio lines do not appear to differ by age group which argues against use of e-cigarettes having much impact on the quit ratio. However, even among the age group that uses e-cigarettes the most (18-24 year olds), the prevalence of current e-cigarette users is only 5.1% (Schoenborn and Clarke 2017).

Figure 6: The Quit Ratio* among US ever smokers aged > 18 years
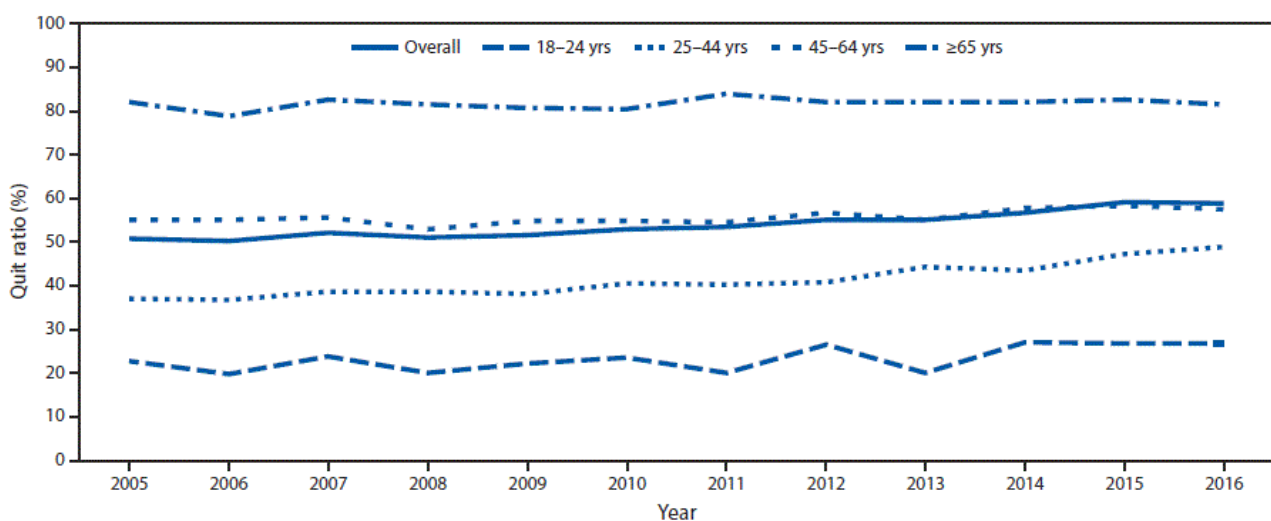
* Quit ratio is defined as the ratio of former smokers to ever smokers for each survey year.
The ethnicity- and age-adjusted trend is significant overall and for all age groups

11.4   Key findings

- There is no apparent change in the decreasing trend of age-adjusted Chronic Obstructive Pulmonary Disease deaths over the period of 2000-2014 in the US when use of e-cigarettes was increasing in prevalence.

- The trend for no change in the prevalence of age-adjusted hypertension over the period 1999-2016 in the US does not show any break in trend that could be attributed to e-cigarettes.

- Consistent with the trend towards less current smokers, the Quit ratio (the ratio of former smokers to ever smokers) is slowly increasing over 2005-2016 in the US. There is no break in trend to indicate an effect of e-cigarettes although the low prevalence of e-cigarettes use would not be expected to have a marked impact.

12 Modelling studies

12.1 Introduction

Modelling studies are a possible approach to estimating the health impact of a factor in a complex system. Mathematical models are always simplifications and are often developed in the context of incomplete information. Assumptions are required to be made to construct models, and some of the model parameters may need to be estimated rather than measured. For this reason, while models may be informative, a weakness is their dependence on specific conditions and assumptions.

12.2 Population health benefits and harms from e-cigarettes in the United States.

Researchers from the US undertook simulation modelling (Soneji 2018) to quantify the health benefits and harms of e-cigarette use in the United States. The approach taken was firstly, to estimate the number of years of life gained among the additional number of current cigarette smokers who quit smoking through the use of e-cigarettes as a cessation tool, compared to those who did not use e-cigarettes as a cessation tool, and remain continually abstinent from smoking for seven years or more. Smokers who are abstinent for seven years rarely relapse, and the risk of death for ex-smokers after seven years approaches that of never smokers. For current cigarette smokers who use e-cigarettes to successfully quit smoking, harm reduction is assumed to be 95%. The second step was to quantify the number of years of life lost among the additional number of never-cigarette smoking adolescents and young adults who eventually become current daily cigarette smokers (and also smoked > 100 cigarettes in lifetime) at age 35–39 years through the use of e-cigarettes.

Four key parameters were varied in a sensitivity analysis. These were:

1) the adjusted odds ratio of smoking cessation (i.e. adjusted for using e-cigarettes or not);

2) the adjusted odds ratio of cigarette smoking initiation;

3) the age-group-specific prevalence of current e-cigarette use among current cigarette smokers who tried quitting within the past year;

4) the age-specific prevalence of ever having tried e-cigarettes among never cigarette smokers.

Finally, the relative harm of e-cigarette use, compared to cigarette smoking, in terms of the number of years of life gained from quitting cigarette smoking was varied from 0% to 100%.

The model estimated that the 2,070 additional long-term quitters would gain 3,000 years of life (95% CI: -325,000 to 351,000). The model also estimated the additional 168,000 adolescent and young adult cigarette smoking initiators who eventually become daily cigarette smokers at age 35-39 years would lose 1,510,000 years of life (95% CI: 1,030,000 to 2,060,000). Considering all population subgroups, the model estimated that e-cigarette use in 2014 would lead to 1,510,000 years of life lost (95% CI: 920,000 to 2,160,000) assuming an approximate 95% relative harm reduction of e-cigarette use compared to cigarette smoking. The model was not very sensitive to the percentage of relative harm reduction of e-cigarette use compared to cigarette smoking because the impact of quitting smoking because of e-cigarettes was overwhelmed by the impact of taking up smoking because of e-cigarettes.

The authors conclude, based on currently available evidence on the e-cigarette associated transition probabilities of cigarette smoking cessation and initiation, that e-cigarettes will result in more harm than they confer benefit at the population level.

The authors did not model an effect of e-cigarette use among current smokers to reduce the amount of conventional cigarettes smoked, although there is uncertainty about whether this occurs. The result for year of life lost would improve if e-cigarettes were a much more effective means of cigarette cessation than other methods – the threshold for an overall positive result is that e-cigarettes would need to be at least 2.55 times more effective than other smoking cessation methods. It should be emphasised that many parameters in the model are not known – for example, the transition to smoking from e-cigarette use for youth, the rate of smoking cessation and relapse using different smoking cessation methods.

However this model highlights the very large public health issue of young people initiating cigarette smoking because of trying e-cigarettes (if this is, in fact, a causal relationship – there is some strong observational evidence for it following meta-analysis (Soneji, Barrington-Trimis et al. 2017)).

A second US modelling study (Warner and Mendez 2018) simulated the effects of vaping induced smoking initiation and cessation to the year 2070 with contrasting results. In this model the base case considered vaping to increase smoking initiation by 2% and smoking cessation by 10%. Under this scenario, the US population gains 3.3 million life years by 2070. If it is assumed that all people who quit smoking by vaping lose 10% of the benefit of quitting smoking, the life year gain falls to 2.4 million life years. Under their worst case scenario (where vaping increases smoking initiation by 6% and smoking cessation by 5%, with all those who quit smoking by vaping losing 10% of the health benefit, the population still gains over 580,000 years of life.

Thus two recent modelling studies provide opposite conclusions despite including an effect of e-cigarettes to increase both smoking initiation and smoking cessation.

12.3 Potential deaths averted in the US by replacing cigarettes with e-cigarettes

The US study by Levy et al (Levy, Borland et al. 2018) aimed to demonstrate the potential health impact from replacing all or most cigarette smoking in the US by e-cigarette use. This tobacco industry funded study is considered in detail in Part 4 (The impact of e-cigarettes in smokers) because it does not consider any possibility that non-smokers would take up smoking because of using e-cigarettes. The positive results of the optimistic modelling study therefore only relate to public health benefit to smokers.

12.3.1 What the new studies add to what is already known about e-cigarettes

Modelling studies are somewhat premature at this stage as a greater understanding of the health effects of e-cigarettes is needed before accurate models can be developed. Further studies are required to identify the variables that should be included in such modelling simulations and to make appropriate assumptions and estimations regarding health outcomes.

12.4 Key findings

- None of the population models incorporated possible harms coming from e-cigarettes in non-smokers (other than transitioning to tobacco smoking) probably because understanding of the magnitude of such harms is not yet conclusive.

- Modelling of different scenarios in the US population is hampered by lack of knowledge of the correct parameters for the impact of e-cigarettes, to the extent that there cannot yet be agreement about the direction of any future health impact.

- There is support from population based models for a positive or a negative health overall impact of e‑cigarette use on the US population.

PART 4: Impact on health of e-cigarettes and personal vaporisers in smokers

Executive summary

Health risks of e-cigarettes for smokers

- The Public Health England report concluded that risk of cardiovascular disease has not been quantified for e-cigarettes. No new evidence on cardiovascular disease is available to alter this conclusion, however limited new results for cardiovascular risk factors suggest that:
    o The blood pressure of smokers can be lowered over a month when e-cigarettes are used instead of conventional cigarettes.
- There may be limited benefits for respiratory function immediately after using an e-cigarette. In the short-term, small improvements in lung function has been reported in smokers who use e-cigarettes. This is consistent with conclusions from the recent US Academies of Science review.
- No new studies report on lung disease in smokers who use e-cigarettes.
- The level of specific carcinogenic compounds and resulting metabolites is lower after e-cigarette use compared to conventional cigarette use. This is consistent with conclusions in previous reports.
- Long term studies are lacking however it is speculated that the cancer risk is much lower (and unknown) for e-cigarettes than for conventional cigarettes based on exposure levels to carcinogens.
- The range of toxic compounds is not the same for e-cigarettes and combustible tobacco. For e-cigarettes, potentially toxic compounds arise from the e-fluid which varies in composition, and from the heating elements (which typically contribute metal vapour for example).
- There is no consistency in results of nicotine absorption and nicotine dependency in smokers who use e-cigarettes. This may be because the way in which devices are used in terms of puffs and intensity can determine the amounts of nicotine inhaled. Furthermore, some studies included people using both conventional and e-cigarettes making it difficult to draw conclusions.
- Results from single studies on broader health outcomes suggest:
    o Oral lesions are worse in e-cigarette users compared to former smokers, suggesting that smoking cessation was superior to e-cigarette use for improving the oral health of smokers.
    o Smokers who use e-cigarettes demonstrate low levels of skin hypoxia (limited oxygen)
    o More needs to be understood about the relationship between depression and use of e-cigarettes in smokers.
    o The use of e-cigarettes may prevent weight gain in smokers who quit.

13 Introduction

This report reviews the recent literature relevant to the assigned task to 'review the impact of e-cigarettes and personal vaporisers on individual health as an alternative to smoking'. In order to achieve this, studies were reviewed where a health outcome related to e-cigarette use was examined in conventional smokers or ex-smokers.

Therefore, studies were included where the health outcome of e-cigarette use was examined in smokers or ex-smokers. These consisted of studies where subjects had ceased smoking (i.e. where e-cigarettes were substituted as an alternative for smoking) and where subjects continued to smoke cigarettes at a reduced rate to previously, in addition to using e-cigarettes (called dual users).

In total, 24 recent papers were extracted that examined the health outcomes of e-cigarettes in conventional cigarette smokers or ex-smokers, alone or relative to other groups (i.e. relative to users of e-cigarettes only, or to non-smokers). Seven of these papers reported on RCT studies, nine reported on cross-sectional data collection (largely collected in surveys), three reported on short-term experimental studies, four reported on larger prospective cohort studies, and one reported on a case control study. Description of the studies and their results are categorised by the body systems involved.

14 Health effects of e-cigarettes on smokers or former smokers

14.1 Cardiovascular system

A UK industry-funded prospective cohort study (Walele, Bush et al. 2018) enrolled former smokers (n=206, mean age 36.6 years, range 21 to 65 years) who were asked to use an electronic vapour product (EVP) (Puritane, with 16mg/g of nicotine) used as often as desired for a period of two years. Subjects were required not to use any other nicotine containing product for the duration of the study. Use of conventional cigarettes during the study did not lead to termination, but subjects were reminded to use the Puritane device. Subjects were identified for this study because they had participated in a previous 12 week trial where they had used either conventional cigarettes or an electronic vaping product.

Only 102 subjects completed the trial, with 69 withdrawing consent, 22 lost to follow-up, five based on an investigators decision and 11 due to adverse events stated to be unrelated or unlikely to be related to the use of the product.

During the two year follow-up period, subjects attended the study centres for assessment at months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24 (end of study). At each visit, exhaled carbon monoxide (eCO) and blood carboxyhaemoglobin (COHb) were measured, adverse events recorded and subjects completed a questionnaire to assess nicotine withdrawal (MWS-R) and a questionnaire to assess smoking desire (QSU-Brief). Weight, vital signs, a 12-lead ECG, lung function, clinical chemistry, haematology and urinalysis were checked at months 1, 3, 6, 12, 18 and 24.

The mean use of conventional cigarettes dropped over the first eight months of the study to an average of about one cigarette a day. Baseline characteristics of subjects who had been on a conventional cigarette treatment in the 12 week trial prior to this study were similar to those who had been on an EVP treatment except for eCO and COHb.

Mean systolic blood pressure, diastolic blood pressure and pulse rate remained steady throughout the study. There were some instances of increased systolic (n=16, 7.8%) and diastolic (n=11, 5.3%) blood pressure (shifts from normal blood pressure at baseline to high blood pressure at one of the study visits). There were no increases in the heart rate-corrected QT interval (QTcB) from baseline of 60ms or greater. ECG parameters were considered stable with some abnormal ECG results found although not considered clinically significant. Although some out of range clinical chemistry or haematology values were observed, most were considered clinically insignificant. Weight also remained stable throughout the study. The authors conclude that there were no changes in blood pressure, heart rate or weight for participants.

 Adverse events were recorded for a high proportion of subjects (n=159, 76.1%), the commonest being headache (28.7%), nasopharyngitis (28.7%), sore throat (19.6%) and cough (16.7%). During the first 8-9 months of the trial, the group who had changed from conventional cigarette use in the previous 12 week trial experienced more adverse events than those who had used an EVP in the previous trial. The selection process for the study raises concern about selection bias. A higher

proportion of the subjects who had been using the EVP in the previous 12 week trial joined the two year study compared to the subjects who had been using conventional cigarettes. Of these a higher proportion of the subjects previously using EVP completed the study. Unsurprisingly, subjects who were switching directly from conventional cigarettes were less likely to join the study and more likely to drop out of the study. This has implications for generalisability from the study results because the selection process means subjects were more likely to have familiarised themselves with EVP prior to the study, and liked or tolerated it.

In the Walele et al. study (Walele, Bush et al. 2018) measurements indicating exposure to carbon monoxide (CO) were undertaken, including exhaled CO (eCO) and carboxyhaemoglobin (COHb). The group that had been involved in the conventional smoking group in the prior 12-week trial showed a rapid decline in both eCO and COHb by month one, reaching levels similar to the group that had been in the EVP arm of the 12 week trial. Levels of eCO decreased for all subjects over the two year study (mean concentration 8.7ppm (SD 6.5) at month one and 4.1 ppm (SD 3.1) at two years). Previously reported eCO in non-smokers is a mean of 3.6 ppm, and 17.1 ppm for smokers (Deveci SE 2004).The mean COHb level remained stable in both groups from month one at 4.33% (SD 1.37%) to 4.27% (SD 0.87%) at two years. Previously reported levels for COHb in non-smokers is up to 3%, while values up to 10-15% have been reported in smokers (Deveci SE 2004).

A Greek study reported in a research letter by Ikonomidis and colleagues (Ikonomidis, Vlastos et al. 2018) was a randomised cross-over trial (n=70) which sought to examine the effects of e-cigarettes on **aortic stiffness** (as measured by pulse wave velocity [PWV] and augmentation index [AIW75]) (as well as exhaled **carbon monoxide** (eCO) and oxidative stress, as measured by malondialdehyde [MDA] plasma concentrations). The study involved two phases, an acute phase where conventional cigarette smokers either smoked a conventional cigarette, or an e-cigarette (half of the group used nicotine free e-fluid, and the other half nicotine containing e-fluid (12mg/mL) for **one seven-minute period**, then subjects crossed over after one hour. In the chronic phase, the same 70 smokers were asked to replace conventional cigarettes by e-cigarettes (with 12mg/dL nicotine in the e-fluid) for **one month** (Ikonomidis, Vlastos et al. 2018). There was also a control group (n=20) of conventional cigarette smokers who maintained their smoking habit.

Results showed that both conventional cigarette and e-cigarette use adversely affected arterial elasticity in the acute phase. PWV increased from 10 ± 0.2 m/s to 10.5 ± 0.2 m/s for e-cigarettes, and to 11.0 ± 0.2 m/s for conventional cigarettes, both $p<0.05$ while AIX75 increased from $28.4\pm7\%$ to $32.1\pm7\%$ for e-cigarettes and $38.2\pm9\%$ for conventional cigarettes, both $p<0.05$). However, nicotine-free e-cigarettes resulted in a comparatively smaller increase of arterial stiffness. Exhaled CO was lower after e-cigarette vaping than after conventional cigarette smoking (12.1 ± 0.5 ppm compared to 14.2 ± 0.8 ppm for the nicotine containing e-cigarette group, $p<0.05$; $12.0+0.6$ppm compared to $15.6+0.7$ppm for the nicotine free e-cigarette group, $p<0.05$). In the chronic phase, at follow-up 60% self-reported using only e-cigarettes, 34% reported using e-cigarettes and conventional cigarettes and 6% were non-compliant (used only conventional cigarettes).

Replacement of conventional cigarette by nicotine-containing e-cigarettes (for both the dual user group and e-cigarette only groups) resulted in **reduced central systolic blood pressure** (dual users 124.9 ± 8mmHg to 123.1 ± 9, $p=0.04$; e-cigarette use only 124.1 ± 9 to 122.2 ± 8, $p=0.04$) **and reduced brachial systolic blood pressure** (SBP) (dual users 127.5 ± 9mmHg to 123.9 ± 7, $p=0.04$; e-cigarette

use only 127.1±6 to 124.5±9, p=0.03) and **reduced augmentation index** (AIW75, 29.3±8% to 25.6±9%, p=0.01 for the dual user group and 28.9±9% to 23.9±7%, p=0.001 for the e-cigarette only group) within one month, likely because of the reduction in smoking conventional cigarettes. In the chronic phase, reductions in exhaled CO compared to baseline were significant for both the dual users (15±0.6 to 12.5±0.6 ppm, p=0.04) and e-cigarette only users (13.9±0.7 to 4.2±0.6 ppm, p<0.001). Heart rate, pulse wave velocity and diastolic blood pressure were unchanged for both groups.

This study provides a good comparison of outcomes using a non-randomised control group and a longer time frame than other studies (detailed below) to try and capture more real world effects. It was clear that a small percentage of cigarette users could not switch to e-cigarettes (6%). However, there appeared to be benefits for those that did, at least in the short-term, and even if they continued to use cigarettes.

An industry funded randomised trial (n=105) by D'Ruiz et al. involved a clinician measuring **systolic (SBP) and diastolic blood pressure (DBP)** and **heart rate (HR)** following four days of use of different types of e-cigarettes (D'Ruiz, O'Connell et al. 2017). The objective of the study was to measure changes in select physiological endpoints such as cardiovascular, pulmonary function and safety and tolerability following short-term (four days) *ad libitum* (as desired) use of e-cigarettes by established adult smokers under exclusive use, dual use and cessation of all tobacco and nicotine product conditions. Participants (mean age=37.8 years) were conventional cigarette smokers in the US who were randomised into groups that either completely (n=45) or partially (n=45) switched to e-cigarette use or completely discontinued using tobacco and nicotine products (n=15).

Subjects in the e-cigarette and dual use groups tested six e-cigarette products (n=15 in each flavour group). All e-cigarette products contained 24 mg/ml (2.4%) USP grade nicotine, USP grade vegetable glycerol (~50% in cherry flavour and ~80% in tobacco flavour), USP grade propylene glycol (~45% in cherry flavour and ~10% in tobacco flavour), distilled water, and flavourings. Each e-cigarette contained ~1 ml of e-liquid per volume. On day 1 subjects smoked their usual conventional cigarettes *ad libitum* (as desired). All e-cigarette product use was ad libitum from 7.30am to 23.00pm on days 2 to 5. Subjects in the dual use group were required to reduce their consumption of conventional cigarettes.

The results showed small reductions in **blood pressure (BP)** and **heart rate (HR)** in most of the participants that either ceased tobacco and nicotine product use altogether, or switched completely to use of e-cigarettes.

Overall, this study indicated limited cardiovascular system benefits for smokers when switching to e-cigarette products however the results are not compelling because of design issues. A major limitation for this study was the short-term use (i.e. 4 days) of e-cigarettes in the trial, and the lack of a control group that continued to smoke conventional cigarettes. Blood pressure and heart rate might be expected to drop over the course of a short study without any treatment as subjects become familiar with measurement processes.

A randomised cross-over study (n=64) from the US sought to test the hypothesis that different liquid nicotine concentration in e-cigarettes, and users' prior experience with e-cigarettes, directly influences outcomes such as plasma nicotine delivery, **heart rate (HR)**, puff topography (duration of puffs, volume of vapour inhaled per puff and period of time between puffs) and subjective effects for the user (Hiler, Breland et al. 2017). Subjects (mean age=30.3 years) were either conventional cigarette smokers who had smoked e-cigarettes (n=33) or conventional smokers who had not smoked e-cigarettes (n=31). Participants used an 'eGo' 3.3V e-cigarette, with 1,000 mAh battery and a 1.5, dual-coil, 510-style cartomizer (7.3W), loaded with 1 ml of flavoured liquid (tobacco or menthol) (70%PG and 30%VG). This device was chosen after testing indicated that its nicotine emissions approached those of a tobacco cigarette under some conditions. Different nicotine concentration levels (0mg/ml, 8mg/ml, 18mg/ml and 36 mg/ml) were tested across four sessions. There were **two 2.5 hour bouts of smoking** this device (two 10 puff e-cigarette use bouts separated by 60 minutes), separated by 48 hours. Participants completed four double-blind sessions (according to the four levels of nicotine) at the laboratory, and session order was randomised.

For both e-cigarette users and e-cigarette naïve groups, HR increased significantly from baseline immediately after bout 1 and 2 in all active liquid nicotine concentrations (8, 18 and 36 mg/ml) but not the 0 mg/ml condition. In the **8mg/ml** nicotine group, mean **HR** increased from 66.4bpm (SD6.5) before bout 1 to 73bpm (SD7.4) after bout 1 and from 65.1 bpm (SD6.5) before bout 2 to 69.9 bpm (SD7.8) after bout 2 (both significant increases, $p<0.05$). In the **18mg/ml** group, **HR** increased from 66.4bpm (SD7.6) before bout 1 to 75.8bpm (SD8.2) after bout 2 (increases both significant $p<0.05$). In the **36 mg/ml** group, **HR** increased from 66.6bpm (SD7.1) before bout 1 to 77bpm (SD8.6) after bout 1 and from 67.3 (SD7.8) before bout 2 to 72.7bpm (SD9.3) after bout 2 (increases both significant, $p<0.05$). There were no significant between group differences in HR at baseline or immediately after bout 1 or 2 (*ts* (37) all >-2.1, ns).

This study focused only on the acute effects of e-cigarette use (within 48 hours) but indicates that nicotine delivered through e-cigarettes is physiologically active as shown by its observable and predictable impact on HR. The study of Hiler et al. also highlighted the association between **user experience with e-cigarettes and nicotine delivery**, with experienced users taking longer and more frequent puffs and achieving higher levels of nicotine in plasma (see nicotine section, below).

A small (n=20) randomised crossover study reported in an abstract by Kerr et al. included only male smokers from the UK and considered **systolic** (SBP) and **diastolic blood pressure** (DBP), **reactive hyperaemia index** (RHI) and **aortic stiffness** via the augmentation index (AI) immediately after vaping and smoking a traditional cigarette (Kerr, Touyz et al. 2017).

It was found that following vaping an e-cigarette, there was a significant increase in RHI (2.0 ± 0.4 vs 1.7 ± 0.3; p=0.006) and decrease in AI (-6.9 ± 13.5 vs -10.5 ± 13.2%; p=0.010). However, no such significant changes were found before and after smoking a traditional cigarette. Heart rate increased after both vaping (73 ±0 vs 65 ±9 bpm; p<0.001) and smoking a traditional cigarette (86 ±13 vs 64 ±8 bpm; p<0.001). There were no significant changes in SBP or DBP immediately after vaping or smoking a traditional cigarette. Tobacco smoking resulted in a significant increase in exhaled CO (20.3±9.5 vs 8.6±10 ppm p<0.001) that was not evident among vapers. Without

further data on longer term implications, it is difficult to interpret these findings in terms of likely health outcomes for users of e-cigarettes although reduced exposure to CO is likely to be beneficial if maintained over the long term.

In a very small UK trial (n=15, only seven of whom were smokers) using convenience sampling among young adults (mean age 26 years), Pywell et al considered whether smoking **nicotine** e-cigarettes had any effect on **blood flow** in the hand (superficial and deep measurements of hand microcirculation) in the **short term** (10 inhalations) as compared with smoking nicotine free e-cigarettes, and compared results between conventional cigarette smokers (average 0.3-3 packs per week) and non-smokers (Pywell, Wordsworth et al. 2018).

Baseline measures of blood flow in smokers and non-smokers showed no significant differences. Comparing smokers and non-smokers confirmed that there was a statistically significant difference between the effects of vaping the 24mg nicotine e-cigarette ($p < 0.05$) for all time points (during and after inhalation) and the 0mg e-cigarette ($p < 0.05$ for all time points after inhalation) on **superficial blood flow**. Smokers and non-smokers were then analysed independently, and it was found that **smokers had a significant reduction in superficial blood flow** at all time points after inhaling a 24mg nicotine e-cigarette, with the maximum reduction of superficial blood flow being 76.9% ($p < 0.05$) at 10 to 15 minutes. Non-smokers had no significant change in superficial blood flow during or after inhaling either 24mg or 0mg e-cigarettes.

Regarding deep blood flow, comparing smokers with non-smokers showed a statistically significant difference between the effects of smoking 24mg nicotine e-cigarettes (< 0.05) for all time points after inhalation, but no difference with 0mg cigarettes. When analysing the **deep blood flow** of smokers and non-smokers independently, **smokers had a significantly reduced blood flow** at all points during and after inhaling a 24mg nicotine cigarette. There was a mean **reduction in flow of 19.3%** ($p < 0.05$) during e-cigarette use and a maximum **reduction of 28.4%** (< 0.05) **after 10 to 15 minutes**. Smokers had no significant change in deep blood flow after inhaling a 0mg nicotine e-cigarette. **Non-smokers had no significant change in deep blood flow** during or after inhaling either 24mg or 0 mg nicotine e-cigarettes.

The study concluded that the results should be considered when counselling smokers in a hand surgery setting, and that further studies are required to determine if the blood flow reduction found during and following vaping could result in impaired wound healing.

A small (n=27) US cross-sectional (analytic) study by Boas et al. sought to consider the effect of e-cigarettes and conventional cigarettes on activation of the **Splenocardiac Axis**[3] among healthy young adults (21-45 years old) (Boas, Gupta et al. 2017). Subjects were healthy non-users (n=9), habitual conventional cigarette smokers (n=9) or habitual e-cigarette users (not dual users, n=9) who had smoked their respective products for a **minimum of one year**.

F-fluorodeoxyglucose (FDG) positron emission tomography/computer tomography was performed to measure FDG uptake in the spleen. FDG uptake is a measure of the metabolic activity of cells, particularly glycolytic activity, so that increased FDG uptake indicates more metabolically active

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[3] an inflammatory signalling network underlying acute cardiac ischemia

cells. This can occur in physiological conditions (e.g. activated inflammatory cells) and in pathological conditions (e.g. malignant cells), and it also varies according to the fasting/non-fasting state.

FDG uptake in the spleen (in units of maximum standardised uptake value) increased from non-user controls (1.62 ± 0.07) to the e-cigarette users (1.73 ± 0.04) and was highest in tobacco cigarette smokers (1.82 ± 0.09); (p for trend=0.05). FDG uptake in bone marrow was lowest in the controls (1.88 ± 0.06) and was higher in both e-cigarette users (2.17 ± 0.12) and tobacco cigarette smokers (2.14 ± 0.15), but the monotonic trend did not reach significance (p for trend=0.12). FDG uptake in skeletal muscle was not different between groups. Aortic wall metabolic activity was increased from nonuser controls (1.87 ± 0.07) to the e-cigarette users (1.98 ± 0.07) and was highest in tobacco cigarette smokers (2.10 ± 0.07); p for trend=0.04) [differences were not found when measured by another method]. Plasma cotinine was weakly correlated with bone marrow activity (r=0.39, p=0.05).

These findings are difficult to interpret in terms of the future risk of cardiovascular events for both conventional cigarette smokers and e-cigarette users. However, this is a small cross-sectional study based on indirect measurement of presumed susceptibility to cardiovascular events and in any case, by design does not directly address the impact of e-cigarettes on smokers.

14.1.1 Conclusion

For cardiovascular system associated outcomes, the new studies add some information.

One small study (Kerr et al, 2017) concluded that acute effects following the use of a single e-cigarette compared to smoking a conventional cigarette by smokers reduced some indicators of cardiovascular risk (e.g. aortic stiffness) but showed no difference for others such as blood pressure or heart rate. Where conventional cigarettes were replaced by e-cigarettes for four days (D'Ruiz et al 2017), a reduction in systolic blood pressure was seen for most e-cigarette groups. However, this study had no control group, and the effects on BP may have been related to the known reduction of BP that occurs in clinical trials. When e-cigarettes replaced conventional cigarettes for a month (Ikonomidis et al. 2018), reductions in systolic blood pressure were seen. However, a follow-up of smokers who had used e-cigarettes for two years (Walele et al, 2018) showed no difference in blood pressure, heart rate or weight. This trial had no control group, suffered from poor retention and subjects continued to smoke at a lower rate than previously.

A small study (Boas, Gupta et al. 2017) showed differences between conventional cigarette users and never smokers in the metabolic activity of the aorta and the spleen (but not the bone marrow) with users of e-cigarettes having an intermediate position. It was suggested this represented the relative risk of cardiac ischemia among the groups however results were somewhat inconsistent.

A final small study (n=7 smokers) showed a significant reduction in superficial blood flow and deep blood flow in the hand following use of an e-cigarette, an effect which did not occur in non-smokers (Pywell, Wordsworth et al. 2018). It is not clear whether this is relevant to cardiovascular health.

14.2 Respiratory system

Three of the studies summarised above also assessed respiratory function outcomes (D'Ruiz, O'Connell et al. 2017, Kerr, Touyz et al. 2017, Walele, Bush et al. 2018).

In the UK prospective cohort study by Walele et al. (Walele, Bush et al. 2018), a closed system electronic vapour product (EVP) was tested for 24 months in a real life setting (n=209 started, n=102 completed the study). Lung function was measured via spirometry. One single cartomizer provided 300-350 puffs and contained 1ml of e-liquid, with 67.5-69% of propylene glycol (PG), 30% glycerol, 1.6% nicotine (16mg/g) and 0.54-1% flavouring (tobacco or menthol flavour). A small decrease from baseline in each mean lung function test parameter was observed, for FVC (4%), FEV_1 (5.4%), FEF25-75 (8.3%) and Peak Expiratory Flow (PEF) (2.5%), which were all statistically significant from 3 months into the study ($p<0.05$). It should be noted that participants continued to smoke some cigarettes, and, because there was no control group, it is not clear whether lung function would be different if subjects used conventional cigarettes exclusively, or neither e-cigarettes or conventional cigarettes.

The industry funded US randomised trial by D'Ruiz et al. summarised above (D'Ruiz, O'Connell et al. 2017) (n=105) also measured **lung function** following short term (4 day) use of e-cigarettes in conventional tobacco smokers. Exclusive e-cigarette use (n=45) (three groups testing three flavourings), dual use (n=45) (three groups testing three flavourings) and those who ceased both tobacco and nicotine products (n=15) were compared.

Observed changes in measured forced vital capacity (FVC) from baseline to day 5 were small (from -0.9% to 3.1%), with small increases for exclusive tobacco flavoured rechargeable e-cigarette use (p= 0.02) and cherry flavoured rechargeable (p=0.01) e-cigarette groups. There were no significant differences between any of the product use groups and nicotine cessation group on FVC. Increases in forced expiratory volume (FEV_1) were observed (from baseline to day 5) for the exclusive e-cigarette tobacco flavoured rechargeable (p=0.015), exclusive cherry rechargeable (p=0.028) and dual cherry rechargeable product use groups (p=0.019). There were no differences in FEV_1 between any of the product use groups and nicotine cessation groups. No measurement of conventional cigarette use was given for the smoking cessation control group, but the study took place in a clinic environment, so it is assumed that cessation was successful. Frequent Adverse Events (AE) reported were headache, followed by cough and sore throat (2-7/15 subjects across all groups and 1 in the cessation group reported AEs). This study would have benefited by having a

control group, and has questionable statistical power to detect differences between groups over a relatively short time period.

In a randomised crossover trial design, Kerr et al. (Kerr, Touyz et al. 2017) compared the immediate effects of vaping an e-cigarette with conventional smoking in 20 male smokers from the UK on various respiratory outcomes. Following smoking an e-cigarette, there was a significantly smaller Peak Expiratory Flow (PEF) (531 ± 97 vs 567 ± 62 L/min, p=0.03) whereas no significant change was observed with conventional cigarette smoking. There were also no statistically significant changes observed in FEV_1, FVC and FEV_1/FVC after vaping or conventional cigarette smoking (all p>0.05).

A private foundation funded randomised crossover study (n=54) by Lappas et al. conducted in Greece also considered the immediate effects of e-cigarette use in dual smokers who were either mild asthmatics (MA, n=27) or healthy smokers (HS, n=27) (Lappas, Tzortzi et al. 2018). There was a control session where there were no liquid or resistance coils used and an experimental session where participants puffed on an e-cigarette for 5 minutes only (containing propylene glycol 46.13% w/v, glycerol 34.3% w/v, nicotine 1.18% w/v, 12mg/ml nicotine, set to 3.7V). **Lung function** spirometry was used to test forced expiratory flow (FEF) (FEF25-75%, FEF 25, FEF 50%, FEF 75%), forced expiratory volume in 1s (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio and resonance frequency (f_{res}), as well as fractional exhaled nitric oxide (FeNO) and parameters of the impulse oscillometry system (IOS). Mild asthmatics exhibited lower baseline values on **spirometry** tests for all parameters (p<0.05) except FVC. Mild asthmatics showed higher baseline **IOS** (Impulse Oscillometry System) **values** than healthy smokers for respiratory system total impedance at 5Hz (Z5), respiratory system resistance at HZ (R10) and resonance frequency (f_{res}) (all p<0.05). FeNO values at baseline were not significantly different between groups for the control or experimental groups.

For the experimental sessions, immediately post e-cigarette use, both groups (healthy and mild asthmatic) exhibited a significant increase in respiratory system total impedance (as shown by IOS values) at 5Hz (p<0.001), respiratory system resistance at 5Hz (p<0.001) at 10Hz (p<0.001) and 20 Hz (p<0.05), resonant frequency (p<0.001) and reactance area (p<0.05). Mild asthmatics also showed greater effects (higher degree of change over time) after smoking an e-cigarette than healthy smokers, as indicated by differences between respiratory system total impedance at 5Hz (P<0.022), respiratory system resistance at 5Hz (p<0.01) and respiratory system resistance at 10Hz (p<0.01). **Fractional exhaled nitric oxide** (FeNO) decreased significantly in both groups immediately after e-cigarette use (p<0.001). For FeNO, healthy smokers returned to baseline values in ≤ 15 minutes while the mild asthmatics maintained significantly lower values for an additional 15 minutes (p<0.05) and returned to baseline values at 30 minutes post e-cigarette use.

The study showed that use of EVP was associated with greater short-term respiratory effects indicating increased airway obstruction in dual users with mild asthma compared with those without.

A prospective cohort study focussing on chronic obstructive pulmonary disorder (COPD) (Oelsner, Hoffman et al. 2017) included a cross sectional analysis of **lung density** amongst its (self-reported)

ever-smokers (n=981), including ever e-cigarette users (n=125) with and without COPD (Oelsner, Hoffman et al. 2017). The study undertook CT scans to determine the lung density of dual users of conventional and e-cigarettes (n=16), current conventional cigarette smokers without e-cigarette use (n=326), former conventional cigarette smokers with current e-cigarette use (n=9) and former smokers without e-cigarette use (n=628). Lung density was measured by Low Attenuation Areas in the lungs (LAA-910) – this is defined as a percentage of total lung voxels less than -910 Hounsfield Units on inspiratory CT (LAA-910) (higher scores show a lower lung density/lung attenuation).

It was found that the mean LAA-910 was higher in 16 dual users of conventional and e-cigarettes compared to 326 current smokers without e-cigarette use (27% vs 19%) and in 9 former smokers with current e-cigarette use versus 628 former smokers without e-cigarette use (38% vs 31%). Current use of e-cigarettes was associated with significantly higher LAA-910 (p=0.028) whereas conventional cigarette use was associated with lower LAA-910 (p < 0.001). In adjusted models, **current e-cigarette use showed a trend towards higher LAA-910** (+5.1%, 95% CI -0.7% to 10.9%, p=0.086), however this association was not independent of total lung volume on CT, which was significantly higher in e-cigarette users (+0.60 L, 95%CI 0.16 to 1.05, p=0.008).

The study (reported in abstract form) concluded that current e-cigarette use showed a trend towards association with lower CT lung density, attributed to larger lung volume. There was only a small number of current e-cigarette users in the study (i.e. only 9 former smokers with current e-cigarette use) and further investigation is required. It was also unclear how long the e-cigarette users had used e-cigarettes based on information reported.

Reidel et al.'s US cross-sectional study (n=44) sought to understand how exposure to e-cigarette vapours modifies **human airway biology** compared with traditional cigarette smoking, to identify the effects e-cigarettes might have on lung physiology and to determine how the use of e-cigarettes and conventional cigarettes impacts the airway innate immune response (Reidel, Radicioni et al. 2018). The primarily in-vitro study collected sputum, plasma and urine samples (the latter two samples in order to test cotinine and NNAL, discussed elsewhere) from 14 current cigarette smokers, 15 current e-cigarette users and 15 never smokers. Compared with non-smokers, induced sputum from e-cigarette users contained approximately 81 proteins with significantly altered abundance, compared with approximately 44 proteins with altered abundance in sputum from cigarette smokers.

The Reidel et al. study particularly noted:

- The increased abundance in the sputum of e-cigarette users of secreted proteins related to the innate defence functions of leukocytes: these included primary neutrophil granule proteins, such as neutrophil elastase (NE), proteinase 3, azurocidin 1 and myeloperoxidase (MPO) where levels were significantly higher in e-cigarette users than in cigarette smokers or non-smokers, with slightly (but non-significantly) increased levels in the cigarette user group.

- E-cigarette users had significantly higher aldehyde-detoxification and oxidative stress-related proteins associated with cigarette smoke compared with non-smokers.

- In cigarette smokers, there was an upregulation of markers known to be associated with smoking (the secreted aldehyde-detoxifying enzyme aldehyde dehydrogenase 3A1

ALDH3A1, microseminoprotein B and nucleobindin-1 and antithrombin 3) as well as oxidative stress response proteins (e.g. thioredoxin and gluthione S-transferase). However, the levels of other known in vivo and in vitro markers of cigarette smoke exposure were also elevated in the e-cigarette users (e.g. ALDH3A1, thioredoxin and glutathione S-transferase).

- There were elevated levels of mucosal defence proteins in the sputum of cigarette smokers but not e-cigarette users. Conversely, levels of defence proteins such as deleted in malignant brain tumors 1 (DMBT1) and Endoproteinase Lys-C (LYSC) were significantly lower in e-cigarette users when compared with non-smokers.

- Levels of innate defence proteins associated with chronic obstructive pulmonary disease, such as elastase and matrix metalloproteinase-9, were also significantly elevated in e-cigarette users.

- E-cigarette users' sputum also exhibited significant abundance of neutrophil granulocyte-related and NET related proteins, such as myeloperoxidase (MPO), azurocidin 1, and protein-arginine deiminase 4, despite no significant elevation in neutrophil cell counts. Peripheral neutrophils from e-cigarette users showed increased susceptibility to phorbol 12-myristate 13 acetate-induced NETosis.

- A compositional change in the gel-forming building blocks of airway mucus (i.e. elevated concentration of mucin) was observed in both cigarette smokers and e-cigarette users (Reidel, Radicioni et al. 2018).

The Reidel et al. (Reidel, Radicioni et al. 2018) study adds support to other research on chemical exposure from e-cigarette use regarding aldehydes and on oxidative stress, particularly in relation to its findings regarding sputum containing aldehyde detoxification and oxidative stress related proteins. However, in two animal studies cited in the US Academies of Sciences review, levels of the antioxidant enzyme glutathione S transferase decreased rather than increased as they had in Reidel et al.'s study. In regards to conventional cigarette versus e-cigarette use, the authors conclude that e-cigarette use alters airway physiology in humans in some ways that are similar to the effects of conventional smoking, and in others that differ.

In cross sectional study (n=203) (Gucht, Adriaens et al. 2017), vape shop owners referred their customers (mean age 46 years), most of whom had been conventional cigarette smokers, to an online survey. The most frequently reported benefits of vaping e-cigarettes were improved breathing (44.7%, 95% CI 0.37, 0.53), less coughing (34.9%, 95% CI 0.28,0.43), better physical health (34.2%, 95% CI 0.27, 0.42), feeling fitter (17.1%, 95% CI 0.12, 0.24), improved sense of taste (15.1%, 95% CI 0.10, 0.22), improved sense of smell (11.1%, 95% CI 0.07, 0.17), improved skin (9.2%, 95% CI 0.05, 0.15) and improved gums and teeth (5.9%, 95% CI 0.03, 0.11). The most obvious limitation of this study is the bias inherent in selection, and the reliance on self-reporting. However, it may represent the perceptions of improved health of many vapers who had previously smoked.

14.2.1 Conclusion

There appears to be little immediate difference on the lung function of smokers following smoking a cigarette compared to vaping an e-cigarette (Kerr, Touyz et al. 2017), and a suggestion of small improvement in FEV_1 after four days among smokers who switched to e-cigarettes or dual use (D'Ruiz, O'Connell et al. 2017) which were statistically significant for some groups only. There was not a statistically significant difference in FEV_1 after four days in the group of smokers who ceased cigarette use (and all sources of nicotine). Over two years, Walele et al. (Walele, Bush et al. 2018) reported small decreases in lung function for former smokers who used e-cigarettes which the authors classify as not clinically relevant. However, this study had an attrition rate above 50%, and did not have a comparison group of continuing smokers to assess whether the smokers switching to e-cigarettes had a benefit in lung function over continuing smokers. The literature reviewed does not provide strong evidence that use of e-cigarettes improves lung function in smokers.

Two studies (Oelsner, Hoffman et al. 2017, Reidel, Radicioni et al. 2018) highlight that e-cigarettes have an impact on the lungs that is different to that of conventional cigarettes, however the implications of these differences on lung health is not known.

> **Previous reviews**
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> The US Academies of Science Review (Stratton, Kwan et al. 2018) concluded in relation to respiratory diseases that:
> - There is **limited evidence** for improvement in lung function and respiratory symptoms among adult smokers with asthma who switch to e-cigarettes completely or in part (dual use).
> - There is **limited evidence** for reduction of chronic obstructive pulmonary disease (COPD) exacerbations among adult smokers with COPD who switch to e-cigarettes completely or in part (dual use).
>
> Key findings from the Public Health England (McNeill A 2018) review were that:
> - 'Comparative risks of ... lung disease have not been quantified but are likely to be also substantially below the risks of smoking.
> - '… small scale or uncontrolled switching studies from smoking to vaping have demonstrated some respiratory improvements.'

14.3 Exposure to toxins and carcinogens

The US cross-sectional study (n=44) by Reidel et al. (Reidel, Radicioni et al. 2018) considered carcinogens including NNAL levels in the urine samples of 14 current cigarette smokers (smoking 11 cigarettes/day on average), 15 current e-cigarette users and 15 never smokers. For e-cigarette users in this study, the average number of puffs inhaled per day was 280 (they had been predominantly exclusive users for six months, but 12/15 had previously smoked cigarettes and 5/15 still occasionally smoked cigarettes). Average urine NNAL levels were significantly lower in e-cigarette users compared with smokers. In smokers, NNAL levels were significantly correlated

with the number of cigarettes smoked per day (p<0.05). NNAL levels were not correlated with number of puffs per day in e-cigarette users. Most e-cigarette users had urine NNAL levels comparable with those observed in non-smokers – which was said to indicate exclusive e-cigarette use.

Another US cross sectional study (Rubinstein, Delucchi et al. 2018) sought to assess in **adolescents** (aged 13-18 years, n=103) the presence of certain **carcinogenic toxicants** linked to e-cigarette use and examine how specific behavioural patterns of use may influence exposure to toxicants. The study population was 67 e-cigarette only users, 16 dual users of conventional cigarettes and e-cigarettes and 20 age matched controls (not using e-cigarettes or conventional cigarettes).

The groups substantially differed in their use of e-cigarettes, with e-cigarette only users reporting their e-cigarettes use to be a mean of 12.8 days/month (SD 8.9) compared with 25.5 days/month (SD6.6) for dual users (p<0.001). E-cigarette only users who used nicotine containing e-cigarettes also reported using these more frequently, with an average use of 15.1 days/month (SD9.2) compared with 7.6 days/month (SD5.6) (p<0.001) for e-cigarette users who did not use nicotine containing e-liquids. The study tested for the presence of five carcinogenic Volatile Organic Toxicants (VOCs): acrylonitrile (CNEMA), acrolein (3-HPMA), propylene oxide (2-HPMA), acrylamide (AAMA) and crotonaldehyde HMPMA). It also considered biomarkers of nicotine (see below) and tobacco-specific nitrosamine.

Urine excretion of metabolites of benzene (PMA), ethylene oxide (HEMA), acrylonitrile (CNEMA), acrolein (3-HPMA), and acrylamide (AAMA) was significantly higher in dual users compared to e-cigarette only users and controls (all p<0.05). Urine excretion of PMA, HEMA, CNEMA, 3-HPMA, and AAMA was significantly higher in dual users versus e-cigarette–only users and controls. However, excretion of metabolites of the five VOCs was significantly higher in e-cigarette only users compared with controls (all p<0.05): acrylonitrile (341% higher than controls but 327% lower than in dual users), acrolein (20% higher than controls but 11% lower than in dual users), propylene oxide (51% higher than controls but 8% lower than in dual users: 2HPMA), acrylamide (30% higher than controls but 23% lower than dual users), and crotonaldehyde (20% higher than controls but 7% lower than in dual users: HMPMA). The average number of sessions of e-cigarette use per day was associated with increased levels of CNEMA (r=0.36, p=0.003). Days of e-cigarette use in the past month was not associated with any increases in urinary VOC levels among e-cigarette users only. There were no differences in levels of the five VOCs that were based on the type of e-cigarette product used. Participants who reported using fruit flavours in the past month had higher CNEMA levels than those who did not (p=0.03).

The study also notes that among e-cigarette users only, the VOCs CNEMA and AAMA were higher in users of nicotine containing e-cigarettes. Levels of the three other significant and likely toxic VOCs were just as high in users of non-nicotine products - this was considered important because adolescents often initiate e-cigarette use with nicotine free products. The use of fruit flavoured products produced significantly higher levels of the metabolites of acrylonitrile. Fruit flavours were also the most popular choice among the adolescent e-cigarette users in the study. Levels of VOCs detected in adolescent e-cigarette users were on average lower than those reported among adults in other studies. In the absence of a group that used conventional cigarettes only, it is relevant that the urinary levels of the five VOCs were higher in the dual users than the e-cigarette only

group. This suggests that replacing conventional cigarettes with e-cigarettes lowers exposure to these chemicals.

A small (n=20) Polish experimental study (a two week trial with no control group) by Goniewicz et al. examined exposure to **selected carcinogens and toxicants** as a result of e-cigarette use (Goniewicz, Gawron et al. 2017). Subjects (aged 20-52 years, mean age 31 years) switched from smoking conventional cigarettes (for an average of 12.1 years, and 16 cigarettes per day) to smoking e-cigarettes for a period of just two weeks (pen-style M201 e-cigarette with nicotine levels 8.4 ± 1.1mg with 150 puffs). However, subjects did not give up smoking completely: the average number of conventional cigarettes smoked per day declined at week 1 to 0.8 (p<0.001) and at week 2 to 0.6 (p<0.001) per day for all participants (nine had ceased altogether). The study measured seven nicotine metabolites and 17 tobacco smoke biomarkers in urine. Biomarkers were metabolites of 13 major carcinogens and toxicants in cigarette smoke: one tobacco specific nitrosamine (NNK), eight volatile organic compounds (1,3-butadiene, crotonaldehyde, acrolein, benzene, acrylamide, acrylonitrile, ethylene oxide, and propylene oxide) and four polycyclic aromatic hydrocarbons (naphthalene, fluorene, phenanthrene and pyrene). Expired carbon monoxide was also measured. **Statistically significant declines in 12 out of 17 measured biomarkers of exposure to toxicants were observed**.

Exposure to several tobacco related carcinogens was substantially reduced, namely NNK, 1,3-butadiene and benzene. Declines in some biomarkers (PAHs) were mainly driven by participants who switched completely from tobacco cigarettes to e-cigarettes. Total mean levels of nicotine (p=0.53) and some polycyclic aromatic hydrocarbon metabolites remained largely unchanged after switching from tobacco to e-cigarettes (nicotine results reported below). All other biomarkers aside from nicotine significantly decreased after one week of using e-cigarettes (p<0.05). After one week, the greatest percentage reductions in biomarker levels were observed for metabolites of 1,3-butadiene, benzene, and acrylonitrile (all p<0.05). Total nitrosamine (NNAL)[4], a metabolite of NNK, declined by 57% and 64% (p<0.001) after one and two weeks respectively.

Among biomarkers of exposure to PAHs, mean levels of 1-hydroxyflourene, 2-hydroxyflourene and 3-hydroxyfluorene significantly declined (all p<0.05). Levels of 3-hydroxyfluorene levels declined by 46% at week one, and 34% at week two. There were no statistically significant changes in mean levels of 3-, 4-hydroxyphenanthrene (p=0.38), 1-hydroxypyrene (p=0.32), 2-hydroxyphenanthrene (p=0.126), 1-hydroxyphenanthrene (p=0.076) or 2-naphthol (p=0.095). The overall decline in levels of 3-hydroxyfluorene were significant among those who were abstinent at week one (p=0.004) and those who were abstinent at week two (p=0.001) whilst no statistically significant declines were observed among those who continued to use conventional cigarettes. Significant improvements in chest tightness (p=0.024) and visual disturbances (p=0.02) were also reported. Notably, the M201 model of e-cigarette used in the study was screened for selected toxicants and

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[4] The CDC states that 'NNAL is a product formed after 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) enters the body. NNK belongs to a group of chemicals called tobacco-specific *n*-nitrosamines (TSNA)…NNK causes cancer in people.' It is known as a lung carcinogen. https://www.cdc.gov/biomonitoring/NNAL_FactSheet.html

it was found that it generated aerosol with significantly less potential toxicants when compared with other similar e-cigarette models.

In a UK cross-sectional study by Shahab et al. (n=71, mean age 37.8 years), exposure to **carcinogens and toxins** (and nicotine, reported below) was considered among long term users of e-cigarettes (Shahab, Goniewicz et al. 2017). The study sought to compare such exposure among five groups:

1. Smokers of conventional cigarettes only (average of > 5 per day for at least 6 months).
2. Former smokers (ceased for at least 6 months) with long-term e-cigarette use (at least weekly for ≥6 months) only.
3. Former smokers with long-term nicotine replacement therapy (NRT) use (at least weekly for ≥6 months) only.
4. Long-term dual users of both conventional cigarettes and e-cigarettes.
5. Long-term users of both conventional cigarettes and NRT.

Long term NRT use or e-cigarette only use among former smokers was associated with substantially reduced levels of selected carcinogens and toxins compared with conventional cigarette smoking, but dual use of NRT and conventional cigarettes and dual use of e-cigarettes and conventional cigarettes did not show the same reductions. E-cigarette use only was not associated with greater benefits than NRT use only. The NRT only and e-cigarette only users had significantly lower NNAL levels than conventional cigarette only, dual conventional cigarette-NRT and dual conventional cigarette-e-cigarette users ($p<0.001$). **E-cigarette only users had significantly lower NNAL levels** than all other groups, a **97% reduction** compared with levels of conventional cigarette-only users. Compared with conventional cigarette only users, there were no large differences in NNAL levels for dual conventional cigarette-e-cigarette users, but dual conventional cigarette-NRT users had 'somewhat' lower NNAL levels. **E-cigarette users had the lowest levels of VOCs overall**; compared with all other groups, NRT only and e-cigarette only users had at least half of the reference values of conventional cigarette only users, and had significantly lower levels of all major metabolites of selected toxic and carcinogenic VOCs (all $p<0.001$). E-cigarette only users had a level of acrylonitrile that was 2.9% of that of conventional smoker levels (range 1.7%-4.7%), whilst for NRT-only users it was 10.5% (range 5.4%-20.6%). Dual conventional cigarette-NRT, dual conventional cigarette-e-cigarette and conventional cigarette only users all had very similar urinary VOC metabolite levels.

The study concludes that e-cigarettes are likely to be beneficial only if there is complete cessation of conventional cigarette smoking, and that full cessation of nicotine products is the best option.

In Walele et al.'s (Walele, Bush et al. 2018) two year industry-funded UK study in which an electronic vapour product (EVP) was tested by former smokers for two years in a real life setting (n=206), the following compounds were measured in 24 hr urine collections: 3-hydroxypropyl mercapturic acid (3-HPMA; a biological marker of exposure to acrolein), S-phenylmercapturic acid (S-PMA; a biological marker of exposure to benzene), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL, a biological marker of exposure to 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone [NNK]) and Propylene Glycol (PG). Over the

course of two years, where most subjects continued to also smoke conventional cigarettes, the urinary level of PG increased, with the other biological markers remaining steady (haven fallen over the first month for subjects smoking only conventional cigarettes immediately prior to the initiation of the study).

A US cross-sectional study (Aherrera, Olmedo et al. 2017) focused on exposure to metals from e-cigarette use and aimed to assess whether e-cigarette use is associated with increased nickel (Ni) and chromium (Cr) exposure as determined by non-invasive biomarkers (urine, saliva and exhaled breath condensate, EBC). The investigators hypothesized a positive association between Ni and Cr biomarkers with increased e-cigarette use and increased Ni and Cr concentrations in the aerosol and tank samples.

For nickel, the US Centre for Disease Control notes health complications in the respiratory tract, immune system and reproductive system following inhalation and/or oral exposure (ATSDR 2014). Chromium is a recognised carcinogen which when inhaled is a respiratory irritant and can cause pulmonary sensitisation (ATSDR 2013).

Subjects (n=59) were **users of e-cigarettes only** and **dual users** of conventional and e-cigarettes who usually used second or third generation tank style/mechanical modified devices. Participants completed four double blind, 2.5 hr sessions where in each session they completed two 10-puff e-cigarettes use bouts (with a 30 sec interpuff interval), separated by 60 minutes. Liquid nicotine concentrations differed by session (0, 8, 18, or 36 mg/ml).

The study found that compared to dual users, **e-cigarette users only had higher levels of Ni and Cr in urine**. Increased tertiles of e-liquid consumption per week was associated with higher urinary, saliva and EBC Ni levels, but in fully adjusted models the association was only statistically significant for the second tertile of e-liquid per week and saliva Ni (Geometric Mean Ratio (GMR) 2.88, 95% CI 1.11, 7.51). Participants who vaped within 15 minutes of waking had a 79% (GMR 1.79, CI 95%, 1.14,2.82) higher urine Ni levels compared to those taking longer to vape. For self-reported use of higher voltage devices, there was a non-statistically significant trend with higher urine Ni levels, with the association only observed for the second tertile (4.06-4.47 V) (GMR 3.65, 95% CI, 1.47,9.07). Changing coils more than three times per month was associated with 91% higher (1.91, 95% CI, 1.23,2.98) urinary Ni levels. Tertiles 2 and 3 of urinary cotinine were associated with 38% and 80% higher urinary Ni levels (p-trend 0.04). Ni levels in e-cigarette dispensers were not associated with Ni biomarkers.

For Cr biomarkers, although adjusted associations were not statistically significant, the two highest compared to the lowest tertile of liquid consumption per week were associated with 28% and 71% higher levels in EBC (p for trend 0.08), 21% and 56% higher in saliva (p for trend 0.26) and 14% and 30% higher levels in urine (p for trend 0.29). Cr levels in dispenser samples were not associated with Cr biomarkers. In adjusted models, comparing the two highest to the lowest aerosol Cr levels was associated with 98% and 193% higher saliva Cr (p for trend 0.02) and Tertile 3 of Cr in tank samples was associated with 178% higher Cr levels in saliva (GMR 95% CI, 1.19, 6.49).

The higher biological levels of nickel and chromium associated with use of e-cigarette suggests that attention should be given to preventing the metals entering the e-cigarette aerosols.

A secondary analysis of the National Health and Nutrition Examination Surveys in US adults examined concentrations of metals in blood (n=483), serum (n=315) and urine (n=321) in people

exclusively using cigarettes, cigars or e-cigarettes (Jain 2018). Metals analysed included 15 different metals in analyses comparing levels between the three groups. For analysis of zinc, copper and selenium the investigators controlled for dietary intake using values estimated from dietary data collected as part of the survey. Adjusted means were significantly different for cobalt and antimony with urine levels lower in the cigar sample compared to the cigarette smokers. Blood levels of **manganese were significantly higher (23.3%) in e-cigarette users but only when compared to cigar smokers**. There were no differences between e-cigarette users and conventional cigarette smokers for any of the 15 metals. It should be noted that the sample size was as low as 14 e-cigarette users in the analysis of urine and serum metals which raises doubt about the power to detect meaningful differences. According the US Centre for Disease Control, toxic levels of manganese can affect neurological function. Normal serum levels range from 4-15µg/L (ATSDR 2012) and e-cigarette users in this study had a mean level of 10.3µg/L.

A large US cross-sectional study by Wei et al. (n=1572) (Wei, Goniewicz et al. 2018) examined whether the use of e-cigarettes potentially increases the body burden of flame retardants in e-cigarette users (n=14), by testing urinary metabolites of organophosphate flame retardants (OPFRs). Also tested were users of smokeless tobacco products (STP) (n=15), conventional cigarette users (n=298), and cigar users (n=22) and non-users (n=1201). The chemicals diphenyl phosphate (DPhP), bis(1,3-dichloro-2-propyl) phosphate (BDCPP), bis(2-chloroethyl) phosphate (BCEP), and dibutyl phosphate (DBUP) were detected in all e-cigarette users. The adjusted geometric mean (GM) of BCEP, the metabolite of tris(2-chloroethyl) phosphate (TCEP), was **81% higher in e-cigarette users** than non-users (p=0.012) and significantly higher than that for both conventional cigarette and cigar users (p<0.05) where the GM for both was similar to non-users. The adjusted GM of DBUP, DPhP and BDCPP for e-cigarette users, and for cigarette users, was not significantly different to that of non-users.

It should be noted for this study that the number of subjects in the e-cigarette and the smokeless tobacco product group was small (n=14 and n=15 respectively).

14.3.1 Conclusion

The studies reviewed here provide a consistent picture of lower or reduced carcinogens and toxicants in people who use e-cigarettes exclusively relative to conventional cigarette use. These conclusions are consistent across the different study conditions including duration of use. Studies also indicated higher levels of nickel and chromium in exclusive e-cigarette users (Aherrera, Olmedo et al. 2017) and flame retardants (Wei, Goniewicz et al. 2018), indicating that there may be toxicant risk specific to the e-cigarette device.

Previous reviews

The US National Academies of Sciences, Engineering and Medicine Review [3] concluded that:

- 'There is **no available evidence** whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for comparisons of e-cigarette use compared with combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products.

14.4 Nicotine exposure and dependency

In Walele et al.'s (Walele, Bush et al. 2018) two year industry-funded UK study in which an electronic vapour product (EVP) was tested by former smokers for two years in a real life setting (n=206), nicotine equivalents (NEQ) were measured in urine. In this study, subjects were allowed to continue smoking conventional cigarettes. The study found that **NEQ levels had decreased by 12.4% from baseline to month 1, but increased to the end of the two year study**, and at the end of the study, mean NEQ levels for all subjects were 10.1% higher than at baseline (95%CI). Nicotine withdrawal effects were measured using the Minnesota Nicotine Withdrawal Scale (MWS-R). The overall mean MWS-R score initially slightly increased from baseline 4.6 (±6.1) rising to 5.4 (±5.5) at month one, before decreasing to 3.3 (±4.2) at the end of the study. Smoking desire as measured by QSU-brief also decreased, going from an overall mean baseline score of 19.2 (±11.5) to 13.3 (±5.2) at 12 months, and remained stable to be 12.4 (±5.5) by the end of the study. The authors make the important point that the study had a high attrition rate, with only 102 subjects completing the study. Desire to smoke conventional cigarettes might be higher amongst those who left the study.

In Goniewicz et al.'s small and short term experimental study (n=20) conducted in Poland, where conventional smokers switched to e-cigarette use, the effects of e-cigarettes on nicotine delivery was measured as well as exposure to selected carcinogens (as described above). Subjects (average age 31 years) were smokers who switched to pen-style M201 e-cigarettes (containing 11.0 ± 1.5mg of nicotine in a mixture of propylene glycol and vegetable glycerin (50:50), which under laboratory conditions generated nicotine levels of 8.4 ± 1.1mg with 150 puffs) for two weeks. It was found that total mean **levels of nicotine equivalents** measured in urine did not change (p=0.53) and some polycyclic aromatic hydrocarbon metabolites also **remained largely unchanged** after switching from tobacco to e-cigarettes. At week one, four (20%) participants increased total nicotine equivalents by greater than 50%, while six (30%) experienced a reduction in total nicotine levels. Results on the Minnesota Nicotine Withdrawal Scale showed an overall significant **decline in withdrawal symptoms** (reduction in MNWS scores) over the two-week period (n=0.005), driven by significant declines in 'desire or craving to smoke' (p=0.002) and 'restlessness' (p=0.049).

In a US cross-sectional study with adolescents (aged 13-18 years, mean age of e-cigarette only users 16.3 years and dual users 17.1 years), Rubinstein et al. (Rubinstein, Delucchi et al. 2018) found the levels of salivary cotinine among e-cigarette only users to be significantly associated with the number of days using an e-cigarette in the past 30 days (r=0.34, p<0.01) and the mean

number of use sessions a day (r=0.75, p<0.001). **Dual users** of e-cigarettes used their e-cigarettes more frequently than e-cigarette only users (25.5 (SD 6.6) days versus 12.8 days (SD 8.9), p<0.001). E-cigarette with nicotine only users reported using their e-cigarettes more frequently than e-cigarette only users who did not have nicotine in their e-cigarettes, with an average use of 15.1 days (SD 9.2) per month compared to 7.6 days (SD 5.6) per (p<0.001), and averaged 2.5 (SD 4) sessions per day versus 0.65 (SD 0.61) sessions per day (p<0.01).

In Shahab et al.'s UK cross-sectional study (Shahab, Goniewicz et al. 2017), nicotine was measured in conventional cigarette only users, formers smokers with long term (>6 months) e-cigarette only or NRT use, and long term dual conventional cigarette-e-cigarette or conventional cigarette-NRT users (n=36 to 37 per group, total n=181). In the adjusted analysis, users of all products had nicotine equivalent levels (urinary biomarkers) at least as high as conventional cigarette only users, however findings related to salivary biomarkers varied. In adjusted models with adjusted nicotine biomarker levels by group as a proportion of cigarette-only smoker levels, nicotine (in saliva) was lowest in e-cigarette only users (60.4, 35.8-101.8) and dual cigarette-NRT users (64.2, 39.2-104.9) and highest in dual cigarette-e-cigarette users (152.2, 90.7-255.1) and NRT-only users (135.1, 68.1-268.0). As nicotine intake from e-cigarette use was considered to be largely similar with NRT only use, greater craving reductions observed in e-cigarette users from previous studies was linked to the greater similarity between conventional smoking and vaping e-cigarettes.

Hiler et al.'s (Hiler, Breland et al. 2017) US randomised crossover study (n=64) tested whether liquid nicotine concentration and users' experience with e-cigarettes influenced outcomes such as nicotine delivery (as measured by plasma nicotine levels) in smokers who were experienced with e-cigarettes (n=33) and those who were new to e-cigarettes (n=31). Participants used an 'eGo' 3.3V, 1000 mAh battery with a 1.5, dual-coil, 510-style cartomizer (7.3W), loaded with 1 ml of flavoured liquid (tobacco or menthol) (70%PG and 30%VG) and differing nicotine levels (0, 8, 18, 36 mg/ml). This device was chosen after testing revealed that their nicotine emissions approached those of a tobacco cigarette under some conditions. **Plasma nicotine levels were higher for those who were more experienced with e-cigarettes**: when using 36mg/ml nicotine e-cigarettes, mean plasma nicotine increase for e-cigarette experienced individuals was 17.9 mg/ml (SD 17.2) and 6.9 mg/ml (SD7.1, p<0.05) for individuals unfamiliar with the use of e-cigarettes. Between group differences were attributed to longer/larger puffs being taken by experienced e-cigarette users. E-cigarette use suppressed nicotine/tobacco abstinence symptoms in both groups.

A number of studies have considered nicotine dependence. Ashford et al.'s US prospective cohort study sought to ascertain the patterns and predictors of prenatal dual cigarette use (n=117) and studied pregnant women (18-44 years) in their first trimester who used conventional cigarettes, e-cigarettes and dual users (Ashford, Chavan et al. 2018). Nicotine dependence was measured using the Fagerstrom Test for Nicotine Dependence (FTND – a questionnaire of six questions) which has a range of 0-10. The study found that prenatal **dual use** of both conventional and e-cigarettes and increased depressive symptoms were significantly associated with higher nicotine dependence (p=0.007). Dual users also had an average of one point higher on the Fagerstrom Test

for Nicotine Dependence (beta =0.93; p=0.034) compared to conventional cigarette users. Every 5-point increase in depressive symptoms was associated with a 0.5 point increase in nicotine dependence (p=0.019).

In Gonzalez-Roz et al.'s cross-sectional study (Gonzalez Roz, Secades Villa et al. 2017) conducted in Spain, nicotine dependence was evaluated in e-cigarette users (who were former smokers) (n=39) and current conventional tobacco users (n=42), using the Fagerstrom Test for Nicotine Dependence (FTND) and the Nicotine Dependency Syndrome Scale (NDSS), along with a urinary cotinine analysis. It was found that e-cigarette users were dependent on e-liquids containing nicotine but were less nicotine dependent than current tobacco cigarette smokers. Biochemical measures of carbon monoxide and self-reported questionnaires found nicotine dependence on e-cigarettes to be lower than was observed in cigarette smokers. On the FTND measure, the overall difference between groups was significant (e-cigarette 4.38±1.93 vs tobacco 5.57±1.48, t-3.1,p=0.003) as were the differences for the NDSS-T (e-cigarette 26.26±5.9 vs tobacco 40.50±8.14, t-9.4, p<0.001), NDSS Impulsivity (e-cigarette 10.46±4.72 vs tobacco 19.98±5.14, t-8.7, p<0.001), NDSS Priority (e-cigarette 4.82±1.57 vs tobacco 7.81±3.07, t-5.5, p<0.001), NDSS Tolerance (e-cigarette 14±3.41 vs tobacco 22.19±3.93, t-10.0, p<0.001), NDSS-Continuity (e-cigarette 23.13±3.91 vs tobacco 25.90±4.86, t-2.8, p=0.006) and NDSS Stereotype (e-cigarette 11.64±2.95 vs tobacco 13.21, t-2.2, p=0.031) sub-scales. It was noted that validated measures of the scales were not able to be used in the study due to the small sample size of e-cigarette users. Lack of a randomised trial design means that the difference in nicotine dependence cannot be attributed to the use of e-cigarettes – people who are less nicotine dependent may be more likely to become e-cigarette users and maintain that use, for example.

Finally, Brown and Todd (Browne and Todd 2018) report on e-cigarette use in a sample of former smokers recruited online from discussion forums. The 436 participants (80% male) completed the FTND, a version modified to suit current vaping, and various measures of consumption. Questions on past behaviours were asked retrospectively. Average cigarettes per day among ex-smoking vapers in this sample was reported to have dropped dramatically from 15.72 to 0.28 after users starting vaping. The investigators found a strong and consistent reduction in dependence after transitioning to vaping. However they also report that nicotine levels increased over time; noting that this is moderated by intention to reduce nicotine intake. Overall, dependence did not increase with the number of years a subject had been vaping.

14.4.1 Conclusion

While a Spanish study suggested that e-cigarette users may be less addicted to nicotine relative to conventional smokers (Gonzalez Roz, Secades Villa et al. 2017), another in pregnant women suggests that dual users may be more addicted than conventional cigarette smokers (Ashford, Chavan et al. 2018). The Walele et al (Walele, Bush et al. 2018) study suggests a decline in the desire to smoke over 12 months which remains consistent at two years, however the high attrition rate means that this applies only to those who remained in the study.

In terms of nicotine levels associated with e-cigarette use in smokers, the results are mixed. Walele et al (Walele, Bush et al. 2018) reported an initial decrease in nicotine level followed by an increase over the following two years based on their real world study where smokers combined cigarettes and e-cigarette use. Whether e-cigarettes are used in combination with conventional cigarettes, and whether the subjects are aiming for smoking cessation are likely to be important factors in regard to ongoing nicotine dependency amongst smokers. Each of these studies reports on designs with various levels of control over use of conventional cigarettes along with e-cigarettes and participant compliance to use the product. Additionally, the Hiler et al. study demonstrated that nicotine exposure with e-cigarettes is associated with how they are used, with experienced e-cigarette users having longer and more frequent puffs of e-liquid and therefore receiving higher amounts of nicotine.

14.5 Other health outcomes

14.5.1 Oxidative stress

Chaumont et al. (Chaumont, Bernard et al. 2018) engaged 23 occasional smokers to test e-cigarettes, and found that a single session of e-cigarette use (25 puffs) did not lead to a rise in plasma oxidative stress biomarkers or superoxide anion production in human umbilical vein endothelial cells incubated with participants sera over two hours. There was no difference compared to sham vaping (i.e. same puffing procedure without the e-cigarette turned on).

However, a Greek study (Ikonomidis, Vlastos et al. 2018) in smokers indicated increased oxidative stress (MDA plasma concentrations increased) immediately following use of e-cigarettes and conventional cigarettes, however the increase in MDA concentration was less for e-cigarettes than for conventional cigarettes (P<0.05). After use for one month, MDA concentration was significantly reduced in both a dual use group and an e-cigarette group, however this was in a context where conventional cigarette use was strongly reduced in both groups. A lower number of cigarettes smoked per day was associated with a lower MDA concentration (r=0.32, p=0.02).

Previous reviews

The US Academies of Science review concluded that

'There is substantial evidence that components of e-cigarette aerosols can promote formation of reactive oxygen species/oxidative stress. Although this supports the biological plausibility of tissue injury and disease from long-term exposure to e-cigarette aerosols, generation of reactive oxygen species and oxidative stress induction is generally lower from e-cigarettes than from combustible tobacco cigarette smoke.'

14.5.2 Skin microcirculation

A small study from Belgium (Chaumont, Bernard et al. 2018) also considered **skin microcirculatory flow** after smoking just **one e-cigarette** for just 25 puffs (as compared with sham vaping). Subjects were young occasional smokers (mean age=23 years, 0.25 pack/year) who were selected on the basis of their 'vaping tolerability' (Chaumont, Bernard et al. 2018). The e-cigarette fluid dose used contained 24mg of nicotine (propylene glycol mix (50:50), vaporised at 60 watts). The study found that exposure to this e-cigarette led to a skin tissue hypoxia (assessed by the PeriFlow system 5000, PF5040) with the nadir reached 30 minutes after exposure (mean ±SEM) (84 ± 2 mmHg to 70 ± 4 mmHg; $p < 0.001$ vs baseline).

14.5.3 Cognitive performance and mental health

Caponnetto et al.'s (Caponnetto, Maglia et al. 2017) small, industry-funded Italian randomised cross-over study of cigarette users (n=34) sought to determine if different e-cigarette models (use for around 1 day per product) and/or smokers' conventional cigarette use had an impact on cognitive performance, craving and gesture. In relation to craving measures, craving significantly increased in the conventional cigarette ($F_{(5,29)}=18.3$, $p < 0.001$), second generation cigalike with 24mg nicotine ($F_{(5, 29)}=3.9$, $p < 0.001$) and personal vaporiser with 24mg nicotine groups ($F_{(5,29)}=4.19$, $p < 0.001$), but not in the first generation rechargeable with 24mg nicotine or second generation rechargeable with 0mg nicotine. The authors report that all cognitive measures of attention, executive function and working memory were not influenced by the different e-cigarettes (including those with and without nicotine) or by gender. Therefore, Caponnetto et al.'s short term study showed an increase in withdrawal symptoms for some types of e-cigarettes but no effects on cognitive function.

Ashford's (Ashford, Chavan et al. 2018) US prospective cohort study demonstrated an association between nicotine dependence and depression in pre-natal women: every 5 point increase in depressive symptoms was associated with a 0.5 point increase in nicotine dependence ($p=0.019$) as determined by the Fagerstrom Test for Nicotine Dependence.

The Lechner study (Lechner, Janssen et al. 2017) also highlights that young people with depression take up and maintain use of e-cigarettes. The US prospective cohort study (Lechner, Janssen et al. 2017) considered the bi-directional relationship between e-cigarette uptake and sustained use and depressive symptoms in adolescents (n=3,383, mean baseline age 14.1 years). Higher baseline depressive symptoms predicted subsequent use of cigarette (OR=1.02, 95% CI=1.01-1.05), e-cigarette (OR=1.01, CI=1.003-1.02), and dual use of both products (OR=1.02, CI=1.003-1.04) but the odds ratios are very small. Conversely, sustained use of e-cigarettes over 12 months was associated with a greater rate of increase in depressive symptoms over time (when compared with non-users) (b=1.272, SE=0.513, $p=0.01$).

It should be noted that for depressive symptoms at 12 months follow up, only self-reported symptoms for the past week were used in analysis (based on Center for Epidemiological

Studies-Depression Scale, CES-D). Therefore the study suggests that young people with depression are more likely to use e-cigarettes (and/or conventional cigarettes) and, conversely, people who use e-cigarettes over a 12 month period are more likely to show an increase in depressive symptoms. However, this is the expression of an association rather than implying causality.

14.5.4 Oral health

A Saudi Arabian case-control study (n=94) by Javed et al. (Javed, Abduljabbar et al. 2017) assessed and compared periodontal parameters (via a clinical periodontal examination) and self-reported oral symptoms among those exclusively vaping e-cigarettes, conventional cigarette smokers (CS) and never-smokers (NS). Full mouth plaque index (PI), bleeding on probing (BOP), probing depth (PD) ≥ 4mm, and clinical attachment loss (AL) were measured, along with marginal bone loss (MBL) around teeth recorded using digital radiographs and number of teeth missing (MT). **Plaque index** (PI%) (52.1±6.6 (CS) vs 23.3±3.4 (vapers), p<0.01) and **probing depth ≥ 4mm** (PD%) (29.3±1.7 (CS) vs 5.1±1.2 (vapers) p<0.01) were significantly higher for smokers than for e-cigarette users and also never smokers (who did not differ from each other). Bleeding on probing (BOP) was significantly higher in never smokers than for cigarette smokers (27.5±3.2 (NS) vs 5.8±0.8 (CS), p<0.01) and e-cigarette user groups (27.5±3.2 (NS) vs 4.6±2.9, p<0.01). There were no differences in number of missing teeth (MT), clinical attachment loss (AL) and marginal bone loss (MBL) across all groups. Gingival pain was more often self-reported among cigarette smokers than by individuals in the e-cigarette (p<0.01) and never smoker (p<0.01) groups.

The e-cigarette users in this study had been using e-cigarettes daily and exclusively for at least the previous 12 months, so this study does not directly address the impact of e-cigarettes on the oral health of smokers. It does, however, suggest that the oral health of regular vapers is better in some respects than conventional cigarette smokers.

14.5.5   Microbiota

Stewart et al (Stewart, Auchtung et al. 2018) recruited a small group (n=30) of e-cigarette users, tobacco smokers and matched controls in the Houston area in an effort to determine if smoking influences gut and mouth microbiota. They collected and analysed once-off faecal samples, buccal cheek cells and saliva samples and performed gene sequencing. The investigators calculated a diversity score (Simpsons Index) in order to assess the relative abundance of difference species of bacteria. Reduced bacterial diversity can be associated with inflammatory bowel disease, obesity, colorectal cancer and asthma (Stewart, Auchtung et al. 2018). Results indicated that regular use of e-cigarettes did not influence oral or gut bacterial communities. However, tobacco use did when compared to control participants. Specifically tobacco smokers had reduced diversity in faecal samples at levels at which the authors describe as "striking". Given the small sample and the fact that this was designed as a pilot study, these results should be interpreted cautiously. Nonetheless, they provide an interesting direction for further understanding the health effects of smoking.

14.5.6   Body weight

Russo et al (Russo, Cibella et al. 2018) used hospital records obtained from four Italian hospitals to determine any relationship between smoking cessation and weight gain in e-cigarette users. Records over three and a half years were collected and those from patients with cardiorespiratory conditions were divided into three groups: e-cigarette users (n=86, including 50% dual users), and age and sex matched smokers (n=93) and patients who had stopped smoking for at least six months (n=44). 1,258 medical records were reviewed. Data were taken from six and 12 months follow-up visits. The primary outcome of interest was body weight at one year. Body weight change extracted from the paper is shown in Figure 7. Quitters gained 4.8% of their body weight over one year whereas e-cigarette users gained 1.5% of their baseline weight. This study was conducted only among people with cardiorespiratory conditions and may not be generalisable to the general population. The investigators suggest that e-cigarettes may help smokers minimise post-cessation weight gain.

Figure 7: Body weight change of smokers and ex-smokers at 12 months follow-up. Figure from (Russo, Cibella et al. 2018).

15   Modelling studies

A modelling study explored the potential mortality avoided by conventional cigarette smokers taking up e-cigarettes.

In a US study funded by the tobacco industry (Levy, Borland et al. 2018), the aim was to demonstrate the potential health impact from a strategy directed at replacing all or most cigarette smoking by e-cigarette use (taking into account current smokers, never smokers and e-cigarette users). A model is used to consider potential health outcomes/deaths averted if cigarette smokers switched to vaping e-cigarettes (comparing a status quo scenario with a substitution model where vaping replaces cigarettes over a 10-year period). Considering the population aged 15 to 99 years in 2016, modelling included groups such as e-cigarette users that never smoked, e-cigarette users among former smokers, former e-cigarette users and current and former smokers who have not yet switched to e-cigarette use.

In the status quo scenario, the number of smoking attributable deaths for current smokers was calculated by age, sex and year as the product of their excess mortality risks (i.e. current smoker mortality rate minus never smoker mortality rate) multiplied by the number of smokers. A similar rate was calculated for former smokers, then smoking attributable deaths combined for current and former smokers. In the optimistic scenario (e-cigarette use) it is assumed that the prevalence of cigarette use will be reduced to 5% residual prevalence of cigarette use.

In the pessimistic scenario, a 10% residual prevalence of cigarette use is assumed. It is claimed that replacement of conventional cigarettes with e-cigarettes over a 10-year period will prevent 6.6 million deaths and result in 86.7 million fewer life years lost in the 'optimistic scenario'. In the pessimistic scenario, 1.6 million deaths would be averted and 20.8 million fewer life years lost. Separate analyses were provided for cohorts aged 15 years and 35 years in 2016.

It is estimated that the largest gains in terms of life expectancy as a result of switching to e-cigarettes would be among the younger cohort (age 15 cohort).

The Levy et al. study is included in the Public Health England review (McNeill A 2018), Modelling studies have highlighted the harm reduction potential of e-cigarettes where conventional tobacco smokers switch to e-cigarettes. Modelling studies are somewhat premature at this stage, however, as a greater understanding of the health effects of e-cigarettes is needed before accurate models can be developed. Further studies are required to identify the variables that should be included in such modelling simulations and to make appropriate assumptions and estimations regarding health outcomes.

16   Summary of health effects of e-cigarettes for smokers

The health effects of e-cigarettes for smokers are a combination of the reduction in conventional smoking in addition to the increase in use of e-cigarettes. Conventional cigarette smoking has health effects for a period after smoking has ceased, and e-cigarette use can be presumed to have a latent period before its effects are apparent. Chronic health effects occur in the context of the effects of ageing. Ideally, health effects of the use of e-cigarettes in smokers would be examined where they could be compared to the health effects of continuing to smoke. They would also be examined over sufficient time for health effects to occur, and the possibility of results being influenced by more health conscious smokers switching to e-cigarettes, while less health conscious smokers continue smoking could be avoided (by randomisation of smokers seeking to quit for example). However, for a range of reasons, published studies may not achieve an ideal design.

In total, this review included 24 recent studies that addressed health outcomes associated with e-cigarette use in smokers. These studies used a range of designs which provide different information relevant to this relationship. For example, Caponnetto et al. (Caponnetto, Maglia et al. 2017) had smokers use e-cigarettes over a short time period (one day) to observe any immediate effects while Ikonomidis et al (Ikonomidis, Vlastos et al. 2018) had people smoke either a cigarette or an e-cigarette for a month. Very few of the studies included a control group which would allow the observation of the effects of e-cigarette use relative to continued use of tobacco products. No study included long-term follow-up (beyond two years in the study of Walele et al) or were of a size to allow the assessment of disease endpoints such as rate of heart attack or incidence of cancers. Therefore, these studies provide only a weak to moderate level of evidence on health outcomes of e-cigarette use in smokers. Nonetheless, these studies do provide some guidance about risk of cardiovascular disease, respiratory implications, exposure to carcinogens/toxicants, nicotine dependence, oral and skin health as well as mental health.

The results were most consistent for observations about exposure to carcinogens (Reidel, Radicioni et al. 2018, Rubinstein, Delucchi et al. 2018). Most of the studies report that equivalent use of e-cigarettes result in less exposure to carcinogens compared to smoking conventional cigarettes. However, studies also provide evidence about use of e-cigarettes leading to exposure to metals and other compounds inherent in e-cigarettes that are not present in conventional cigarettes (Aherrera, Olmedo et al. 2017). This suggests that attention needs to be given to the constituents of the various e-cigarette products and liquids.

While reductions in systolic blood pressure are reported for smokers using e-cigarettes in some short term studies (D'Ruiz et al.; Caponnetto et al.), in the flawed longer term study of Walele et al no change was seen.

New studies about the impact of e-cigarette use on respiratory function for smokers do not show benefit in the short term (one to four days). It is apparent that e-cigarettes change lung biology in different ways to conventional cigarettes, but the implications of these differences on health are not yet clear.

Finally, a single cross-sectional study suggests that e-cigarette use may be associated with better oral health for many outcomes relative to conventional cigarettes. However, it does not assess whether oral health improves in smokers who switch to e-cigarettes. Another single study suggests that e-cigarette use may be beneficial in order to prevent weight gain for smokers who have quit smoking, although this observation was made on subjects with cardiorespiratory conditions.

16.1.1 What the new studies add to what is already known about e-cigarettes

Overall, the results from this review of recent studies are largely consistent with the conclusions drawn in previous reviews. There is still a need for studies which can appropriately allocate treatments to sufficient subjects for a sufficient time to quantify the health effects of e-cigarettes for conventional cigarette smokers. It is recognised that this is challenging.

- The Public Health England report states that e-cigarettes are 'unlikely to exceed 5% of the harm from smoking tobacco' and that risks of cardiovascular disease are likely to be substantially lower for e-cigarettes (McNeill A 2018). In relation to cardiovascular risk, this review identified studies suggesting lower cardiovascular risk for those switching to e-cigarettes. Switching to e-cigarettes could be associated with either no changes or reduced systolic and diastolic blood pressure. However, a small study linked increased cardiac sympathetic nerve activity to the nicotine in e-cigarettes (Kerr, Touyz et al. 2017).

17 Tables

Table 17: Health outcomes in studies of cigarette smokers

Study	Design	Duration	Population	Groups/comparisons	Funding
Aherrera et al. 2017	Short-term experimental study.	Participants completed four double blind, 2.5 hr sessions where in each session participants completed two 10-puff e-cigarette use bouts (with a 30 sec interpuff interval) separated by 60 minutes.	64 e-cigarette users: 50 sole users of e-cigarettes and 14 dual users (used combustible cigarettes at least weekly). Analyses restricted to the 59 tank style/mods device users (59). There were 14 dual users in the study – it was not clear how many of the dual users were among the 59 final participants of the study. Male and female, numbers not specified, 18 years and older, mean age not specified.	No control group. Analyses restricted to the 59 tank-style/mods device users. Considered variables: e-liquid consumption per week (tertiles), time to first vape from waking (within 15/more than 15min), preferred voltage for e-cigarette use (tertiles), coil change per month (1-2/3 times or more per month) and urinary cotinine (tertiles) as well as corresponding metal levels in samples obtained from the dispenser, aerosol and tank (tertiles).	Cigarette Restitution Fund, State of Maryland. In 2000, the Maryland General Assembly created the Cigarette Restitution Fund (CRF) Program with funds derived from the 1998 Master Tobacco Settlement Agreement with the tobacco industry.
Ashford et al. 2018	Part of a larger prospective cohort study.	Cross-sectional snapshot of those in a larger prospective study.	117 prenatal women. Dual users n =27. Conventional cigarette users n= 90, e-cigarette users. Aged 18-44 years.	Compared dual users with conventional cigarette users.	NR.
Boas et al. 2017	Cross-sectional analytic.	Short-term. NR.	Habitual tobacco cigarette smokers or habitual e-cigarette users (not dual users) who had used tobacco cigarettes or e-cigs, respectively, most days for a minimum of 1 year, in who plasma cotinine levels were elevated. 31 patients enrolled, 3 excluded. 9 healthy nonuser controls, 9 e-cigarette users, 9 tobacco cigarette smokers. M=20, F= 7. Non user control M=6 F=3, e-cigarette users, M=7, F=2, Tobacco cig smoker M=7, F=2. Aged 21-45 years old.	Considered activation of the splenocardiac axis (increased metabolic activity of the hematopoietic and vascular tissues) across the 3 groups (e-cigarette users, tobacco users, non-users).	Tobacco-Related Disease Research Program; American Heart Association, Western States Affiliate, Grant in Aid; the National Institute of Environmental Health Sciences, National Institutes of Health; Training Grant in Molecular Toxicology; Irma and Normal Switzer Dean's Leadership and Science Scholarship and UCLA Clinical and Translational Science Institute.
Browne, Todd 2018	Cross-sectional.	Retrospective	436 current vape users recruited via discussion forums. Participants from UK, Australia, Finalnd, Ireland and the US. 80% Male; mean 41.4(13.1) years old	No comparison group.	Block funding to the School of Health, Medical and Applied Sciences, Central Queensland University.
Caponnetto et al. 2017	Randomised crossover trial.	Each product tried in one experimental session (15m) and then for the next 10 hours.	34 cigarette users, mean age 34.8 years.	No control group. Participants were randomised to use one of five different e-cigarette products, unclear if crossover occurred.	Industry funded – Happy Liquid.
Chaumont et al. 2018	Randomised crossover, single	1 week: 2 experiments occurred 7 days apart.	Healthy occasional smokers, mean age 23 years.	Control condition was sham vaping (e-cigarette turned off).	Fonds Erasme pour la Recherche Medicale, Belgium, Fondation pour la Chirurgie Cardique, Belgium, the Fondation Emile Saucez-Rene Van

Study	Design	Duration	Population	Groups/comparisons	Funding
	blinded, placebo controlled trial.				Poucke Belgium, Prix Docteur & Mrs Rene Tagnon, Belgium, Fondation IRIS Belgium, Prix de l'Association Andre Vesale, Belgium, a research grant of Astra Zeneca Belgium, the Fonds Fruit de Deux Vies Belgium, the Fond David & Alice Van Buuren Belgium.
D'Ruiz et al. 2017.	Randomised, forced-witch parallel arm study.	Use of e-cigarettes occurred for 4 days (days 2-5).	Participants were conventional cigarette smokers randomized into groups that either completely or partially switched to e-cigarette use or completely discontinued using tobacco and nicotine products.	45 in e-cigarette use groups (15 in each flavour group), 45 in dual use groups (15 in each flavour group). Complete tobacco and nicotine product cessation group (15).	Industry funded - Fontem Ventures B.V, owned by Imperial Brands plc, the manufacturer of the e-cigs used in the study.
Goniewicz et al. 2017	Short-term experimental study.	2 weeks.	Subjects (n=20) were healthy current cigarette smokers (>5 per day within the last 12 months). Subjects smoked an average of 12.1 (SD 7.5) years and smoked an average 16 cigarettes (SD 9) per day. Average age 31 years. 60% female.	No control group.	Ministry of Science and Higher Education of Poland and National Institutes of Health.
Gonzalez-Roz et al. 2017	Cross-sectional analytic.	Short-term. NR.	81 in total: 39 e-cigarette users, 42 current tobacco smokers. E-cigarette users were former smokers or current tobacco cigarette smokers. E-cigarette users males 77%, conventional smokers 57% male. Age not recorded.	Compared e-cigarette users with current tobacco smokers on nicotine dependence.	BBVA Foundation. Described as a large multinational financial group here: http://terravivagrants.org/grant-makers/group-2-biodiversity-conservation-wildlife/bbva-foundation/
Hiler et al. 2017	Randomised crossover trial.	Sessions separated by 48 hrs. No follow up.	40 participants were Caucasian, 15 were African American, 2 were Hispanic/Latino, 1 was Hawaiian/other Pacific Islander, 1 reported more than one race and 5 reported 'other'. Mean age 30.6 years (9.1) across groups.	64 included in the analysis, smokers who were 33 e-cigarette experienced individuals and smokers who were e-cigarette naive (31).	National Institute on Drug Abuse of the National Institutes of Health.
Ikonomidis et al. 2018.	Randomised crossover trial.	1 month follow up. Acute phase (group that smoked conventional cig and one that smoked e-cigarette at hospital) and chronic phases (1 month chronic phase).	Subjects were attending hospital's smoking cessation unit. 70 experimental and 20 in control group.	70 in experimental group: 35 were assigned to use nicotine-free e-cigarette fluid during the acute-phase protocol, while the remaining 35 were assigned to an e-cigarette liquid with concentration of 12 mg/ml (PG 74.3%, G 20%, flavouring 4.5%, nicotine, 1.2%). 20 in control group.	Hellenic Cardiology Society and Hellenic Society of Lipidiology and Atherosclerosis.
Jain 2018	Cross sectional. Analytic.	Short-term.	Participants of the National Health and Nutrition Examination Surveys (NHANES) from 2013 to 2014. Blood metals n=483 (e-cigarette only 5.5%; cigars 9.6%; cigarettes only 84.9%); Serum metals n=315 (e-cigarette only 5.4%; cigars 8.5%; cigarettes only 86.1%); Urine metals n=321 (e-cigarette only 5.4%; cigars 8.8%; cigarettes only 85.8%).	Compared smoker types between cigarettes only, cigars only and e-cigarettes only. Dual users, pregnant women, and those with missing smoking data excluded.	No funding received.

Study	Design	Duration	Population	Groups/comparisons	Funding
Javed et al. 2017	Cross sectional.	Subjects accumulated over 9 months.	Study participants were 94 male only outpatients at the College of Dentistry, King Saud University, Riyadh, Saudi Arabia. Study period June 2016 to Feb 2017. Mean age 41.3 ± 2.8 (cigarette smokers), 37.6 ± 2.1 (e-cigarette users) and 40.7 ± 1.6 (never smokers).	Compared groups: Group 1 cigarette smoking - those who had been smoking up to 5 cigarettes daily for at least 12 months. Group 2 e-cigarette users - those who were exclusively e-cigarette vaping at least once per day for 12 months. Group 3 Never smokers - never used tobacco in any form. Mean duration in years of smoking in group 1: 5.4 ± 1.6 years. Mean duration of years vaping in group 2: 2.2 ± 0.2 years. Mean daily frequency of smoking in group 1: 13.3 ± 2.6 times. Mean daily frequency of vaping in group 2: 6.8 ± 0.8 times.	King Saud University.
Kerr et al. 2017	Randomised crossover trial.	NR. Immediate physiological effects of vaping measured.	20 male smokers.	Compared vaping with tobacco smoking. No control group.	NR (abstract only).
Lappas et al. 2018	Randomised crossover trial.	Three consecutive sessions. No further info provided regarding days elapsed.	54 dual smokers (27 healthy, and 27 with intermittent asthma (mild asthma)) underwent a control session (no liquid, no resistor coil inside e-cigarette cartridge) and an experimental session. 33/54 male. Average age 23 years.	Control: no liquid, no resister coil. Crossover trial.	Behrakis Foundation, Boston, MA.
Oelsner et al.	This is a cross sectional component of a broader prospective cohort study.	Cross sectional snapshot of larger prospective cohort study.	Part of the SPIROMICS prospective study examining people with and without COPD. 2981 participants with and without COPD. 981 of these were ever smokers, with 125 ever using e-cigarettes (13%) and 25 (3%) having used e-cigarettes on the day of the CT for the study.	Compared lung density of ever smokers and e-cigarette users.	National Heart, Lung and Blood Institute. (Abstract only).
Pywell et al. 2018	Short-term experimental study.	5 minute smoking protocol of a nonnicotine e-cigarette was commenced with the participant inhaling at a rate of 1 inhalation every 30 seconds, a total of 10 inhalations.	7 smokers and 8 non-smokers. Mean age smokers: 26 years, mean age non-smokers: 25 years.	Compared results across conventional cigarette users and non-smokers. No control group.	NR.
Reidel et al. 2017	Cross-sectional.	Short-term. NR.	Collected sputum samples from 14 current tobacco cigarette smokers, 15 current e-cigarette users and 15 never smokers. Mean age and gender not recorded.	Compared e-cigarette users with tobacco smokers and never smokers. E-cigarette use, average number of puffs inhaled per day was 280 (had been predominantly exclusive users for 6 months, but 12/15 had previously smoked cigarettes. 5/15 occasionally smoked cigarettes). Conventional cigarette users, average number smoked per day was 11.	National Institutes of Health and the Family Smoking Prevention and Tobacco Control Act.

Study	Design	Duration	Population	Groups/comparisons	Funding
Rubinstein et al. 2018	Cross-sectional.	Short-term. NR.	67 e-cigarette only users and 16 dual users. There were 20 age matched controls who did not use e-cigarettes or cigarettes. Male: 49 e-cigarette only (73%), 12 dual users (80%), 7 controls (35%). Aged 13-18 years.	Compared e-cigarette only users with dual users and age-matched controls. E-cigarette users only reported using their e-cigarettes a mean of 12.8 days/mon (SD 8.9) compared with 25.5 days (SD6.6) for dual users (<0.001). E-cigarette only users who used nicotine in their e-cigarettes reported using their e-cigarettes more frequently with an average use of 15.1 days/month (SD9.2) compared with 7.6 days/month (SD5.6) (p<0.001).	National Institutes of Health.
Russo, Cibella et al. 2018	Prospective cohort.	3.5 years of hospital records from March 2012 to December 2015.	Patients with cardiorespiratory conditions at four Italian hospitals.	Patients reporting regular daily use of e-cigarettes on at least 2 visits n=86 (67.4% male, 54.2 years); age and sex matched cigarette smokers n=93; smokers who reported sustained smoking abstinence (>6mo) n=44.	This research was supported by university grant No. 21040100 of "Ricerca Scientifica Finanziata dall'Ateneo di Catania"
Shahab et al. 2017	Cross-sectional.	Short-term. Study done from Jan to Jun 2014. No follow-up. Cross sectional. 'Spot sampling of biomarkers.'	Total n=181. 71 female (39.2%). Proportion of women ranged across groups, from 19.% in e-cigarette only group to 61.1% in dual combustible cigarette-NRT users. Mean age 37.8 years.	Five groups compared: Current smokers of conventional cigarettes. Former smokers with long term e-cigarette use (≥ 6 mths) only. Former smokers with long-term NRT use only. Long term dual users of conventional cigs and e-cigarettes. Long terms users of both conventional cigs and NRT. N=36 to 37 per group.	Cancer Research UK.
Stewart, Auchtung et al. 2018	Cross-sectional.	Short-term	Group of 30 individuals recruited in Houston area. Provided single biological samples for analysis.	10 e-cigarette users (daily for at least 6mo) aged 29y (median); 10 tobacco smokers (nicotine dependent, min 10 cigarettes/day) aged 35y (median); 10 matched controls aged 31y (median). Only 2/30 participants were female.	This work was supported by NCI (3P30CA0125123-09S1); the Veteran Health Administration (VHA5I01CX000994); and the McNairMedical Institute. This material is partly the result of work supported with resources and the use of facilities at the Michael E. DeBakey VA Medical Center, Houston, TX. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Walele et al. 2018	Prospective cohort study.	2 years	A closed system electronic vapour product (EVP) was used by former smokers of conventional cigarettes (CCs) for 24 months in a real life setting. 209 started. 206 used the product once, 102 (48.8%) went on to use the product for 24 months. 110 were compliant - used EVP for 80% of study days. Both male (115, 55%) and female (94, 45%). Completers: 57 male, 45 female. Aged between 21 and 65 years.	No control group. Compared results of all subjects with EVP compliant subjects (n=110) and completers (n=102).	Fontem Ventures B.V. Imperial Brands Group plc is the parent company of Fontem Ventures B.V., the manufacturer of the EVP used in this study.

Study	Design	Duration	Population	Groups/comparisons	Funding
Wei et al. 2018	Cross-sectional analytic	Short-term. NR.	Participants of the National Health and Nutrition Examination Surveys (NHANES) from 2013 to 2014. N=1572. Male non user 534/1201, Male cigarette user, 170/298, male cigar user 18/22, male e-cigarette user 8/14, male user of smokeless tobacco products 15/15. Mean age NR.	Compared groups such as non users (if not using tobacco or nicotine products within 5 days prior to the NHANES examination), exclusive e-cigarette users, exclusive cigarette smokers, exclusive cigar smokers and exclusive users of smokeless tobacco products (if using such products within the five days prior to examination).	NR. The NHANES is a study conducted by the National Center for Health Statistics (NCHS) and the US Centers for Disease Control and Prevention (CDC). One researcher reported receiving a research grant from Pfizer and being a member of an advisory board to Johnson & Johnson.

PART 5: Potential for e-cigarettes and personal vaporisers to reduce rates of smoking in Australia

Executive summary

The prevalence of regular smoking in Australia has been declining since at least 1945, from very high levels, particularly in men. The most recent national data indicates that 14% of Australian adults are current regular smokers.

E-cigarette use in Australia has generally increased from 2013 and 2016, however current regular use has a prevalence below 8% amongst all adolescent and adult age groups. Among 'ever users' of e-cigarettes, the largest percentage is people who have used e-cigarettes only once or twice. This group is larger than current users and ex-users for all age groups, but is particularly large in adolescents and younger adults. E-cigarette use beyond once or twice is very uncommon amongst people who are not current or ex cigarette smokers.

The most common reason for using e-cigarettes among adolescents and younger adults is 'out of curiosity', while among older adults the reasons for use are more likely to be related to tobacco smoking (to cease smoking, to reduce the number of cigarettes smoked, or to avoid recommencing smoking).

E-cigarettes are stated to be the preferred smoking cessation method for smokers wishing to cease smoking or to cut down on smoking. Nicotine containing e-cigarettes have been shown to be effective at reducing the withdrawal symptoms of smokers who have abstained from cigarettes for a short period, and more effective than non-nicotine e-cigarettes or nothing at reducing the number of cigarettes smoked by smokers wanting to reduce smoking or to quit.

There is insufficient information about the effectiveness of e-cigarettes for smoking cessation compared to other smoking cessation methods. Such evidence should compare methods over an appropriate period of time with the aim being to cease both smoking and the cessation method used. This information is critical to assess the potential for e-cigarettes to reduce the smoking rate in Australia.

While it is plausible that e-cigarettes could increase the smoking rate among people who are not currently tobacco smokers, the evidence for this to occur in Australia to any great extent is not compelling in the current context. However, there are clear similarities between e-cigarette use and regular cigarette use, and if regular e-cigarette use were to become more widespread, there is at least potential to undermine the progress to decrease the use of tobacco products. However, it is difficult to assess whether social 'normalisation' of personal devices for inhaling vapour would impact acceptance of cigarette smoking, or regulations to discourage the smoking of cigarettes.

It is reasonable to consider the potential impact of e-cigarettes among groups that have a high prevalence of smoking, such as Indigenous Australians or people from a socially disadvantaged background. Unfortunately there is a paucity of information among such groups, and development of effective smoking cessation methods amongst such groups should be a priority.

18   Introduction

This section responds to the assigned task 'to identify any potential for e-cigarettes to reduce rates of smoking in Australia'. The information summarised in other parts in this report are relevant to Australia, as is the context in which smoking and e-cigarette use occurs. Therefore this report includes an examination of the data on e-cigarette use in the Australian context, and also trends for conventional smoking in Australia. A summary is provided of the funding that the Australian National Health and Medical Research Council has provided for research studies relevant to the use of e-cigarettes that are yet to be completed.

19   Use of e-cigarettes in Australia

19.1   Prevalence of e-cigarette use in Australia

Williams et al (Williams and White 2018) analysed data from the Australian Secondary Schools Alcohol and Drug survey collected from June to December 2014 but restricted their analysis to one state (Victoria). Based on 4,576 adolescents aged 12 to 17 years, they reported a prevalence of 14% ever-use of e-cigarettes and 13% ever-use of shisha tobacco with most students using e-cigarettes in combination with conventional cigarettes.

In 2016/17, Musk et al (Musk 2018) surveyed 812 adults aged 51-71 years as part of the Busselton Baby Boomers Study. Of the current smokers, 30% had tried e-cigarettes however only 3% were current or recent users (in the last 30 days). Of the responders, 46.6% were never smokers, 48.5% were ex-smokers, and 4.9% were current smokers. Over 60% of the sample felt they did not know enough about e-cigarettes to say whether they were more or less harmful than tobacco cigarettes, however 15% believed that e-cigarettes were equally or more harmful than conventional cigarettes.

Bonevski et al (Bonevski, Guillaumier et al. 2017) surveyed 427 people at substance use centres by telephone and reported 39% 'ever use' of e-cigarettes and that 70% had used them to try to stop smoking.

The 2016 National Drug Strategy Household Survey (AIHW 2017) indicated that the majority of Australians had never used e-cigarettes, except for the youngest age group (12-17 years – Table 18, Figure 8).

Table 18: Prevalence of e-cigarette use (%) in Australia by age group (2016).

	Age group (years)								
	12-17	18-24	25-29	30-39	40-49	50-59	60-69	70+	18+
Currently user	4.3	6.8	3.6	5.9	4.3	3.3	2.9	0.8	4.4
Ex user	3.4	9.3	5.5	7.9	7.6	5.9	4.0	4.3	6.8
Tried once or twice	43.1	33.1	28.4	25.3	14.3	11.6	11.8	6.5	19.6
Never used	49.2	50.9	62.4	61.0	73.8	79.1	81.3	88.4	69.2

Figure 8: Percentage of e-cigarette use in Australia 2016
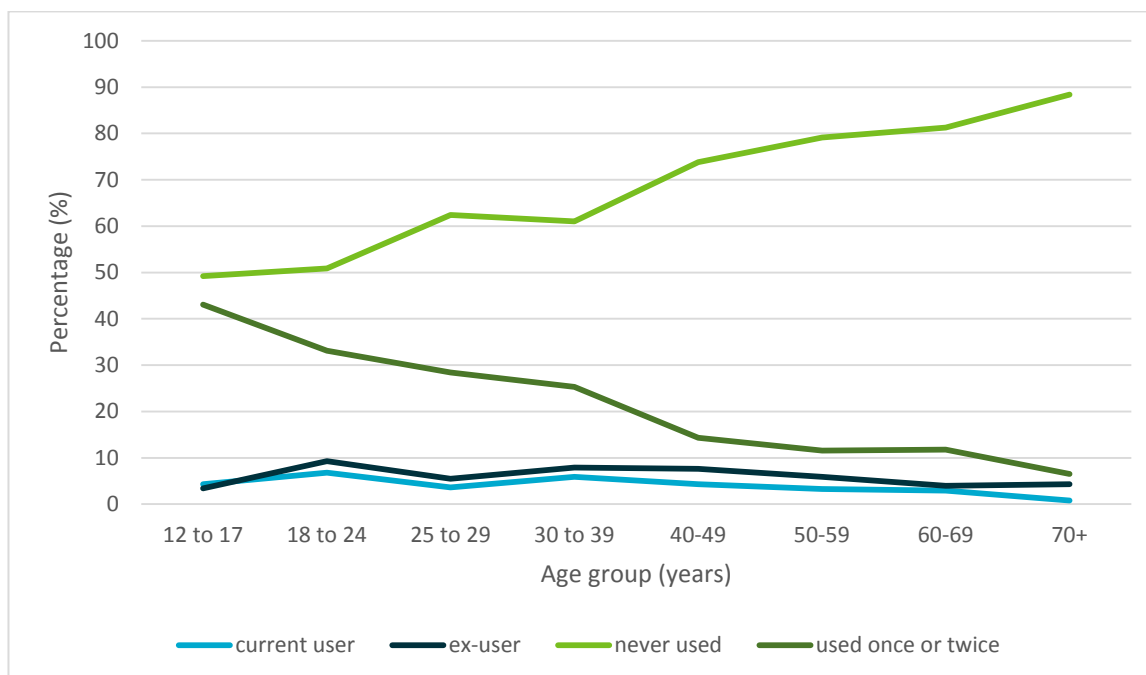
From Figure 8 it can be seen that the percentage of people who have never used e-cigarettes increases with age, driven mainly by the percentage of people who try e-cigarettes (but don't continue) being high at a young age but decreasing with age. The percentage of people currently using e-cigarettes is low, and lower than the percentage of people who are ex-users except for the youngest age group.

From the same AIHW survey, more than 98% of current or ex tobacco smokers used conventional tobacco cigarettes prior to using e-cigarettes. Only about 0.5% of current or ex-tobacco smokers stated that they had used e-cigarettes prior to using conventional cigarettes.

Table 19: Prevalence of e-cigarette ever use (%) in Australia for males and females by age group (2013 and 2016).

	Age group (years)								
	12-17	18-24	25-29	30-39	40-49	50-59	60-69	70+	18+
Males (2013)	53.7	36.2	26.6	21.1	13.4	8.4	7.4	7.4	18.5
Males (2016)	46.0	47.9	41.8†	39.0†	29.3†	19.4†	15.6†	8.8	31.4†
Females (2013)	43.4	24.1	25.4	16.3	14.2	15.1	10.1	11.8	17.1
Females (2016)	52.1	50.4†	32.5	39.1†	22.2†	22.5†	22.6†	15.3	30.0†

† - statistically significant difference between 2013 and 2016

The percentage of 'ever use' of e-cigarettes in the Australian adult population has increased between 2013 and 2016 (Table 19) particularly for age groups between 19 and 69 years. At all ages, experimentation with e-cigarettes once or twice makes up the largest percentage of the 'ever use' category.

Table 20: Prevalence of e-cigarette use (%) in Australia by smoking status (aged 14 years +, 2016).

E-cigarette use	Cigarette use			
	Smokers	Ex-smokers	Never smokers	Total
Daily	1.5	0.8	0.2	0.5
At least weekly (but not daily)	1.2	0.1	<0.1	0.3
At least monthly (but not weekly)	0.7	<0.1	<0.1	0.1
Less than monthly	1.0	0.2	0.2	0.3
Ex-user	6.8	1.7	0.3	1.6
Only used once or twice	19.9	4.7	3.2	6.0
Never used	69.0	92.5	96.1	91.2

As Table 20 shows, conventional cigarette smokers are more likely to be current users and 'ever users' of e-cigarettes.

19.2 Qualitative information from Australian e-cigarette studies

The 2016 National Drug Strategy Household Survey (AIHW 2017) collected data on reasons why e-cigarette users used e-cigarettes. Table 21 shows that curiosity to try e-cigarettes was a reason for a large percentage of younger people, but that smoking cessation or reduction was a reason for the largest percentage of older people. Older people were also more likely to have the belief that e-cigarettes are less harmful than regular cigarettes as a reason for use.

Table 21: Reasons for using e-cigarettes (%) in Australia by age group (2016).

	Age group (years)								
	12-17	18-24	25-29	30-39	40-49	50-59	60-69	70+	18+
To help me quit smoking	2.3	13.1	19.5	39.0	45.0	51.0	59.3	61.2	32.3
To try to cut down on the number of cigarettes I smoke	2.0	8.8	15.6	25.8	23.4	30.5	29.5	20	19.7
To try to stop me going back to smoking	1.9	7.2	11.6	17.1	18.9	30.0	22.7	12.7	15.3
I think they are less harmful than regular cigarettes	11.1	15.9	14.0	22.6	23.1	22.3	24.7	38.9	19.8
They are cheaper than regular cigarettes	4.3	5.9	8.5	12.7	12.8	17.4	16.6	17.0	10.9
I think they taste better than regular cigarettes	10.8	12.8	11.4	9.8	6.2	8.0	6.9	N/A	9.8
You can smoke in places where you can't smoke regular cigarettes	N/A	6.8	9.5	7.7	8.1	7.7	8.7	4.3	7.8
They seem more acceptable than regular cigarettes	6.7	3.6	5.2	8.2	5.9	5.4	11.5	N/A	5.9
Out of curiosity	78.9	70.7	70.4	53.5	36.3	27.7	20.6	24.8	53.6
Other	16.4	8.2	7.6	6.0	5.7	4.2	5.1	3.3	6.6

N/A– not available – numbers too small in sample

When respondents are categorised by their regular cigarette or e-cigarette use (Table 22), a large percentage of current e-cigarette users have a reason to use e-cigarettes that is related to smoking current cigarettes, whereas a high percentage of ex e-cigarette users give curiosity as a reason for using e-cigarettes. This is consistent with the large percentage of younger people who have used e-cigarettes once or twice and who give curiosity as a reason why they used them. Perhaps surprisingly, the reason given by the highest percentage of smokers and ex-smokers for using e-cigarettes is also curiosity, followed by 'to help me to quit smoking'.

 Byrne S, Brindal E, Williams G, Anastasiou KM, Tonkin A, Battams S and Riley MD (2018), E-cigarettes, smoking and health. A Literature Review Update. CSIRO, Australia.

Table 22: Reasons for using e-cigarettes (%) in Australia by smoking or e-cigarette use status (2016).

	Usage group			
	Current e-cigarette user	Ex-e-cigarette user	Current smoker	Ex-smoker
To help me quit smoking	46.7	28.0	38.9	44.6
To try to cut down on the number of cigarettes I smoke	36.0	16.0	28.8	14.1
To try to stop me going back to smoking	31.2	11.9	18.5	19.4
I think they are less harmful than regular cigarettes	42.4	15.6	23.0	20.4
They are cheaper than regular cigarettes	29.6	7.6	15.3	8.9
I think they taste better than regular cigarettes	28.8	7.1	10.0	10.1
You can smoke in places where you can't smoke regular cigarettes	12.7	6.5	10.1	5.9
They seem more acceptable than regular cigarettes	14.1	4.7	7.8	4.5
Out of curiosity	30.5	59.2	46.9	46.0
Other	7.2	7.1	5.0	8.3

Two of the relevant Australian qualitative studies focussed on very specific subgroups of e-cigarette users: Indigenous Australians (Yuke, Ford et al. 2018) and people with schizophrenia (Brown 2018).

Brown's ethnographic study used observations in Australia and the UK to explore experiences of smoking and vaping. Few details are available on the quantity of observations and an in-depth discussion of experiences is provided with the ultimate conclusion that this sample emphasised the harm from smoking relative to vaping.

Interviews and focus groups were held with a small number of Indigenous Australians (n=27) living in Brisbane and who were smokers with the aim of understanding the acceptability of new nicotine products. While the majority of Indigenous women reported no willingness to try e-cigarettes (70%), a majority of men were willing (82%). Therefore, in this specific and select group there was a very pronounced difference in willingness to try e-cigarettes. However, no recent data exist that quantify prevalence of use of e-cigarettes in this population.

The final qualitative study (Keane, Weier et al. 2017) analysed data from an open-ended question included as part of another survey using Theories of Social Practice. Discussion is strongly grounded in the context of this theory which is beyond the scope of the current summary. However, the authors conclude that health and freedom are important for vaping and that word of mouth is a driver of uptake.

Williams et al (Williams and White 2018) analysing data from the Australian Secondary Schools Alcohol and Drug survey for Victoria noted a high rate of shisha use which is not generally reported in other countries.

Bonevski et al (Bonevski, Guillaumier et al. 2017) surveyed 427 people at substance use centres and reported 39% ever-use of e-cigarettes and that 70% had used them to try to stop smoking. A survey of 1,127 people in treatment centres across the US (Gubner, Pagano et al. 2017) showed the prevalence of e-cigarette use was 59.8% which is much higher than that in the Australian sample.

In the final Australian study (Lee, Yong et al. 2018), the authors used data collected as part of the 2014 International Tobacco Control Survey to compare vaping among people in Australia and the UK. The sample for this survey was people who have smoked at least 100 cigarettes over their lifetime. Data analysed were from 2,849 adults, including 1,430 Australians. The prevalence of current vaping in the Australian subjects was 11.9% with 2.5% using e-cigarettes daily. Compared to the survey subjects in the UK, the Australian subjects had lower rates of vaping, stronger opinions about it, and felt that there were less social constraints.

Data collected in New Zealand focussed on vaping as a means of smoking cessation through an online survey with 218 vapers (Truman, Glover et al. 2018) and 20 semi-structured interviews (Robertson, Hoek et al. 2018). Despite their different research approaches, both papers conclude that vaping may be useful for smoking cessation in New Zealand.

19.2.1 Conclusion

Recent data from Australia is limited but provides a mixture of depth through qualitative studies and reach through quantitative surveys. The percentage of people who have ever used e-cigarettes has increased from 2013 to 2016 however the rate of people currently using e-cigarettes appears to be well under 10% of the population. For adolescents and young adults, the main reason for use of e-cigarettes appears to be out of curiosity and most users experiment and cease using them. For older adults, however, the reason for use is related to wanting to stop, cut down or avoid recommencing regular cigarette smoking. With older age groups, a smaller percentage use e-cigarettes only once or twice compared to younger age groups, but it is still a higher percentage than ex-users or current users.

There does not appear to be a striking difference between males and females in percentage who have ever used e-cigarettes. E-cigarette use, for all frequencies of use, is much more prevalent among people who are current smokers, or ex-smokers of regular cigarettes.

A single small study of Indigenous Australian smokers suggested a large difference between males and females in willingness to try e-cigarettes with a large majority of males willing to try (more than for any other smoking cessation method), but only a small minority of females (the equal lowest of any smoking cessation method). The reason for the large difference in preference is not clear, however the study was small and none of the subjects had any experience with e-cigarettes.

Amongst Victorian secondary school students (in 2014) the 'ever use' of shisha tobacco was almost as prevalent as the 'ever use' of e-cigarettes, however both may represent use 'out of curiosity' that is prevalent in this age group.

19.3 Prevalence of smoking in Australia

When first measured in 1945, the prevalence of current tobacco smoking in Australia was 72% for males and 26% for females (Cancer Council Victoria 2018). Since that date the rate among males has been steadily decreasing, while the prevalence rate for females increased in the 1970s and has decreased since.

Figure 9: Daily smoking in the general population people aged 18 years and older and key tobacco control measures implemented in Australia since 1990
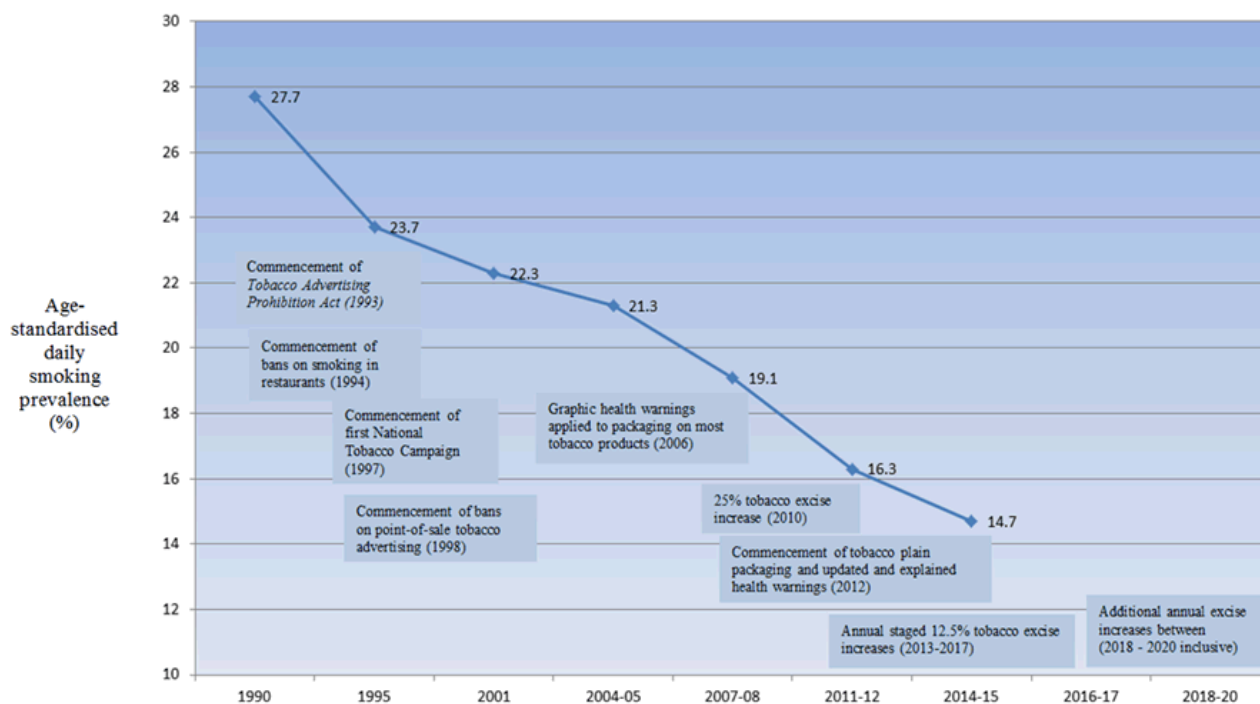
Source: National Health Survey results: 1990, 1995, 2001, 2004-05, 2007-08, 2011-12 and 2014-15.

The decline in prevalence rate for daily smoking from 1990 is shown in Figure 9, with the difference between male and female rates now being only a few percentage points. As highlighted in the figure, the declining rate of regular tobacco use has been assisted by many public health measures.

In some population groups, the tobacco smoking prevalence rate remains stubbornly high. In 2014-15, the prevalence of daily smoking among Aboriginal and Torres Strait Islanders aged 15 years and above was 39%, with little difference between males and females. After adjusting for differences in age-structure, Indigenous Australians over the age of 15 years were almost 3 times as likely to smoke cigarettes as non-Indigenous Australians (Cancer Council Victoria 2018).

Socially disadvantaged groups tend to have higher smoking rates than socially advantaged groups.

19.4   Key findings

- The prevalence of regular smoking in Australia has been declining since at least 1945, from very high levels, particularly in men. The most recent national data indicates that 14% of Australian adults are current regular smokers.

- E-cigarette use has generally increased from 2013 and 2016, however current regular use has a prevalence below 8% amongst all adolescent and adult age groups.

Byrne S, Brindal E, Williams G, Anastasiou KM, Tonkin A, Battams S and Riley MD (2018), E-cigarettes, smoking and health. A Literature Review Update. CSIRO, Australia.

- Among 'ever users' of e-cigarettes, the majority percentage is people who have used e-cigarettes only once or twice. This group is larger than current users and ex users for all age groups, but is particularly large in adolescents and younger adults.

- E-cigarette use beyond once or twice is very uncommon amongst people who are not current or ex cigarette smokers.

The most common reason for using e-cigarettes among adolescents and younger adults is 'out of curiosity', while among older adults the reasons for use are more likely to be related to tobacco smoking (to cease smoking, to reduce the number of cigarettes smoked, or to avoid recommencing smoking).

20 The potential for e-cigarettes to reduce smoking rates in Australia

It is desirable that tobacco smoking rates continue to decline in Australia and elsewhere. In the absence of better information, it is too simplistic to view the use of e-cigarettes as only another potential tool to reduce smoking among smokers by either reducing the number of cigarettes smoked, or by facilitating smoking cessation.

Focusing only on smoking rates (i.e. leaving aside health consequences of using e-cigarettes), the issue should be considered from the point of view of

1) the potential for the use of e-cigarettes to reduce the smoking rate of people currently smoking regular cigarettes and
2) the potential for the use of e-cigarettes to influence the future smoking behaviour of people who are currently not smoking regular cigarettes.

20.1 The potential for the use of e-cigarettes to reduce smoking among people currently smoking regular cigarettes

The second report in this series sets out a number of issues relating to the use of e-cigarettes for smoking cessation. The first point is that smokers in many populations have stated that they prefer e-cigarettes as a smoking cessation method. However, preference for the method may reflect the smokers comfort with the method rather than whether it effectively achieves smoking cessation. There is limited evidence for the effectiveness of using e-cigarettes for smoking cessation compared to using other methods.

There is good evidence that nicotine containing e-cigarettes are more effective at reducing conventional cigarette use among smokers than non-nicotine containing e-cigarettes, or than no treatment. This is likely to be due to the nicotine replacement effect of e-cigarettes, similarly for trials that indicate that e-cigarettes reduce withdrawal symptoms after a short period of cigarette abstinence in smokers.

In order to assess the potential for e-cigarettes to reduce smoking rates among smokers, methods using e-cigarettes need to be compared with other smoking cessation methods over a moderate time period.

Ideally, an effective smoking cessation method should result in the complete cessation of regular smoking without its long term replacement by other harmful behaviours.

20.2 The potential for e-cigarettes to change smoking behaviour among people who are not currently smoking regular cigarettes

While there has been considerable interest in whether the use of e-cigarettes can result in a gateway effect to use of conventional cigarettes (especially in young people), the evidence for this being an important route to smoking initiation in Australia does not appear strong. The majority of e-cigarette use in young Australians appears to be short term experimentation out of curiosity. Most 'ever users' of e-cigarettes have used them once or twice and then not again. Only a very small percentage (about 0.5%) of current or ex-smokers of regular cigarettes had used e-cigarettes prior to their use of regular cigarettes. In Australia, only a small percentage (4%) of never smokers have reported using e-cigarettes, and most of these people have used them once or twice only. Less than 1% of never smokers have used e-cigarettes on a more intensive basis than once or twice.

However, these observations about use of e-cigarettes in Australia have occurred under the current regulatory restrictions for use. It is plausible that some continuing users of e-cigarettes could develop a preference for regular cigarettes. There is a much smaller percentage of smokers in Australia than non-smokers, and therefore even small effects in the non-smoking population may be important.

E-cigarette use is similar to cigarette use in that it is a personal device from which a user inhales smoke or vapour that is most often aromatic. It is not possible to easily assess whether there is a social impact of e-cigarettes to reverse the social disapproval of smoking, to normalise the use of personal devices to inhale smoke or vapour, or to make regulation that has been resulting in a decline in tobacco smoking less effective, or future measures less successful.

20.3 Key findings

- While it is plausible that e-cigarettes could increase the smoking rate among people who are not currently tobacco smokers, the evidence for this to occur in Australia to any great extent is not compelling in the current context.

- In order to assess the potential for e-cigarettes to reduce smoking rates among smokers, cessation methods using e-cigarettes need to be compared with other smoking cessation methods over a moderate time period. There are no long-term studies on e-cigarettes for smoking cessation in Australia.

- Observations about use of e-cigarettes in Australia have occurred under the current regulatory restrictions for use, thus changes in regulations may lead to different observations.

- It is difficult to assess whether social 'normalisation' of personal devices for inhaling vapour would impact acceptance of cigarette smoking, or regulations to discourage the smoking of cigarettes.

20.4 NHMRC Funding related to e-cigarettes

Funding awarded by the National Health and Medical Research Council (NHMRC) to projects and programs related to e-cigarettes, and their descriptions, are listed in Table 23. A substantial commitment of over $6 million has been made and the results of many of these studies are expected to be reported in the next 3-5 years. This will provide much needed information of relevance directly for Australia, but also more broadly.

Table 23: E-cigarette projects funded by NHMRC grants.

Grant Title	Years active	Budget	Chief investigator	Institution	Project description
The health effects of electronic-cigarettes	2017 – 2019	$571,260	Associate Professor Alexander Larcombe	University of Western Australia	The health effects of electronic cigarette use are virtually unknown. They have only recently been introduced into widespread use, and as such their effects on human health will not be known for many years. We will use our expertise in exposure models and health outcome measurement to provide timely hard-data on their potential to impact health – data that are urgently required to guide policy makers in this area.
Adding an electronic-cigarette to standard behavioural treatment for low-socioeconomic status smokers: A randomised trial.	2017 – 2020	$1,381,127	Professor Richard Mattick	University of New South Wales	Behavioural and pharmacological approaches to smoking cessation are effective at helping people to quit but long-term quit rates remain low, especially among low-SES Australians. The electronic cigarette may complement current treatment approaches. We will conduct a large-scale trial to determine if "e-cigarettes" can improve on the efficacy of existing treatments. The findings would have immediate practical implications that could reduce the preventable deaths of many tobacco smokers.
A Pragmatic Randomised Clinical Trial of Nicotine Vaporisers added to Smoking Cessation Treatment for Priority Populations Living with Comorbidities	2017 – 2021	$1,499,145	Dr Coral Gartner	University of Queensland	Smoking is a leading cause of early death for people with certain health conditions because they are more likely to smoke and are also at greater risk of tobacco-related disease. This clinical trial will test whether encouraging people living with Hepatitis C Virus, people on opiate substitution therapy and people living with HIV who smoke to use nicotine vaporisers long-term, in addition to current smoking cessation treatments, will help them to stay abstinent from smoking.
Understanding the impacts of Vaporised Nicotine Products on smoking in Australia	2016 – 2020	$1,603,159	Professor Ron Borland	Cancer Council Victoria	Vaporised nicotine products (e.g. e-cigarettes) are widely used in Australia, even though possession of the nicotine fluid without a permit is an offence. They are primarily used by smokers as a means of quitting. However, there is concern about their potential attractiveness and uptake by non-smokers. The aim is to identify how these products might be used to both maximise smoking cessation and minimise nicotine use, especially smoking uptake by non-smokers.

Grant Title	Years active	Budget	Chief investigator	Institution	Project description
Cardiometabolic Health of People with Severe and Persistent Mental Illness	2016 – 2019	$187,322	Associate Professor Dan Siskind	University of Queensland	People with schizophrenia have much higher rates of smoking, obesity and diabetes. To date, psycho-social interventions to reduce these physical health risk factors have had limited success. This research aims to conduct clinical trials among people with schizophrenia of 1. a novel diabetes medication to help people lose weight and gain better control of their sugars, and 2. newly developed vaporised nicotine products to help reduce cigarette smoking.
Public health policies and interventions to reduce tobacco-related harms among socially disadvantaged populations and 'low probability quitters'	2014	$404,844	Dr Coral Gartner	University of Queensland	Tobacco continues to be a leading cause of preventable death and disease in Australia. Those who are socially disadvantaged are at higher risk of smoking, which contributes to the health gap between the rich and poor. This research will provide evidence for policy makers on interventions which could reduce smoking among the most disadvantaged in society. It will also examine whether less harmful nicotine products could a reduce health risks in smokers who find quitting difficult.
An open-label randomised pragmatic policy trial of nicotine and smokeless tobacco products for short-term cessation assistance or long-term substitution in smokers	2012 – 2017	$1,014,392	Dr Coral Gartner	University of Queensland	Many smokers who try to quit fail in their attempt. Medicinal nicotine is currently only used as a short-term quit aid. This trial will test if offering smokers the option of using these products as long-term substitutes for cigarettes will help more smokers to successfully quit. We will also determine if offering smokers low toxicity smokeless tobacco and electronic nicotine devices in addition to medicinal nicotine products further increases the number of smokers who quit successfully.

Adapted from: (NHMRC 2018).

PART 6: Smoking rates in countries where e-cigarettes and personal vaporisers are available

Executive summary

This report aimed to compare the rates of tobacco smoking in countries where e-cigarettes and similar smoking alternatives are available with rates in countries where such products are not available.

Data about the availability of e-cigarettes and associated products are not comprehensively available. An examination of regulatory regimes in different countries, suggests that countries where e-cigarettes are not available by regulation may tend to have a higher prevalence rate of tobacco use, however at least one country with a low tobacco use prevalence rate (Panama at 11.9% for men and 2.8% for women) also has a ban on use and sales of e-cigarette devices and supplies.

Within a country, the prevalence rate of e-cigarette use is highest for current smokers, lower for ex-smokers and lowest for never smokers. However, across countries, those countries with the highest prevalence rate of current smokers do not necessarily have the highest prevalence rate of e-cigarette use. There appears to be a weak positive association between prevalence of current smokers and 'ever use' of e-cigarettes.

The determinants of the country adult prevalence of e-cigarette use may include regulations impacting availability, but also the history of use in a country, how the products are marketed, previous tobacco use and other cultural determinants.

21   Introduction

This report responds to the assigned task 'to compare the rates of tobacco smoking in countries where e-cigarettes and similar smoking alternatives are available with rates in countries where such products are not available'.

21.1 Regulation and Policy relating to e-cigarettes

Electronic cigarettes are a class of Electronic Nicotine Delivery Systems (ENDs) or Electronic Non-Nicotine Delivery Systems (ENNDs). Both are characterised by heating a solution (called an e-liquid) to create an aerosol which frequently contains flavouring compounds, usually dissolved into propylene glycol or/and glycerin (WHO 2016 ENDS report).

A number of different devices have been developed, designated first to third generation devices, and evolution of devices is likely to continue. The devices vary in their performance and users in their behaviour leading to a difference in exposure to active components such as nicotine. For example, the user's puffing style, the choice of e-liquid, the wattage and resistance of the device are all relevant variables determining the user's experience. There are close to 8,000 reported e-liquid flavours.

While the mechanism to replace burning tobacco with flavoured, smokeless steam was invented in 1963, the first commercial device became available in 2004. E-cigarettes arrived in the United States in 2006.

By 2015, about 56% of the global market was accounted for by the United States, 12% by the United Kingdom and a further 21% by China, Germany, France, Italy and Poland (3-5% each) (WHO 2016 ENDS Report).

Researchers from the United States (Kennedy, Awopegba et al. 2017) examined the regulatory regimes of 68 countries (current in October 2016). The most common forms of regulation included sale bans, use restrictions, age of purchase requirements, and advertising and promotion bans. The types of regulation existing in a large range of countries are summarised in Table 24 and broadly categorised in Table 25. Within the broad categories of e-cigarette regulation in Table 25, countries are listed along with the age-standardised male current tobacco use prevalence rate for 2013 (taken from Table 26). The male current tobacco use prevalence is selected as an indicator of national tobacco use because some countries show a very wide difference between male use and female use - for example, the female current tobacco use prevalence for Jordan, Cambodia and Panama is 10.2%, 3.2% and 2.8%, compared to 65.5%, 44.7% and 11.9% for males. The prevalence for women and the spread of prevalence is much reduced for women. In general, in Western countries male and female rates are much more similar.

The most restrictive regulatory regime listed in Table 25 is where there is a complete use and sales ban. Countries in this category include those with a high prevalence of male current tobacco use such as Jordan (65.5%) and Cambodia (44.7%), but also countries with low prevalence such as Panama (11.9%). To examine the extent to which tobacco use prevalence rate is related to e-cigarette regulatory regime, a simple average of the country age standardised male and female tobacco use prevalence rate was calculated for each category and included in Table 26. A simple average is used to represent country-level data rather than a population weighted average because regulatory regimes are country level characteristics.

In each of the regulation categories, there is a wide range of tobacco use prevalence – while the highest average male current tobacco use prevalence and male daily cigarette prevalence is in the most restrictive e-cigarette regulatory category (Table 26), the pattern is not the same for women, and there does not appear to be a strong trend across categories.

The data on smoking prevalence by country shown in Table 27 is selected because it is for the same year and it is age-adjusted – current smoking prevalence changes with time with many countries successfully deploying campaigns to reduce tobacco use. These prevalence rates are therefore comparable to each other.

While tobacco use is a behaviour of very long standing, it would appear that e-cigarette regulation is only one factor relevant to the rate of e-cigarette use. Other factors might be expected to be the history of use of e-cigarettes (i.e. when it was introduced), the penetration and type of marketing, and the nature of tobacco regulation (because one stated reason for using e-cigarettes is to use them in circumstances where smoking cigarettes is not allowed, or socially unpopular).

22   Prevalence of e-cigarette use

National level data collections on the rate of e-cigarette use are more sparse than similar data on tobacco use. Standard data items and surveys to collect these items have been developed for tobacco, but standard protocols have not yet been similarly developed for e-cigarettes. In many countries, their use is uncommon and therefore there is no imperative to measure their (low) use.

A standard data collection was achieved for countries in Europe (Table 28) for 2014. The overall prevalence of current e-cigarette use was low – it ranged from less than 1% to 4% in France and Belgium and 5% in the United Kingdom. The prevalence for ever use of e-cigarettes was much higher ranging up to 24% of the population.

22.1 Comparison of e-cigarette use with conventional cigarette use

A broader data set was developed by including prevalence estimates from adjacent years, with information on national rates of conventional tobacco use for the same period (Table 29).

For example, an estimate of e-cigarette use for Australia is sourced from a NSW survey (Harrold, Maag et al. 2015) which measured current e-cigarette use at 1.3% and e-cigarette ever use at 8.4%. For 2014, the national current smoking rate was 16.7% for men and 13.1% for women. For the US, for 2014-15, the prevalence of current e-cigarette users was 2.4%, and the prevalence rate for ever use was 8.5%.

This database was used to develop scatterplots (Figures 10-13) to demonstrate any relationship between e-cigarette use and conventional cigarette use. For each scatterplot, a Pearson's correlation coefficient was calculated to express the linear relationship between the variables plotted. For most countries the prevalence rate for smoking was higher for men than for women. In some countries, the prevalence rate was 20 times higher for men than for women. Generally, the e-cigarette use rate was low and not segregated by gender. The scatter plots therefore use a single e-cigarette use rate for each country, but are plotted using a tobacco smoking rate for men, and a tobacco smoking rate for women. The smoking prevalence rate in women was not correlated to the smoking prevalence rate in men across the 44 countries used in generating the scatter plots (r=0.03, p=0.86).

The between-country relationship for current smokers with current e-cigarette users was not statistically significant when either the male smoking rate (Figure 10) or the female smoking rate (Figure 11) was used to represent smoking rate. The between-country relationship for current smokers with 'ever-use' of e-cigarettes was not statistically significant when the male smoking rate was used to represent smoking rate (Fig 12), but was statistically significant when the female smoking rate was used to represent smoking rate (Fig 13).

Figure 10: Prevalence of current e-cigarette use vs current male tobacco cigarette use
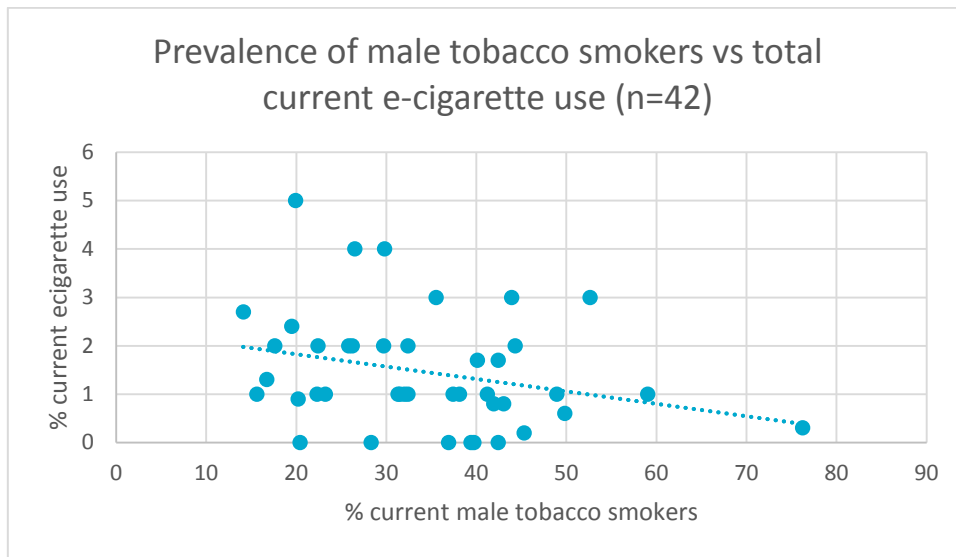
Correlation coefficient=-0.28, p=0.07 (i.e. the correlation is not statistically significant)

Figure 11: Prevalence of current e-cigarette use vs current female tobacco cigarette use
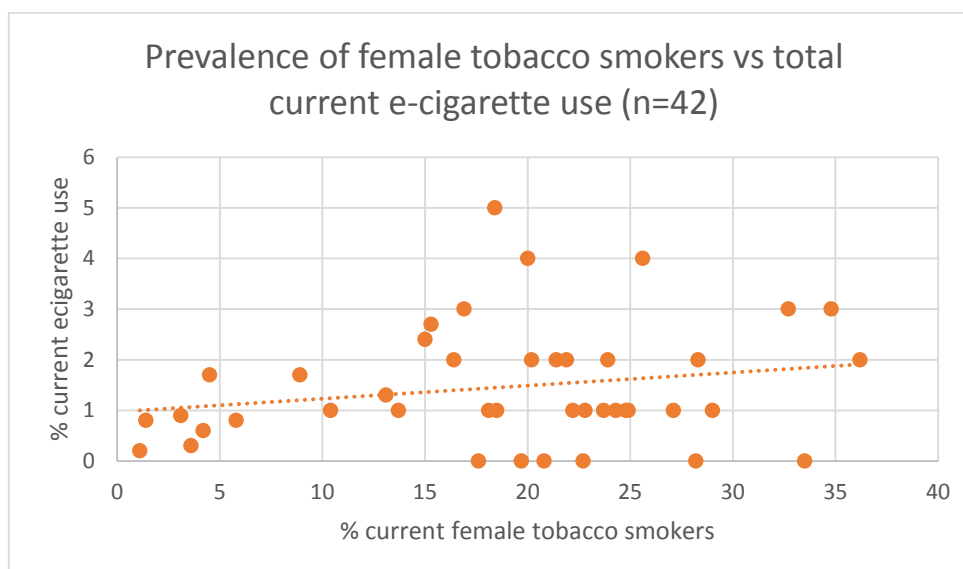
Correlation coefficient=0.20, p=0.20 (i.e. the correlation is not statistically significant)

Current e-cigarette use is rarely categorised by sex, so two plots are shown – the first comparing current e-cigarette use against current male smoking prevalence, the second against current female smoking prevalence. The scale for smoking prevalence is different for Figure 10 and Figure 11 because the prevalence rate for females is generally less than the prevalence rate for males, and substantially different in some countries. Six countries have a female smoking prevalence of less than 5%, while no country has a male smoking rate of less than 10%. Also only one country in this dataset has a female smoking rate over 35% (Serbia), while the male smoking rate is above 35% for close to half of the countries.

Within a country, rates of e-cigarette use are generally highest among current smokers, lower among ex-smokers and lowest among never smokers for adults. However the same principle does not operate across countries – it is not the countries with the highest tobacco smoking rates that have the highest e-cigarette use.

The scatterplot for current e-cigarette use against male current tobacco smoking shows a negative trend (albeit not statistically significant). This suggests that the higher the male current smoking rate, the lower the current e-cigarette use. The highest male tobacco smoking rate (Indonesia at 76.2% of males) and the highest current e-cigarette use (UK at 5%) may be exerting high leverage. However, omitting both points still results in a negative coefficient for the remaining 40 points (smaller, and still non-significant).

Prevalence of male tobacco smokers vs ever used e-cigarettes (n=36)

Correlation coefficient = 0.28, p=0.09 (i.e. the correlation is not statistically significant)

Figure 13: Prevalence of ever used e-cigarettes vs current female tobacco cigarette use

Prevalence of female tobacco smokers vs ever used e-cigarettes (n=36)
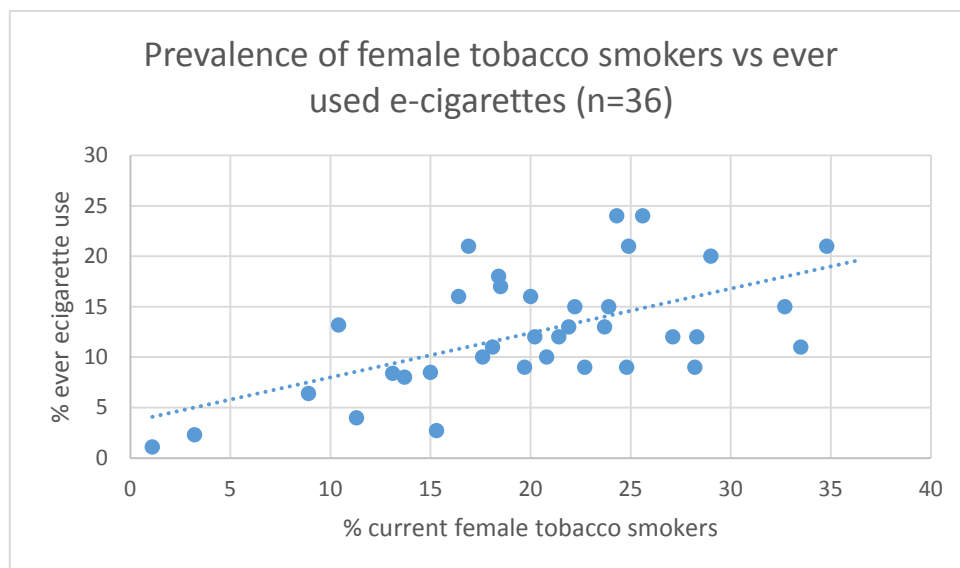
Correlation coefficient=0.58, p>0.001 (i.e. the correlation is statistically significant)

The prevalence for 'ever use' of e-cigarettes is higher than current use (because most people who try e-cigarettes do not continue to use them). Here there is a strong positive association between ever use of e-cigarettes and smoking prevalence rate for females, but not for males. Higher rates of smoking in women are generally associated with higher rates of 'ever use' of e-cigarettes. Nevertheless, for any level of ever used e-cigarettes, there are countries across a broad range of current smoking prevalence for both males and females.

23   Tables

Table 24: Regulations relating to e-cigarettes by country

Country	E-cigarette laws
Argentina	A ruling bans the sale, advertisement, distribution and importation of e-cigarettes. A decree classified these as tobacco products, thus use is inherently prohibited in enclosed public spaces/transport by the national tobacco control law.
Australia	A law classifies nicotine as a restricted poison if it is not used for therapeutic purposes. Non-nicotine e-cigarettes are classified as legal consumer products.
Austria	E-cigarettes can be classified as medicines if they are marketed with medicinal claims and thus regulated under the Austrian Medicinal Products Act, or as tobacco related products and regulated by the Amended Austrian Tobacco Act 2016.
Bahrain	Classified as tobacco products and referred to as e-cigarettes in the decision that bans their sale, importation and distribution.
Barbados	The Health Service Amendment Bill 2017, which classifies e-cigarettes as electronic smoking devices, extends the prohibition on smoking to e-cigarettes.
Belgium	According to a science policy advisory report nicotine-containing e-cigarettes can be brought to the market as medicinal products and have to obtain marketing authorization. The medicines act stipulates rules on advertising of medicines.
Brazil	Classified as tobacco products. A resolution prohibits the sale, advertisement, distribution and importation of e-cigarettes. As tobacco products, their use in public places and public transportation is prohibited by a decree.
Brunei Darussalam	Classified as tobacco imitation products. The Tobacco Order prohibits the sale, offer for sale or importation of items that imitate tobacco products.
Bulgaria	E-cigarettes are regulated by Decree 89 (to Promulgate the Law on Amending and Supplementing the Law on Tobacco and Tobacco Products), which contains a requirement to notify the Ministry of Economy prior to introducing a product to the market and notification requires compliance with a range of product specifications including on pack warnings. Manufacturers or importers must also submit an annual report to the Ministry of Economy as specified in the law.
Cambodia	Classified as e-cigarettes by a circular which bans their sale, importation and use.
Canada	A notice by Health Canada classifies nicotine-containing e-cigarettes as new drugs under the Food and Drug Regulations. As such, there are restrictions on their sale, advertisement, promotion, sponsorship, importation and manufacturing.
Chile	Nicotine-containing e-cigarettes are classified as medicinal products per a resolution.
Colombia	The tobacco control law classifies these products as tobacco imitations, banning sale, manufacturing and marketing/advertising. There are bans on the use of these products in enclosed public places and on public transport.
Costa Rica	Referred to as ENDS in a decree and classified as tobacco products. In accordance with the tobacco control law, they cannot be sold to minors (under 18 years).
Croatia	E-cigarettes are regulated by the Law restricting the use of tobacco and related products of May 10, 2017, which contains a requirement to notify the Ministry of Health prior to introducing a product to the market.

Country	E-cigarette laws
Cyprus	Nicotine-containing e-cigarettes are regulated by the Law on Health protection (Tobacco Control Law) of 2017 and the Health Protection (Tobacco Control) Regulations of 2017, which require specific notification and reporting obligations on manufacture.
Czech Republic	Decree No. 37/2017 regulates e-cigarettes that contain nicotine.
Denmark	E-cigarettes will be regulated as medicinal products under the Danish Medicines Act if they are marketed as products for the prevention or treatment of diseases, e.g. nicotine dependence and cessation.
Ecuador	Classified as ENDS per a decree. Minimum age of purchase is 18 years. Advertising is restricted to venues accessed solely by adults. The tobacco control law bans use in public spaces/transport.
England	E-cigarettes may be brought to market either as medicines or as consumer products. Those seeking medicines approval undergo the standard licensing process.
Estonia	E-cigarettes are classified as tobacco related products and regulated by the Tobacco Act 2016. E-cigarettes may also be classified/brought to the market as medicinal products and thus be regulated by the Medical Devices Act.
Fiji	A tobacco control (amendment) decree applies to both nicotine-containing and non-nicotine e-cigarettes. E-cigarettes cannot be sold to minors (under 18 years), advertised or used in public transportation and certain enclosed public places.
Finland	E-cigarettes are classified as tobacco related products (non-nicotine single use e-cigarettes are classified as tobacco substitutes) and regulated by the Tobacco Act 2016.
France	E-cigarettes maybe be brought to market either as medicines or as consumer products.
Gambia	Classified as electronic nicotine delivery systems. The sale, offer for sale, possession, distribution, importation of nicotine-containing and non-nicotine e-cigarettes are prohibited.
Georgia	Nicotine-containing e-cigarettes or similar nicotine-delivery devices are classified and regulated as tobacco products in accordance with the Law of Georgia on Tobacco Control. Sale of nicotine-containing e-cigarettes to minors under 18 years is prohibited, as is sale at certain locations (e.g. education institutions, sections of retail stores where children's toys are sold, etc.).
Germany	Nicotine-containing e-cigarettes are classified as tobacco related products and regulated by the Federal Government law on the Implementation of the Tobacco Products Directive and Related Products 2016 and by the ordinance on the implementation of the Tobacco Products Directive and related products 2016. Non-nicotine e-cigarettes are regarded as consumer products.
Greece	A law bans the sale, display, manufacture and commercialization of e-cigarettes. Use of all types of e-cigarettes in enclosed public places is prohibited.
Honduras	A decree classified e-cigarettes as tobacco derivative products, thus subject to tobacco control laws. Minimum age of purchase is 21 years.
Hungary	Classified as consumer products. Marketing authorization is required for sale. Sale is permitted at tobacco shops.
Iceland	Nicotine-containing e-cigarettes are classified as medicinal products, thus marketing authorization must be obtained prior to marketing these products and they must meet all requirements on sale, advertising/promotion, distribution, manufacture.
Ireland	Non-nicotine e-cigarettes are regulated as consumer products, while nicotine-containing e-cigarettes and refill containers are regulated by the European Union (Manufacture, Presentation and Sale of Tobacco and Related Products) Regulations 2016 (S.I. No. 271 of 2016), which transposed the Tobacco Products Directive 2014/40/EU.
Israel	N/A
Italy	E-cigarettes are classified as tobacco related products and regulated by a legislative decree.
Jamaica	Nicotine-containing e-cigarettes are classified as medicinal products under the Food and Drugs Act. As such they must be registered before they can be imported (no approval has been granted for these products to date).

Country	E-cigarette laws
Japan	Non-nicotine e-cigarettes are currently not being regulated. However, nicotine- containing e-cigarettes are classified as medicinal products and are regulated under the Japanese pharmaceutical affairs law.
Jordan	Jordan bans the sale, advertising, manufacturing, importation and use of e-cigarettes via an official letter.
Kuwait	The sale and marketing of e-cigarettes is banned in accordance with a decision by health ministers of gulf countries.
Latvia	E-cigarettes are described as "electronic smoking devices".
Lebanon	A decision bans the importation and trading of all types of e-cigarettes and orders the withdrawal of all e-cigarettes from the Lebanese market.
Lithuania	E-cigarettes are classified as tobacco related products and regulated by the Tobacco, Tobacco Products and Related Products Control Law 2016.
Luxembourg	E-cigarettes are regulated by the Law of 13 June 2017 transposing the Directive 2014/40/EU, amending the amended law of 11 August 2006 on tobacco control.
Malaysia	Nicotine is classified as a class C poison under the Poisons Act and Control of Drugs and Cosmetics Regulations. Devices without nicotine are classified as electrical appliances.
Malta	The manufacture, presentation and sale of e-cigarettes are regulated by the Subsidiary Legislation 315.10, Manufacture, Presentation and Sale of Tobacco and Related Products Regulations, enacted under the Tobacco (Smoking Control) Act (CAP 315 of Laws of Malta).
Mauritius	A public health regulation prohibits the sale, offer for sale or distribution of products that look like tobacco or cigarettes.
Mexico	The national tobacco control law prohibits the sale, distribution, exhibition, promotion or manufacture of an object that imitates a tobacco product. These prohibitions are specific to nicotine-containing e-cigarettes.
Nepal	The Tobacco Product Control and Regulatory Directive, 2014 bans the sale (including single unit sale), advertising, promotion and sponsorship, importation, manufacture, as well as distribution and use of e-cigarettes in public places and transportation.
Netherlands	Nicotine-containing and non-nicotine e-cigarettes and e-liquids are regulated under the amended Tobacco and Smoking Commodities Act (and delegated legislation: the Tobacco and Smoking Commodities Decree and the Tobacco and Smoking Commodities Order.
New Zealand	Under the Medicines Act, nicotine-containing e-cigarettes or non-nicotine e-cigarettes promoted as therapeutic products are classified as medicinal. As medicinal products, there are restrictions on sale, advertising and distribution.
Nicaragua	The national tobacco control law prohibits the sale, importation or manufacture of objects imitating tobacco products.
Northern Ireland	E-cigarettes may be brought to market either as medicines or as consumer products. Those seeking medicines approval undergo the standard licensing process.
Norway	E-cigarettes can be classified either as medicinal products or as tobacco surrogates.
Oman	A decision by the Public Authority for Consumer Protection bans the sale and marketing of e-cigarettes and electronic shisha.
Panama	A decree classifies e-cigarettes as tobacco products. Sale, advertising, promotion and sponsorship, distribution and importation of e-cigarettes with or without nicotine are prohibited.
Philippines	An order classifies e-cigarettes as medicinal products and medical devices.
Poland	E-cigarettes are classified as tobacco related products and regulated by the Polish Anti-Tobacco Act (2016).
Portugal	Nicotine-containing e-cigarettes (like all tobacco products) are regulated by Law no 37/2007 of 14th August, with language provided in Law no 108/2015 of 26th August.
Qatar	A circular strictly prohibits the sale, distribution and advertising of e-cigarettes in pharmacies; another circular strictly prohibits their importation into the country.

Country	E-cigarette laws
Republic of Korea	Non-nicotine containing e-cigarettes are considered consumer products. Nicotine-containing e-cigarettes are classified as tobacco products, thus their sale is prohibited to minors (under 19 years).
Romania	E-cigarettes are classified as tobacco related products and regulated by Law no. 201/2016 (establishing the conditions for manufacture, presentation and sale of tobacco products and related products and amending Law no. 349/2002 for preventing and combating the effects of tobacco products).
Saudi Arabia	The sale and marketing of e-cigarettes is banned in accordance with a decision of health ministers of gulf countries.
Scotland	E-cigarettes may be brought to market either as medicines or as consumer products. Those seeking medicines approval undergo the standard licensing process.
Serbia	The law on advertising (Official Gazette of RS, No. 6/2016) provides restrictions in advertising, promotion and sponsorship related to e-cigarettes, e-liquids and e-cigarette components.
Seychelles	The Tobacco Control Act prohibits the manufacture, importation, supply, display, distribution or sale of imitation tobacco products.
Singapore	E-cigarettes are classified by the tobacco control act as imitation tobacco products banning their sale, distribution and importation.
Slovakia	E-cigarettes are regulated by the Act of 25 November 2015 (No. 89/2016) on the Manufacture and Labelling of Tobacco Products and related Products and Amending Certain Acts, which classifies them as tobacco related products.
Slovenia	E-cigarettes are regulated by the Restriction on the Use of Tobacco or Tobacco-related Products Act (OUTP), which classifies them as tobacco related products.
South Africa	Nicotine-containing e-cigarettes are regulated by the Medicines Control Council as schedule 3 medicines.
Spain	Law 28/2005 on health measures against smoking and regulating the sale, supply, consumption and advertising of tobacco products bans the sale of ENDS or similar products to minors (under 18 years).
Suriname	The Tobacco Law prohibits the importation, distribution and sale of electronic cigarettes.
Sweden	E-cigarettes are regulated by Law (2017:425) on electronic cigarettes and refill containers.
Switzerland	In a statement by the Federal Office of Public Health, non-nicotine e-cigarettes are regulated within the scope of the food act as commodities. However, the sale of nicotine-containing e-cigarettes is prohibited.
Thailand	E-cigarettes are prohibited under several regulatory mechanisms. The Medicine Act prohibits manufacturing, sale and importation of modern medicinal products.
Togo	The tobacco control law classifies nicotine-containing e-cigarettes as derivative products.
Turkey	Ministry of Health issued a circular (not available online) indicating that the sale and importation of e-cigarettes and related devices are banned. However, other legislation seem inconsistent with this statement.
Turkmenistan	E-cigarettes are classified as tobacco products.
Uganda	Classified as electronic nicotine delivery systems. The sale, offer for sale, distribution, importation, manufacture, or processing of nicotine-containing and non-nicotine e-cigarettes are prohibited.
Ukraine	A law classifies these products as e-cigarettes and prohibits their use in public spaces/transport, with the exception of designated areas. The prohibition on sale and use of tobacco by minors under 18 years is extended to e-cigarettes.
United Arab Emirates	The sale and marketing of e-cigarettes is banned in accordance with a decision of health ministers of gulf countries. The Ministry of Health has also banned their use.

Country	E-cigarette laws
United States	The US Food and Drug Administration (FDA) classifies e-cigarettes and other electronic nicotine delivery systems (ENDS) as tobacco products, except in cases when they are marketed as drugs, devices or combination products (e.g., as a therapeutic product to help people quit smoking). The US FDA regulates the sale, advertising, promotion, distribution, manufacture, import, packaging and labeling of e-cigarettes classified as tobacco products based on the laws set forth in the Tobacco Control Act and the Food, Drug, and Cosmetic Act (FD&C Act).
Uruguay	Nicotine and non-nicotine e-cigarette sale, importation, registration as a brand/patent and promotion is explicitly banned by an amendment/ decree.
Venezuela (Bolivarian Republic of Venezuela)	Companies wishing to import e-cigarettes must indicate whether the product should be classified as a medicinal, consumer good or tobacco derivative. If regulated as a tobacco- derivative, e-cigarettes cannot be sold to minors, advertised/promoted or used in enclosed public spaces or transport, as dictated by the tobacco control law. If indicated as medicinal or consumer products, they must be subject to extensive clinical trials like other nicotine replacement therapies before being sold, promoted, distributed or used.
Viet Nam	E-cigarettes are classified as tobacco products. The national tobacco control law bans sale to minors and marketing/advertising.
Wales	E-cigarettes may be brought to market either as medicines or as consumer products. Those seeking medicines approval undergo the standard licensing process.

Table from *Country Comparison Database,* (Global Tobacco Control. nd.)

Table 25: Categories of national e-cigarette regulation

Countries with complete use and sales ban	Countries with a sales ban and restricted public use	Countries with sales ban	Countries with restricted public use	
Cambodia (44.7)*	Australia (17.8)	Argentina (31)	Austria -	Portugal (31.9)
Jordan (65.5)	Brazil (20.3)	Canada (18.5)	Belgium (27.5)	Slovenia (23.2)
Nepal (37.9)	Columbia (16.8)	Japan (35.4)	Croatia (39.5)	South Korea (51.1)
Panama (11.9)	Costa Rica (19.3)	Kuwait -	Denmark (19.9)	Spain (33)
Turkmenistan -	Greece (53.8)	Malaysia (44.4)	Ecuador (14.7)	Togo -
United Arab Emirates -	Thailand (41.9)	Mexico (22.5)	Estonia (42.8)	Ukraine (50.6)
	Turkey (41.6)	New Zealand (18.5)	Fiji (40)	Venezuela -
		Nicaragua -	Finland (24.6)	Vietnam (47.3)
		Oman (19.5)	France (30.6)	
		Saudi Arabia (26.8)	Germany (33.1)	
		Suriname -	Honduras (35.9)	
		Switzerland (27.7)	Lithuania (39.8)	
		Uganda (17.5)	Philippines (44.8)	
		Uruguay (28.8)	Poland (34)	

*country (2013 age-standardised male current tobacco use rate);

Table 26: Average of the country prevalence rate (%) for tobacco and cigarette use by sex within e-cigarette regulation categories

| | | E-cigarette Regulation category | | | |
		Countries with complete use and sales ban*	Countries with a sales ban and restricted public use*	Countries with sales ban*	Countries with restricted public use*
Current smoking of any tobacco product	Males	40	30.2	27.3	35
	Females	7.3	13	11.6	17.1
	Total	23.3	21.4	19.8	25.7
Daily smoking of cigarettes	Males	26.4	21.6	19.5	24.7
	Female	3.6	8.3	8.3	11.4
	Total	14.8	14.8	14.1	17.8

*simple average of each country rate

Table 27: Country-specific Age-Standardised Smoking Prevalence Rates for 2013

| Country | Current smoking of any tobacco product (age-standardized rate) | | | Daily smoking of any tobacco product (age-standardized rate) | | | Current smoking of cigarettes (age-standardized rate) | | | Daily smoking of cigarettes (age-standardized rate) | | |
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
Albania	29.7	51.7	8	23.8	41.7	6.2	24.5	44.4	5	21.3	38.4	4.6
Andorra	33.1	38.1	28.1	27.9	32.2	23.6	27.2	31.4	22.9	22	25.3	18.7
Argentina	25.3	31	19.9	18.1	22.2	14.3	22.9	28.2	18	17.3	21.4	13.5
Armenia	28	54.2	1.7	24.7	48.1	1.3	26.2	50.8	1.5	22.7	44.2	1.1
Australia	16	17.8	14.3	13.7	15.1	12.4	13	14.9	11.3	11	12.3	9.6
Azerbaijan	23.5	47.8	0.4	18.6	38	0.3	18.7	38.2	0.3	15.5	31.7	0.3
Bahrain	30.3	42.7	7.1	27.1	38.5	5.9	25.3	37.6	2.3	21.2	31.9	1.4
Bangladesh	21.8	42.4	0.9	19.6	38.1	0.8	15.2	29.8	0.3	12.5	24.5	0.3
Barbados	7	13.1	1	5	9.3	0.7	5.4	10.2	0.8	3.8	7.1	0.5
Belarus	27.9	48.2	10.9	22.6	40.7	7.6	25.6	44.3	10	21.1	38.4	6.7
Belgium	23.9	27.5	20.5	19.7	22.6	16.9	19.8	22.5	17.2	15.5	17.4	13.7
Benin	8.8	16.9	1	7.4	14.2	0.8	5	9.9	0.2	4.6	9	0.2
Bosnia and Herzegovina	39.2	48.3	30.8	32.1	40.6	24.1	31.7	38.9	25	28.2	35.9	21.1
Brazil	16.1	20.3	12.1	12.7	16.3	9.4	14	17.9	10.3	11.5	15	8.3
Brunei Darussalam	16.4	29.2	3.3	12.9	23.2	2.5	13.2	23.4	2.7	10.5	18.9	1.9

Country	Current smoking of any tobacco product (age-standardized rate)			Daily smoking of any tobacco product (age-standardized rate)			Current smoking of cigarettes (age-standardized rate)			Daily smoking of cigarettes (age-standardized rate)		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
Bulgaria	36.8	44.3	29.8	30	37.5	23.1	33.7	40.6	27.2	27.1	33.6	21
Burkina Faso	19.1	34.1	4.8	16.2	28.7	4.3	12.4	24.7	0.7	7.7	15.1	0.6
Cabo Verde	12.2	20.8	3.7	9.7	16.6	2.8	7.9	14.9	1.1	6.1	11.4	0.9
Cambodia	23	44.7	3.2	19.8	38.5	2.7	19.4	37.6	2.8	16.8	32.4	2.5
Cameroon	18.8	36.9	0.9	13.6	26.8	0.6	11.4	22.6	0.4	9.8	19.5	0.2
Canada	16.2	18.9	13.6	11.9	13.9	9.9	15.6	18.3	13	11.7	13.7	9.7
Chile	38.9	41	36.8	27.5	29.4	25.8	32.7	34.9	30.5	23	25	21.1
China	25.9	48.7	1.9	22.4	42	1.6	23.7	44.6	1.7	20.4	38.5	1.3
Colombia	11.6	16.8	6.6	8.1	11.8	4.6	9.5	13.8	5.5	5.7	8.7	2.9
Comoros	15.3	23.8	6.7	12.5	20.1	5	11.9	19.3	4.5	6.3	10.9	1.7
Congo	18.5	35.5	1.7	13	25	1.1	12	23.3	0.8	9.8	19.2	0.5
Costa Rica	14.2	19.3	8.9	8.3	11.3	5.1	11.9	16.1	7.6	6.9	9.4	4.2
Croatia	36	39.5	32.7	31.1	34.9	27.6	28.9	32	26	24.7	28.9	20.8
Cuba	36.1	53.1	19.1	23.4	33.2	13.7	28.5	42.2	14.8	21	30.8	11.3
Czechia	33.4	37.8	29.2	24.7	29.4	20.3	28.1	32	24.3	24.1	28.5	20
Denmark	18.9	19.9	18	15.6	16.2	14.9	15.8	15.9	15.6	11.5	11.6	11.4
Dominican Republic	14.5	19	10	11.3	14.7	8	10.4	13.6	7.2	8.9	11.6	6.2
Ecuador	9	14.7	3.5	4.5	7.1	1.9	7.3	11.9	2.8	3.9	6.4	1.4
Egypt	23.8	47.5	0.4	20.3	40.5	0.3	17.9	35.7	0.2	14.8	29.7	0.1
Estonia	33.2	42.8	25.3	26.1	35.7	18.1	27.2	35.3	20.5	23.6	32.2	16.5
Ethiopia	4.7	8.9	0.5	3.3	6.3	0.3	3.8	7.5	0.2	2.9	5.7	0.1
Fiji	26.5	40	12.7	18.1	28	8	20.9	31.8	9.8	15.1	23.2	6.8
Finland	21.8	24.6	19.3	16.8	19.3	14.5	16.9	18.8	15.1	13.6	14.8	12.4
France	28.1	30.6	25.8	23.5	25.5	21.5	22.8	24.9	20.8	20.1	22.3	18.1
Georgia	30	58.5	5.8	24	47.7	3.9	27	52.5	5.3	21.7	43.3	3.4

Country	Current smoking of any tobacco product (age-standardized rate)			Daily smoking of any tobacco product (age-standardized rate)			Current smoking of cigarettes (age-standardized rate)			Daily smoking of cigarettes (age-standardized rate)		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
Germany	30.7	33.1	28.5	24.2	27.6	21	28.3	30.4	26.4	23.1	25.9	20.4
Ghana	6.3	12.4	0.5	4.9	9.8	0.4	4.4	9	0.1	3.9	8	0.1
Greece	43.4	53.8	33.5	35.2	45.8	25.1	36.5	45	28.4	29.7	37.6	22.1
Haiti	11.8	21.5	2.7	8.6	15.6	2	9.8	17.8	2.3	4.8	8.9	1
Honduras	18.9	35.9	2.3	11.1	21.1	1.4	13.8	26.1	1.8	9.9	18.8	1.1
Hungary	29.6	33.6	26	25.1	28.9	21.7	24.1	27.8	20.7	22.1	25.2	19.4
Iceland	17.5	18.6	16.3	13.1	13.1	13.1	13.4	14.2	12.7	11.5	12.4	10.7
India	12.4	21.9	2.3	10.7	19.1	1.9	5.2	9.4	0.8	3.1	5.6	0.6
Indonesia	38.5	73.3	3.8	33.1	63.9	2.4	33.2	63	3.5	30.8	59.4	2.3
Iran	11.7	22.4	1	10.4	20	0.8	7.8	15	0.6	5.6	10.8	0.4
Ireland	23.2	23.6	22.9	19.2	19	19.4	23.2	23.6	22.9	19.2	19	19.4
Israel	30.4	41.5	19.8	23.3	31.9	15	25.1	34.3	16.4	21.6	30.3	13.4
Italy	24.2	28.8	19.9	22	26.1	18.3	23.2	27.5	19.3	21.1	24.5	18.1
Jamaica	17.6	29.7	6.2	13	21.8	4.7	14.7	24.8	5.2	9.3	15.3	3.5
Japan	22.8	35.4	11	18.1	28.6	8.4	22.8	35.4	11	18.1	28.6	8.4
Jordan	38.4	65.5	10.2	31	54	7.2	33.2	56.8	8.6	22	41.2	2.1
Kazakhstan	26.3	45.3	9.5	17.4	30.3	5.9	24.2	42.2	8.1	16.1	27.6	5.9
Kenya	13.6	25.1	2.2	9.8	18.5	1.2	10.2	20	0.6	8.7	17.1	0.6
Kiribati	54	66.2	42.2	45.6	56.8	34.7	41.5	51.8	31.6	24.2	29.9	18.8
Kyrgyzstan	26.4	50.5	3.7	20.9	40.1	2.7	23.1	44.5	2.9	19.9	38.4	2.5
Lao	34	58.7	10.1	29	50.7	8	27.4	47.5	8.2	23.6	42.7	5.3
Latvia	35.9	50	24.4	30	44.4	18.3	29.1	40.3	20	26.8	38.2	17.6
Lebanon	37	43.9	29.9	28.7	36	21.1	30.7	37	24.2	16.9	27.4	6.1
Lesotho	25.4	51.7	0.4	19.9	40.4	0.3	18.3	37.3	0.2	14.9	30.3	0.2
Liberia	14.2	25.9	2.6	11.2	20.5	1.9	10	19.3	0.7	7.5	14.5	0.6

Country	Current smoking of any tobacco product (age-standardized rate)			Daily smoking of any tobacco product (age-standardized rate)			Current smoking of cigarettes (age-standardized rate)			Daily smoking of cigarettes (age-standardized rate)		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
Lithuania	30.1	39.8	22.2	23.6	34.1	14.9	24.6	32.8	17.8	18.9	26.2	13
Luxembourg	24.4	26.8	22	18.8	20.2	17.3	20.1	22.3	17.9	15.8	17	14.6
Malawi	16.3	26.3	6.4	11.9	20.1	3.8	11.7	22.4	1.2	9.7	18.1	1.2
Malaysia	22.3	44.4	1.5	18.2	36.5	1.1	18	36	1.2	16.1	32.4	0.9
Mali	18.6	33.9	3.3	14.9	27.5	2.5	13.2	25.5	1.1	8.5	16.5	0.6
Malta	25.9	30.9	20.9	20.7	25.3	16.1	21	25.3	16.8	18.3	22.4	14.2
Mauritania	22.3	40.6	3.9	19	35.1	2.9	14.9	28.7	1	8.7	16.5	0.9
Mauritius	21.9	41	3.4	16	31	1.6	19.6	36.8	3	14.5	28.4	1.2
Mexico	14.5	22.5	7.3	8.3	13.1	4	13.3	20.7	6.6	8	12.6	3.8
Mongolia	26.8	48.7	5.6	22.7	41.6	4.5	21.7	39.5	4.5	20.2	36.9	4.1
Morocco	22	43.6	1.6	17.9	35.8	0.9	18.5	36.8	1	14.1	28.4	0.5
Mozambique	18.8	32.7	6.1	13.4	23.7	3.9	12.8	24.8	1.8	10.5	20.3	1.5
Myanmar	20	33.9	7.2	15.8	27.1	5.5	16.2	27.4	5.9	10	16.8	3.8
Namibia	23.8	37	11.7	18.9	29.8	8.9	15.6	25.7	6.5	12.3	20.4	4.9
Nauru	48.9	44.3	53.5	39.8	36.8	42.8	38.2	35.8	40.6	28	26	30
Nepal	24.6	37.9	12.9	18.1	27.7	9.6	20.5	32.1	10.3	16.9	26.4	8.6
Netherlands	25.7	27.3	24.2	19.6	20.6	18.6	21.1	22.4	19.8	18.8	20	17.7
New Zealand	17.6	18.5	16.7	15.5	16.4	14.7	16.7	17.6	15.9	15.1	15.9	14.3
Niger	8.4	16.7	0.2	6	11.8	0.2	6.3	12.6	0	5.6	11.3	0
Nigeria	8.9	16.4	1.2	7	13	0.9	5.7	10.9	0.3	4.8	9.2	0.2
Niue	16.6	21.5	11.8	11.7	15.6	7.9	13.9	18.1	9.8	9.3	12.1	6.5
Norway	24.1	24.3	23.9	17.2	17.2	17.2	18.9	18.9	18.9	14.7	14.5	15
Oman	13.5	19.5	1	10.9	15.8	0.7	10.5	15.3	0.5	8.2	12.1	0.2
Pakistan	22.6	41	3.4	18.6	33.8	2.8	14.1	26	1.6	11.6	21.6	1.1
Panama	7.4	11.9	2.8	3.9	6.2	1.5	6.4	10.4	2.4	3.4	5.6	1.3

Country	Current smoking of any tobacco product (age-standardized rate)			Daily smoking of any tobacco product (age-standardized rate)			Current smoking of cigarettes (age-standardized rate)			Daily smoking of cigarettes (age-standardized rate)		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
Paraguay	19.5	30.3	8.6	11.9	18.6	5.1	15.6	24.2	7	9.9	16	3.7
Philippines	26.7	44.8	8.9	20.6	35	6.4	23.8	40.6	7.4	18.6	31.5	5.9
Poland	29.4	34	25.2	23.2	27.9	18.9	26.8	31.3	22.8	22.6	27.1	18.4
Portugal	22.6	31.9	14	17.7	26.1	10	18.5	26.2	11.3	15.2	22.2	8.6
Republic of Korea	27.4	51.1	4.3	25.7	48.5	3.5	27.4	51.1	4.3	25.7	48.5	3.5
Republic of Moldova	23.8	44.8	5.4	20.1	38.1	4.3	21.6	40.7	4.8	17.9	34	3.8
Romania	30.5	38.5	23.1	25.7	33.4	18.6	26.7	34.1	19.8	23.8	30.4	17.7
Russian Federation	39.5	59.8	22.7	33.4	51.9	18.1	36.1	55	20.6	31	48.2	16.8
Samoa	32	43.5	19.8	24.4	34	14.1	25	34	15.5	21.5	29.7	12.8
Saudi Arabia	17.1	26.8	3	14.5	23.1	1.8	12.9	20.2	2.2	10.2	16.8	0.6
Senegal	11.1	22.4	0.8	9.5	19.2	0.6	7.7	15.9	0.2	6.8	14.1	0.2
Serbia	42.1	44.6	39.7	33.5	36.4	30.8	33.8	36.3	31.4	31.1	33.6	28.7
Seychelles	26.7	43.7	9	20.7	34.3	6.6	20.3	34.7	5.5	15.7	27.7	3.1
Sierra Leone	34.4	56.4	12.9	25.7	43.4	8.5	23.5	43	4.5	20.6	38.5	3.2
Singapore	16.2	27.8	5.2	13.2	23.1	3.6	14.5	24.8	4.5	12.4	21.8	3.5
Slovakia	28.8	40.4	18	22	31.8	12.9	23.7	33.4	14.6	18.8	27.5	10.8
Slovenia	20.9	23.2	18.7	17.7	20	15.4	17.1	19.3	14.8	14.9	16.8	12.9
South Africa	18.9	31.9	7	16.1	27.1	6	13.3	24	3.6	11.7	20.3	3.9
Spain	30.3	33	27.8	25.7	28.2	23.2	26.7	29.1	24.3	23	25	21.1
Sri Lanka	14.1	28.8	0.4	10.9	22.2	0.3	9.8	20.1	0.2	7.5	15.3	0.1
Swaziland	10.2	18.4	2.3	7.1	12.7	1.7	8.7	16.5	1.3	4.8	8.9	0.9
Sweden	21.9	21.7	22.1	11.8	10.6	13	16.8	16.6	17.1	11.8	10.6	13
Switzerland	24.1	27.7	20.6	19.5	21.5	17.6	23.5	27.1	20.1	19.1	20.8	17.5
Thailand	21.5	41.9	2.4	18.2	35.7	1.8	20.5	39.9	2.2	17.4	34.2	1.6
Tonga	30.2	47.9	13.1	25.8	41.6	10.6	23.8	38	10.2	19.7	31.1	8.7

Country	Current smoking of any tobacco product (age-standardized rate)			Daily smoking of any tobacco product (age-standardized rate)			Current smoking of cigarettes (age-standardized rate)			Daily smoking of cigarettes (age-standardized rate)		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
Turkey	27	41.6	13.2	22.4	35.7	9.9	24.7	38.1	12	21.4	33.9	9.6
Uganda	10.3	17.5	3.1	6.6	11.5	1.8	8	15	0.9	5.3	9.9	0.8
Ukraine	30.7	50.6	14.3	25.4	44.2	9.9	28.3	46.9	13	24.1	42.2	9.1
United Kingdom	20.3	21.1	19.5	20.3	21.1	19.5	20.3	21.1	19.5	20.3	21.1	19.5
Tanzania	16.3	28.8	3.9	11.9	21.4	2.4	11.4	22.1	0.8	10	19.2	0.8
United States	18.1	20.3	15.9	14.3	16.1	12.6	18.1	20.3	15.9	14.3	16.1	12.6
Uruguay	24.8	28.8	21.1	18.9	22.3	15.7	22.1	25.9	18.6	17.6	20.8	14.6
Uzbekistan	13.3	25.6	1.3	10.4	20.1	1	11	21.3	1	8.5	16.5	0.8
Viet Nam	23.7	47.3	1.3	19.2	38.4	1	18.7	37.4	1	14.3	28.6	0.8
Zambia	15.9	27.1	4.7	10.5	17.8	3.2	12.5	23.9	1.2	8.2	15.4	1

Table 28: Prevalence of e-cigarette use. Data from 2017 Eurobarometer Report (survey conducted in 2014).

Country	Current e-cigarette use (%)				Have ever tried e-cigarettes (%)					
	Total	Current smokers	Ex-smokers	Never smokers	Total	Current smokers	Ex-smokers	Never smokers	Males	Females
Austria	3	7	3	1	21	42	24	8	26	16
Belgium	4	8	6	1	16	50	14	5	18	14
Bulgaria	0	0	1	0	9	22	10	1	12	8
Croatia	0	0	2	0	11	26	8	2	17	7
Czech Republic	1	3	2	0	20	48	24	5	26	16
Denmark	2	7	2	0	16	50	14	4	16	15
Estonia	1	3	1	1	21	49	24	8	29	14
Finland	1	4	2	0	17	47	18	4	19	14
France	4	8	6	0	24	54	19	2	29	20
Germany	2	6	1	0	12	35	10	2	15	9
Greece	3	4	5	0	15	31	13	2	17	12
Hungary	1	0	3	0	9	19	12	2	10	6
Ireland	2	4	7	0	13	44	19	2	15	12
Italy	0	0	1	0	9	20	19	2	12	6
Latvia	1	3	0	0	24	46	28	7	36	15
Lithuania	1	3	0	0	15	31	18	4	24	7
Luxembourg	2	7	0	0	12	35	10	4	12	12
Malta	2	6	3	0	12	40	5	2	15	9
Poland	1	3	1	0	13	35	12	2	17	10
Portugal	1	3	1	0	8	28	2	1	10	6
Republic of Cyprus	3	6	1	1	21	47	24	6	30	12
Romania	0	1	1	0	9	25	3	3	14	6
Slovakia	0	1	0	0	10	27	11	2	15	5
Slovenia	1	1	1	0	11	27	9	3	14	7
Spain	1	2	0	0	12	32	8	2	13	10

Sweden	0	0	1	0	10	40	13	3	12	8
The Netherlands	2	5	1	0	15	52	9	3	15	15
United Kingdom	5				18					

Table 29: Tobacco smoking rates in countries where e-cigarette use has been recently measured.

Country (source)	Year	E-cigarette use		Tobacco smoking rate	
		Current use of e-cigarettes	Ever used e-cigarettes	Male	Female
Australia (NSW) (Harrold, Maag et al. 2015)	2014	1.3	8.4	16.7	13.1
Austria (European Commission 2017)	2014	3	21	35.5	34.8
Belgium (European Commission 2017)	2014	4	16	26.5	20
Brazil (Gravely, Fong et al. 2014)	2012-13		4	19.3	11.3
Bulgaria (European Commission 2017)	2014	0	9	42.4	28.2
Canada (Reid JL 2017)	2015	1	13.2	15.6	10.4
Croatia (European Commission 2017)	2014	0	11	39.4	33.5
Czech Republic (European Commission 2017)	2014	1	20	37.4	29
Denmark (European Commission 2017)	2014	2	16	17.6	16.4
Estonia (European Commission 2017)	2014	1	21	41.2	24.9
Finland (European Commission 2017)	2014	1	17	23.2	18.5
France (European Commission 2017)	2014	4	24	29.8	25.6
Germany (European Commission 2017)	2014	2	12	32.4	28.3
Greece (European Commission 2017)	2014	3	15	52.6	32.7
Hong Kong (Jiang, Chen et al. 2016)	2014		2.3	18.6	3.2
Hungary (European Commission 2017)	2014	1	9	32	24.8
Indonesia (Palipudi, Mbulo et al. 2016)	2011	0.3		76.2	3.6
Ireland (European Commission 2017)	2014	2	13	22.4	21.9
Italy (European Commission 2017)	2014	0	9	28.3	19.7
Kazakhstan (Ministry of Healthcare and Social Development of the Republic of Kazakhstan. 2014)	2014	1.7		42.4	4.5
Latvia (European Commission 2017)	2014	1	24	48.9	24.3
Lithuania (European Commission 2017)	2014	1	15	38.1	22.2
Luxembourg (European Commission 2017)	2014	2	12	25.8	21.4
Malaysia (Palipudi, Mbulo et al. 2016)	2011	0.8		43	1.4
Malta (European Commission 2017)	2014	2	12	29.7	20.2
Philippines (Republic of the Philippines Department of Health 2017)	2015	0.8		41.9	5.8
Poland (European Commission 2017)	2014	1	13	32.4	23.7
Portugal (European Commission 2017)	2014	1	8	31.5	13.7
Qatar (Palipudi, Mbulo et al. 2016)	2013	0.9		20.2	3.1
Republic of Cyprus (European Commission 2017)	2014	3	21	43.9	16.9
Romania (European Commission 2017)	2014	0	9	36.9	22.7
Russia (Ernst & Young 2016)	2013-15	1		59	22.8
Serbia (Kilibarda, Mravcik et al. 2016)	2014	2		44.3	36.2
Slovakia (European Commission 2017)	2014	0	10	39.7	17.6
Slovenia (European Commission 2017)	2014	1	11	22.3	18.1
South Korea (Ernst & Young 2016)	2013-15	0.6		49.8	4.2
Spain (European Commission 2017)	2014	1	12	31.3	27.1
Sweden (European Commission 2017)	2014	0	10	20.4	20.8
Taiwan (Chang, Tsai et al. 2017)	2015	2.7	2.7	14.1	15.3

The Netherlands (European Commission 2017)	2014	2	15	26.2	23.9
UK (European Commission 2017)	2014	5	18	19.9	18.4
Ukraine (Ministry of Health of Ukraine. 2017)	2017	1.7		40.1	8.9
USA (Zhu, Zhuang et al. 2017)	2014-15	2.4	8.5	19.5	15
Viet Nam (Ministry of Health Viet Nam 2016)	2015	0.2	1.1	45.3	1.1

PART 7: Supplementary Report: exploring the use of e-cigarettes

Executive summary

- Most data about the use of e-cigarettes are being produced based on samples in the US.

- Many papers aim to describe prevalence and/or predictors of e-cigarette use in order to understand if certain types of people use these products. Results for sociodemographic variables are not consistent internationally.

- Few studies consider factors beyond sociodemographic profiles. However, those that do provide a fairly consistent picture of an association between psychological and personality characteristics such as mental health and impulsivity and e-cigarette use.

- Youth samples are represented in almost half the papers about e-cigarette use and are a key interest in the literature. Papers on youth focus on susceptibility to use and wider factors such as social and environmental ones that may predict uptake.

- LGBTI people appear to have higher rates of e-cigarette use than people in sexual and gender majorities – at least in the US.

- Data from Australia does not provide a clear indication of e-cigarette use. However, it highlights some interesting considerations such as gender differences in Aboriginal Australians' willingness to try and the possible role of shisha in e-cigarette use.

- Despite some idiosyncrasies, the wide range of data considered is largely consistent with observations and conclusions made in previous reports.

24   Introduction

This section reviews recent studies describing the characteristics of e-cigarette use.

Supplementary data extraction and synthesis were performed to provide an additional level of understanding about e-cigarette use. For example, whether certain people are more likely to use them than others, reasons for use, whether certain factors predict use of e-cigarette and so on. As this section was exploratory, it includes a wide range of relevant papers and specific topics.

24.1 Data extraction

Full text was examined for 177 published papers that were categorised based on title to be relevant to pattern of use of e-cigarettes.

During the data extraction process, 32 papers were removed for the following reasons:

- reviews (n=10);
- viewpoint/commentary articles (n=8);
- no full text was available (n=7);
- out of scope (i.e. about use of cannabis; n=3);
- not in English (n=1),
- research protocol (n=1);
- news article (n=1);
- duplicate (n=1).

This review only considered original research results (either experimental or observational) and therefore did not review viewpoint or commentary articles, research protocols, news articles or other reviews. The review was restricted to papers published in English and did not review articles where the full text was published but not available.

Full data were extracted for 145 papers and conference abstracts. Due to the high number of studies based on data from the US, the results are separated into the US (n=92) and other countries. Separating the data this way also allows for easier comparison to existing knowledge from previous international reports.

In May 2018, the search was updated and an additional 13 papers were found. One of these was about cannabis use and excluded. The remaining 12 papers were mostly from the US (n=8). These papers have been incorporated into the summaries that follow.

25 US data on e-cigarette use

Description of the results based on US data is categorised as secondary analysis of large datasets, investigator developed surveys/interviews and any other research methods. The reason for this is because secondary analysis provide a good snapshot of large numbers of respondents but may be limited regarding the depth of exploring specific research questions as questions included in large surveys are usually broad-sweeping. Finally, studies reporting on e-cigarette use amongst sexuality and gender minorities (n=11) were separated from others due to their narrow and specific focus.

25.1 Analysis of large national datasets

The previous US report from the Surgeon General refers to data from the National Youth Tobacco Survey (NYTS; up to 2015), Population Assessment of Tobacco and Health (PATH) study (Wave 1 2013-2014), National Adult Tobacco Survey (NATS; 2013-2014), HealthStyles and Monitoring the Future survey (MTF; 2015) as well as literature retrieved in a search performed as late as March 2016 (US Dept of Health and Human Services 2016). Twenty of the studies we extracted used these data sets or older versions of the same survey data. Therefore, results of these papers are only briefly synthesised. Despite using the same datasets, these papers report on different sample sizes due to slightly different parcelling of the data to different research questions. Discussion of papers based on national US datasets is divided into those focussing on youth/adolescents (n= 18; Tables 30 and 31) and those on adults (n=15; Tables 32 and 33).

25.1.1 Youth samples (n=18)

Largely these papers add limited new insights to what has been previously reported based on youth samples (Chapter 2 of the Surgeon General's report)(US Dept of Health and Human Services 2016). For example, papers report on increased use of e-cigarettes in Hispanic populations (Hammig, Daniel-Dobbs et al. 2017, Lanza, Russell et al. 2017), perceptions that e-cigarettes are less harmful than cigarettes (Dobbs, Hammig et al. 2017), and that other substance use is related to e-cigarette use (Owotomo and Maslowsky 2017).

One paper compared participation in different sports and found that sports such as baseball and wrestling were associated with greater likelihood of e-cigarette use (Veliz, McCabe et al. 2017). Chen et al (Chen, Yu et al. 2017) used data from the 2014 NYTS and performed survival analysis to predict when youth are at greater risk of initiation of e-cigarette smoking. Their results suggested that e-cigarette use may begin earlier than use of conventional cigarettes, starting from as young as seven years old. However, it should be noted that there was significant variations by race and gender.

One paper included analysis of the 2016 NYTS data which was not included in the Surgeon General's report (Tsai, Walton et al. 2018). This analysis included 20,675 school-children and sought to understand reasons for e-cigarette use. The most commonly selected reasons for e-cigarette use were, "friends or family member used them," "they are available in flavours, such as mint, candy, fruit, or chocolate," and "they are less harmful than other forms of tobacco, such as cigarettes." These reasons largely echo those reported based on earlier data in the Surgeon General's report (US Dept of Health and Human Services 2016). Results from Merianos et al (Merianos, Yockey et al. 2017) based on only Hispanic youth (n=6,044) in the 2014 NYTS reiterates the increased probability of initiating use of e-cigarettes for youth who have friends and family who use e-cigarettes.

One recent publication used PATH data from Wave 1 (n=9853) to better understand how psychological factors may predict susceptibility to e-cigarette use (Kwon, Seo et al. 2018). Psychological factors have received limited attention in previous reports. The authors suggest 24.2% of youth who had never used e-cigarettes were susceptible to future use. Rebelliousness and psychological problems were also associated with increased susceptibility.

Two papers reported a summary of PATH data including both Waves 1 and 2 of data. The PATH survey retained 87.9% of wave 1 respondents at wave 2. Follow-up data were used to assess progression to smoking in adolescents by Chaffee et al (Chaffee, Couch et al. 2017). The authors report that ever-use of e-cigarettes was a significant predictor for current established smoking and conclude that the use of e-cigarettes may be associated with progression to cigarette smoking. This is consistent with Coleman et al (Coleman, Rostron et al. 2018) who noted that almost half of e-cigarette users had discontinued use by the time of Wave 2 data collection which they interpret as "transitory experimentation". Based on changes in prevalence of different tobacco use groups, the authors of the US Academy of Sciences report (McNeill A 2018) also suggest that:

> "There is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults."

Two papers were based on analysis of the Youth Risk Behaviour Survey. These data were collected in schools based on a stage clustered design. One of these studies refers only to only students in North Carolina (Giovacchini, Pacek et al. 2017) while the other describes national data (Demissie, Everett Jones et al. 2017). Demissie et al report 15.8% e-cigarette use amongst a sample of 15,624 9-12 graders which is in the vicinity of the 16% reported in the Surgeon General's report (US Dept of Health and Human Services 2016). The authors also assessed the relationship between e-cigarette and conventional cigarette use with other health risk behaviours beyond substance use such as unintentional injuries and violence, substance use, and sexual risk behaviours. They report associations between health risk behaviours and use of e-cigarettes with youth showing patterns of risky behaviours.

25.1.2   Adult samples (n=15)

Recent analyses (n=3) of National Adult Tobacco Survey data were used to explore a variety of questions around prevalence of e-cigarette use (Anic, Holder-Hayes et al. 2018) and patterns of e-cigarette use (Sharapova, Singh et al. 2018) which appear in previous reports. One paper explored what kinds of people switch from conventional cigarettes to e-cigarettes (Park, Duncan et al. 2017) and reported that compared with current dual users, those with higher education and those who were not single were more likely to switch to e-cigarettes from conventional cigarettes.

Two other large datasets, the 2014 Tobacco Use Supplement-Current Population Survey (TUS-CPS) (Levy, Yuan et al. 2017) and the 2014 National Health Interview Survey (NHIS) (Park, Lee et al. 2017, Shah, Paliwal et al. 2017, Stokes, Collins et al. 2018) were analysed. These studies include large samples of 158,626 and 642,848 respectively which are recruited based on methods designed to obtain representative populations. However, both samples include response rates around 50%.

Papers based on the NHIS sought to understand e-cigarette use amongst people with Chronic Obstructive Pulmonary Disease (COPD) (Shah, Paliwal et al. 2017), cardiovascular disease (Stokes, Collins et al. 2018) or to explore whether e-cigarette use is associated with psychological distress (Park, Lee et al. 2017).

Park et al. separated the NHIS sample in to those who ever used e-cigarettes, current dual users of e-cigarettes and conventional cigarettes, those with former cigarette and ever use of e-cigarette and current user of conventional cigarettes only. The authors report increased risk of psychological distress for all four groups. Due to the methods used, it is difficult to determine the direction of this relationship which means it is difficult to know if people with higher levels of distress are attracted to substances or whether substances can cause these issues based on these data alone.

Analysis of TUS-CPS data suggested 7.7% ever use of e-cigarettes and 2.1% current use (Levy, Yuan et al. 2017). The authors report that the odds of regular e-cigarette use was higher among males than females at age 18–34, those with a high school and associate degree, and for those living in metropolitan areas, and was lower among age 45–64 and 65+, among Blacks and Asians compared to Whites, and among Hispanic compared to non-Hispanic. The authors also analyse use of e-cigarette by conventional cigarette smokers with the conclusion that e-cigarettes are effective for smoking cessation. This conclusion is not held more generally (see Part 2).

Data on the Tobacco and Attitudes Beliefs Survey (Yao, Max et al. 2017) and the Tobacco Products and Risk Perceptions Survey (Jones, Majeed et al. 2017, Spears, Jones et al. 2018) are also based on national data. Unfortunately both rely on research panel data which is likely to include a biased sample as these include participants who have chosen to be part of a research panel rather than people randomly contacted. Spears et al (Spears, Jones et al. 2017) extend findings on psychological distress by Park et al (Park, Lee et al. 2017) by examining e-cigarette use amongst people with mental health conditions. They found that participants reporting mental health conditions were approximately 1.5 times more likely to have used e-cigarettes in their lifetime and almost twice as likely to currently use e-cigarettes as those without one.

Other papers based on national datasets explored smoking cessation in one region (Henry, Gettens et al. 2017), aimed to develop a profile for predicting ever-use of e-cigarettes (Pericot-Valverde, Gaalema et al. 2017), understand e-cigarette use in substance users (Gubner, Pagano et al. 2017) or examined whether people are comfortable asking people not to use e-cigarettes relative to conventional cigarettes (Bigman, Mello et al. 2018).

25.2   Literature from other US datasets

Twenty-five papers (n=25) reported on secondary analysis of data from non-national datasets. Most of these were based on adolescent samples (n=16; 64%) (Tables 34 and 35).

Multiple papers reported on: the Texas Adolescent Tobacco and Marketing Surveillance System (TATAMS) (n=4), the Marketing and Promotions across Colleges in Texas Project (Project M-PACT) (n=5), the California Healthy Kids Survey (n=2), the Southern California Children's Health Survey (CHS) (n=3), and the AWARE intervention (n=2). As is apparent from the titles, many of these surveys are based on data of specific regions (e.g. Texas). Due to the fact that these samples are largely less representative than those based on nationally collected data, synthesis of these papers is limited to those adding novel insights.

Papers reporting on adolescent samples covered similar aims to those already captured in national datasets. For example, estimating prevalence and profiling e-cigarette users (Kristjansson, Mann et al. 2017, Kristjansson, Mann et al. 2017), reasons for use (Hong, Barrington-Trimis et al. 2017) and predicting use of tobacco products in Texas (Creamer, Loukas et al. 2018) and Florida (Lee, Pepper et al. 2018). Lee et al (Lee, Pepper et al. 2018) slightly extended national observations using the Florida YTS. They found that the perception that cigarettes are easy to quit is predictive of combined use of conventional and e-cigarettes.

TATMAS data was used to explore how psychological factors such as subjective experiences (Creamer, Delk et al. 2017) and sensation seeking (Case, Harrell et al. 2017) may be associated with e-cigarette use. Creamer et al (Creamer, Delk et al. 2017) describe the experiences that youth have with using different tobacco products. Subjective experiences included feeling good, dizzy or coughing. The authors took data from never-users at baseline (n=1,999) and assessed future use or susceptibility to use 6 months later. Logistic regression models suggested no experiences were significantly associated with increased odds of using e-cigarettes. Case et al (Case, Harrell et al. 2017) used data from baseline (n=3,907) and follow-up (n=2,488) to understand whether sensation seeking is related to e-cigarette use in Texan Youth. They reported that adolescents with higher mean sensation seeking scores had significantly higher odds of being susceptible to e-cigarette use compared to adolescents with lower sensation seeking scores. People high in sensation seeking are more likely to be looking for new experiences that can also be more intense. Therefore, generally it has been related to risk taking behaviours.

In papers reporting on secondary analysis of non-national adult samples (Tables 36 and 37), three reported on data based on college students (Case, Loukas et al. 2017, Creamer, Loukas et al. 2018) whereas other samples were based on random-digit dialling (Amato, Boyle et al. 2017, Mendy, Vargas et al. 2017, O'Gara, Sharma et al. 2017) or a smoking cessation intervention program delivered through primary care (Kalkhoran, Alvarado et al. 2017).

Case et al (Case, Loukas et al. 2017) extended their observations of the association between sensation seeking and e-cigarette use in to Texan college students with similar results. In a sample of people understanding a smoking cessation program (n=718), Kalkhoran et al (Kalkhoran, Alvarado et al. 2017) observed that ever users of e-cigarettes had higher prevalence of mental health conditions than never users which reinforces observations made by Park et al (Park, Lee et al. 2017) based on a national sample. One study explored the bidirectional relationship between e-cigarette use and depression (Bandiera, Loukas et al. 2017) which extends other studies about the relationship between e-cigarette use and mental health. These authors were able to do this through the use of longitudinal data collected from Texan colleges over 6 months and 1 year. The authors conclude that elevated depressive symptoms predicted e-cigarette use 6 months later, thus adding to previous observations about mental health and e-cigarette use (Park, Lee et al. 2017).

Agarwal et al (Agarwal, Loukas et al. 2017) explored how the social environment could also predict use of e-cigarettes using M-PACT data collected over one year. They report that having peers or being happy to date someone who uses e-cigarettes increases the odds of initiating the use of e-cigarettes. This is consistent with observations in the NYTS about how peer influences can increase use of e-cigarettes (Merianos, Yockey et al. 2017).

Recently, these observations were extended by analysis of two waves of the Southern California Children's Health Survey (n=1441) (Urman, McConnell et al. 2018). Urman et al (Urman, McConnell et al. 2018) assessed the bidirectional relationship between social environment and e-cigarette use and initiation. The authors observed that 11th and 12th graders with 3-4 friends using e-cigarettes at baseline had four times in the probability of initiating use. Other social variables that predicted initiation were, having friends who had a friendly reaction to e-cigarette use, and students with a person at home using them. Meanwhile, for those students who had used e-cigarettes at baseline, there were changes in their environment. They were more likely to have friends who used e-cigarettes, and have friends who were supportive of the use. These results are interesting because they describe not only what social factors may lead to initiation but also how social factors may change once e-cigarette use has begun.

25.3 US literature based on investigator-developed surveys and other research methods

Twenty-nine papers reported on studies that performed primary analysis on data collected by the investigators (Tables 38 and 39). Nine of these were conducted with high school students (Bold, Kong et al. 2017, Bold, Morean et al. 2017, Camenga, Kong et al. 2017, Johnson, Mays et al. 2017, Temple, Shorey et al. 2017, Westling, Rusby et al. 2017, Fite, Cushing et al. 2018, Pepper, Farrelly et al. 2018, Vogel, Ramo et al. 2018) and eight were performed using college students (Abadi, Couch et al. 2017, Copeland, Peltier et al. 2017, Franks, Hawes et al. 2017, Lee, Lin et al. 2017, Lee, Nonnemaker et al. 2017, Cheney, Gowin et al. 2018, King, Reboussin et al. 2018).

The author-described aims of these papers was used to thematically code the purpose of the 29 papers. The following themes were identified: Use and/or perception of e-cigarettes (n=11), influences on use of e-cigarettes (n=10), and characteristics of users (n=4). The remaining four papers did not fit into any of these themes and included an expert discussion (Bold, Sussman et al. 2018), development of tools for assessing e-cigarette use or perception (Bold, Kong et al. 2017, Copeland, Peltier et al. 2017) and a study exploring the topographies of e-cigarettes (Lee, Nonnemaker et al. 2017).

Papers on use and perception of e-cigarettes added limited, novel insights regarding the use of e-cigarettes. Two papers explored use in military personnel (Chin, Lustik et al. 2018, Hall, Austin et al. 2018). These samples included large numbers of males (85 and 86%). Chin et al (Chin, Lustik et al. 2018] obtained reponses from 1,288 army members with a response rate of 95%. They observed an ever-use prevalence of 61% which appears much higher than other statistics reported for the US, which was 35.8% based on the 2013-2014 NATS. However, in a sample of Navy members, the ever-use rate was 31.4%{Hall, 2018 #4652) which is lower than nationally representative data. It may be that different service types have different rates of e-cigarette use due to job demands. However, a direct comparison would be needed to understand prevalence in military samples.

Two papers exploring influences on e-cigarette use investigated impulsivity in children (Bold, Morean et al. 2017) and adults (Hershberger, Connors et al. 2017). Results from both samples suggest impulsivity is associated with e-cigarette use. This finding is interesting in the context of sensation seeking papers. Hershberger et al (Hershberger, Connors et al. 2017) provide a summary figure of the relationships (Figure 14). There may be a parcel of personality traits associated with e-cigarette use. Whether or not this is unique to e-cigarette use or general substance use is yet to be determined in the literature.

Figure 14: Summary of the relationship of urgency, deficits in conscientiousness and sensation seeking to e-cigarette use
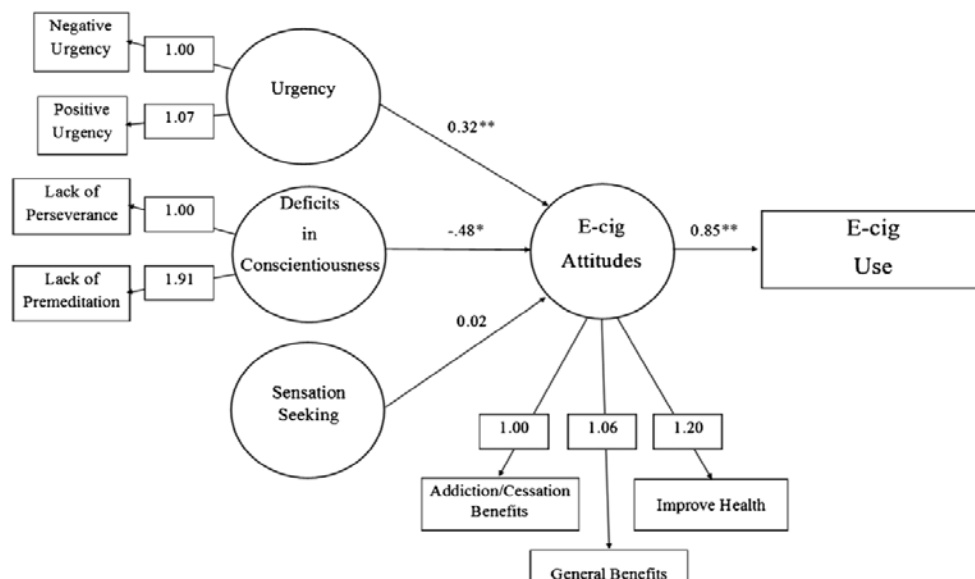
Figure from Hershberger, Connors, Um, Cyders, 2017. International Journal of Mental Health and Addiction.

One paper reported on semi-structured interviews with 33 college student vapers (Cheney, Gowin et al. 2018). This qualitative data provides more in-depth data from smaller numbers of people. Supporting previous survey data, the authors report that social and physical environment influences determine how and when college students choose to vape. Using a survey, Fite et al (Fite, Cushing et al. 2018) extended these and similar observations by also suggesting that parental attitudes are predictive of e-cigarette use in adolescents. Finally, Abadi et al (Abadi, Couch et al. 2017) reported on the perceived differences in risks and benefits of e-cigarettes relative to conventional cigarettes. Similar data has been reported based on national datasets and in the Surgeon General's report (US Dept of Health and Human Services 2016). However, Abadi et al compared specific risks and reported that bad breath, a friend being upset, getting in trouble and feeling nervous were seen as more likely for cigarettes relative to e-cigarettes in their small college sample (n=91).

Finally, papers on the characteristics of e-cigarette users explored whether e-cigarette use was associated with eating disorders (Morean and L'Insalata 2018), mental health (King, Reboussin et al. 2018) or general demographic characteristics (Lee, Lin et al. 2017, Sussan, Shahzad et al. 2017). King et al's (King, Reboussin et al. 2018) observations based on 2,370 college students were slightly different to those previous reported for mental health. They suggested that stress and depression predicted e-cigarette use but that mental health diagnosis did not. Morean et al's (Morean and L'Insalata 2018) observations of e-cigarette use in those with eating disorders suggested that e-cigarettes were more likely to vape. Motivations and the way in which vaping was done reflected behaviours generally associated with disordered eating which may suggest that these people use e-cigarettes to extend their problematic behaviours.

25.4   Gender/sexuality minorities

Eleven papers had a focus on understanding e-cigarette, or more widely, tobacco product use in sexual orientation or gender minorities of youth and adults (Tables 40 and 41). These papers were exclusively from US Samples. These papers reported on large national datasets of over 300,000 students (Coulter, Bersamin et al. 2017) to 29 focus group interviews with LGBTQ adults (Giachello, Thanh-Huyen et al. 2017). Despite different methods, the results for this subset of papers are highly consistent and suggest that gender and sexuality minorities are at greater risk of e-cigarette use. It is likely that this is due to higher use of other substances (Goldbach, Mereish et al. 2017) which would be in keeping with the Common Liability Use Model. One paper also provides further insight into disparities by suggesting that school harassment may be an early driver of differences (Coulter, Bersamin et al. 2017).

25.5   Conclusion

Large quantities of data have been produced based on US samples. Many of these are also based on large, national samples which offer a large scale snapshot into e-cigarette use. There is keen interest in the US in youth and adolescent samples. Approximately one in five of the papers that have been produced since the Surgeon General's report use the same (or older) datasets and add little new knowledge to the understanding of the use of e-cigarettes.

Papers reporting on secondary analysis of national youth datasets in the US add limited new insights into use of e-cigarettes to that included in the Surgeon General's report (US Dept of Health and Human Services 2016) or the Academy of Science report (McNeill A 2018). The Surgeon General's report discusses the Common Liability Model to describe substance use and the fact that the use of one substance may promote the use of others. It is important to note that the parcelling of e-cigarette use with other health-risk behaviours (Demissie, Everett Jones et al. 2017) as well other substance use (Owotomo and Maslowsky 2017) suggests that there may be 'downstream' effects for youth beyond directly associated with e-cigarette use and beyond other substances.

There are some interesting themes amongst the other papers. These include the association between certain personality characteristics (impulsivity, sensation seeking) and e-cigarette use in multiple samples of adults and youth. Likewise, there appears to be a consistent link between mental health, stress and depression and e-cigarette use. One unexpected theme was that of sexuality and gender minorities who seem to be disproportionately heavy users of e-cigarettes.

Some of the papers explored provide greater depth into observations already made. For example, the powerful influence of social and environment factors on e-cigarette use. This may be particularly relevant for youth who generally have more sources of social influence.

More or less, the picture painted based on US data is fairly consistent with previous reports that e-cigarette use is increasing, that males, young people and certain racial groups are more likely to be ever-users of e-cigarettes. There also appears to be an association with level of education. However, the direction of this association is unclear with some datasets suggest that use is lowest amongst those with a college degree (2013-2014 NATS) (US Dept of Health and Human Services 2016), whilst others indicate that it is highest amongst those with a high school and associate degree (TUS-CPS)(Levy, Yuan et al. 2017) and others still suggest that those who switch from smoking conventional cigarettes to e-cigarettes have a higher level of education (Park, Duncan et al. 2017).

26 Non-US data on e-cigarette use

Data from the UK (n=8) were analysed separately to allow easier comparison to the Public Health England report (Stratton, Kwan et al. 2018). Given the specific interest in Australian data (n=6), these papers were also analysed separately from the others. Due to cultural and physical proximity, two papers from New Zealand are also summarised with these data.

26.1 Australian Studies

Of the six Australian studies found, half were qualitative studies (Keane, Weier et al. 2017, Brown 2018, Yuke, Ford et al. 2018) with the remaining studies being a telephone survey, a national, school-based survey (Williams and White 2018) and an international tobacco survey (Lee, Yong et al. 2018) (Tables 44 and 45).

Two of the qualitative studies focussed on very specific subsamples of e-cigarette users: Indigenous Australians (Yuke, Ford et al. 2018) and people with schizophrenia (Brown 2018). Brown's ethnographic study used observations in Australia and the UK to explore experiences of smoking and vaping. Few details are available on the quantity of observations and an in-depth discussion of experiences are provided with the ultimate conclusion that this sample emphasised harm from smoking relative to vaping.

Interviews with Indigenous Australians were performed with the aim of understanding the acceptability of new nicotine products (Yuke, Ford et al. 2018). While the majority of women reported no willingness to try e-cigarettes (70%), a majority of men were willing (82%). Therefore, in this specific group there may be very pronounced difference in uptake of e-cigarettes. However, no recent data exist that quantify prevalence of use in this population.

The final qualitative study (Keane, Weier et al. 2017) analysed data from an open-ended question included as part of another survey using Theories of Social Practice. Discussion is strongly grounded in the context of this theory which is beyond the scope of the current summary. However, the authors conclude that health and freedom are important for vaping and that word of mouth is a driver of uptake.

Williams and White (Williams and White 2018) analysed data from the Australian Secondary Schools Alcohol and Drug survey but restricted their analysis to one state (Victoria). Based on 4,576 adolescents, they report a prevalence of 14% ever-use of e-cigarettes and 13% ever-use of shisha tobacco with most students using in combination with conventional cigarettes. This rate of e-cigarette use is similar to that reported in the Public Health England report for 11-16 year olds (7-18%) (Stratton, Kwan et al. 2018). What is very interesting about this study is the high rate of shisha use. In the YTS in the US, the rate of ever-use of Hookah is usually combined with other combustible tobacco products such as pipes. Harrell et al (Harrell, Naqvi et al. 2017) report that past 30-day use of hookah was 22.6% while e-cigarette use was 16.1% in a sample of past-month tobacco users in the YTS. The Surgeon General's report (US Dept of Health and Human Services 2016) refers to Hookah lounges and Shisha cafes are also commonplace in Australia.

Bonevski et al (Bonevski, Guillaumier et al. 2017) surveyed 427 people at substance use centres and reported 39% ever-use of e-cigarettes and that 70% had used them to try to stop smoking. One of the international studies (Table 38), also surveyed people in treatment centres across the US (Gubner, Pagano et al. 2017). Based on 1,127 people surveyed in this study, the prevalence of e-cigarette use was 59.8% which is much higher than that in the Australian sample.

In the final Australian study (Lee, Yong et al. 2018), the authors used data collected about part of the 2014 International Tobacco Control Survey to compare vaping in people in Australia and the UK. People in this sample are slightly different to the general population as they have smoked at least 100 cigarettes throughout their lifetime. Data analysed included 2,849 adults of which 1,430 were Australian. The prevalence of current vaping in Australians was 11.9% with 2.5% using daily. Compared to those in the UK, Australians had lower rates of vaping, higher opinions about it, and felt that there were less social constraints.

Both of the papers based on data collected in New Zealand focussed on vaping as a means of smoking cessation through an online survey with 218 vapers (Truman, Glover et al. 2018) and 20 semi-structured interviews (Robertson, Hoek et al. 2018). Despite their different research approaches, both papers conclude that vaping may be useful for smoking cessation in New Zealand.

26.1.1 Conclusion

Recent data from Australia is limited but provides a mixture of depth through qualitative studies and reach through quantitative surveys. While none of these data are appropriate to draw conclusions about use of e-cigarettes in Australia, they give some indication that rates of use may be lower than in the UK – which is already lower than that reported in the US. One of the interesting discoveries from Australian data is the role of shisha and how this may have a similar prevalence to e-cigarette use in youth.

26.2   Data from the UK

The search process revealed nine studies based on samples in the UK. Five of these used adolescent samples (Tables 42 and 43).

Three papers reported on analysis of datasets included in the Public Health England report (McNeill A 2018), including ASH Smoke-free Great Britain (Simonavicius, McNeill et al. 2017), the Scottish Schools Adolescent Lifestyle and Substance Use Survey (Kaufmann and Currie 2017), and the School Health Research Network (de Lacy, Fletcher et al. 2017, Fat, Scholes et al. 2017) and one combined data based largely on these datasets (Bauld, MacKintosh et al. 2017). The remaining five studies used data from the Health Survey for England 2013–2014 (Fat, Scholes et al. 2017), a smoking initiation prevention program for adolescents (Conner, Grogan et al. 2017), hospital records from patients with irritable bowel disease (Loonat, Sagar et al. 2018) and two investigator-led surveys (Clarke and Lusher 2017, McKeganey, Barnard et al. 2018).

An analysis of the Health Survey for England 2013–2014 was available as a conference abstract only (Fat, Scholes et al. 2017) and examined 3,039 current smokers aged 16 years and older. It found that 12% were current users and 20% were past users of e-cigarettes. Compared to 'never-use' of e-cigarettes, current use was not associated with age, while past use was associated with being younger. Conversely, current and past users of other nicotine delivery devices were more likely to be older than smokers who had never used other nicotine delivery devices.

Data taken from the intervention program were collected across a 4-year period from control schools (those who did not have an active intervention) (Conner, Grogan et al. 2017). Conner et al used these data to model prediction of e-cigarette initiation. Reported ever-use of e-cigarettes was 34.2% in their sample of 2,836 adolescents. Initiation was predicted by having ever used e-cigarettes. It was also high in those who had a few or most friends and/or family who smoked. Intentions to not smoke appeared protective. Ever-use in this sample was in the vicinity of similar age groups from the SALSUS survey (32%) but higher than those reported in other samples in the Public Health England report (YTPS reported 17%) (McNeill A 2018).

The final two papers explore reasons for initiation of use of e-cigarettes. McKeganey et al (McKeganey, Barnard et al. 2018) used semi-structured interviews with 50 young adults who use e-cigarettes. People in interviews reinforced observations seen in US data (page 59 of the Surgeon General's report), that vaping is perceived as being associated with lower levels of harm than smoking. It also suggested, as US data did, that people had initiated use through social contacts.

The final study was an investigator developed survey performed in schools throughout the UK (Clarke and Lusher 2017). Willingness to try an e-cigarette was largely predicted by smoking status with those already smoking more willing. The authors also observe that flavours increase appeal to use e-cigarettes for this sample. Both of these observations are established based on larger datasets in the Public Health England report (Stratton, Kwan et al. 2018).

26.3   International data

Purposes of international research were coded thematically into different categories (Tables 46 and 47). Most of the international papers were classified as being focussed on use and perception of e-cigarettes (including prevalence; n=18). This was followed by those exploring influences on use (n=8), characteristics of users (n=8), and reporting on e-cigarette use and smoking (n=5). One paper did not fit into these categories and explored smoking topography in Japan (Gee, Prasad et al. 2018). There was a total of forty-one studies.

A summary of the international data reporting primarily on prevalence is included in part 6 of this report.

26.3.1   Other studies on e-cigarettes use

Most of the studies from European Union countries reported on prevalence which is summarized in the Eurobarometer study. A single study reported on data from the Russian Federation (Kong, Idrisov et al. 2017) using a convenience sample of 716 high school students from the Republic of Bashkortostan. The authors report on prevalence as well as predictors of use. In addition to reporting on the typical predictors of e-cigarette use (being male, having professional education) the authors also assessed personality characteristics and found that having a rebellious spirit, being adventurous, being impulsive and being less apt at making friends predicted e-cigarette use. These findings add to previous observations in US samples regarding sensation seeking and impulsivity and fill a gap left in the literature by simultaneously assessing a variety of characteristics. Unfortunately, the sampling and exclusive adolescent sample limit the generalisability of these findings.

A cohort study of 2,186 Germany high school students also extended observations about sensation seeking in combination with other personality variables (Morgenstern, Nies et al. 2018). Rather than exploring e-cigarette use, these authors assessed the onset of conventional cigarette smoking from e-cigarette use over a 6 month period and what factors may predict this. Of the nine personality variables that the authors assessed, two significantly predicted initiation of conventional cigarette use: Sensation seeking and hopelessness. This finding adds more strength to the possible role of sensation seeking in e-cigarette use as well as the progression to smoking. The fact that a feeling of hopelessness was also significant is in line with observations about depression and e-cigarette use from US samples (Park, Lee et al. 2017). Hopelessness is strongly linked to depression. These findings are supportive of observations made about e-cigarette use but extend this to better understanding of the transition to conventional cigarette use.

The final nine studies extracted did not report on specific regions or report on data collected via the internet with no specific regional requirements.

Two papers analysed discussion forum content including 3.3 million tweets (Ayers, Leas et al. 2017) and 3,263 Reddit comments (Sharma, Wigginton et al. 2017). These methods allow investigators to get an unobtrusive snapshot of what people are talking about and any related sentiment. Sharma et al (Sharma, Wigginton et al. 2017) analysed Reddit posts about e-cigarette use and mental illness. The authors identify six themes that could be broken into benefits (freedom, self-medication, smoking cessation, freedom, hobby, social connectedness and motivation) and draw backs (unsatisfactory substitute for cigarettes and psychiatric medicines, interactions with other drugs, nicotine addiction, risks of e-liquid and general practical difficulties).

Observations based on Twitter data sought to summarise the reasons people give for vaping (Ayers, Leas et al. 2017). The authors conclude that data suggest the reasons people vape are shifting away from cessation and toward social image. However, given the high impression management that occurs on social media, it would be expected that these data are somewhat influenced by an individual's image management. Using more conventional survey methods, Browne et al (Browne and Todd 2018) report that reasons for vaping were health benefits (74.1%), other nicotine replacement therapies ineffective (45.2%), more enjoyable (35.1%) and for pleasure (22.7%), less offensive to others (31.8%), and being easier than quitting nicotine completely (35.1%).

Berry et al (Berry, Burton et al. 2017) performed a web-based experimental study to understand how addiction warning labels influence willingness to try e-cigarette products. They conclude that warnings may be effective in changing risk beliefs which may ultimately be persuasive.

Etter (Etter 2017) performed a web-based survey following 3,868 vapers between 2012 and 2016 to assess smoking cessation and its relationship with vaping. He concludes that enjoyment and relapse prevention were the most important reasons to vape and that smoking relapse was low. This may also be reflected by the low (23%) retention rate with those who were more successful more likely to complete follow-up surveys.

The final four studies (Alexander and Williams 2017, Chesaniuk and Sokolovsky 2017, De Genna, Goldschmidt et al. 2017, Nahin, Bispo et al. 2017) were based on conference abstracts only and added no new insights to other papers.

26.4   Conclusion

The new papers reviewed that have used data obtained in the UK are consistent in their findings to what has already been reported in the Public Health England report (Stratton, Kwan et al. 2018). Likewise papers from other regions mostly report on prevalence of e-cigarette use which adds limited novel insight into e-cigarette use.

27   Summary of e-cigarette use

Most data being published about e-cigarette use is being analysed based on samples in the US. Fortunately, many of these are also based on national datasets that have been collected through surveys using methods attempting to attract representative samples. As a whole, results are consistent with observations made in the Surgeon General's report about the type of people who may be more likely to use e-cigarette. These include males, people with different levels of education, different ethnic groups and current smokers. There are some inconsistencies about which level of education is predictive of e-cigarette use.

Many investigators have sought to describe prevalence and/or predictors of e-cigarette use. Few studies consider factors beyond sociodemographic profiles. However, when they do, they provide interesting results about psychological variables that may be predictive of use. In fact, personality variables have the potential to be more predictive for explaining e-cigarette use than sociodemographic variables, as these can be more reliable predictors of behaviour. Indeed, observations for characteristics such as sensation seeking and impulsivity paint a clearer picture of e-cigarette than factors such as age and level of education. For example, in the UK there appears to be limited association between gender and age and e-cigarette use whereas, relationships are consistent observed between these variables in the US. Meanwhile, observations on the association between personality and e-cigarette use seems consistent across European and US samples. Personality variables may also be predictive of any gateway effects of e-cigarettes. However, there is a need for future research to consider a combination of psychological and personality variables alongside with sociodemographic variables to truly understand their impact on e-cigarette use.

There has been a strong focus on youth samples internationally with most of the papers analysed using samples of school children, youth or college students. Young people provide a good opportunity to assess changes in uptake and many papers have tracked use over time to understand what predicts uptake of e-cigarette use in youth. Largely, observed influences on e-cigarette use are consistent with wider models designed to explain general behaviour. For example, the socio-ecological model which considers individual, interpersonal, community, organizational, and policy/enabling environment factors that determine behaviour (UNICEF 2015). In youth, the findings that their use of e-cigarette is influenced by the use of family and friends is consistent with Bandura's classic Social Learning Theory. While papers have considered some cognitive/attitudinal predictors such as perceived risk/harm, motivational factors are possible psychological predictors have been neglected. Nonetheless, it appears as though wider models of behaviour also apply to e-cigarette use.

Data from Australia is sparse and varied. It does not provide a clear indication of e-cigarette use. However, it provides some points for consideration, for example about Aboriginal Australians willingness to try and the role of shisha in e-cigarette use.

Despite some idiosyncrasies, the wide range of data considered is largely consistent with previous reports. It adds some new insights but does not dramatically challenge conclusions made by the Surgeon General's report (US Dept of Health and Human Services 2016), the Public Health England report (McNeill A 2018) or the Academy of Science report (Stratton, Kwan et al. 2018) about

predictors of e-cigarette use, prevalence of use, use of flavours, reasons for use and perceptions of risk/harm associated with use.

28 Tables

Table 30: Characteristics of studies from US national level youth

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Abouk, Adams 2017	Model data to test for effects of restricting youth access to e-cigarette on smoking traditional combustion cigarettes.	Monitoring the Future (MTF)	US national	2007-2014	50,000 12th graders	NR	NR	30-day smoking prevalence and intensity (number of cigs on a daily basis)
Owatomo, Maslowsky et al 2017	To examine the relationship between e-cigarette and marijuana use in adolescents.	Monitoring the Future (MTF)	US national	2014-15	12,743, Grades 8 and 9, 48% male	NA	NA	Past 30 day e-cigarette use; perceived availability of marijuana; peer marijuana use; parental monitoring; religiosity; risk-taking propensity; paid employment; sociodemographics
Veliz, McCabe et al 2017	To determine whether physical activity lowers the risk of e-cigarette use among adolescents.	Monitoring the Future (MTF)	US national	2014-15	12th grade school students, 49% male	NR	NR	30-day e-cigarette use and traditional cig smoking; participation in sports (13 different sports)
Chaffee, Couch, Gansky 2017	To evaluate trends from 2011-2015 in electronic cigarette (e-cigarette) use among U.S. adolescents, grades 6-12, including prevalence and associations with past month use of cigarettes and other tobacco products, cigarette smoking intensity, quit attempts, and quit contemplation.	National Youth Tobacco Survey	US national	2011-2015	101,011 Grades 6-12, 51% male	Three-stage cluster sampling design	Self-administered	Ever use e-cigarettes 30-day use e-cigarettes Also nine other tobacco products Intensity of cigarette smoking (users only) Quit attempts
Dobbs, Hammig, Henry 2017	To examine the influence of perceived addiction and harm of e-cigarettes on e-cigarette use among adolescents.	National Youth Tobacco Survey	US national	2014	22,007 9-19 year olds, 48% male			Ever use e-cigarettes 30-day use e-cigarettes Perceived harm of e-cigarettes Perceived addictiveness of e-cigarettes Smoking history (lifetime cigarettes)
Lanza, Russell, Braymiller 2017	To examine rates of both products by age and examine differences in	National Youth Tobacco Survey	US national	2014	22,007 average age 14.5yrs, 51% male			Demographics 30-day cig and e-cigarette use

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	age-varying rates by sex and race/ethnicity.							
Chen, Yu, Wang 2017	To better understand age of initiation of e-cigarette use.	National Youth Tobacco Survey	US national	2014	20,680 11-19 year olds, 51% male	207 schools	NR	Age e-cigarette smoking initiation Ever use e-cigarettes 30-day use e-cigarettes Demographics
Hammig, Daniel-Dobbs, Blunt-Vinti 2017	To examine factors associated with e-cigarette initiation among minority youth in the United States.	National Youth Tobacco Survey	US national	2014	27,294,454 (weighted)			
Harrell, Nqvi, Plunk et al 2017	The present study was designed to identify patterns of youth tobacco use and examine associations with sociodemographic characteristics and tobacco dependence.	National Youth Tobacco Survey	US national	2012/2013	6,958 tobacco users, 61% male			Past month use of tobacco products tobacco dependence demographics
Merianos, Yockey, Wood et al 2017	To examine the influence friend and family factors have on lifetime e-cigarette use, past year e-cigarette use, and perceptions of trying e-cigarettes soon in a national sample of Hispanic junior high and high school students.	National Youth Tobacco Survey	US national	2014	6,044			
Lippert 2017	To examine temporal changes in the correlates of experimental and current e-cigarette use and associations with tobacco quit attempts.	National Youth Tobacco Surveys	US national	2011,2012, 2013 (and 2014)	2011 n=17,741 2012 n=23,194 2013 n=16,858 2014 n=22,007 Regression based on n=18, 971			Lifetime and 30-day e-cigarette use; Age of initiation e-cigarettes Addictivity relative to cigarettes Perceived harm of e-cigarettes Cig smoking status Demographics
Tsai J, Walton K et al 2018	Reasons for Electronic Cigarette Use Among Middle and High School Students.	National Youth Tobacco Survey	US national	2016	20,675	Cross-sectional, nationally representative sample of students in grades 6-12	School based pencil and paper questionnaire	Self-reported reasons for e-cigarette use
Chaffee, Watkins, Glantz 2018	We evaluated associations between e-cigarette use and progression to established smoking among adolescents who had already tried cigarettes.	Population Assessment of Tobacco and Health survey (PATH)	US national	2013-2014; 2014-2015	13,651, mean age 15.5 years, 54% male	4-stage stratified probability design oversampling tobacco users. Completers got $25	In home, in person, computer assisted	Ever use e-cigarettes 30-day use e-cigarettes Demographics Alcohol use Receptivity to tobacco advertising Sensation seeking

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
								Cig label exposure Ever use other tobacco products
Coleman, Rostron et al 2018	Transitions in e-cigarette use among adults.	Population Assessment of Tobacco and Health (PATH)	US national	2013-2015 (Wave 1 and 2)	32,320 in Wave 1 and 28362 in Wave 2, 49% males	Stratified address-based, area-probability sampling design that oversampled adult tobacco users, young adults and African American adults	Interviews	Demographics; e-cigarette use;
Kwon, Seo et al 2018	Predictors of e-cigarette susceptibility in youth.	Population Assessment of Tobacco and Health (PATH)	US national	2013-2014 (Wave 1)	9,853, 51% male, 12-17 years	Four-stage stratified area probability sampling	Computer-assisted personal interviewing	Susceptibility to e-cigarette use Demographics Substance use Attitudes toward advertisments Perception of addictiveness/harmfulness Psychological and personality factors (Global Appraisal of Individual Needs – Short Screener (GAIN-SS)) Parental factors
Nicksic, Snell, Barnes 2017	The current study not only measures e-cigarette advertisement exposure, but also determines participants' receptivity to e-cigarette advertisements by randomizing exposure to common e-cigarette advertisements.	Population Assessment on Tobacco and Health survey (PATH)	US national	2013-2014 (Wave 1)	13,651, 52% 15-17 years old, 52% male	Using a four-stage stratification design, mailing addresses were used to sample household participants	NR	E-cigarette use E-cigarette susceptibility Cigarette use Cigarette susceptibility E-cigarette advertising exposure E-cigarette advertising receptivity Other tobacco product use Demographics
Demisse, Everett Jones, Clayton et al 2017	To measure the prevalence and frequency of cigarette smoking and EVP (electronic vapour products) use among high school students, and associations between health-risk behaviours and both cigarette smoking and EVP use.	Youth Risk Behaviour Survey	US national	2015	15,624 9-12th graders	NR	School 69% Student 86%	Survey is self-administered and students record their responses directly on a computer-scannable questionnaire or answer sheet
Giovacchini, Pacek, McClernon, Que 2017	To describe the lifetime use and perceived risk of e-cigarette use in the context of other risk-taking	Youth Risk Behaviour Survey (North Carolina)	North Carolina, US	2015	503 middle school, 444 high school e-cigarette use restricted to high school sample	49.1	Response above 99%	Self-report. Administered in test conditions

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	behaviours among adolescents in North Carolina.				Grades 6-12			

Table 31: Results from studies of US national level youth

Study reference	Purpose	Results	Author conclusion
Abouk, Adams 2017	Model data to test for effects of restricting youth access to e-cigarette on smoking traditional combustion cigarettes.	Modelled 15% reduction in smoking after e-cigarette bans	E-cigarette and cigarettes are complementary. This evidence suggests that not only are e-cigarettes and smoking regular cigarettes positively related (and not substitutes) for young people, banning retail sales to minors is an effective policy tool in reducing tobacco use
Owatomo, Maslowsky et al 2017	To examine the relationship between e-cigarette and marijuana use in adolescents.	Positive association between e-cigarette use and marijuana use among adolescents who have never smoked conventional cigarettes. A sizable proportion of these adolescents use marijuana (5.2%) and e-cigarettes (5.6%), with 24.2% of e-cigarette users concurrently using marijuana. Adolescents who refrain from smoking conventional cigarettes are still at risk of using either marijuana, or e-cigarettes, or both. Among these adolescents, those who use e-cigarettes are 3 times more likely (than those who do not use e-cigarettes) to also be marijuana users.	Marijuana use was strongly associated with e-cigarette use, with about a quarter of e-cigarette users being concurrent marijuana users. Adolescent e-cigarette users who have never smoked conventional cigarettes are particularly more likely than non-e-cigarette users to be current marijuana users. High perceived availability of marijuana and high peer marijuana use were significantly associated with marijuana use among these adolescents while parental monitoring and religiosity were protective.
Veliz, McCabe et al 2017	To determine whether physical activity lowers the risk of e-cigarette use among adolescents.	Adolescents who participated in at least one competitive sport were less likely to engage in past 30-day traditional cigarette smoking (AOR=0.73, 95% CI=0.538, 0.973) and past 30-day dual use of traditional cigarettes and e-cigarettes (AOR=0.66, 95% CI=0.438, 0.982) when compared with their nonparticipating peers. Adolescents who participated in baseball/softball and wrestling were at greatest risk of e-cigarette use. Of the 13 assessed sports, none were found to lower the odds of e-cigarette use.	Some athletes are at elevated risk of e-cigarette use and prevention efforts targeted at these sports should be considered by school administrators (wrestling and baseball/softball)
Chaffee, Couch, Gansky 2017	Evaluate trends from 2011-2015 in electronic cigarette (e-cigarette) use among U.S. adolescents, grades 6-12, including prevalence and associations with past month use of cigarettes and other tobacco products, cigarette smoking intensity, quit attempts, and quit contemplation.	Overall, e-cigarette ever use increased 10-fold among females (from 2.5% in 2011 to 24.8% in 2015) and nearly 7-fold among males (from 4.3% in 2011 to 29.4% in 2015) Ever and past month e-cigarette use was strongly associated with ever and past month use of cigarettes and other tobacco products. Expanding e-cigarette ever and past month use occurred simultaneously with a demonstrable shift in youth consumption of other tobacco products. Although past month combustible tobacco use declined, more U.S. middle school and high school students reported past month use of some form of tobacco and/or e-cigarettes in 2014–2015 than in 2011–2013. Although e-cigarette past month users were less likely to be past month multi-product users in 2014–2015 than in previous years (2011–2013), in all years and both sexes, past month e-cigarette users were several times more likely than past month e-cigarette non-users also to use one or more other tobacco product in the past month, and those who also smoked cigarettes in the past month were not more likely to have attempted or contemplated quitting.	Adolescent past month e-cigarette use is associated with past month use of other tobacco but not with cigarette quit attempts or quit contemplation among cigarette users. Over five years, the average characteristics of U.S. adolescents who use e-cigarettes have shifted, increasingly including more adolescents who do not use non e-cigarette tobacco products.
Dobbs, Hammig, Henry 2017	To examine the influence of perceived addiction and harm of e-cigarettes on e-cigarette use among adolescents.	19.4% reported trying an e-cigarette 9.2% current users e-cigarette Perceived less harm and less addictiveness is associated with lifetime use of e-cigarettes Strongest predictor of ever use e-cigarette was smoking history - more cigs, higher probability of trying e-cigarette.	The perception that e-cigarettes are less addictive and harmful than their conventional counterparts may be an important risk factor for the use of e-cigarettes.

Study reference	Purpose	Results	Author conclusion
Lanza, Russell, Braymiller 2017	We examine rates of both products by age and examine differences in age-varying rates by sex and race/ethnicity.	E-cigarette use was most common among Hispanic adolescents (10.8%), followed by White (10.4%) and Black (5.0%) adolescents. The prevalence of e-cigarette use increased rapidly between ages 12 and 16 yrs, when it peaked at approximately 0.15; between ages 16 and 19 yrs the rate of e-cigarette use remained constant. Sex differences emerged at around age 14 yrs, with males using e-cigarettes at a higher rate than females; this difference was only present between ages 14 and 17.5. Among older adolescents, the rate of e-cigarette use was not significantly different for males and females. Between ages 12 and 14 yrs Hispanic adolescents emerged as the heaviest e-cigarette users.	Young Hispanic adolescents are at elevated risk for use of e-cigarettes and traditional cigarettes during early adolescence. During early adolescence, youth using e-cigarettes are more likely to smoke traditional cigarettes compared to youth not using e-cigarettes.
Chen, Yu, Wang 2017	To better understand age of initiation of e-cigarette use.	18.7% ever use e-cigarettes The estimated mean age of e-cigarette initiation was 17.50 (95% CI=17.47, 17.52) years. The estimated hazard of e-cigarette use initiation was 0 up to age 6 years, increased slowly from age 7 to 11 years, and continued with an accelerated increase up to age 17 years before it slowed down. There were significant gender (male>female) and racial/ethnicity (from high to low: multiracial, white, Hispanic, African, and Asian) differences in the age pattern.	E-cigarette smoking is initiated as young as age 7 years. Different from conventional cigarette smoking with peak initiation risk at age 14-15 years, the likelihood of initiating e-cigarette smoking continues to increase up to age 18 years.
Hammig, Daniel-Dobbs, Blunt-Vinti 2017	To examine factors associated with e-cigarette initiation among minority youth in the United States.	Odds of e-cigarette initiation was highest among Hispanic youth [adjusted odds ratio (AOR)=2.70; 95% confidence interval (CI)=1.60-4.56]. Exposure to e-cigarette advertising (AOR=1.64; 95% CI=1.07-2.50), perceptions of little to no harm (AOR=7.08; 95% CI=4.03-12.46), and believing e-cigarettes were less addictive than tobacco (AOR=2.15; 95% CI=1.52-3.02) were associated with e-cigarette initiation.	Odds of initiating e-cigarette use was highest among Hispanic youth. Among minority youth, e-cigarette initiation was associated with perceptions of harm and addiction potential, as well as exposure to e-cigarette advertising.
Harrell, Nqvi, Plunk et al 2017	The present study was designed to identify patterns of youth tobacco use and examine associations with sociodemographic characteristics and tobacco dependence.	Nine classes emerged: cigarette smokers (33.4% of sample, also included small probabilities for use of cigars and e-cigarettes), cigar smokers (16.8%, nearly exclusive), smokeless tobacco users (12.3%, also included small probabilities for cigarettes, cigars, snus), hookah smokers (11.8%), tobacco smokers/chewers (10.7%, variety of primarily traditional tobacco products), tobacco/hookah smokers (7.2%), tobacco/snus/e-cigarette users (3.3%), e-cigarette users (2.9%,), and polytobacco users (1.7%, high probabilities for all products). Compared to cigarette smokers, tobacco/hookah smokers and hookah smokers were more likely to report Hispanic ethnicity. Polytobacco users were more likely to report dependence (AOR:2.77, 95% CI:[1.49-5.18]), whereas e-cigarette users were less likely (AOR:0.49, 95% CI:[0.24-0.97]).	Findings are consistent with other research demonstrating shifts in adolescent tobacco product usage towards non-cigarette tobacco products. Continuous monitoring of these patterns is needed to help predict if this shift will ultimately result in improved public health.
Merianos, Yockey, Wood et al 2017	To examine the influence friend and family factors have on lifetime e-cigarette use, past year e-cigarette use, and perceptions of trying e-cigarettes soon in a national sample of Hispanic junior high and high school students.	Over one-fifth (22.8%) of Hispanic students have used e-cigarettes in their lifetime, 11.1% used in the past 30 days, and one-fifth (20.5%) think they will try e-cigarettes soon. Results revealed students who reported that young people who use e-cigarettes have more friends were 3-4 times more likely to report lifetime use, recent use, and think they will try e-cigarettes soon. Students who reported that if one of their best friends offered an e-cigarette that they would use were nearly 27 times more likely to report lifetime use, 38 times more likely to report recent use, and 77 times more likely to try e-cigarettes soon. Students who lived with someone who used e-cigarettes were 5-6 times more likely to report lifetime use, recent use, and think they will try e-cigarettes soon. Junior high school students who reported that young people who use e-cigarettes have more friends were 4-5 times more likely to report lifetime use, recent use and think they will try e-cigarettes soon. Junior high school students who reported that if one of their best friends offered an e-cigarette that they would use were 29 times more likely to report lifetime use, 44 times more likely to report recent use, and 74 times more likely to try e-cigarettes soon. Junior high school students who lived with someone who used e-cigarettes were 5-6 times more likely to report lifetime use, recent use, and think	Results supported the ideas that family and friend use of e-cigarettes strongly influenced use among Hispanic adolescents. Prevention messages and interventions to reduce smoking among Hispanic students are necessary efforts in improving their health.

Study reference	Purpose	Results	Author conclusion
		they will try e-cigarettes soon. Similar findings were indicated in high school students, although, lower odds ratios were found based on friend factors.	
Lippert 2017	To examine temporal changes in the correlates of experimental and current e-cigarette use and associations with tobacco quit attempts.	Lifetime use was higher among students in medium- (odds ratio [OR]=2.30, 95% confidence interval [CI]=1.82, 2.89) and high- (OR=4.66, 95% CI=3.67, 5.90) versus low-use schools. Past 30-day use followed a similar pattern. Multilevel ordinal logistic models revealed that initiates from high-use schools reported more days of use in the past month (OR=2.25, 95% CI=1.52, 3.33) and higher age-at-first-use (OR=1.45, 95% CI=1.08, 2.00) than students at low-use schools. Expectations for future use were higher among abstainers from medium- and high- versus low-use schools, and among all students, perceived addictivity and harm caused by e-cigarettes were lower in medium- and high- versus low-use schools	The current study demonstrates a link between school prevalence of e-cigarette use and student-level use, as well as perceived risks of e-cigarette use, age of initiation and frequency of use among users, and intentions to use among abstainers.
Tsai J, Walton K et al 2018	Reasons for Electronic Cigarette Use Among Middle and High School Students.	Among students who had ever used e-cigarettes in 2016, the most commonly selected reasons for e-cigarette use were "friend or family member used them," "they are available in flavours, such as mint, candy, fruit, or chocolate," and "they are less harmful than other forms of tobacco, such as cigarettes."	The prevalence of e-cigarette use among youths increased substantially during 2011–2015. In 2016, e-cigarettes were the most common tobacco product used among adolescents, although the overall prevalence of use declined from previous years
Chaffee, Watkins, Glantz 2018	We evaluated associations between e-cigarette use and progression to established smoking among adolescents who had already tried cigarettes.	Versus e-cigarette never use, having ever used e-cigarettes was positively associated with progression to established cigarette smoking (19.3% vs 9.7%), past 30-day smoking (38.8% vs 26.6%), and current established smoking (15.6% vs 7.1%). In adjusted models, e-cigarette ever use positively predicted current established smoking (OR: 1.80; 95% CI: 1.04-3.12) but did not reach statistical significance (alpha=.05) for established smoking (OR: 1.57; 95% CI: 0.99-2.49) and past 30-day smoking (OR: 1.32; 95% CI: 0.99-1.76).	Among adolescent cigarette experimenters, using e-cigarettes was positively and independently associated with progression to current established smoking, suggesting that e-cigarettes do not divert from, and may encourage, cigarette smoking in this population.
Nicksic, Snell, Barnes 2017	The current study not only measures e-cigarette advertisement exposure, but also determines participants' receptivity to e-cigarette advertisements by randomizing exposure to common e-cigarette advertisements.	Ever use among youth was higher for conventional cigarettes than e-cigarettes (15% vs. 12%). The same pattern was observed for current use (5% for conventional cigarettes vs. 3.5% for e-cigarettes. A third of youth who were never-users were susceptible to future use of both e-cigarettes (34.7%). Additionally, 34% were exposed to at least one e-cigarette advertisement, while 57% were receptive. Youth exposed and receptive to e-cigarette advertisements are 6.8 percentage points (PP) more likely to be e-cigarette ever users compared to non-exposed, non-receptive youth (16.4% vs 9.6%). Our results document an association between e-cigarette advertising exposure and e-cigarette ever use, current use, and susceptibility to future use among youth.	Our study illustrates the critical association between advertising exposure and receptivity with e-cigarette and conventional cigarette use behaviours and can inform policies at federal, state, and local levels aimed at restricting e-cigarette advertising to prevent initiation of and continued tobacco use among youth.
Demisse, Everett Jones, Clayton et al 2017	We assessed the prevalence and frequency of cigarette smoking and EVP (electronic vapour products) use among high school students, and associations between health-risk behaviours and both cigarette smoking and EVP use.	15.8% used EVP and 7.5% dual users EVP use is associated with other health-risk behaviours. For a majority of the behaviours examined in this study, cigarette-only smokers and EVP-only users were as likely to engage in that behaviour, suggesting that the associations between health-risk behaviours and EVP use mirror the associations between health-risk behaviours and conventional cigarettes. Cigarette-only smokers, EVP-only users, and dual users were more likely than nonusers to engage in several injury, violence, and substance use behaviours; have >/=4 lifetime sexual partners; be currently sexually active; and drink soda >/=3 times/day. Only dual users were more likely than nonusers not to use a condom at last sexual intercourse.	EVP use, alone and concurrent with cigarette smoking, is associated with health-risk behaviours among high school students.

Study reference	Purpose	Results	Author conclusion
Giovacchini, Pacek, McClernon, Que 2017	To describe the lifetime use and perceived risk of e-cigarette use in the context of other risk-taking behaviours among adolescents in North Carolina.	Ever-use of e-cigarettes (37.2%) Most (73.7%) perceived cigarette use to pose a great health risk, while 33.6% perceived e-cigarette use to pose a great health risk. The majority perceived that their friends (95.4%) and parents (95.3%) would perceive e-cigarette use to be wrong or very wrong. Compared to non-users, ever-users of e-cigarettes were more likely to be African American (13.6% versus 22.8%) and less likely to be Asian (16.0% versus 8.6%; P=0.006). A greater proportion of e-cigarette users than non-users reported Hispanic ethnicity (22.8% versus 15.2%). There was a statistically significant association between being an ever-user of e-cigarettes and higher school grade; among those reporting ever-use of e-cigarettes, 18.9% were in 9th grade compared to 32.9% in 12th grade (p<0.001). Ever-users of e-cigarettes had significantly higher odds of having ever used alcohol and/or illicit drugs.	E-cigarette use among adolescents in North Carolina correlates positively with perceived friends' views of e-cigarettes, and use correlates negatively with personal perception of the risk of e-cigarettes.
Kwon, Seo et al. 2018	Predictors of e-cigarette susceptibility in youth.	Overall, 24.2% (n=2410) of youth who have never used e-cigarettes were susceptible to e-cigarette use. Psychological problems and rebelliousness were associated with increased susceptibility. Ever use of alcohol, marijuana, and other substances and household secondhand smoke exposure were found to be risk factors. Perceptions of e-cigarettes as addictive and harmful worked as protective factors	The results revealed determinants of e-cigarette use susceptibility. Multi-level intervention approach is needed to prevent youth from being susceptible to e-cigarette initiation.
Coleman, Rostron et al 2018	Transitions in e-cigarette use among adults.	Half (48.8%) of adult e-cigarette users at Wave 1 discontinued their use of e-cigarettes at Wave 2. Among dual users of e-cigarettes and cigarettes at Wave 1, 44.3% maintained dual use, 43.5% discontinued e-cigarette use and maintained cigarette smoking and 12.1% discontinued cigarette use at Wave 2, either by abstaining from cigarette smoking only (5.1%) or discontinuing both products (7.0%). Among dual users at Wave 1, daily e-cigarette users were more likely than non-daily users to report smoking abstinence at Wave 2 (aPR=1.40, 95% CI 1.02 to 1.91).	The observed patterns of e-cigarette use and discontinuation between Waves 1 and 2, particularly among infrequent users, suggest a high level of transitory experimentation at Wave 1. As an emerging product on the US market in 2013–2014, the novelty of e-cigarettes may have prompted some people to try them out of curiosity, perhaps without any intention for sustained use. Indeed, curiosity about e-cigarettes is understandable when considering the context in which they emerged— namely, a marketplace of nicotine delivery products that had remained largely unchanged for decades. Moreover, e-cigarettes—and the culture that developed around them—received widespread media attention, potentially fuelling curiosity

Table 32: Characteristics of studies from US national level adults

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Anic, Holder-Hayes, Ambrose	To estimate the prevalence of e-cigarette, smokeless tobacco use and switching amongst current and recent former adults cigarette smokers.	National Adult Tobacco Survey	US national	2012-2013 Analysed 2016	2012/13 n=8,891 2013/14 n=11,379 Past-year smokers. Ages: 2012/13 Median 41.0 (IQR29-53.2) 2012/13 Median 41.4 (IQR29.6-53.7) % males: 2012/13 57.5% 2013/14% 55.5%	Random digit dialling	Landline and cellular phone administered survey based on random-digit dialling	Smoking status based on quit attempts Ever use e-cigarette Frequent use e-cigarette Use smokeless tobacco Switch from cig to e-cig Switch from cig to smokeless tobacco Demographics
Bigman, Mello, Sanderrs-Jackson, Tan	This study examines psychosocial predictors of intentions to ask others not to use e-cigarettes (vape) and smoke - i.e., assertive communication intentions.	Survey paired with Annenberg National Health Communication Survey (ANHCS)	US national	Dec-13	474 (heard of e-cigarettes) 510 recruited Mean age: 48.91(16.03) Male: 47%	Panel that is originally selected via probability-based random-digit dial	Online The ANHCS was a rolling cross-sectional survey among adults aged 18 years and older that surveyed the public from 2005 to 2013. ANHCS participants were U.S. adults who were members of GfK's Knowledge Panel (previously Knowledge Networks).	Assertive Communication Intention (adapted from CDC NATS) Perceived health risks of exposure (adapted from CDC NATS) Attitude toward exposure (Theory of Planned Beh) Perceived normative support for assertive communication (Theory of Planned Beh) Self-efficacy toward assertive communication (Theory of Planned Beh) Demographics Cigarette use e-cigarette use
Conway, Green, Kasza et al	This study examined co-occurrence of tobacco use, substance use, and mental health problems, and its moderation by gender.	Population Assessment of Tobacco and Health survey (PATH)	US national	2013-2014	32,202 with valid data Age: 47.1% between 18 and 44 Male: 48%	Address-based area probability sampling approach that oversampled tobacco users	Audio Computer Assisted Self-Interviews administered in English or Spanish	Self-reported current cigarette, e-cigarette, traditional cigar, cigarillo, filtered cigar, hookah, smokeless tobacco and other tobacco product use; past year alcohol, marijuana, and other drug use; and past year substance use, internalizing and externalizing problems. GAIN-SS - mental health disorders

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Gubner, Pagano, Tajima, Guydish	This research examined electronic cigarette (e-cigarette) use by individuals in treatment for substance abuse, a population with a high prevalence of tobacco use and poor smoking cessation outcomes.	Part of a larger study unnamed	US national	2015	1127 Wave 2 Mean age: 33.3(9.0) years Male: 54%	24 substance abuse treatment centres (10 residential, 7 methadone maintenance, and 7 outpatient clinics) affiliated with the NIDA Clinical Trials Network (CTN).	Qualtrics, self-administered on site using iPads $20 gift card	Demographics lifetime use e-cigarettes 30-day use e-cigarettes Details of e-cigarette device types Smoking status
Henry, Gettens, Savageau et al	We used surveys conducted in 2008 and 2014 to examine changes in smoking abstinence rates among MassHealth members identified as smokers and to identify factors associated with being a former smoker.	MassHealth Smoking Cessation (MHSC) Surveys	US national (Massachusetts only)	2008 and 2014	2008 n1,635 2014 n793 Age: 2008 31.4% 45-54 2014 33.1% 55-64 years % male: 2008 41.5% 2014 36.7%	People involved with MassHealth smoking cessation	Mail and phone	Current and prior smoking behaviour attempts to quit chronic health conditions demographics Plus some open-ended items
Jones, Majeed, Weaver et al.	We aimed to determine whether the prevalence of current use of smokeless tobacco products (STPs) changed during 2014-2016 and examine factors associated with use among adults in the United States.	Tobacco Products and Risk Perceptions Surveys	US national	2014, 2015, 2016	5,717, 6,051, 6,014	Gfk's Knowledge Panel Probability based web panel	Web-based	Current STP use Other tobacco use Demographics
Levy, Yuan, Li	While most studies consider a subset of these characteristics with weak measures of regular e-cigarette use, this study uses a large, recent U.S. survey to simultaneously consider the association of each of these factors with different use measures.	Tobacco Use Supplement-Current Population Survey (TUS-CPS)	US national	2014	158,626 Age: 36.7% 45-64 years Male: 45%	A probability sample employs stratified clusters of households drawn from an initial sampling frame that covers the civilian, non-institutionalized population ages 18 and older.	Telephone and in-person interviews conducted by US Census Bureau	Ever use e-cigarettes 30-day e-cigarette use Regular e-cigarette use Lifetime cigarette use Current cigarette use, intensity and frequency Smoking cessation Demographics Cig taxes and tobacco control spending data from records
Park, Duncan et al	To investigate the individual characteristics and state-level prevalence of U.S. adults who have switched to e-cigarettes from traditional cigarettes.	National Adult Tobacco Survey	US national	2012-14	44,00 completed surveys	Stratified sample were selected by random-digit dialling	Telephone survey	Switching to e-cigarettes; former smokers who quit without switching; current dual e-cigarette and cig users; sociodemographics

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Park SH, Lee L et al 2017	Investigated the possible association between individuals' levels of psychological distress and e-cigarette use.	National Health Interview Survey (NHIS)	US national	2014	36,697 Ages: 18+ years 48% male	Cross-sectional nationally representative survey of the non-institutionalized US civilian population. The survey uses a complex, multistage, stratified probability design	Face-to-face interviews	Kessler 6 scale to measure psychological distress e-cigarette use demographics
Pericot-Valverde I et al 2017	To estimate and update knowledge on rates and predictors of awareness, perceived harmfulness, and ever use of e-cigarettes among adults and (b) to utilize that information to identify risk-factor profiles associated with ever use.	Health Information National Trends Survey (HINTS)	US national	2015	3,738 Mean age: 30.4 (29.8, 30.8) 49% male	Stratified sample of households received the questionnaire. - A nationally-representative, cross-sectional survey of the U.S. non-institutionalized population.	Mail (pen and paper)	Demographics; sociodemographics incl sexual orientation; current use of other tobacco products and e-cigarette awareness, perceived harm and ever use
Roberts ME, Doogan NJ et al 2017	To examine urban–rural differences in US prevalence's of traditional and emerging tobacco product use as well as dual or polytobacco use of these products.	Population Assessment of Tobacco and Health (PATH) (Wave 1)	US national	2013-14	32,320 Mean age: 46.6 ±0.4 48% male	Sampled from 150,000 mailing addresses	Ongoing household-based, nationally representative, longitudinal cohort study	Urban vs rural, tobacco use, dual and poly-tobacco use, demographics
Shah A et al 2017	Prevalence and characteristics of e-cigarette users among COPD patient population.	National Health Interview Survey (NHIS)	US national	2014	642,848 38% male	Self-selection; cross-sectional survey	Face-to-face interviews	Current e-cigarette user; ever e-cigarette user; sociodemographics
Sharapova, Singh et al	Patterns of E-cigarette Use Frequency.	National Adult Tobacco Survey	US national	2012-2014	60,192 Ages: 18+ years	Nationally representative cross-sectional survey	Telephone based survey	Current e-cigarette use; cigarette and other tobacco product use
Spears CA, Jones DM et al 2017	To assess the use of ENDS among adults with mental health conditions.	Tobacco Products and Risk Perceptions Survey	US national	2015	6,051	Cross-sectional survey of a national random probability sample with an over sample of current smokers from GfK's Knowledge Panel	Online questionnaire	Mental health condition; smoking status; ENDS use; ENDS use during smoking quit attempts; susceptibility to future ENDS use
Stokes, Collins et al 2018	The objectives of the present study therefore were to assess the prevalence of e-cigarette use in individuals with CVD using nationally representative	National Health Interview Survey (NHIS)	US national	2014	4,966 (with CVD) By e-cigarette status: Never 47.0% male, 64.8(15.8) years	Nationally representative	Not reported in paper	E-cigarette use current/ever Smoking history

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	data on adults in the United States and to characterize patterns of e-cigarette use by tobacco smoking status.				Former 49.4% male, 49.4(16.3) years Current 45.3% male, 52.0(15.4) years Ever 45.4% male, 50.3(16.0) years			
Yao T, Max W et al 2017	Relationship between spending on electronic cigarettes, 30-day use, and disease symptoms.	Tobacco and Attitudes Beliefs Survey	US national	August 20–31, 2015	539 24 yrs and older 40% male	Recruited by the Qualtrics Research Company (an online survey company) using a probability-based sampling approach. Participants received $10.	Online survey	Disease symptoms; current (last 30 days) e-cigarette use; total spending on e-cigarettes in past month; Ave no of conventional cigs smoked per day; demographics
Anic, Holder-Hayes, Ambrose	To estimate the prevalence of e-cig, smokeless tobacco use and switching amongst current and recent former adults cigarette smokers.	National Adult Tobacco Survey	US national	2012-2013 Analysed 2016	2012/13 n=8,891 2013/14 n=11,379 Past-year smokers. Ages: 2012/13 Median 41.0 (IQR29-53.2) 2012/13 Median 41.4 (IQR29.6-53.7) % Male: 2012/13 57.5% 2013/14% 55.5%	Random digit dialling	Landline and cellular phone administered survey based on random-digit dialling	Smoking status based on quit attempts Ever use e-cigarette Freq use e-cigarette Use smokeless tobacco Switch from cigarette to e-cigarette Switch from cigarette to smokeless tobacco Demographics

Table 33: Results of studies from US national level adults

Study reference	Purpose	Results	Author conclusion
Anic, Holder-Hayes, Ambrose	To estimate the prevalence of e-cig, smokeless tobacco use and switching amongst current and recent former adults cigarette smokers.	E-cigarette use increased between years for all smoking status groups. More freq among smokers with unsuccessful attempt (10.4%; 14.8%) and recent quitters (9.1%; 15.8%) than smokers with no attempts (5.9%; 10.7%). Sig increase for recent quitters (7.7%; 11.9%), no quite attempt (1.5% 2.4%). No sig change over time for unsuccessful quit attempt (3.4%; 4.4%). Complete switch to e-cigarette at some point increased from 15.3% to 25.7%. 13/14 age diff: Recent quitters who switched more likely to be 18-24yo. Switchers more like to have history of daily cig smoking from >6mo and current daily cig use. No diffs or sex, race, education.	E-cigarette more popular than smokeless tobacco. Recent quitters are considerably more like tot have switched to e-cigarette at some point in the past 12mo than smokeless tobacco.
Bigman, Mello, Sanderrs-Jackson, Tan	This study examines psychosocial predictors of intentions to ask others not to use e-cigarettes (vape) and smoke - i.e., assertive communication intentions.	Tried e-cigarette 11.60%. Participants in this study were more willing to communicate assertively about smoking than vaping. The findings align with the fact that, on average, participants reported more risk for smoking than vaping, and perceived more normative support and efficacy for assertive communication for asking someone not to smoke.	Although a majority of respondents indicated they were unlikely to intervene to voice objections about SHSe and SHVe in public venues, this study suggests that incidental or intentional messages and policies that influence perceptions of risk, norms, and efficacy could affect willingness to voice objections about others' vaping and smoking in public.
Conway, Green, Kasza et al	This study examined co-occurrence of tobacco use, substance use, and mental health problems, and its moderation by gender.	The associations of current e-cigarette use and current traditional cigar use with internalizing problems were stronger among females compared to males	Female tobacco users are at increased risk for substance use and mental health problems. These findings may point to gender differences in vulnerability and suggest that interventions incorporate gender-specific approaches.
Gubner, Pagano, Tajima, Guydish	This research examined electronic cigarette (e-cigarette) use by individuals in treatment for substance abuse, a population with a high prevalence of tobacco use and poor smoking cessation outcomes.	59.8% ever use e-cigarettes; 23.6% past month e-cigarette use. Being at methadone clinic, former tobacco smoker predicted daily versus weekly e-cigarette use. Daily e-cigarette users were more likely to report using e-cigarettes as a way to reduce health risk, and because they cost less than tobacco cigarettes, while weekly e-cigarette users were more likely to use e-cigarettes at times and places where they could not smoke tobacco cigarettes. Daily e-cigarette users were more likely to report using their e-cigarette continuously throughout the day, while weekly e-cigarette users were more likely to use e-cigarettes at times or places where they could not smoke tobacco cigarettes. Interestingly, especially among weekly users, more individuals did not know the concentration of nicotine used, than what flavour they used.	Daily e-cigarette users in substance abuse treatment were more likely to be from methadone clinics and former cigarette smokers. However, the majority of daily e-cigarette users were current cigarette smokers (73.6%). While a majority of e-cigarette users in substance abuse treatment were current cigarette smokers, daily e-cigarette users were more likely to be former cigarette smokers. Administrators of substance abuse treatment programs should evaluate potential benefits and harms of e-cigarettes when developing program policies.
Henry, Gettens, Savageau et al	We used surveys conducted in 2008 and 2014 to examine changes in smoking abstinence rates among MassHealth members identified as smokers and to identify factors associated with being a former smoker.	The use of e-cigarettes within the last 30 days was significantly associated with a decreased odds of being a former smoker (OR=0.1, 95% CI=0.02–0.2). Of the factors identified by MassHealth members as 'helping the most' in quitting or quit attempts, three factors differed between smokers and former smokers: health concerns; influence of family members; and use of electronic cigarettes Almost one-quarter of smokers had used e-cigarettes within the past 30 days suggests that use of these devices may be a growing trend among Medicaid enrolees.	Compared to smokers, former smokers more frequently reported health concerns, the influence of family members, and the use of e-cigarettes as helping the most in quitting. Additionally, smokers' concerns about health and the influence of family and friends provide opportunities for targeted intervention and messaging about quitting.
Jones, Majeed, Weaver et al.	We aimed to determine whether the prevalence of current use of smokeless tobacco products (STPs) changed during 2014-2016	The prevalence of current STP (smokeless tobacco products) use was 2.3% in 2014, 3.6% in 2015, and 2.7% in 2016 Males, adults aged less than 60 years old, those with less than a college degree, those who resided in the Midwest or West, and current cigarette smokers had higher odds of being a current STP user. Being a current hookah smoker (AOR: 3.70; 95% CI: 1.51, 9.12) and current ENDS user (AOR: 2.71; 95%	The prevalence of current STP use peaked in 2015. In 2016, current STP use was more prevalent among males and adults with lower education. Continuous monitoring of STP use is needed, particularly non-cigarette tobacco product users.

Study reference	Purpose	Results	Author conclusion
	and examine factors associated with use among adults in the United States.	CI: 1.40, 5.24) was associated with statistically higher odds of being a current STP user, compared to a non-current user	
Levy, Yuan, Li	While most studies consider a subset of these characteristics with weak measures of regular e-cigarette use, this study uses a large, recent U.S. survey to simultaneously consider the association of each of these factors with different use measures.	The prevalence of ever, current (at least 1 of the last 30 days), and regular (at least 20 of the last 30 days) e-cigarette use were 7.7%, 2.1% and 0.9%, implying that 27.0% of ever users were current users of which 45.3% were regular users. The odds of regular e-cigarette use was higher among males than females at age 18–34, among those with a high school and associate degree, and for those living in metropolitan areas, and was lower among age 45–64 and 65+, among Blacks and Asians compared to Whites, and among Hispanic compared to non-Hispanic. Among the policy variables, the only consistent finding that emerged was lower e-cigarette use in states at the highest quarter of tobacco control spending. The odds of regular use were about 140 times greater for former smokers who quit in the last year than never smokers. We found that e-cigarette ever use increased with the number of cigarettes smoked per day for those who were smokers one year ago. However, that relationship reverses, i.e., current smokers who smoke more CPD are less likely to be regular users, suggesting that e-cigarettes are particularly effective in enabling heavy smokers to quit	Our results indicate that it is essential to distinguish infrequent, experimental use from more established, regular use in analysing the role of e-cigarette use in the uptake and cessation of cigarette and other tobacco product use
Park SH, Lee L et al 2017	Investigated the possible association between individuals' levels of psychological distress and e-cigarette use.	In a multivariate model, psychological distress was significantly associated with the following groups: (a) exclusive e-cigarette ever-use (aOR=3.7; 95% CI=1.6, 8.6), (b) current dual use of e-cigarettes and cigarettes (aOR=4.6; 95% CI=3.1, 6.7), (c) former cigarette use and ever use of e-cigarette (aOR=3.2; 95% CI=2.2, 4.8) and (d) current use of cigarettes only (aOR=2.1; 95% CI=1.7, 2.6)	As is true for cigarettes, e-cigarette use is associated with increased levels of psychological distress
Park, Duncan et al	To investigate the individual characteristics and state-level prevalence of U.S. adults who have switched to e-cigarettes from traditional cigarettes.	Overall, the number of individuals who switched from traditional cigarettes to e-cigarettes increased by approximately 100% over the 1-year interval. Those living in the South and West were more likely to switch to e-cigarettes, compared to former smokers who did not switch. Compared with current dual users, those with higher education and those who were not single were more likely to switch to e-cigarettes.	There is an increase in the progression from traditional cigarette use to e-cigarette use
Pericot-Valverde I et al 2017	To estimate and update knowledge on rates and predictors of awareness, perceived harmfulness, and ever use of e-cigarettes among adults and (b) to utilize that information to identify risk-factor profiles associated with ever use.	Most respondents were aware of e-cigarettes (83.6%) and perceived them to be not at all or moderately harmful (54.7%). Prevalence of e-cigarette ever use was 22.4%. Current cigarette smoking and ever use of alternative tobacco products were powerful predictors of use. Other predictors of use of e-cigarettes were age, race/ethnicity, and educational attainment. Awareness and perceived harm were significant predictors among particular smoker subgroups. Fifteen risk profiles were identified across which prevalence of e-cigarette use varied from 6 to 94%.	New knowledge regarding risk-profiles associated with striking differences in prevalence of e-cigarette use that have the potential to be helpful when considering the need for or impact of e-cigarette regulatory policies.
Roberts ME, Doogan NJ et al 2017	To examine urban–rural differences in US prevalence's of traditional and emerging tobacco product use as well as dual	Cigarette use and smokeless tobacco use, as well as dual or polytobacco use of traditional products, were more prevalent in rural than in urban areas. There was no significant urban–rural difference in use of e-cigarettes	Longitudinal data are needed to examine whether use of e-cigarettes will create a shift away from the predominance of cigarette and smokeless tobacco use that has been the mainstay of rural tobacco users for decades. The question of whether e-cigarette use aids cessation is complex and continues to be

Study reference	Purpose	Results	Author conclusion
	or polytobacco use of these products.		debated; how the use of e-cigarettes and other emerging tobacco products will contribute to the rise or decline of rural tobacco use remains to be seen.
Shah A et al 2017	Prevalence and characteristics of e-cigarette users among COPD patient population.	Among COPD individuals with current e-cigarettes use (N=642,848), user percentages were higher significantly (p<0.05) among individuals: Between 45 and 64 years age (56.96%), Among divorced (30.75%), Residing in south (53.88%), Currently unemployed(87.50%), Working for a private firm (77.73%), Currently smoking tobacco (68.48%), Have tried quitting the use of tobacco at least once in past 12 months (62.20%).	With the increase in awareness of e-cigarette use for smoking cessation, its usage were found to be higher in COPD individuals who are current smokers and among those who want to quit tobacco use.
Sharapova, Singh et al	Patterns of E-cigarette Use Frequency.	Among current e-cigarette users, 19.3% used daily, 29.3% used some days, and 51.4% used rarely. Daily use was lowest among younger adults, Hispanics, and those who were single, never married, or not living with a partner; and greatest among non-Hispanic Asians (p<0.0001). Among current e-cigarette users, 25.3% were cigarette-only smokers, 52.8% smoked cigarettes and used other tobacco products, 5.5% used other tobacco products only, 6.5% were former cigarette-only smokers, 6.7% were former users of cigarettes and other tobacco products, 1.3% were former other tobacco product users only, and 1.8% never used cigarettes or other tobacco products.	E-cigarette use frequency varies by sociodemographic characteristics and other tobacco use. Further surveillance, particularly related to frequency of e-cigarette use and its impact on cigarette cessation, could inform public health policy, planning, and practice.
Spears CA, Jones DM et al 2017	To assess the use of ENDS among adults with mental health conditions.	Participants with MHC were approximately 1.5 times more likely to have used ENDS in their lifetime and almost twice as likely to currently use ENDS as those without MHC. MHC status was most strongly linked to higher ENDS use among former smokers, and former smokers with MHC were more likely to report using ENDS during past smoking quit attempts than those without MHC. Among participants who had not tried ENDS, former smokers with MHC were especially susceptible to future ENDS use.	The potential advantage of ENDS for cessation purposes should be balanced with the risk of attracting former smokers with MHC to ENDS
Stokes, Collins et al 2018	The objectives of the present study therefore were to assess the prevalence of e-cigarette use in individuals with CVD using nationally representative data on adults in the United States and to characterize patterns of e-cigarette use by tobacco smoking status.	11.0% ever used e-cigarette (3.7% current) Compared with never users of e-cigarettes, those who had ever used e-cigarettes were younger, more likely to be non-Hispanic whites, and report some college without completion and current/recent former smokers.	Individuals with CVD who recently quit smoking or reported a recent quit attempt were significantly more likely to use e-cigarettes than current smokers and those who did not report a quit attempt
Yao T, Max W et al 2017	Relationship between spending on electronic cigarettes, 30-day use, and disease symptoms.	The most commonly reported disease symptoms were coughing (54.5%) and waking up feeling tired (52.0%), and the least common symptoms were having sores or ulcers in mouth (8.3%) and having more than one cold (6.8%). For each $100 increase in e-cigarette expenditures, the odds of reporting chest pain (versus not reporting chest pain), noticing blood when brushing teeth (versus not noticing blood when brushing teeth), having sores or ulcers in their mouth (versus not having sores or ulcers in their mouth), and having more than one cold (versus not having more than one cold) significantly increased by factors of 1.25, 1.23, 1.36, and 1.36, respectively.	E-cigarette expenditures might be a more useful measure of intensity of e-cigarette use. The additional health effect of e-cigarette use or expenditures among smokers independent of the effect of CPD suggests that e-cigarette use adds adverse health effects even among cigarette smokers.

Table 34: Characteristics of studies that were US non-national level youth

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Barrington-Trimis, Gibson, Halpern-Felsher et al	Report the prevalence of using different device types among a combined 2,166 adolescent and young adult e-cigarette users across eight different studies.	Combination of 8 studies	California (3 studies), Texas (2 studies), Connecticut (1 study), or randomly selected from the US population (2 studies).	Fall 2014 and Spring 2016	2,166 adolescents	NR	Surveys were administered in school (2 studies), online (5 studies), or by phone (1 study).	Demographics e-cigarette use e-cigarette device type
Bersamin, Paschall, Fisher	The current study extends previous research and examines possible differences in the association between school-based health centre exposure and adolescent alcohol, tobacco, and other drug use by race/ethnicity, sex, and socioeconomic status.	California Healthy Kids Survey	California, US	2013	504 schools 330,764 9-12 graders Mean age: 15.4(1.2) 49% males	Survey conducted by WestEd.	Anonymous, self-administered in classrooms as written or internet-based	Lifetime and past-month substance use Demographics
Case, Harrell, Perez et al	This study examined cross-sectional and longitudinal associations between sensation seeking and a variety of e-cigarette use behaviours among Texas adolescents.	Texas Adolescent Tobacco and Marketing Surveillance System (TATAMS)	Texas, US	2014-2015	N=2,488 at follow up 3,907 at baseline Baseline 51.1% males	TATAMS is a three-year longitudinal study. Complex probability sampling representative of grades 6,8,10 in 4 largest cities in Texas.	NR	Susceptibility to e-cigarette use Ever use e-cigarettes Current use e-cigarettes Sensation seeking Demographics Use of other tobacco products
Choi, Bestrashniy, Forster	We assessed trends in e-cigarette and snus in a cohort of young adults from the US Midwest.	Minnesota Adolescent Community Cohort (MAconventional cigarette) study	Minnesota, US	2010-2013	2010-2011 2622 2011-2012 2550 2012-2013 2420 Mean ages: 2010-2011 24.0(1.7) 2011-2012 25.0(1.7) 2012-2013 26.0(1.7) % male: 2010-2011 47.3% 2011-2012 47.6% 2012-2013 46.8%	Complex probability sample used to sample one adolescent per household among eligible households. Clearwater Research, Inc. conducted sampling and recruitment.	Telephone surveys that included questions about tobacco use and attitudes towards tobacco were completed every 6 months. $25 for participation.	Awareness e-cigarette Use e-cigarettes 30-day use e-cigarettes Beliefs about e-cigarettes Demographics

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Creamer, Delk, Case et al	This study examines if outcome expectations at baseline, among an adolescent cohort of never users of tobacco products, predicts tobacco product use (i.e., cigarettes, hookah, e-cigarette, cigar, or smokeless tobacco) or susceptibility to use at 6-month follow-up.	Texas Adolescent Tobacco and Marketing Surveillance System (TATAMS)	Texas, US	2014-2015	Never users only at baseline n=1,999	TATAMS surveyed 3907 6th, 8th, and 10th grade students in the 5 counties that surround the 4 largest metropolitan areas	NR	Ever use smoking products Susceptibility to any smoking product Outcome expectancies for tobacco Demographics
Delk, Creamer, Perry, Harrell	Given the high rate of adolescent obesity and the rise in e-cigarette use in adolescents, this relationship should be investigated.	Texas Adolescent Tobacco and Marketing Surveillance System (TATAMS)	Texas, US	2015-2016 Wave 3	2,733 Grades 7, 9 , 11 n=1090 boys n=1434 girls	As above	NR	Weight status Ever use e-cigarette Past 30-day use e-cigarette Demographics
Dunbar, Tucker, Ewing et al	E-cigarettes (e-cigarettes) are increasingly popular among adolescents, who perceive them as "safer" than cigarettes. Although research has examined risk factors for adolescent e-cigarette use, little is known about how e-cigarette use correlates with health status and protective health behaviours.	CHOICE intervention program (wave 7)	Los Angeles, US	2014-2015	2,488 Mean age: 17(0.67) 46% males	Part of the intervention program delivered in schools. Intervention program ended at wave 2.	Web-based	E-cigarette use Cig and tobacco use Health status (physical and mental) Health protective behaviours (PA, Healthy diet, Sleep) Health Risk Behaviours (alcohol and drug use, sedentary behaviour) Demographics
Hong, Barrington-Trimis, Liu et al	Examine reasons for e-cigarette use in Southern California cohort of adolescents.	Southern California Children's Health Survey (CHS)	California, US	2015-2016	614 Mean age: 18.8	NR	Online	Reasons for use e-cigarette Ever use e-cigarette demographics history of e-cigarette and cig use Type of e-cigarette use
Kristjansson, Mann, Smith	The objective of this study was to compare the prevalence of substance use in e-cigarette-only users with conventional cigarette-only users, dual users, and nonusers in a large sample of middle school-aged adolescents.	AWARE intervention	West Virginia, US	2015	6,547 Grades 6-8 50% males	The sampling frame included all students in 15 public and private middle schools (grades 6–8) in the 3 counties	Collected by teachers	Smoking status Chewing tobacco Alcohol use Use of illicit and licit drugs Demographics
Kristjansson, Mann, Smith, Sigfusdottir	The purpose of this study was to assess the similarities and differences in the social profile of middle school-aged children that have used e-cigarette-only versus conventional cigarette use only	AWARE intervention	West Virginia, US	2015	6,547 Grades 6-9 50% males	The sampling frame included all students in 15 public and private middle schools (grades 6–8) in the 3 counties	Collected by teachers	Smoking status Parents and family domain School environment domain

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	and to compare those groups against non-users and dual users.							Peer group domain Leisure time domain Demographics
Lee, Pepper et al 2018	Examining youth dual and polytobacco use with e-cigarettes.	Florida Youth Tobacco Survey	Florida, US	2014	2,756 middle and highschool students	Two-stage cluster probability sample design	Pencil and paper questionnaire	Psychosocial variables; e-cigarettes, cigarette and OTP use
Leventhal, Urman, Barrington-Trimis et al	Perceived stress was examined as a predictor of later tobacco product use in a population-based cohort of southern California adolescents.	Southern California Children's Health Study (CHS)	California, US	2003-	1,851 (4-year FU) Mean ages: 13.5(0.6) baseline 17.3(0.6) FU 49% males	12 communities across Southern California	Participants completed questionnaires in school classrooms under the supervision of study staff	Perceived Stress (PSS) Tobacco product ever and 30-day use (cigarette, e-cigarettes, hookah, cigar) Demographics
Mantey, Harrell, Case et al	In this paper, we assessed the prevalence of subjective experiences at first use across four different nicotine products (cigarettes, e-cigarettes, hookah, and cigars/cigarillo/LFC) and the associations between each subjective experience and current use of the four products.	Texas Adolescent Tobacco and Marketing Surveillance System (TATAMS)	Texas, US	2014-2015 (Wave 1)	3,907 Grades 6,8,10 51% males			Subjective experience of first use (if EVER use) Current use of tobacco products Demographics
Owusu D,Aibangbee et al 2017	To estimate the prevalence of e-cigarette use and examine association of e-cigarette use with two tobacco products among school-going adolescents.	Lunch and Learn Tobacco Use Survey	Tennessee, US	2016	894 Age: 14-22 (mean=16 yrs ± 1.4) 42% males	All schools in county invited to participate, 4 accepted and all students eligible to participate	Face-to-face interviews	Current e-cigarette use (ever use, current use, age of initiation, and intention to quit of these three nicotine products); demographics
Urman, McConnell et al 2018	We used two waves of data from the Southern Children's Health Study to examine prospectively (1) whether the e-cigarette social environment was associated with subsequent initiation of e-cigarettes and (2) whether ever use of e-cigarettes at baseline was associated with the development of a social environment more supportive of e-cigarette use at follow-up.	Southern California Children's Health Study	California, US	2014	1,441, 17.3 years (median), 47.6% male	11 and 12 graders from 12 Southern California communities	In-class on paper Follow-up online	Tobacco product use Social environment Demographics
Wong, Fan 2018	This study sought to determine e-cigarette use prevalence and its relation to alcohol use as a potential	California Health Interview Survey (CHIS)	California, US	2014/2015	1,806, 14.5 years (mean), 51.1% male	cross-sectional, multistage sampling representative of	Telephone (CATI)	Ever-use e-cigarettes Ever-use alcohol

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	gateway drug, and how this may differ by sex and ethnicity in a multi-ethnic sample of California adolescents.					the non-institutionalised population	household phones and then cell phones	Demographics
								Ever-use cigarettes
								Fruit and vegetable consumption
								Levels of physical activity

Table 35: Results of studies that were US non-national level youth

Study reference	Purpose	Results	Author conclusion
Barrington-Trimis, Gibson, Halpern-Felsher et al	Report the prevalence of using different device types among a combined 2,166 adolescent and young adult e-cigarette users across eight different studies.	Use data in supplementary table [need to download from journal] Past 30-day e-cigarette use ranged from 3.5% to 13.2% Across the eight studies, 8.0% reported primary use of a disposable/cigalike device and 77.0% used later generation device	Among adolescent and young adult e-cigarette users, primary use of disposable/ cigalike devices was rare
Bersamin, Paschall, Fisher	The current study extends previous research and examines possible differences in the association between school-based health centre exposure and adolescent alcohol, tobacco, and other drug use by race/ethnicity, sex, and socioeconomic status.	E-cigarette use lifetime 27.2%; past 30-days 14.3% Strongest predictor of e-cigarette use was male followed by parent not graduating from college -- similar for cigarettes (plus being African American for cigs). The current study found that SBHCs had a differential association with substance use behaviours among (1) African Americans and Asian/Pacific Islanders compared to white youth; and (2) youth whose parent(s) did not complete college compared to those who did. Among African Americans, access to an SBHC was inversely associated with alcohol use, binge drinking, cigarette, and e-cigarette use. Among Asian/Pacific Islanders, SBHC access was inversely associated with cigarette and marijuana use. In contrast, among white youth, there were positive associations between SBHC access and alcohol and marijuana use, no association between SBHC access and cigarette use, and a weak inverse association between SBHC access and e-cigarette use.	SBHC exposure appears to be inversely related to substance use among youth in some ethnic minority groups and youth of lower SES.
Case, Harrell, Perez et al	This study examined cross-sectional and longitudinal associations between sensation seeking and a variety of e-cigarette use behaviours among Texas adolescents.	30.9% of never e-cigarette use were susceptible to future use 7.3% reported current use. Adolescents with higher mean sensation seeking scores had significantly higher odds of being susceptible to e-cigarette use as compared to adolescents with lower mean sensation seeking scores (AOR=1.25, 95% CI=1.07, 1.47). Similarly, adolescents with higher mean sensation seeking scores had significantly higher odds of ever e-cigarette use (AOR=1.24, 95% CI=1.08, 1.43) as compared to adolescents with lower mean sensation seeking scores.	Higher sensation seeking scores were consistently and significantly related to experimentation with e-cigarette use among Texas adolescents.
Choi, Bestrashniy, Forster	We assessed trends in e-cigarette and snus in a cohort of young adults from the US Midwest.	Ever use e-cigarette 2010-2011 7%; 2011-2012 11.1%; 2012-2013 15.5% young adults in our sample were increasingly likely over time to believe that e-cigarettes are less harmful than cigarettes and can help people quit smoking. Trends did not vary by smoking status.	The increasingly favourable beliefs about e-cigarettes may explain the increasing prevalence of their use particularly among young adults, both among smokers and non-smokers.
Creamer, Delk, Case et al	This study examines if outcome expectations at baseline, among an adolescent cohort of never users of tobacco products, predicts tobacco product use or susceptibility to use at 6-month follow-up.	78 (3.6%) never users 63.2% of ever users tried e-cigarette (denominator n78) Outcome expectancies reported for total tobacco use only	This study extends the literature regarding outcome expectations among adolescents regarding tobacco products. It is important that interventions offer alternative solutions to stress relief that do not include tobacco products.
Delk, Creamer, Perry, Harrell	Given the high rate of adolescent obesity and the rise in e-cigarette use in adolescents, this	Compared with healthy-weight boys, obese boys had higher odds of past 30-day e-cigarette use (AOR=3.45, 95% CI=1.34, 8.33) and cigarette smoking (AOR=4.52, 95% CI=1.32, 15.51). There was no significant relationship between weight status and cigarette or e-cigarette use in girls.	This study supports that there is a positive relationship between weight status and past 30-day cigarette and e-cigarette use for boys, but that there is no association for girls

Study reference	Purpose	Results	Author conclusion
	relationship should be investigated.		
Dunbar, Tucker, Ewing et al	Investigate how e-cigarette use correlates with health status and protective health behaviours.	Sig predictor of e-cigarette in e-cigarette users only: Did not limited consumption of unhealthy foods/drink; alcohol use; heavy drinking; marijuana use; other drug use. User groups were similar on physical health and engagement in protective health behaviours (physical activity, sleep duration/quality, healthy diet), but e-cigarette-only users reported fewer mental health symptoms and less AOD use than dual or cigarette-only users. Among e-cigarette-only users, AOD use (all p<0.0001) predicted more frequent e-cigarette use; healthy diet predicted less frequent use (p<0.01).	E-cigarette-only use is associated with lower engagement in risky behaviours, but not better health status or higher engagement in protective health behaviours, compared with cigarette smoking. Dual e-cigarette/cigarette users may represent a particularly high-risk group due to their greater AOD use and cigarette consumption. Among "intermediate-risk" e-cigarette-only users, AOD use and unhealthy diet correlated with heavier use, and may be important targets for preventing escalation to more harmful tobacco use.
Hong, Barrington-Trimis, Liu et al	Examine reasons for e-cigarette use in Southern California cohort of adolescents.	56.6% smoked e-cigarette because it had flavours they like, 51% because they taste better than cigarettes and 46.7% due to perceived less harm to themselves or others (43.7%).	Flavourings were cited as the most common reason for e-cigarette use and few cited use for smoking cessation.
Kristjansson, Mann, Smith	The objective of this study was to compare the prevalence of substance use in e-cigarette-only users with combustible cigarette-only users, dual users, and nonusers in a large sample of middle school-aged adolescents.	4.3% had used e-cigarette but not conventional cigarette, 4.5% had used conventional cigarette but not e-cigarette, and 5.5% had used both e-cigarette and conventional cigarette Nonusers have significantly lower odds of substance use than e-cigarette users and the e-cigarette users are not significantly different from conventional cigarette users in terms of odds for substance use. The dual users are at increased odds for substance use over e-cigarette users.	Among middle school-aged adolescents, e-cigarette-only users do not differ from conventional cigarette-only users in odds for other forms of substance use.
Kristjansson, Mann, Smith, Sigfusdottir	The purpose of this study was to assess the similarities and differences in the social profile of middle school-aged children that have used e-cigarette-only versus conventional cigarette use only and to compare those groups against non-users and dual users.	The results show that compared to never smokers, e-cigarette-only users possessed a weaker social support and parental monitoring profile and performed worse in school. Additionally, e-cigarette-only users were more likely to feel alienated from school, to associate with delinquent peers, to spend time outside late at night, and to engage in unsupervised gatherings with their friends. In 11 of 13 statistical models no difference was observed between e-cigarette-only users compared with conventional cigarette-only users. However, dual users (that had used both e-cigarette and conventional cigarette in their lifetime) demonstrated a significantly greater risk profile compared with e-cigarette-only users.	We conclude that middle school-aged kids that use e-cigarette share a similar risk profile as kids of the same age that use conventional cigarette.
Lee, Pepper et al 2018	Examining youth dual and polytobacco use with e-cigarettes	Most e-cigarette-using youth used at least one other product (81%). Perceiving cigarettes as easy to quit was significantly associated with greater likelihood of combined e-cigarette/OTP use (relative risk ratio (RRR)=2.51, p<0.001) and combined e-cigarette/cigarette/OTP use (RRR=3.20, p<0.0001). Thinking you will be smoking cigarettes in 5 years was associated with product combinations that include cigarettes	Given that specific psychosocial factors put youth at risk for concurrent use of e-cigarettes with tobacco products, public health efforts should address polytobacco use specifically, instead of individual product use. Youth perceptions about the ease of quitting cigarettes, intentions to continue smoking cigarettes and receptivity to tobacco company marketing are promising areas for messaging aimed at reducing e-cigarette polytobacco product use.

Study reference	Purpose	Results	Author conclusion
Leventhal, Urman, Barrington-Trimis et al	Perceived stress was examined as a predictor of later tobacco product use in a population-based cohort of southern California adolescents.	14.1% ever use e-cigarette; 9.7% past 30-day use A standardized baseline perceived stress score predicted electronic cigarette, hookah, combustible cigarette, and cigar use and a poly-tobacco use index at the 4-year follow-up in the overall sample.	In the current era in which teen use of alternative tobacco products is increasingly common, adolescent tobacco use and poly-use research and prevention strategies should address gender-specific origins of tobacco product use risk and consider perceived stress and other emotional endophenotypes in such risk pathways.
Mantey, Harrell, Case et al	In this paper, we assessed the prevalence of subjective experiences at first use across four different nicotine products (cigarettes, e-cigarettes, hookah, and cigars/cigarillo/LFC) and the associations between each subjective experience and current use of the four products.	The weighted prevalence rates of ever use of/tobacco products were: 19.5% for e-cigarettes. E-cigarette ever users had the lowest reported rates of almost all subjective experiences, including dizziness, coughing rush/buzz and relaxed/good, although ever hookah users had the lowest prevalence of sick/nausea. No first use subjective experiences were significantly associated with increased odds of using e-cigarettes or hookah.	Subjective experiences at first use differ by tobacco product.
Owusu D,Aibangbee et al 2017	To estimate the prevalence of e-cigarette use and examine association of e-cigarette use with two tobacco products among school-going adolescents.	11% of the participants currently used e-cigarettes, and 35% had ever used e-cigarettes. About 6% of the participants were current users of both e-cigarettes and cigarettes; 4% were current users of e-cigarettes and smokeless tobacco; 3% were current users of all three products, and 15% had ever tried all three products. More than one-half of current e-cigarette users (52%) also smoked cigarettes. Adjusting for covariates, current e-cigarette use was positively associated with cigarette smoking [Odds Ratio (OR) 27.32, 95% confidence interval (CI) 14.4-51.7] and smokeless tobacco use [OR 7.92, 95% CI 3.8-16.5]	E-cigarette use was more common among the high school students than cigarette and smokeless tobacco use, and a significant proportion of users either smoked cigarettes, used smokeless tobacco, or both. Thus, there is a critical need for preventive policies and programs to address dual and poly-use of these products.
Urman, McConnell et al 2018	We used two waves of data from the Southern Children's Health Study to examine prospectively (1) whether the e-cigarette social environment was associated with subsequent initiation of e-cigarettes and (2) whether ever use of e-cigarettes at baseline was associated with the development of a social environment more supportive of e-cigarette use at follow-up.	Participants with 3-4 friends using e-cigarettes at baseline (vs. no friends) had an odds ratio (OR) of 4.08 of subsequent initiation (95% confidence interval (CI): 1.96, 8.49); those with best friends who would have a very friendly (vs. unfriendly) reaction to e-cigarette use had OR 2.54 of initiation (95%CI: 1.57, 4.10); and those with someone in the home using e-cigarettes had OR 1.94 of initiation (95%CI: 1.19, 3.15). Participants who had ever used e-cigarettes at baseline developed a supportive social environment at follow-up (OR 2.06 of having any friends who used e-cigarettes (95%CI: 1.29, 3.30) and OR 2.33 of having friends who were friendly toward use (95%CI: 1.32, 4.11). Similar bidirectional associations were observed between ever cigarette use and a supportive cigarette social environment	The bidirectional relationship between a supportive e-cigarette social environment and ever use of e-cigarettes was similar to that previously observed between cigarette social environment and cigarette use.
Wong, Fan 2018	This study sought to determine e-cigarette use prevalence and its relation	9.1% ever-use of e-cigarettes	Our study has shown that e-cigarette use varies by sex and ethnic groups, is particularly high in White boys and Asian girls, and is

Study reference	Purpose	Results	Author conclusion
	to alcohol use as a potential gateway drug, and how this may differ by sex and ethnicity in a multi-ethnic sample of California adolescents.	e-cigarette use highest in boys among non-Hispanic Whites (15.1%) and in Asian girls (13.3%). The logistic regression odds of alcohol use, adjusted for age, ethnicity, body mass index, cigarette smoking status, socioeconomic status, parents' education level, and insurance status among e-cigarettes users (compared with non-users) was 9.2 in girls and 3.1 in boys (both $p<0.01$). Asians/others, non-Hispanic whites and Hispanics were similarly at increased odds: 17.8, 5.4, and 3.0, respectively ($p<0.01$ for Asians/others and for whites) of using alcohol compared with their non-e-cigarette using counterparts, respectively.	closely related to alcohol use, especially among females, Caucasians, and Asians/others.

Table 36: Characteristics of studies that were US non-national adults

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Agarwal, Loukas, Perry	To examine the role of the social environment, normative beliefs, and attitudes in predicting subsequent ENDS initiation across a 1-year period among 18- to 29-year-old college students.	Marketing and Promotions across Colleges in Texas Project (Project M-PACT)	Texas, US	Nov 2014 to Mar 2015	2,110 of a 5482 cohort for longitudinal study where data are collected every 6mo Mean age: 20.27 (2.17) 34% male	E-mail invitations were sent that described the purpose of the study and included a link to an eligibility survey.	Not clearly reported	ENDS use: reported use, peer use, household use, social acceptability, inclination to date END user, demographics
Amato, Boyle, Levy	Investigated the predictive validity of ENDS use frequency as a measure for likelihood of continued use, and cigarette smoking abstinence.	Recontacted people from 2014 Minnesota Adult Tobacco Survey 1171 consented to recontact	Minnesota, US	2015	601 18–24 4% (n=24) 25–44 32% (n=193) 45–64 47% (n=285) 65 or older 16% (n=99) 49% male	Recruitment: dual-frame random digit dialling sampling procedure	Telephone surveys	ENDS use; cigarette smoking
Bandiera, Loukas, Li et al	The main objective of the current study was to establish a potential bi-directional relationship between e-cigarette use and elevated depressive symptoms among college students in Texas, across a 1 year period of time.	Marketing and Promotions Across Colleges in Texas Project (Project M-PACT)??? Not actually specified but very similar methods	Texas, US	Nov 2014 – Feb 2015	5,445 Mean ages: Wave 1 20.5(2.4); Wave 2 20.4 (2.3); Wave 3 20.5 (2.3) % male: Wave 1 36.2%; Wave 2 35.6%; Wave 3 35.5%	Participants were recruited from 24 colleges in Texas.	Online	Demographics Current tobacco use (four types) Current e-cigarette use Depressive symptoms (CES-D)
Case, Loukas, Harrell et al	To examine the associations between sensation seeking and ever and current e-cigarette use in Texas young adults (18–29 years old).	Marketing and Promotions across Colleges in Texas Project (Project M-PACT)	Texas, US	2014/2015	n=5,418 Mean age: 20.5(2.36) 46% male	Recruited from colleges and vocational/technical programs in Texas via e-mail, and student consent was obtained online prior to study enrolment.	NR	Ever use e-cigarettes Current use e-cigarettes Brief Sensation Seeking Scale 4 (BSSS-4) Demographics Cig use Alcohol use Impulsivity (Substance Use Risk Profile Scale)
Creamer, Loukas, Clendennen et al	The purpose of this study is to examine differences between current and non-current cigarette users, focusing on	Marketing and Promotions Across Colleges in Texas	Texas, US	2014/2015	4,296 (Wave 1)	The 24 colleges were recruited from five counties	Email invitation to online survey	Current use e-cigarettes Other non-cigarettes

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	sociodemographic factors, non-cigarette tobacco product use, parental and friend use, and alcohol and marijuana use; and to identify predictors of cigarette use at six-month follow-up.	Project (Project M-PACT)			Mean ages: 20.3(2.2) non-current cigarette user; 21.2(2.8) current cig user % male: 33.6% non-current cigarette user (denominator n3547); 45.6% current user (denominator n749)	that included the four largest metropolitan areas in Texas.		tobacco product use Drug and alcohol use Parental and peer variables Demographics
Kalkhoran, Alvarado, Vijayaraghavan et al	Identify how and why smokers in primary care use e-cigarettes.	Sample based on a smoking cessation program delivered through primary care	California, US	2014-2015	788 Mean ages: 53.8(10.3) (Never use e-cigarette); 48.4(11.2) (Ever use e-cigarette) % male: 63% (Never use e-cigarette); 64% (Ever use e-cigarette)	Cross-sectional secondary data analysis from a randomized controlled trial of a tablet intervention to deliver the 5As for smoking cessation in primary care.	Computer tablet prior to appointment. Then 72h later phone or in-person interview	Demographics type of health insurance smoking habits readiness to quit smoking habits and e-cigarette use, e-health records
Kalkhoran, Yuan, Alvarado, Satterfield	We aimed to identify how and why smokers in primary care use e-cigarettes.	Sample based on a smoking cessation program delivered through primary care	California, US	NR	718	Cross-sectional secondary data analysis from a randomized controlled trial of a tablet intervention to deliver the 5As for smoking cessation in primary care.	NR	
Mendy, Vargas, Cannon-Smith et al	To identify differences and associations in e-cigarette use by sociodemographic characteristics and describe the reported reasons for initiating use among Mississippi adults.	Mississippi Behavioural Risk Factor Surveillance System	Mississippi, US	2015	6,035 Mean age: 46.8 48% male	State-based, random-digit-dialled telephone survey	BRFSS data included both landline and cell phone surveys	E-cigarette use, frequency and reasons for trying Demographics
O'Gara, Sharma, Boyle, Taylor	This study examines patterns of exclusive cigarette and polyuse among adult smokers in Minnesota.	Minnesota Adult Tobacco Survey (MATS)	Minnesota, US	1999-2014	1999 n=5,968 2003 n=8,782 2007 n=12,580 2010 n=7,057 2014 n=9,304	Random digit dealing sample method for landlines and (starting in 2010) cell telephones	Telephone interviews	Demographics Current use cigarette, e-cigarette. Use of other tobacco products e-cigarette only added in 2010 Smoking dependence Recent quit attempts Smoking intensity

Table 37: Results of studies that were US non-national adults

Study reference	Purpose	Results	Author conclusion
Agarwal, Loukas, Perry	To examine the role of the social environment, normative beliefs, and attitudes in predicting subsequent ENDS initiation across a 1-year period among 18- to 29-year-old college students.	2,110 never users at baseline. By Y1, 15.6% initiated use of ENDS, 10% at Wave 2, 6% at Wave 3. 329 initiators, and 27% did not use tobacco products at baseline. Males and Hispanics more likely to initiate by Wave 3. Asians less likely. Age and number of other tobacco products ever used predicted initiation of ENDS use. Peer ENDS use and inclination to date someone who uses ENDS predicted increased odds of initiating ENDS	Tobacco prevention programs on college campuses should include ENDS as part of comprehensive tobacco control efforts to prevent the use of all types of tobacco products
Amato, Boyle, Levy	Investigated the predictive validity of ENDS use frequency as a measure for likelihood of continued use, and cigarette smoking abstinence.	Daily use of ENDSs at T1 was closely associated with past 30-day use at T2 across smokers and former smokers, while infrequent use at T1 was associated with not using at T2. Intermediate use was not significantly predictive; however, the numerical pattern was similar to infrequent use.	For adult population surveillance surveys, defining current use prevalence as 'any use in the past 30 days' includes many individuals who can be expected to discontinue use within 1 year. Until measures of ENDS use become standardised, researchers should choose definitions carefully because different definitions are likely to yield different results.
Bandiera, Loukas, Li et al	The main objective of the current study was to establish a potential bi-directional relationship between e-cigarette use and elevated depressive symptoms among college students in Texas, across a 1 year period of time.	Elevated depressive symptoms predicted e-cigarette use 6 months later among a young adult college population, even after controlling for a variety of socio-demographics and number of tobacco products used. No evidence that e-cigarette use predicted elevated depressive symptoms. Despite the high levels of stability across time of depressive symptoms and e-cigarette use (betas>0.70), depressive symptoms were robust predictors of subsequent e-cigarette use 6 months later	This study established a temporal relationship, such that elevated depressive symptoms predicted e-cigarette use 6 months later among college students.
Case, Loukas, Harrell et al	To examine the associations between sensation seeking and ever and current e-cigarette use in Texas young adults (18–29 years old).	A higher proportion of ever users were men, current cigarette smokers, and current alcohol users, as compared to never e-cigarette users. The crude OR indicates that young adults with higher mean sensation seeking scores had significantly higher odds of current e-cigarette use as compared to low sensation seekers (OR = 1.86, 95% CI = 1.66, 2.08, results not shown in the table). The association remained significant after controlling for sex, race/ethnicity, age, college type, parental education, current cigarette use, current alcohol use, and mean impulsivity score (AOR = 1.38, 95% CI = 1.22, 1.57).	Sensation seeking is an important factor in identifying college students who may be at increased risk for e-cigarette use behaviours.
Creamer, Loukas, Clendennen et al	The purpose of this study is to examine differences between current and non-current cigarette users, focusing on sociodemographic factors, non-cigarette tobacco product use, parental and friend use, and alcohol and marijuana use; and to identify predictors of	Among current cigarette smokers at follow-up, use of tobacco products at baseline was common: 73% were current cigarette smokers, 41% were current e-cigarette users, 35% were current hookah users, and 22% were current cigar smokers and 8% were smokeless tobacco users.	Prevention programs that target multiple tobacco products are needed in colleges, as it appears that non-cigarette tobacco use and other high risk behaviours are independent risk factors for continued cigarette use in young adults

Study reference	Purpose	Results	Author conclusion
	cigarette use at six-month follow-up.		
Kalkhoran, Alvarado, Vijayaraghavan et al	Identify how and why smokers in primary care use e-cigarettes.	Fifty-two percent (n=408) of patients reported ever using an e-cigarette, and 20% (n=154) reported past-30-day use. Ever e-cigarette use was associated with younger age and negatively associated with being seen at practices at a public safety-net hospital compared to a practice at University-affiliated hospital. The most common reason for having used e-cigarettes among ever e-cigarette users, and for interest in future use of e-cigarettes among never e-cigarette users, was to cut down cigarette use. The mean number of days of e-cigarette use in the past 30 increased with duration of e-cigarette use. Most current e-cigarette users did not know the nicotine content of their e-cigarettes.	Over half of smokers in primary care have ever used e-cigarettes, and one-fifth are currently using them. Most reported using e-cigarettes to cut down or quit cigarettes.
Kalkhoran, Yuan, Alvarado, Satterfield	We aimed to identify how and why smokers in primary care use e-cigarettes.	57% (n=408) of patients reported ever using an e-cigarette and 21% (n=154) reported past 30 day use. Ever e-cigarette users were more likely to be younger, white, more educated, daily smokers, have smoked for more years, and more nicotine dependent than never users. Ever e-cigarette users had higher prevalence of mental illness than never users. The most and second most common reasons for e-cigarette use among current and former e-cigarette users were to cut down on and quit cigarette smoking, respectively. These were also the most common reasons never e-cigarette users reported for why they would use e-cigarettes.	Over half of smokers in primary care use e-cigarettes, with 1 in 5 reporting current use. E-cigarette use is intermittent in this population, with most reporting non-daily use. Most patients report using e-cigarettes to cut down or quit cigarettes.
Mendy, Vargas, Cannon-Smith et al	We identify differences and associations in e-cigarette use by sociodemographic characteristics and describe the reported reasons for initiating use among Mississippi adults.	4.7% of Mississippi adults currently used e-cigarettes, while 20.5% had ever tried an e-cigarette. The prevalence of current e-cigarette use was significantly higher for young adults, whites, men, individuals unable to work, those with income $35,000-$49,999, and current smokers compared to their counterparts. Similar results were observed for having ever tried an e-cigarette. E-cigarette use was associated with age, race, income, and smoking status. Most (71.2%) of current e-cigarette users and over half (52.1%) of those who have ever tried e-cigarettes reported that a main reason for trying or using e-cigarettes was "to cut down or quit smoking."	These findings highlight the need for e-cigarette policies and community interventions addressing the initiation of e-cigarette use among at-risk subgroups in Mississippi.
O'Gara, Sharma, Boyle, Taylor	This study examines patterns of exclusive cigarette and polyuse among adult smokers in Minnesota.	Use of ENDS in combination with cigarettes increased from 3.6% in 2010 to 27.3% in 2014. The most common combination of products in 2014 was combustible cigarettes and electronic nicotine delivery systems (ENDS), a combination that increased significantly between 2010 and 2014.	In this state-based survey, the number of people using multiple tobacco products remains modest but nearly doubled from 1999 to 2014.

Table 38: Characteristics of studies that were US investigator developed

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Abadi, Couch, Chaffee, Walsh	To assess electronic cigarette (e-cigarette) use, factors associated with use, and exposure to e-cigarette-related information from health professionals in a sample of college students attending a public university in northern California, using a web-based survey.	Investigator developed 18-item survey, developed in part by study investigators	San Francisco Bay, US	NR	N=91 College students Ages: 18-21 (33%) 22-24 (12%) 25 and over (10%) 22% male	Through faculty members in three university courses	Link provided in a recruitment letter Online vis Qualtrics Total 18 items, piloted with 10 students	E-cigarette awareness; e-cigarette use; perceptions of harm, addiction, risk, social acceptability for tobacco and e-cigarettes; previous use of healthcare counselling; demographics
Ashford, Rayens, Wiggins et al.	The study examined the relationship between exposure to e-cigarette advertising and e-cigarette use by pregnancy status, including use of flavoured e-cigarette products, among women of childbearing age.	Investigator developed	Kentucky, US	July 2014 to April 2015	n=194 51.5% pregnant Mean age: 29.56(6.71) 0% male	Pregnant women were recruited from two university- affiliated prenatal clinics and non-pregnant women of childbearing age were recruited from one women's health clinic; clinics were located in Central and Eastern Kentucky	Nearly, three- fourths of participants completed the survey via an iPad; the remainder completed a paper form and their responses were entered into the database. $10 gift card	Demographics Exposure to e-cigarette advertising (NIDA 2014 PATH survey 10 items) Cig use past 30 days Ever use e-cigarette Use flavoured e-cigarette
Bauhoff, Montero, Scharf	To examine how smoking status impacts adult perceptions and expectations of e-cigarettes.	Investigator developed	US national	March, 2014	796 Ages: 18-24 18%; 25-34 40%; 35-44 19%; 45-54 14%; 55-64 9% 52% male	Mechanical Turk (MTurk), a "crowdsourcing" platform for participants on a US-based computer	Clicked on a link for a "Social Science Study" and provided informed consent. 35 items	Demographics Cigarette smoking status and history e-cigarette status and history First to learn of e-cigarette Intention to use e-cigarette Reasons for trying/not e-cigarette Perceptions of e-cigarette
Bold, Kong, Cavallo et al.	This study aimed to examine whether items adapted for e-cigarette susceptibility predicted subsequent	Investigator developed	US	Fall 2013, Spring 2014	Wave 1 1,720 e-cigarette users: adolescents Mean age: 14.4(1.9) (matched)	Parents contacted through schools	Teachers administered, pencil and paper	e-cigarette susceptibility e-cigarette use Other substance use

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	e-cigarette use among never e-cigarette users.				Wave 1 46.1% male			
Bold, Morean, Kong et al	The current study examined whether an early age of onset of e-cigarette use mediates the association between impulsivity and e-cigarette frequency.	Investigator developed Two versions - one with impulsivity	Connecticut, US	Spring 2015	927 e-cigarette users (valid data) Original survey of 7045 3474 got the impulsivity survey: adolescents Mean age: 16.2(1.2) 63% male	7 of 9 district reference groups	Pencil and paper during homeroom periods at school	Demographics Impulsivity (Barratts) e-cigarette use e-cigarette use with peers Other tobacco use
Bold, Sussman, O'Malley et al	The Tobacco Center for Regulatory Science (TCORS) Measurement Workgroup was convened to consider aspects to include in a measure of e-cigarette dependence.	NA - Expert discussion	US	Jun-15	6 experts conducted a literature review; 10 external experts reviewed a list of constructs	NR	Search of Google Scholar, provision of written feedback	List of items provided to reviewers
Brikmanis, Petersen, Doran	The purpose of the present study was to prospectively investigate perceptions of e-cigarettes, cigarette smoking intentions, and their associations with e-cigarette use over time.	Investigator developed (longitudinal)	California, US	2015	348 Mean age: 20.5(1.8) 57% male	Facebook posts and referral for intermittent smokers	Online using Survey Monkey. $25+ up to $40 for completion	Demographics cigarette and e-cigarette use Use of e-cigarette to circumvent smoking bans harmfulness of e-cigarettes e-cigarette expectancies Intention to quit smoking Intention to maintain or increase smoking
Camenga, Kong, Cavallo et al	This exploratory study examines the prevalence and predictors of current and former smokers' use of electronic (e-) cigarettes for smoking cessation among a sample of adolescent and young adult established smokers.	Investigator developed	Connecticut, US	2013/2014	middle school n1166; high school n3614; college n625 Data analysis on 189 established smokers with ever use of e-cigarettes; adolescents Mean age: 18.3(2.8) 49% male	School selection based on district reference groups	Teacher distributed paper surveys. College students online.	Cigarette smoking status Ever use e-cigarette e-cigarette frequency Use of e-cigarette to quit smoking Flavour preferences Risk perceptions

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Carroll, Wagener, Thompson	The objective of this small-scaled study was to examine use behaviours and dependence among exclusive ENDS users and dual users of American Indian descent.	Investigator developed	Oklahoma, US	2016	ENDS users n27 Dual users n28 cig users n27 Median age: 41.5 38% male	Posting ads online, staff attending cultural events	Described elsewhere	Hooked on Nicotine Checklist CO_2 measures
Cheney, Gowin, Clawson	The Ecological Model was used to examine the social and environmental influences of the college environment on e-cigarette use (vaping) among college students.	NA - Interviews	Southwest US	2015-2016	33 College students Mean age: 20.4 66% male	Posters placed on campus	Conducted by 2 interviewers based on interview guide, then transcribed	Coded interviews
Chin, Lustik, Pflipsen	The primary outcome of this study was to define the prevalence of ESD use in a US Army division.	Investigator developed	HI, US (?)	2015	1,288 military service members Median age: 26 86% male	Using a randomizer on www. random.org, we randomly selected 20 of 108 companies from the 25th Infantry Division to participate in the study. Each company had 40–100 service members.	Administered by a member of the research team	ESD use ESD opinions Demographics
Copeland, Peltier, Waldo	The present study sought to develop the Risks and Benefits of E-cigarettes (RABE) questionnaire to assess the perceptions about e-cigarette use among college students.	Investigator developed - RABE survey	Southern US	NR	734 Psychology undergrads Mean age: 20.07(1.97) 22% male	Recruited from Department of Psychology research pool at college	Online	Demographics Smoking status Risks and benefits of e-cigarette (RABE)
De Genna, Ylioja, Schulze et al	The objectives of this study were to examine the prevalence of electronic cigarette use among counselled tobacco users admitted to 2 academic hospitals.	NA - observational data	Pennsylvania, US	2015	2,194 Mean age: 50.2(14.2) 64% male	Those admitted to one of 2 hospitals in 2015 24% identified as smokers	tobacco counsellors recorded after interview/counselling	Ever use e-cigarette Reasons for use (categorical) Cigarette history Demographics
Fite, Cushing, Poquiz, Frazer	The goal of the current study was to better understand family influences (i.e., perceptions of parental attitudes and sibling use) of e-cigarette use and determine how these influences on e-cigarette use compared to their influence on other substances (i.e., alcohol,	Investigator developed	Midwest, US	NR	279 Adolescents Mean age: 15.59(1.20) 50% male	Consent forms send home with parents	Administered in school vis computer using an online link Firewall blocked and 54.8% had to complete via paper	Demographics Lifetime substance use Parental approval of substance use Sibling use of substances

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
						traditional tobacco, and marijuana).		
Franks, Hawkes, McCain, Payakachat	Our study evaluated the electronic cigarette (e-cigarette) use, knowledge, and perceptions of health professional students enrolled in one of five colleges at a single academic health centre.	Investigator developed	Arkansas, US	2014	853 College students Ages: 38.7% 21-24 years; 25.0% 25-29 years 26% male	All students currently enrolled in a health professional degree or certificate program in one of five colleges within a single US academic health centre	Online survey (Survey Monkey) Chance to win iPod shuffle	History of tobacco smoking Knowledge (e-cigarette) Perception of smoking cessation, harm reduction and enhanced regulation Demographics
Hall, Austin, Do et al	The purpose of this study was to assess the prevalence and correlates of e-cigarette use in a select population of active duty U.S. Naval personnel.	Investigator developed	Virginia, US	2015-2016	977 Ages: 62.5% older than 25 85% male	US Navy personnel undertaking a health assessment at a specific department	Survey attached to other paperwork	Ever-use of e-cigarette Use of e-cigarette Demographics
Hershberger, Connors, Um, Cyders	The current paper applied the theory of planned behaviour to understand how impulsive personality traits and attitudes concerning e-cigarette use relate to the likelihood of electronic cigarette (e-cigarette) use.	Investigator developed	US national	NR	714 Mean age: 34.01(10.89) 51% male	Amazon's Mechanical Turk (MTurk)	Survey Monkey	Demographics e-cigarette use Impulse related personality traits Comparing E-cigarettes and Cigarettes Questionnaire (CEAC)
Johnson, Mays, Hawkins et al	This study examined youths' perceptions of electronic cigarettes ("e-cigarettes"), sources of e-cigarette exposure, and preferred sources of e-cigarette health information.	Investigator developed	Washington, US		25 Adolescents Mean age: 15(1.5) 44% male	Approached during a primary care visit to a specific clinic	In-depth interview over the telephone	Open and close ended questions regarding e-cigarettes
King, Reboussin, Spangler et al	Individuals with mental health conditions represent a priority population for tobacco control. This population smokes cigarettes at disproportionately higher rates than the general population, but less is known about the relationship between non-cigarette tobacco use and mental health status.	Investigator developed 10-item survey	North Carolina and Virginia, US	2013 (wave 6)	2370 College students Mean age: 21.1(0.4) 36% male	Students in 11 colleges 10,528 invited to complete screener. Surveyed twice a year since 2011. $40 gift card	Online	Mental Health diagnosis (Self-reported) Stress (PSS) Depression (CED-S) Tobacco use (including e-cigarette) Demographics

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Lee, Lin, Seo, Lohrmann	This study investigated characteristics of potential and current e-cigarette users based on four different levels of use acceptability along with the determinants that promote e-cigarette use acceptability among college students.	Investigator developed	US	2015	1,198 College students Mean age: 19.9(1.54) 33% male	Instructors of undergraduate-level general education courses were first contacted via email for permission to either administer paper-and-pencil surveys in class or provide a survey link to an online version of the questionnaire.	Self-administered pencil and paper	Ever use e-cigarette Intention to use e-cigarettes Current e-cigarette use e-cigarette use acceptability Perceived advantages of e-cigarette Compatibility of e-cigarette with preferences Exposure to e-cigarette advertisement Substance use Demographics
Lee, Nonnemaker, Bradfield et al	In this study, we compare e-cigarette topographies of established cigarette smokers and non-established cigarette smokers.	NA - observational data	New York, US	2015	20 College students Ages: 18-25 95% male	Subjects were recruited using posters placed on the Rochester Institute of Technology campus and paid $200 for participating in the study	Observational plus online surveys	Puffing topography was measured with a wireless personal use monitor (wPUM) Puff, session, daily pattern Cig smoking Craving to use e-cigarette Use of e-cigarette
Morean, L'Insalata	The primary study aim was to examine whether rates of using e-cigarettes ("vaping") to lose weight are elevated among American adults who self-report having an eating disorder (ED).	Investigator developed	US national	2016	611 433 no ED; 178 ED Ages: 35.98(11.71) no ED 33.26(8.35) ED % male: 45.3% no ED; 27.5% ED	Participants were recruited through Qualtrics Online Research Panels	Online	Vaping frequency ED status Demographics ED symptoms Cigarette smoking status e-liquid nicotine content SF Vaping consequences questionnaire Vaping motives
Morean, Wedel	The current study evaluated whether a subset of adult e-cigarette users reported vaping to lose or control their	Investigator developed	US national	2015	459 Mean age: 34.42(9.69)	Amazon Mechanical Turk (i.e.,Mturk)	Online	Demographics Cig smoking status Vaping to lose weight Frequency of vaping

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	weight and examined potential predictors of vaping for weight management.				51% male			Nicotine content of e-cigarette Flavour preferences Weight perceptions Weight control strategies Binge eating Impulse control/self-discipline
Oncken, Ricci et al 2017	To investigate reasons for e-cigarette use by women of reproductive age.	Investigator developed	US	Oct 2012-March 2016	55 Mean age: 27.7 0% male	From prenatal clinics or referred from private practitioners	Pen and paper, face-to-face	Use of electronic cigarettes, previous use of treatments for smoking cessation; Fagerstrom Test for Cigarette Dependence; depression; Smoking Cessation Self-Efficacy Questionnaire.
Pepper, Farrelly, Watson 2018	We explored adolescents' use of nicotine-free e-cigarettes and understanding of chemicals in e-cigarettes, including nicotine.	Investigator developed	US	2016	1589 e-cigarette users, 15-17 years, 53.3% male (use without nicotine, 60.7% male (use with nicotine)	Social media (Facebook and Instagram)	Online. Survey was piloted prior to launch.	E-cigarette use with/out nicotine e-cigarette device Cigarette use Vaping use Demographics
Sussan TE, Shahzad FG et al 2017 (2 of the Sussan papers were corrections)	To determine demographics, behaviours, perceptions and motivations underlying the use of e-cigarettes.	Investigator developed	US	Dec 2014 - July 2015	320 Half population younger than 35 yrs 78% male	Survey conducted in 3 vaping stores or online	Pen and paper	Demographics; tobacco use; e-cigarette use; motivations for use
Temple, Shorey et al 2017	To examine associations between e-cigarette use and other substances and identified motives for e-cigarette use among young adults.	Investigator developed (longitudinal)	Texas, US	2010	1042 Adolescents Mean age: 20.3 ±.79 44% male	From mandated classes in 7 public high schools; $30 gift voucher	NR "45 min survey"	E-cigarette use in past year, other drugs use; motivations for using e-cigarettes
Vogel, Ramo, Rubinstein 2018	This study identifies correlates of e-cigarette use frequency and	Investigator developed	San Francisco, US	Not reported	173 e-cigarette users, 16.6(SE1.2) years, 75.1% male	Adolescents (age 13–18) who reported having used an e-cigarette product at	In-person	Frequency of e-cigarette use

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	dependence among adolescent users.					least once in the past 30 days and at least 10 times in their lives recruited through online advertising and posters		Dependence on e-cigarettes Demographics e-cigarette use history current e-cigarette and cig use
Westling E, Rusby J et al 2017	To examine the use of electronic cigarettes (e-cigarettes) among adolescents over time, including correlates of lifetime use by eighth grade and trajectories of current use across ninth grade.	Investigator developed	Oregon, US	2014-16	1091 Adolescents Mean age: 14.4±0.5 47% male	Via schools - selected based on serving above Ave numbers of free lunches (proxy for lower income households)	Online; project staff administered the surveys during regular classes	demographics; lifetime and current substance use

Table 39: Results of studies that were US investigator developed

Study reference	Purpose	Results	Author conclusion
Abadi, Couch, Chaffee, Walsh	To assess electronic cigarette (e-cigarette) use, factors associated with use, and exposure to e-cigarette-related information from health professionals in a sample of college students attending a public university in northern California, using a web-based survey.	Use: Ever user (45%); Current user (9%); Never (41%); Missing (5%) Top reasons for use: Sampling flavours with friends (16%), enjoy watching the vapour (15%), calming effect (9%). Concentration don't know (43%)/missing(33%), 0-6mg (14%), 7-18mg (3%). Flavours: fruit (25%), Mint (13%), Candy (12%), Tobacco (5%), Dessert (5%), Coffee or Cola (4%). Perceived harmfulness of smoking products (extreme ratings reported as %): cigarettes (87%), cigars (89%), smokeless tobacco (75%), Hookah (42%), e-cigarette (47%), marijuana (24%) Sig differences for risks: Bad breath, feel jittery/nervous, get mouth sores, friends will be upset, you will get into trouble. Sig differences for benefits: none, look cool (p=0.07)	Our findings demonstrate a high prevalence of e-cigarette use and experimentation among college students in our sample population. Participants' perceptions related to reduced harm of e-cigarettes may influence their willingness to use such products.
Ashford, Rayens, Wiggins et al.	The study examined the relationship between exposure to e-cigarette advertising and e-cigarette use by pregnancy status, including use of flavoured e-cigarette products, among women of childbearing age.	96.4% ever use of cig; 64.9% ever use e-cigarettes Sig predictor of ever use for e-cigarette were age (young), being white, and media exposure to e-cigarettes Age (younger) only predictor of use of flavoured e-cigarettes	There is a link between advertising exposure and ever use of e- cigarettes, though surprisingly, pregnancy status is not significantly associated with ever use. Use of flavoured e- cigarettes is associated with increased exposure to advertising on social media
Bauhoff, Montero, Scharf	To examine how smoking status impacts adult perceptions and expectations of e-cigarettes.	72% (n=572) of all participants had never tried e-cigarettes. Among those who had tried e-cigarettes, 47% were current smokers 13% of the total sample identified themselves as current e-cigarette users; 15% identified as former e-cigarette users. Participants reported learning about e-cigarettes primarily through internet sources (55%), conversations (53%), TV advertisements (41%), and retail POS locations (30%). Ever smokers were more likely than never smokers to have learned about e-cigarettes from POS locations (37% versus 24%) but less likely to have heard about e-cigarettes on TV (36% versus 45%). Current smokers were more likely than former smokers to have learned about e-cigarettes through in-person conversations (61% versus 48%), from POS locations (42% versus 30%), and through social media (18% versus 9%). Perceptions: e-cigarettes can help smokers quit smoking (58%) and that they are less harmful than conventional cigarettes (64%). Participants were unlikely, however, to believe that they are less addictive than conventional cigarettes (27%). Top reasons for e-cigarette use: to quit or reduce smoking (58%), curiosity/novelty (19%), because e-cigarettes are cleaner/ less smelly or offensive than cigarettes (19%). Current smokers' top reasons for not trying e-cigarettes included safety and health (38%), expense (26%), less satisfaction or enjoyment than from cigarettes (18%), and addictive potential (12%).	Never, former, and current smokers have different reasons for wanting to try or avoid e-cigarettes, and public health messages about e-cigarettes may need to be tailored separately for these groups
Bold, Kong, Cavallo et al.	This study aimed to examine whether items adapted for e-cigarette susceptibility predicted subsequent e-cigarette use among never e-cigarette users.	Comparing demographics between susceptible (n=489) and non-susceptible (n=1231) youth indicated susceptible youth are slightly older (14.7 ± 1.8 vs. 14.5 ± 2.0 non-susceptible, p=0.02), more likely to be male (51.9 vs. 43.8% non-susceptible, p=0.002) and report ever use of other tobacco products (8.2 vs. 1.9% non-susceptible, p<0.001), alcohol (24.7 vs. 10.0% non-susceptible, p<0.001), and marijuana (5.1 vs. 1.5% non-susceptible, p<0.001). Susceptibility did not differ by race or school SES. Six months later, 8.9% (n=153) of youth initiated e-cigarettes and 3.7% (n=63) reported past 30-day use of e-cigarettes. By comparison, 3.1% (n=53) of youth initiated conventional cigarettes	These findings provide initial support for adapting two susceptibility items to identify adolescents at risk for future e-cigarette use. The robust relationship between e-cigarette susceptibility and future use suggests these items can predict which adolescents are at risk for trying e-cigarettes in the future

Study reference	Purpose	Results	Author conclusion
		and 0.9% (n=16) reported past 30-day use of cigarettes 6 months later The results indicated that e-cigarette susceptibility was a significant independent predictor of future initiation and past 30-day use of e-cigarettes	
Bold, Morean, Kong et al	The current study examined whether an early age of onset of e-cigarette use mediates the association between impulsivity and e-cigarette frequency.	Ever use e-cigarette 26.8% of 3474 results indicate that youth e-cigarette users who had greater impaired self-regulation and behavioural impulsivity were more likely to try e-cigarettes at an earlier age, and that earlier initiation was associated with using e-cigarettes on more days in the past month.	Adolescents who endorse aspects of impulsivity, such as acting without thinking, are at greater risk for more frequent e-cigarette use through an early age of e-cigarette initiation.
Bold, Sussman, O'Malley et al	The Tobacco Center for Regulatory Science (TCORS) Measurement Workgroup was convened to consider aspects to include in a measure of e-cigarette dependence.	Constructs to consider: Quantity and frequency of use; tolerance; perceived benefits; withdrawal symptoms; cravings/urges; use despite harm; impaired control; automaticity; preferred over competing rewards; sensory dependence	The purpose of this manuscript is to provide guidance on domains or constructs to consider when developing a measure of e-cigarette dependence
Brikmanis, Petersen, Doran	The purpose of the present study was to prospectively investigate perceptions of e-cigarettes, cigarette smoking intentions, and their associations with e-cigarette use over time.	Ever use e-cigarette 33%; 22% in last 9mo those who smoked cigarettes more frequently also used e-cigarettes more frequently. This association did not change over time. Student status was a significant predictor of e-cigarette use in all models except the expectancies and circumvention models (ds 0.13 to 0.11; zs 2.48 to 2.03; ps .05), indicating that students used e-cigarettes less frequently. No changes over time. Frequency of using e-cigarettes to circumvent smoking bans was also a significant predictor (d 0.24, z 4.08, p .001), such that those who reported doing so more often tended to use e-cigarettes more frequently. The model testing the effect of perceived harmfulness of e-cigarettes versus cigarettes yielded a significant main effect of perceived harmfulness (d 0.10, z 1.97, p .049), suggesting that those who perceived a greater safety advantage for e-cigarettes tended to use e-cigarettes more frequently. More positive baseline expectancies were associated with more frequent e-cigarette use at each assessment, but that the slope of the effect became more negative over time. Intentions to quit not related to e-cigarette use.	The combination of these findings suggests that, at least among nondaily smoking young adults, other factors may influence frequency of e-cigarette use more than harm reduction. Findings instead seem consistent with the hypothesis that e-cigarettes are more often used to complement ongoing cigarette smoking.
Camenga, Kong, Cavallo et al	This exploratory study examines the prevalence and predictors of current and former smokers' use of electronic (e-) cigarettes for smoking cessation among a sample of adolescent and young adult established smokers.	The prevalence of using e-cigarettes to quit smoking was 41.8% among this sample of youth with a history of established smoking. Older students, White race, higher e-cigarette frequency, and preference for "a combination of 2 or more flavours mixed together" predicted increased likelihood of using e-cigarettes to quit smoking.	Among young established smokers, more frequent e-cigarette use and preference for using flavours mixed together, but not perceptions of harmfulness of e-cigarettes or comparative safety of e-cigarettes compared with cigarettes or other smoking cessation medications or helpfulness of e-cigarettes in quitting smoking, are associated with using e-cigarettes for smoking cessation.
Carroll, Wagener, Thompson	The objective of this small-scaled study was to examine use behaviours and dependence among exclusive ENDS users and dual users of American Indian descent.	The vast majority of ENDS users (92.6%) reported being former cigarette smokers Comparing ENDS users with smokers, ENDS users had a lower severity of diminished autonomy (4 vs 8; P=0.0077). Comparing dual users with smokers, median severity of diminished autonomy over cigarettes did not differ (P=0.6865).	This study provides an in-depth description of ENDS use, including both exclusive use and dual use with cigarettes, among AIs.
Cheney, Gowin, Clawson	The Ecological Model was used to examine the social and environmental influences of the	College student vapers report multiple levels of influence on their vaping beyond personal beliefs and peer influences, including parents, explicit campus and community messaging, community	Parents, community members, campus policy, and the physical environment all influence where and when college students vape

Study reference	Purpose	Results	Author conclusion
	college environment on e-cigarette use (vaping) among college students.	member requests, and respect for others. College student vapers also describe constant associations with smokers in allowable public places to vape.	
Chin, Lustik, Pflipsen	The primary outcome of this study was to define the prevalence of ESD use in a US Army division.	Electronic smoking device use 20%; ever use 61% Lower education, current smokers, ex-smokers most likely to use	There is a high prevalence of current and ever use ESD among active duty service members assigned to a US Army Infantry Division
Copeland, Peltier, Waldo	The present study sought to develop the Risks and Benefits of E-cigarettes (RABE) questionnaire to assess the perceptions about e-cigarette use among college students.	Benefits of e-cigarette use differed across smoking status: e-cigarette highest, then dual users, then smokers, then non-smokers No differences in risk	The present results indicate that the RABE is a reliable instrument to measure college student's perceived risks and benefits of e-cigarettes.
De Genna, Ylioja, Schulze et al	The objectives of this study were to examine the prevalence of electronic cigarette use among counselled tobacco users admitted to 2 academic hospitals.	22% had used an e-cigarette Most of these patients used electronic cigarettes to quit or reduce use of combustible cigarettes. Adjusted odds of electronic cigarette use were higher for females (adjusted odds ratio [AOR] 0.60 for male patients, 95% confidence interval [CI] 0.47-0.76), younger patients (AOR 0.98 for older patients, 95% CI 0.97-0.99), and individuals who initiated tobacco use earlier in life (AOR 0.97 for later smoking initiation, 95% CI 0.95-0.99). 52% of smokers had tried e-cigarette to quit; 23% used to cut down smoking cigs	Young, female patients are most likely to use electronic cigarettes and may benefit most from directed discussions about electronic cigarette use and Federal Drug Administration-approved cessation methods during smoking cessation counselling.
Fite, Cushing, Poquiz, Frazer	The goal of the current study was to better understand family influences (i.e., perceptions of parental attitudes and sibling use) of e-cigarette use and determine how these influences on e-cigarette use compared to their influence on other substances (i.e., alcohol, traditional tobacco, and marijuana).	E-cigarette ever use 19.25% Parental attitudes, sibling substance use and age (younger?) predicted e-cigarette use	Findings from the current study indicate the need to educate parents on the dangers of e-cigarette use and for the need for parents to convey their negative viewpoints of e-cigarette use to their children.
Franks, Hawkes, McCain, Payakachat	Our study evaluated the electronic cigarette (e-cigarette) use, knowledge, and perceptions of health professional students enrolled in one of five colleges at a single academic health centre.	99.2% awareness of e-cigarettes 24.2% ever use of these 23.1% used for smoking cessation Participants enrolled in the colleges of public health, pharmacy, and nursing had statistically higher knowledge scores than those from allied health programs. However, mean scores from each of these groups were below 75% correct, indicating substantial gaps in knowledge about e-cigarettes even among the most knowledgeable groups Perceptions relating to smoking cessation, harm reduction, and opposition to enhanced e-cigarette regulation were all associated with using e-cigarettes	Our study is the first to examine the use, knowledge, and perception of e-cigarettes among health professional students from a wide variety of disciplines. We found the highest estimate of e-cigarette use to date among health professional students, as well as notable across disciplines of health professional students. We also found that perceptions of using e-cigarettes as smoking cessation aids, a perceived reduction in harm compared to tobacco, and a preference for reduced e-cigarette regulation were all significantly associated with using e-cigarettes.
Hall, Austin, Do et al	The purpose of this study was to assess the prevalence and correlates of e-cigarette use in a select population of active duty U.S. Naval personnel.	Ever use e-cigarette 31.4% 9.3% current users e-cigarette Having a Bachelor degree and higher income protective against current use e-cig Trying cigarettes was associated with nearly 12 times the risk for trying e-cigarettes compared with those who never tried cigarettes	The findings of increased risk of e-cigarette use among those with lower income and less than a bachelor's degree suggest social determinants of health implications. This study sheds new light on e-cigarette use, characteristics of use, addiction

Study reference	Purpose	Results	Author conclusion
			implications, and highlights concerns for a growing health risk behaviour.
Hershberger, Connors, Um, Cyders	The current paper applied the theory of planned behaviour to understand how impulsive personality traits and attitudes concerning e-cigarette use relate to the likelihood of electronic cigarette (e-cig) use.	30.3% e-cigarette users (y/n). Urgency and deficits in conscientiousness were significantly related to e-cigarette attitudes (CFI=0.99, TLI=0.99, RMSEA=0.02; urgency: β=0.32, p=0.001; deficits in conscientiousness: β=−0.48, p<0.001). E-cigarette attitude scores were significantly higher for e-cigarette users than non-users, β=0.85, p<0.001.	Findings provide initial support for a model in which impulsive traits are related to e-cigarette use through positive e-cigarette attitudes
Johnson, Mays, Hawkins et al	This study examined youths' perceptions of electronic cigarettes ("e-cigarettes"), sources of e-cigarette exposure, and preferred sources of e-cigarette health information.	Most participants (72%) perceived e-cigarettes as "healthier" than cigarettes and reported e-cigarette advertising exposure (80%) and interpersonal exposure (60%). Participants reported that advertisements portray e-cigarettes as less harmful than cigarettes and novel products. Most (72%) indicated their doctor was their preferred source of e-cigarette health information, suggesting paediatric health care providers are well-positioned to counsel patients to prevent e-cigarette use.	Our findings highlight important areas of research to better understand risk factors for youth e-cigarette use.
King, Reboussin, Spangler et al	Individuals with mental health conditions represent a priority population for tobacco control. This population smokes cigarettes at disproportionately higher rates than the general population, but less is known about the relationship between non-cigarette tobacco use and mental health status.	Total 30-day e-cigarette use 5.2% Stress and depression predicted e-cigarette use. Mental health diagnosis not related.	Findings in this study provide further evidence of a potential relationship between non-cigarette tobacco products and mental health status.
Lee, Lin, Seo, Lohrmann	This study investigated characteristics of potential and current e-cigarette users based on four different levels of use acceptability along with the determinants that promote e-cigarette use acceptability among college students.	Approximately 40% of the participants reported ever using e-cigarettes. E-cigarette adopters agreed that e-cigarettes are more socially acceptable than traditional tobacco cigarettes (relative risk ratio [RRR]=1.43, p<0.01). Unique features such as flavour appeared to encourage college students' experimentation with e-cigarettes (ps<0.05). Participants mentioned positive sensory experiences as a reason for e-cigarette use (ps<0.01) and reported caring about their appearance more than their health (ps<0.05) when asked about possible outcomes of e-cigarette use.	Study findings indicate a possible explosive increase in e-cigarette experimentation or use among college students. Unique features of e-cigarettes such as flavour and USB recharge-ability appear to be strong factors making e-cigarettes more acceptable and appealing to young adults regardless of their smoking status.
Lee, Nonnemaker, Bradfield et al	In this study, we compare e-cigarette topographies of established cigarette smokers and non-established cigarette smokers.	The non-established cigarette smokers reported nicotine levels of 17–24 mg and 4.4%, which were relatively high compared to what is typically available in the market. The established cigarette smokers reported a wider range of nicotine levels, including 3–24 mg as well as 0.6%–4.8% and one reported a level of "high." On average, established cigarette smokers in the sample used e-cigarettes for more sessions per day (5.3 s vs. 3.5 s, p=0.14), had longer sessions (566.3 s vs. 279.7 s, p=0.06), had more puffs per session (13.7 vs. 11.9, p=0.481), and had larger puff volume per session (1,509.3 mL vs. 651.7 mL, p<0.05).	A user's topography affects his or her exposure to HPHCs. As this study demonstrates, user characteristics, such as level of smoking, can influence topography.
Morean, L'Insalata	The primary study aim was to examine whether rates of using	Relative to individuals reporting no ED history, those reporting a current ED were significantly more likely to report vaping daily (OR 5 3.75), vaping for weight loss (OR 5 4.06), vaping because	Individuals who self-reported currently having an ED endorsed vaping motives that are consistent with eating pathology (e.g.,

Study reference	Purpose	Results	Author conclusion
	e-cigarettes ("vaping") to lose weight are elevated among American adults who self-report having an eating disorder (ED).	of the availability of sweet flavours (OR 5 1.79), vaping because it is easy to conceal/hide from others (OR 5 2.75), vaping because it is difficult to detect indoors (OR 5 1.63), and using nicotine e-liquid (OR 5 1.82 [and higher concentrations of nicotine e-liquid]), p values<.05	substance-induced weight loss, hiding compensatory behaviours from others). They also were more likely to vape daily and to use higher nicotine concentrations, raising health concerns.
Morean, Wedel	The current study evaluated whether a subset of adult e-cigarette users reported vaping to lose or control their weight and examined potential predictors of vaping for weight management.	13.5% of the analytic sample reported vaping to lose/control weight Participants who reported vaping to lose/control weight vaped more frequently (adjOR=1.15); were currently overweight (adjOR=2.80); reported engaging in calorie restriction (adjOR=2.23); reported poor impulse control (OR=0.59); and reported preferences for coffee (adjOR=2.92) and vanilla-flavoured e-liquid (adjOR=7.44)	A subset of adult e-cigarette users reported vaping for weight loss/control, raising concerns about expanded, scientifically unsubstantiated uses of e-cigarettes. Identifying where individuals obtain information about vaping for weight loss (e.g., e-cigarette ads, Internet) and whether weight-related motives promote e-cigarette initiation among e-cigarette naive individuals is important to informing regulatory efforts.
Oncken, Ricci et al 2017	To investigate reasons for e-cigarette use by women of reproductive age	53% percent (55/103) of participants had previously tried electronic cigarettes. Ever users smoked more cigarettes per day before pregnancy (p=0.049), had a greater number of previous quit attempts (p=0.033), and were more likely to identify as being Hispanic or non-Hispanic white than never users (p=0.027). Fifteen percent of participants (15/103) reported previous use of electronic cigarettes for smoking cessation, which was more common than the use of any specific FDA-approved smoking cessation medication. Fourteen percent of participants (14/103) reported electronic cigarette use during pregnancy, most commonly to quit smoking. A history of substance abuse (p=0.043) and more previous quit attempts (p=0.018) were associated with electronic cigarette use during pregnancy.	Shows that electronic cigarettes are used by women of reproductive age, including pregnant smokers. The implications of this finding are that there is an urgent need to examine the risks and benefits of electronic cigarette use, especially by pregnant women. The study also shows that electronic cigarettes are commonly used as a smoking cessation aid in women of reproductive age. The greater likelihood of electronic cigarette use compared to proven adjunctive smoking treatments suggests that electronic cigarettes should be examined as a potential aid to cessation in this population.
Pepper, Farrelly, Watson 2018	We explored adolescents' use of nicotine-free e-cigarettes and understanding of chemicals in e-cigarettes, including nicotine.	66.3% usually used e-cigarette with nicotine. Older adolescents less likely to usually use without nicotine. Hispanic youth were more likely than non-Hispanic white youth to usually use without nicotine. Current cigarette smokers, cigarillo or little cigar users, and OTP users were less likely to usually use without nicotine than non-users of those products. "Some day" users and 'rarely' users were more likely than 'every day' users to usually use without nicotine. Those endorsing the use of e-cigarettes with other people around and higher perceived health risks were less likely to usually use e-cigarettes without nicotine. Non-nicotine users were less likely to correctly answer the questions about the source of nicotine in e-liquid and whether firsthand e-cigarette aerosol is just water vapour	The adolescents who reported usually using e-cigarettes without nicotine had poorer knowledge of e-cigarettes.
Sussan TE, Shahzad FG et al 2017 (2 of the Sussan papers were corrections)	To determine demographics, behaviours, perceptions and motivations underlying the use of e-cigarettes.	The survey respondents were predominantly young, Caucasian males, 74% of whom identified themselves as former smokers, while 20% identified as current smokers and 6% were never smokers. Former smokers reported a longer history of e-cigarette use and higher nicotine concentrations than current smokers. For former and current smokers, the primary motivation for e-cigarette use was assistance to quit smoking, and nearly half indicated that they plan to reduce their nicotine concentration and eventually quit using e-cigarettes. Among former smokers, self-reports on use and measures of dependence were consistent with nicotine replacement as their primary motivation. The majority of former and current smokers also reported that their respiratory health had improved as a result of e-cigarette use, although this effect was stronger for former smokers. Never smokers reported less frequent e-cigarette use and dependence compared to former and current smokers. Their motivations for use were more commonly for enjoyment and popularity, and they displayed a reduced desire to eventually quit using e-cigarettes.	Never-smoking e-cigarette users are an emerging demographic with different motivations and perceptions than those of current and former smokers

Study reference	Purpose	Results	Author conclusion
Temple, Shorey et al 2017	To examine associations between e-cigarette use and other substances and identified motives for e-cigarette use among young adults.	Hispanic, White, and male young adults reported significantly greater past year e-cigarette use compared to their African American and female counterparts. Bivariate correlations showed that use of e-cigarettes was positively associated with use of combustible cigarettes, alcohol, marijuana, cocaine, amphetamines, inhalants, hallucinogens, ecstasy, and misuse of over-the-counter and prescription medications. E-cigarette users reported a higher prevalence of substance use relative to those who did not use e-cigarettes. The taste of e-cigarettes was identified as an important motive for use.	E-cigarettes appear to be a risk marker for the use of substances that are known to pose substantial health problems. Youth substance use prevention programs should target the reduction of e-cigarette use with particular attention to addressing their taste appeal.
Vogel, Ramo, Rubinstein 2018	This study identifies correlates of e-cigarette use frequency and dependence among adolescent users.	Significant bivariate correlates of frequency of use (p<0.10) were older age, SES , source of first e-cigarette, presence of nicotine in one's first e-cigarette, current use of nicotine in e-cigarettes, device type, having friends who use e-cigarettes, and recent cigarette smoking. Significant bivariate correlates of dependence were younger age of first use, source of first e-cigarette, presence of nicotine in one's first e-cigarette, current use of nicotine in e-cigarettes, source of first hearing about e-cigarettes, device type, having many friends who use e-cigarettes, and recent cigarette smoking.	When assessing problematic e-cigarette use among adolescents, it is important to consider social factors (e.g., friends' and family members' e-cigarette use), device type, and dual use with cigarettes.
Westling E, Rusby J et al 2017	To examine the use of electronic cigarettes (e-cigarettes) among adolescents over time, including correlates of lifetime use by eighth grade and trajectories of current use across ninth grade.	Overall, 27.7% of eighth graders had used e-cigarettes, and 16.8% were current e-cigarette users (used in the past 30 days); use did not significantly differ by gender or ethnicity. Correlates of e-cigarette lifetime use by eighth grade included lifetime and current use of marijuana, alcohol, cigarettes, and chewing tobacco. Five percent of students were "accelerators," on average using e-cigarettes 14 of the last 30 days in eighth grade, increasing to daily use (30/30 days) by the end of ninth grade. Across all substances, those in the accelerator group were more likely to have reported lifetime substance use by eighth grade and current substance use in ninth grade, compared to the "infrequent/no use" group	A sizeable proportion of young adolescents are using e-cigarettes, and e-cigarette use is highly correlated with use of other substances, including marijuana. Adolescents who progress to daily e-cigarette use in high school are more likely to use other substances compared to low or nonusers. E-cigarettes may be a relatively new addition to a constellation of substances being actively used by a segment of the youth population.

Table 40: Characteristics of studies of US LGBTI

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Buchting, Emory, Scout	This national study is the first to report on cigarettes, cigars, and e-cigarettes by examining differences in transgender tobacco use independent of sexual orientation.	Tobacco in a Changing Media Environment	US national	2013	168 transgender; 17,164 cisgender Age: Trans: 53.8% 45-64, Cisgender: 38.2% 45-64 % male: Trans 49.6%, Cisgender 48.0%	Administered by gfK Group online using research panel (75% or participants). Original panel recruited by random digit dialling	Online	Demographics Gender identity Tobacco use behaviours: Ever use cigarettes and e-cigarettes, cigars, mini cigars 30-day use
Coulter, Bersamin, Russell, Mair	We tested three competing models about whether gender- and sexuality-based harassment at school have non-independent, additive, or interactive effects on adolescents' electronic cigarette use (i.e., vaping), cigarette smoking, alcohol use, and heavy episodic drinking (HED).	California Healthy Kids Survey	California, US	2013-2014	316,766 students (adolescents) Grades 7, 9, 11 % cismales 48.2%	Randomly selected classrooms in schools with >900 students per grade.	Eligible students voluntarily completed anonymous confidential surveys, either online or using paper surveys depending on their school's administration method	Gender Sexual identity 30-day use of smoking devices Demographics
Fallin-Bennett, Lisha, Ling	OTP (other tobacco products) use among young adult LGB bar patrons and the relationship among past quit attempts, intention to quit, and binge drinking with OTP use was examined.	Investigator developed	US	2012-2014	8,010 3,906 Females 4,104 Males Age: Females 23.62(1.8); Males 23.88(1.9) 51% male	Time location sampling	Paper survey in pub/bar Received $5 on the spot	Sexual orientation 30-day tobacco product use Demographics Quit attempts 30-day alcohol use
Ganz, Johnson, Cohn et al	The purpose of this study was to examine differences between SGM SGM (sexual and gender minorities) and non-SGM young adults in harm perceptions of various tobacco products and tobacco use behaviour and whether low tobacco-related harm perceptions moderate the relationship between identifying as a SGM and tobacco use behaviour.	Truth Initiative Young Adult Cohort Study (Wave 10)	US national	2016	3,089 Age: 71.1% 25-34 years 49% male	The sample was drawn from GfK's KnowledgePanel®, an online panel of adults ages≥18 that covers both the online and offline populations in the U.S. Additional information about survey methodology have been reported elsewhere	Online self-administration	SGM status Demographics Tobacco use (cigarettes, e-cigarettes, little cigars) Harm perceptions
Gerend, Newcomb, Mustanski	The goal of this study was not to compare gay, bisexual, and transgender individuals to their heterosexual/cis-gender peers, but rather to identify correlates of tobacco	RADAR	Chicago, US	2015-2016 (baseline)	771 Age: 34% 19-21 years, 27% 22-24 years	Various methodologies	NR	Demographics Lifetime e-cigarette, cigarette use

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	use within a large cohort of racially diverse MSM reporting different sexual (e.g., gay, bisexual) and gender identities (e.g., cisgender man, transgender woman).				92% cisgender male			
Giachello, Thanh-Huyen, Payne et al	Cigarette smoking has been reported to be high among Lesbian, Gay, Bisexual, Transgendered and Queer (LGBTQ) populations. However, in-depth information on perception, knowledge, attitudes and behaviours, is limited.	AHA-Tobacco Regulatory Addiction Center (A-TRAC)	Chicago and New York, US	2016	29 focus groups 99 Surveys Age: 18-64 years	NR	Focus group and survey	Lifetime and current smoking history Demographics Perceptions of tobacco use
Goldbach, Mereish, Burgess	This paper investigates the use of risky substances among adolescents, and examines disparities between sexual minority (i.e., mostly heterosexual and lesbian, gay, bisexual; LGB) and heterosexual adolescents in use of novel and emerging substances.	Youth Development Survey (YDS)	North Carolina, US	2014	3,343 for YDS 3,105 with sexual orientation data Adolescents Age: 10-19+ Male: 47%	All public middle and high schools in the County were invited to participate. In total, 75 schools were invited and 74 schools participated. Randomly selected classrooms	Administered in class	Demographics Substance use (lifetime and 30-day) of cigarette, smokeless tobacco, e-cigarette, alcohol, marijuana/hash, synthetic marijuana, prescription drugs (without prescription)
Hinds, Loukas, Perry	This study examined differences in the odds of current use and age of initiation of five tobacco/nicotine products among three groups of SGM young adults who self-identified as (1) gay or lesbian, (2) bisexual, and (3) queer, transgender, or "other," compared to their heterosexual peers.	Marketing and Promotions across Colleges in Texas project (Project M-PACT)	Texas, US	2015	5,482 Wave 3 n4321 adolescents Mean age: 20.45(2.33) Male: 36%	College students aged 18- to 29 years attending 24 two- and four-year colleges in five counties surrounding the four largest metropolitan areas of Texas, Austin, Dallas/Fort Worth, Houston, and San Antonio	Online	Demographics Sexual/gender status Current tobacco product use
Jannat-Khah, Reynolds, Dill, Joseph	Within the United States, alternative tobacco product (ATP) and varies by geographic region, gender and age. Few articles have been published on the usage of these products among the lesbian, gay, bisexual, transgender or queer (LGBTQ) population.	Investigator developed	New York, US	2014	64 Mean age: 33.033(13.89) 51.6% male/ transmale	Through social media	Google Forms	Current, former, experimental tobacco use Beliefs about alternative tobacco products Sources of knowledge about ENDS Stress

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
								Micro aggressions Demographics
Nayak, Salazar, Kota, Pechacek	In this study, we compared rates of novel and other alternative tobacco product use, risk perceptions, and worldview between LGB and heterosexual (HET) adults.	Tobacco Products and Risk Perceptions Surveys	Georgia, US	2014-2015	11,525 (with sexual orientation data) 5,717 2014 6,051 2015 Mean age: 47.15(0.2SE) 50% male	KnowledgePanel	NR	Sexual identity Awareness, ever use and current use of alternative tobacco products Smoking status Dual use Intention to quit/quit attempts Risk perceptions of e-cigarettes Cultural cognition worldview scale
Wheldon, Kaufman et al	To characterize lifetime tobacco use across two measures of sexual orientation and six types of tobacco products.	Population Assessment of Tobacco and Health (PATH)	US national	Sept 2013 - Dec 2014	31,500	Used screener of households	Interviews in the home using audio- computer assisted self-interviewing	Sexual orientation; lifetime tobacco product use

Table 41: Results of studies of US LGBTI

Study reference	Purpose	Results	Author conclusion
Buchting, Emory, Scout	This national study is the first to report on cigarettes, cigars, and e-cigarettes by examining differences in transgender tobacco use independent of sexual orientation.	Current e-cigarette use: Trans 69%; cisgender 5%. Transgender adults reported higher past 30-day use of any cigarette/cigar/e-cigarette product (39.7% vs 25.1%) and current use of cigarettes (35.5% vs 20.7%), cigars (26.8% vs 9.3%), and e-cigarettes (21.3% vs 5.0%) compared with cisgender adults (all p-values </=0.003). Transgender respondents had significantly higher odds of past 30-day tobacco product use for any cigarette/cigar/e-cigarette product (OR=1.97, 95% CI=1.25, 3.1), e-cigarettes (OR=5.15, 95% CI=3.36, 7.88), cigars (OR=3.56, 95% CI=2.27, 5.59), and cigarettes (OR=2.10, 95% CI=1.35, 3.28) versus cisgender respondents (all p-values </=0.0035).	Transgender adults are at higher risk for tobacco use than cisgender adults and risk of specific product use varies by gender.
Coulter, Bersamin, Russell, Mair	We tested three competing models about whether gender- and sexuality-based harassment at school have non-independent, additive, or interactive effects on adolescents' electronic cigarette use (i.e., vaping), cigarette smoking, alcohol use, and heavy episodic drinking (HED).	Our study provides novel insights about disparities for transgender populations and about vaping as a health disparity for LGBT adolescents. Prevalence ranging from 6-6.3% in cisgenders to 40.7% in LGB-only trans for Grade 7; 10.3-11.9 for cisgender to 35.8% for LGB-only trans in Grade 9; 11.6% in cisgender females to 30.2.% in LGB-only trans in Grade 11.	Gender- and sexuality-based harassment at school independently or interactively produced LGBT disparities in substance use. Reducing these types of discrimination in schools will likely mitigate these disparities.
Fallin-Bennett, Lisha, Ling	OTP (other tobacco products) use among young adult LGB bar patrons and the relationship among past quit attempts, intention to quit, and binge drinking with OTP use was examined.	Females LGB (n572) 20.9% e-cigarette use; straight 11.6% Males LGB (n486) 28.5%; straight 21.2% Model results: Females sig predictors of e-cigarette use; sexual orientation (LGB), not being college graduate. Males sig predictors of e-cigarette use; sexual orientation, being younger, not being in college or having graduated college.	LGB bar-going young adults are at higher risk for OTP use than their heterosexual counterparts. Bar-based interventions are needed to address all forms of tobacco use in this high-risk group.
Ganz, Johnson, Cohn et al	The purpose of this study was to examine differences between SGM SGM (sexual and gender minorities) and non-SGM young adults in harm perceptions of various tobacco products and tobacco use behaviour and whether low tobacco-related harm perceptions moderate the relationship between identifying as a SGM and tobacco use behaviour.	Chi-square tests demonstrate that a greater proportion of SGM respondents perceived e-cigarettes to be less harmful than cigarettes compared to non-SGM respondents (44.6% vs. 37.3%; p<0.05). There was no interaction between SGM status and harm perceptions on past 30-day tobacco use	Findings confirm that SGM young adults continue to disproportionately use tobacco products, compared to non-SGM young adults.
Gerend, Newcomb, Mustanski	The goal of this study was not to compare gay, bisexual, and transgender individuals to their heterosexual/cis-gender peers, but rather to identify correlates of tobacco use within a large cohort of racially diverse MSM reporting different sexual (e.g., gay, bisexual) and gender identities (e.g., cisgender man, transgender woman).	40% ever use e-cigarette Black/African American participants were 78% less likely to be e-cigarette users relative to White participants. Participants who completed some graduate school or had a graduate degree were over eight times more likely to be e-cigarette users relative to those with less than a high school education. Transgender women were 4.5 times more likely to be e-cigarette users than cisgender men. Finally, relative to participants who were attracted to only males, those who were attracted to mostly females but some males were over five times more likely to use e-cigarettes.	The present study advances the literature by providing a nuanced understanding of risk factors for tobacco use within a large, diverse cohort of YMSM and transgender women.

Study reference	Purpose	Results	Author conclusion
Giachello, Thanh-Huyen, Payne et al	Cigarette smoking has been reported to be high among Lesbian, Gay, Bisexual, Transgendered and Queer (LGBTQ) populations. However, in-depth information on perception, knowledge, attitudes and behaviors, is limited.	17% reported frequent or occasion use of e-cigarettes, e-hookah or other types of vaping.	Cigarette smoking was high among the LGBTQ individuals in our sample and they seems unlikely to quit. Social stressors appear to be a strong contributing factor. Educational efforts and culturally appropriate messages to this population, are critical.
Goldbach, Mereish, Burgess	This paper investigates the use of risky substances among adolescents, and examines disparities between sexual minority (i.e., mostly heterosexual and lesbian, gay, bisexual; LGB) and heterosexual adolescents in use of novel and emerging substances.	Odds of substance use was higher for mostly heterosexual adolescents than for heterosexual adolescents on lifetime cigarette use (AOR=1.35 [1.0, 1.83], p=0.05), and past 30 day use for e-cigarettes (AOR=1.52 [1.01, 2.29] and prescription drugs (2.10 [1.21, 3.66]). Odds of substance use were higher for LGB adolescents than for heterosexual adolescents over their lifetime and the past 30 days, respectively, on: cigarettes (AORs=2.90 [1.96, 4.31]; 2.77 [1.54, 5.0]); smokeless tobacco (AOR=1.88 [1.23, 3.14], lifetime only); e-cigarettes (AOR=1.92 [1.27, 2.89], lifetime only); alcohol (AORs=2.20 [1.54, 3.14]; 1.70 [1.06, 2.71]); marijuana (AORs=3.06 [2.10, 4.46]; 3.02 [1.96, 4.63]); synthetic marijuana (AORs=2.48 [1.16, 5.31]; 3.77 [1.55, 9.15]), and prescription drugs (AORs =2.55 [1.59, 4.10]; 3.82 [1.98, 7.37]). There were no differences between LGB and heterosexual adolescents on lifetime or past 30-day use of smokeless tobacco and e-cigarette use.	Our results are notable given the dearth of data documenting use of increasingly emerging or "trendy" substances such as prescription drugs.
Hinds, Loukas, Perry	This study examined differences in the odds of current use and age of initiation of five tobacco/nicotine products among three groups of SGM young adults who self-identified as (1) gay or lesbian, (2) bisexual, and (3) queer, transgender, or "other," compared to their heterosexual peers.	E-cigarette use 10.3% for Queer or Trans up to 21.7% for Bisexual. Bisexual and Gay/lesbian higher prevalence	Findings highlight some significant tobacco use disparities among SGM young adults compared to their heterosexual peers.
Jannat-Khah, Reynolds, Dill, Joseph	Within the United States, alternative tobacco product (ATP) and varies by geographic region, gender and age. Few articles have been published on the usage of these products among the lesbian, gay, bisexual, transgender or queer (LGBTQ) population.	Heterosexuals were found to have tried cigarettes, on average, almost a year before the LGBTQ respondents. Social networks were influential to LGBTQ respondents for an introduction to smoking; 48.00% were introduced by friends, 28.00% by family, 12.00% by a significant other and 9.09% by someone else. For heterosexuals, 73.68% reported that friends introduced them to smoking. More heterosexuals reported trying hookah (N=10), snus (N=4) and roll your own cigarettes (N=5). On average respondents knew of eight different tobacco products, regardless of sexual identity	To our knowledge, we present for the first time a comparison of people who tried, current and former users of ATPs, beliefs and knowledge about ATPs, and sources of knowledge of ATPs by sexual identity from NYC
Nayak, Salazar, Kota, Pechacek	In this study, we compared rates of novel and other alternative tobacco product use, risk perceptions, and worldview between LGB and heterosexual (HET) adults.	6% of sample LGB Ever use e-cigarette approx. 15% for heterosexual and 26% for LGB. LGB adults were 1.5 times more likely to have ever used e-cigarettes No difference for 30-day use ~32% A lower percentage of LGB adults, as compared to HET adults (16.7% vs. 19.2%), believed that exposure to vapours from e-cigarettes was "harmful" and reported that they "did not know" of any harm (35.1% vs. 39.8%). LGB were 20% less likely than were HET adults to endorse an individualistic worldview.	These results help to inform LGB-targeted specific health promotion efforts to reduce potential health risks related to the use of tobacco products, specifically, ever e-cigarette use.

Study reference	Purpose	Results	Author conclusion
Wheldon, Kaufman et al	To characterize lifetime tobacco use across two measures of sexual orientation and six types of tobacco products.	Younger lesbian/gay and bisexual women had higher relative odds of experimental use of all six tobacco products compared to heterosexual women, whereas lesbian/gay and bisexual women in both age groups had higher odds of regular use of cigarettes, e-cigarettes, cigars, and hookah than heterosexual women. Younger gay men (but not older gay men) had higher relative odds of experimental and regular use of cigarettes compared to heterosexual men. Older gay men had higher odds of experimental e-cigarette and hookah use, but lower odds of regular cigar and experimental/regular smokeless tobacco use. Measures of sexual orientation identity and sexual attraction resulted in similar estimates of tobacco use with noted differences in those who identified as ''something else,'' as well as among those who indicated asexual attraction.	There is a complex relationship between sexual orientation and tobacco use

Table 42: Characteristics of studies from the UK

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Bauld, MacKintosh, Eastwood, Ford et al.	To assess recent trends in ever and regular use of tobacco and electronic cigarettes.	Youth Tobacco Policy Survey (YTPS); the Schools Health Research Network (SHRN) Wales survey; two Action on Smoking and Health (ASH) Smokefree GB-Youth Surveys; and the Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS)	UK multiple countries	2015-2017	YTPS 1213; SHRN 32,479; ASH Smokefree 1205 (2016); 1361 (2017); SALSUS 13,607 (13yo); 11,697 (15yo) All adolescents Ages: YTPS 11-16; SHRN 11-16; ASH Smokefree 11-16; SALSUS 13/15	YTPS random selection of 82 wards. Interviewers approach households. SHRN all 113 schools approached (87 participated) ASH Smokefree been running annually since 2013 some follow-up, some cross-sectional SALSUS Random, national sample using classes as sampling unit	NR	Smoking prevalence e-cigarette prevalence Combined into never use, ever use and regular
Clarke, Lusher	To investigate factors that lead to willingness to try electronic cigarettes among UK adolescents.	Investigator developed	UK	NR	256 adolescents Ages: 16 to 19 25% males	purposive sampling from two London sixth form schools	Survey data were collected from pupils in class during a series of 45-minute workshops held during school time. Detailed written responses for some pupils	Smoking status Smoking prototypes Willingness to try e-cigarettes + flavoured e-cigarettes
Conner, Grogan, Simms-Ellis	This study assessed whether adolescent e-cigarette use was associated prospectively with initiation or escalation of cigarette use.	4-year cluster randomised controlled trial of a school-based smoking initiation intervention	England	NR	2,836 based on control schools only adolescents Mean age: 13.8(0.39) 50% males	NR	NR	Cigarette use Awareness; ever use e-cigarettes Demographics Health cognitions about smoking Intention to smoke Social norms to smoking Behavioural control to smoking
de Lacy, Fletcher, Hewitt et al	To examine the prevalence and frequency of electronic (e)-cigarette use among young people in Wales, associations with socio-demographic characteristics, smoking and other substances and the sequencing of e-cigarette and tobacco use.	School Health Research Network	Wales, UK	2015	32,479 recruited, 30,917 completers adolescents Years 7-11: 48%; Year 11: 46.6%	77% of schools	Demographics Ever use e-cigarettes Frequency e-cigarette use Age of initiation (cigarettes and e-cigarettes) Frequency current smoking Sequencing of e-cigarette or tobacco use Alcohol use per drinking	Binary logistic regression models

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
							session Prevalence and frequency of cannabis use. Use of mephdrome and laughing gas	
Kaufmann, Currie	This study will provide the first national scale profiling of Scottish adolescent e-cigarette users, which may be used to develop policies towards specific groups.	Scottish Schools Adolescent Lifestyle and Substance Use Survey	Scotland, UK	2013	33,685 pupils (adolescents) Ages: 13-15 years	Students from 283 schools	Further details elsewhere	NR
McKeganey, Barnard, Russell	In this paper we report the views of a small sample of e-cigarette users focussing on the circumstances in which individuals began vaping, their reasons for continuing vaping, their perceptions of the relative harm of vaping compared to smoking, and their views as to whether their use of e-cigarettes had increased their likelihood of smoking.	NA	Scotland and England, UK	NR	50 Mean age: 20.9 64% males	Interviewees were recruited from a range of educational settings (universities/colleges), leisure, and work settings across the North of England and Scotland drawing on social networks of young people within the various settings	Face-to-face interviews	Semi-structured interviews
Loonat, Sagar, Selinger 2018	We aimed to describe current smoking rates in IBD (irritable bowel disease) patients compared with the general population and to ascertain any effects of smoking on disease course.	Hospital records	UK	Not reported	375 people with IBD, 44.7 years (mean age)	Out-patients and clinical data	Records	Disease phenotype treatment history disease status self-reported smoking status
Ng Fat, Scholes, Mindell	This study explores the motivations for current and previous use of e-cigarettes, and whether use is associated with reporting lower or higher cigarette consumption than a year ago.	Health Survey for England, HSE2013–2014	England	2013-2014	3,039 current smokers	NR	NR	Current use e-cigarette Ever use e-cigarette Intentions to quit smoking Cigarette use
Simonavicius E et al 2017	To assess factors associated with ongoing e-cigarette use and discontinuation among smokers.	ASH Smoke free Britain survey annual survey	UK	2016	12,157	Panel members emailed an invitation to participate then members were	online questionnaire	Smoking status + motivation to stop smoking; reasons for and characteristics associated with using

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
						allocated in line with quotas		and discontinuing e-cigarettes

Table 43: Results of studies from the UK

Study reference	Purpose	Results	Author conclusion
Bauld, MacKintosh, Eastwood, Ford et al.	To assess recent trends in ever and regular use of tobacco and electronic cigarettes.	Ever use e-cigarette ranged from 7-18% in 11-16yo. 1/10 to 1/5 of 11–16 year olds report having tried e-cigarettes, only 3% or less report using them at least weekly, most of whom are regular smokers, with less than 0.5% of never smokers reporting weekly e-cigarette use.	In summary, surveys across the UK show a consistent pattern: most e-cigarette experimentation does not turn into regular use, and levels of regular use in young people who have never smoked remain very low.
Clarke, Lusher	To investigate factors that lead to willingness to try electronic cigarettes among UK adolescents.	Smoking status significantly predicted more than one-third of the variance of willingness to try an electronic cigarette and a further 7.8% was significantly predicted by a positive prototype of a smoker (e.g., stylish) and a negative prototype of an electronic cigarette user (e.g., unattractive). Moreover, tobacco-flavoured electronic cigarettes were less favourable than alternative flavours such as fruit, chocolate, and mint.	Findings provide evidence that flavored electronic cigarettes are more appealing to all; adolescents, smokers, non-smokers, current and past electronic cigarette users, and never users
Conner, Grogan, Simms-Ellis	This study assessed whether adolescent e-cigarette use was associated prospectively with initiation or escalation of cigarette use.	Ever use e-cigarette 34.2%. Initiation of cigarette use at follow-up was predicted by having ever used e-cigarettes at baseline (table 4, model 1; OR 5.38, 95% CI 4.02 to 7.22) and remained so when controlling for covariates. Initiation of cigarette use was significantly higher in adolescents who at baseline were ever users of e-cigarettes, had either a few or most friends who smoked and had one, two or three or more family members who smoked, but was significantly lower in adolescents with stronger intentions (not to smoke). Ever use of e-cigarettes is associated with initiation of cigarette use; an effect that remains when controlling for various predictors of smoking.	Ever use of e-cigarettes was robustly associated with initiation but more modestly related to escalation of cigarette use
de Lacy, Fletcher ,Hewitt et al	To examine the prevalence and frequency of electronic (e)-cigarette use among young people in Wales, associations with socio-demographic characteristics, smoking and other substances and the sequencing of e-cigarette and tobacco use.	These data suggest that e-cigarette use among youth is an emerging public health issue, even though there remains no evidence that it represents a new pathway into smoking.	
Kaufmann, Currie	This study will provide the first national scale profiling of Scottish adolescent e-cigarette users, which may be used to develop policies towards specific groups.	1.1% current e-cigarette users 11.6% ever use e-cigarette 26% exclusive e-cigarette; 74% dual users Males, rural adolescents more likely to be current users of e-cigarette. Weekly alcohol use, current drug use and tobacco smoking all significantly associated with current e-cigarette use	The low prevalence of current e-cigarette use contrasts with other countries, but similar factors predict use. Contrasting the profiles of non-smokers who are e-cigarette users with those who solely use tobacco suggests that there are differences in predictive factors which may have implications for subsequent tobacco use indicating the need to carefully monitor the effects of e-cigarette use in longitudinal studies.

Study reference	Purpose	Results	Author conclusion
McKeganey, Barnard, Russell	In this paper we report the views of a small sample of e-cigarette users focussing on the circumstances in which individuals began vaping, their reasons for continuing vaping, their perceptions of the relative harm of vaping compared to smoking, and their views as to whether their use of e-cigarettes had increased their likelihood of smoking.	Our interviewees saw the two activities of vaping and smoking as being associated with very different levels of harm. None of our interviewees felt that their e-cigarette use had increased their likelihood of smoking even if a small number conceded that this might be the case for other people. In terms of how individual interviewees had begun vaping this had largely occurred in the midst of their social contacts with friends in which they had either asked or been offered a try of friends' equipment and within which curiosity seemed to be a key driver of such experimentation. With regard to the decision to continue vaping, attention was drawn to such factors as the lower levels of harm associated with vaping compared to smoking, the availability of different flavours, the lack of an offensive smell associated with vaping (again in contrast to smoking), the fun that was seen to be associated with creating large vapour plumes, the greater range of situations within which one could use e-cigarettes compared to combustible cigarettes, and the lower level of stigma attached to vaping compared to smoking.	The sample of interviewees were evenly split with regard to the perceived justification (or not) for banning vaping in public. Finally, we make the case that it is important to base policy and regulation of e-cigarettes on both robust epidemiological data on the impact of these devices as well as more qualitative, ethnographic, information from users themselves.
Loonat, Sagar, Selinger 2018	We aimed to describe current smoking rates in IBD (irritable bowel disease) patients compared with the general population and to ascertain any effects of smoking on disease course.	"Of 200 ever cigarette smokers 144 had stopped and 56 continued cigarette use, while of 30 ever e-cigarette users 14 had stopped and 16 continued. All e-cigarette users had previously smoked cigarettes and 10 had stopped smoking completely after e-cigarettes. Crohn's disease patients were more likely to smoke cigarettes (19.9% vs. 8.1%) or e-cigarettes (4.1% vs. 3.4%) compared with UC/IBD-U patients (p =0.026). Compared with the general population the proportion of current cigarette smokers (14.9% vs. 17.2%) and e-cigarette users was similar in our cohort (4.26% vs. 4%). "	IBD patients use e-cigarettes as replacement for cigarettes or as an intermediate step for smoking cessation with no de-novo e-cigarette use in our cohort.
Ng Fat, Scholes, Mindell	This study explores the motivations for current and previous use of e-cigarettes, and whether use is associated with reporting lower or higher cigarette consumption than a year ago.	12% were current users, and 20% previous users of e-cigarettes. Compared with never use of e-cigarettes, no association was found with age and current use, while being younger was associated with previous use (45–54 v. 16–34 years, OR=0.68 [95%CI 0.46–0.79]). Conversely, current and previous users of NDPs were more likely to be older than never users of NDPs (45–54 years 2.07 [1.29–3.30]). Quit intentions had a dose response relationship with the odds of current e-cigarette use (e.g. Preparation versus No intention (3.14 [2.24–4.42]); for previous e-cigarette users the magnitude was smaller (1.39 [1.04–1.87]). However, 'Preparation' had stronger associations with other NDPs, for both current (8.93 [5.54–14.40]), and previous use (3.18 [2.47–4.09]). Being a current user of e-cigarettes (1.77 [1.36–3.20]) or other NDPs (1.72 [1.19–2.50]) increased the odds of reporting smoking fewer cigarettes than the previous year; previous use was not significant. E-cigarette use was not associated with reporting smoking more than the previous year, however current use of NDPs was (1.84 [1.13–3.01]).	Current or previous e-cigarette use is unlikely to increase consumption of cigarettes compared with a year ago, but smokers who used them had weaker intentions to quit smoking than smokers who used other NDPs.
Simonavicius E et al 2017	To assess factors associated with ongoing e-cigarette use and discontinuation among smokers.	Current dual users were more motivated to stop smoking than past users; never users or past triers motivation did not differ from past users. Dual users were less dependent on cigs and to deal with smoking restrictions than past users. Smokers mostly discontinued e-cigarette because they did not feel like smoking, did not help with cravings or respondents had just wanted to try them	Among smokers, ongoing use of e-cigarettes is assoc with reasons for reducing smoking and dealing with smoking restrictions, heightened motivation to stop smoking, and lower dependence on smoking.

Table 44: Characteristics of studies from Australia

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Bonevski, Guillaumier, Skelton et al.	Examine nicotine electronic cigarette awareness, use and place of purchase and reasons for use.	Investigator developed	Australia	NR	427 Mean age: 37 years 58% male	Clients from substance use treatment centres	Telephone	Awareness e-cigarettes; ever use e-cigarettes; whether e-cigarette contained nicotine; current use e-cigarettes, reasons (select Y/N)
Brown	This paper explores the experiences of smoking and 'vaping' while being pharmaceutically treated for schizophrenia, as well as what the experiences of breathing smoke and vapour in and out can reveal about health 'care', toward the self and others.	ethnographic data	Australia and UK	2015-2016	NR	NR		
Keane, Weier, Fraser, Gartner	Rather than add to the literature on the health effects of e-cigarettes, this article aims to explore vaping through theories of social practice.	Investigator developed	Australia	2014	705 71% male	Invitations to participate in the survey were distributed through online vaper forums, e-cigarette vendors and word of mouth	Online	'tell us anything you would like to about personal vaporisers'
Lee, Yong, Borland et al	This study examined the prevalence and correlates of (1) perceived social acceptability of personal vaporizer (PV)/e-cigarette use, and (2) reported vaping in public and private places, in the UK and Australia with different regulatory environments for PVs.	International Tobacco Control Survey (ITC4)	Australia, UK	2014	2,849 32.8% aged 18-39 years 56% male	Probability sampling methods using random-digit dialling from the population of each country within strata defined by geographic region and community size,	Web or phone interviews	PV awareness, trial, use (y/n) Extent of current use Social acceptability Perceived harmfulness of PV Friends and family who vape Seen vaping in public places Comfort using PV in public Enjoyment of e-cigarettes Demographics
Sharma R, Wiggington B et al 2017	To determine motivations and Limitations Associated with Vaping among People with Mental Illness.	Qualitative Analysis of Reddit discussions;	Australia (Queensland)	2016	Thematic analysis of 3,263 comments from 133 discussion threads	NA	Systematically searched the website Reddit.com using keywords related to e-cigarettes and mental illness	Coded relevant posts into themes under the framework of motivations for and limitations of vaping for people with mental illness
Williams T, White V et al 2017	To determine what Factors are Associated with Electronic Cigarette, Shisha-Tobacco and Conventional Cigarette Use.	Victorian component of the Australian Secondary Schools	Australia (Victoria)	June - August 2014	4,576 Aged 12-17 years	Principals were approached and their school invited to participate. If a principal declined, a replacement school was selected. Replacement schools were geographically closest within the same education sector. In total, 264 schools were approached and	Pen and paper survey face-to-face with researcher	Outcome categories were based on cross-classifying the sample by ever e-cigarette, ever shisha-tobacco and ever tobacco cigarette use. Eight unique groups were determined: e-cigarettes only (e-cigaretteO), shisha-tobacco only (STO), tobacco cigarettes only (TCO), dual tobacco

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
		Alcohol and Drug survey				63 schools agreed to participate in the study		cigarette and e-cigarette use (Te-cigarette), dual tobacco cigarette and shisha-tobacco use (TCS), dual e-cigarette and shisha-tobacco use (e-cigaretteTS) and use of all three products (EST). Students who had not used any of the three products were classified as never smokers (NS).
Yuke, K, Ford P, et al 2018	Exploration of the acceptability of novel nicotine products, such as e-cigarettes.	Indigenous smokers	Australia (Brisbane)	2014-15	27 63% male	Convenience through health care system	Small size focus groups, 3 individual interviews	Thematic

Table 45: Results of studies from Australia

Study reference	Purpose	Results	Author conclusion
Bonevski, guillaumier, Skelton et al.	Examine nicotine e-cigarette awareness, use and place of purchase and reasons for use.	39% ever use e-cigarettes; 7% current use; 3% daily use. 72% wanted to try e-cigarettes; 70% used to help cut down smoking;	Smokers are trialling e-cigarettes to help quite but few persevere
Brown	This paper explores the experiences of smoking and 'vaping' while being pharmaceutically treated for schizophrenia, as well as what the experiences of breathing smoke and vapour in and out can reveal about health 'care', toward the self and others.		This paper has demonstrated how operations of health 'care' of self and others can be explored in and through experiences of breathing in and out cigarette smoke and e-cigarette vapour. Smoking and vaping are and are not different from general population experiences of smoking where harms are emphasised. Forclozapine-treated schizophrenia patients in my ethnographic study, inhaling nicotine via both cigarettes and e-cigarettes provoked a temporal, not just neuro-chemical, reclamation of self and being in the world
Keane, Weier, Fraser, Gartner	Rather than add to the literature on the health effects of e-cigarettes, this article aims to explore vaping through theories of social practice.	Participants expressed a positive view of vaping, stating that vaping had enabled them to stop or dramatically reduce their smoking. The survey responses produced a picture of vaping as an extensive and flexible practice that had expanded and opened up the possibilities of daily life. The specific temporal capacities of e-cigarettes also contribute to the flexibility valued by respondents. While respondents emphasised that vaping allowed an expansion of the times and places of nicotine consumption, there was no discussion of consequences such as potentially increased ingestion of nicotine or other chemicals. The survey also provided insights into the transmission of vaping as a social practice. The survey responses suggested that vaping is being spread efficiently through word of mouth or personal contact.	Drawing on a survey of Australian vapers, this article has examined elements of vaping as social practice. It has suggested that vaping has temporal and spatial characteristics which enable it to be 'bundled' with other important social practices. Vaping also has a normative significance associated with the notion of health as an individual project of self-improvement and a personal responsibility. Importantly, this positive web of meanings comprising concepts of health, freedom, transformation and choice is currently not affected by uncertainty about the long-term effects of vaping. Vaping takes on these positive meanings through its relationship with smoking and its negative meanings and effects. Vaping also enables a different experience of nicotine addiction, in which dependency on the substance co-exists with experiences of choice and control.
Lee, Yong, Borland et al	This study examined the prevalence and correlates of (1) perceived social acceptability of personal vaporizer (PV)/e-cigarette use, and (2) reported vaping in public and private places, in the UK and Australia with different regulatory environments for PVs.	Prevalence of current vaping (defined as any use of PVs) in the UK was more than twice that of AU (28.2% vs. 11.9%) and prevalence of daily use in the UK was about 4 times that of AU (9.2% vs. 2.5%). UK respondents were more likely to think vaping is socially acceptable than Australians (56.4% vs. 27.9%; p<0.001) and also more likely to believe that PVs are less harmful than conventional cigarettes (63.9% vs. 48.7%, p<0.001) Knowing regular vapers was significantly associated with greater social acceptability in AU but not in the UK UK vapers tended to vape more frequently at home and in SF public places, and had more positive attitudes toward vaping, compared to AU vapers	The acceptability of vaping was greater among those who were more exposed to vaping and not just among those with some personal experience of vaping, suggesting no strong social barriers to increased use. Vaping in SF public places was less common than in homes, and both were more common in the UK than in Australia, suggesting some social constraints on use, particularly in Australia.
Sharma R, Wiggington B et al 2017	To determine motivations and Limitations Associated with Vaping among People with Mental Illness.	6 themes classified as motivations: Self-medication; Quitting smoking; Freedom and control; Hobby; Social connectedness; and Motivation from caregivers and online communities. The limitations of vaping included: Unsatisfactory substitute for cigarettes and psychiatric medicines; Drug interactions; Nicotine addiction; Risks of e-liquid; Practical difficulties and Cost	People with mental illness; and their carers; use online discussion boards like Reddit to discuss the benefits and limitations of e-cigarettes for people with mental illness. Both positive and negative views exist.

Study reference	Purpose	Results	Author conclusion
Williams T, White V et al 2017	To determine what Factors are Associated with Electronic Cigarette, Shisha-Tobacco and Conventional Cigarette Use.	Overall, 14% of students had used an e-cigarette with 3% using e-cigarettes exclusively. 13% had used shisha-tobacco, with 2% using shisha-tobacco exclusively. Most students (65%) using e-cigarette and shisha-tobacco (67%) had also used tobacco cigarettes. After adjusting for demographic factors, students using e-cigarettes only were more likely to have never used cannabis or drink alcohol in the past year compared to tobacco cigarette users. Compared to tobaccocigaretteusers,studentsusingonlyshisha-tobaccowereyounger,lesslikelytousecannabis or alcohol or have friends or parents who smoke	Most Australian adolescents who use alternative nicotine and tobacco-related products do so in conjunction with tobacco cigarettes. Students using e-cigarettes or shisha-tobacco exclusively were less likely to use other substances
Yuke, K, Ford P, et al 2018	Exploration of the acceptability of novel nicotine products, such as e-cigarettes.	82% of men 'very likely to try' e-cigarette, 70% of women 'would never try'. Common views on need to taste good (NRTs) and community endorsement. Divergent views on similarity to cigarette, visible vapour and appearance. Lack of interest in long-term substitution, concern about e-cigarettes being attractive to children.	Some participants were interested in long-term substitution if acceptable products were available. Improvements in current products and access to novel products are needed if tobacco harm reduction is to be acceptable.

Table 46: Characteristics of studies from other countries

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Adriaens, van Gucht, Baeyens	To discover elements to be included in an intervention aiming at dual users who want to quit smoking completely in the future.	Investigator developed – 5-part survey	Netherlands	Feb/Mar 2016	217 Mean age: 42.57(11.23) 75% male	Distributed a link to an online Dutch questionnaire through social media (Facebook and Twitter) and a Dutch forum for vapers (www. dampforum.nu)	Self-administered, 13-18 minutes, 25Euro voucher, Qualtrics	Section 1: demographics section 2: smoking behaviours Section 3: e-cigarette use Section 4: attitudes of vaping/smoking Section 5: Dual uses rate situations where they would use one versus the other
Ajjandaleh, Bolze, Khoury, Melchior, Mary-Krause.	Understand factors associated with e-cigarette use in young adults in France.	Data collected from French Trajectoires Epide´miologiques en Population (TEMPO)	France	2015	Restricted to smokers=358 adults Ages: 23 to 42 years	NR	Self-administered questionnaire	Family status, quality of family relations, educational attainment, occupation and type of work contract, chronic health problems, psychoactive substance use, as well as perception of e-cigarettes.
Alexander, Williams	Reasons for initiation and current use qualitatively explored among users of e-cigarettes.	NA	NR	NR	42 adolescents Ages: 14-17	NR	Four focus groups	NR
Ayers, Leas, Allem et al.	We demonstrate the feasibility of a data-driven protocol that allows the public to describe why they vape in their own words by passively monitoring public tweets.	NA	Internet	2012-2015	3.3 million tweets	3.3 million public tweets from 2012 and 2015 that was collected from the Twitter API by searching for the following ENDS-related keywords: electronic cigarette(s), electronic cig(s), e cig(s), e-cig(s), eking(s), e cigarette(s), e-cigarette(s), e-cigarette(s), vape(s), vaper(s), and vaping	Screened data for irrelevant and spam tweets using machine learning then identified reasons for use	NA
Azagba	The current study examined associations between e-cigarette use, dual use of e-cigarettes and tobacco cigarettes, and frequency of cannabis use.	2014-2015 Canadian Student Tobacco,	Canada	2014-2015	23,429 in survey 23,429 students in grades 9 to 12		NR	Cannabis use e-cigarette use Cigarette use Students' perceptions

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
		Alcohol and Drugs Survey The CSTADS			51% male			about the risk of regular cannabis use
Azagba, Baskerville, Foley	This study examined the association between e-cigarette use and future intention to smoke cigarettes among middle and high school students who had never smoked cigarette.	2014-2015 Canadian Student Tobacco, Alcohol and Drugs Survey	Canada	October 2014 and May 2015	42,094 original respondents 25,637 (restricted to Grades 7-12) 50.9-49.8% male	Stratified, single stage cluster design with strata based on health region smoking rates and type of school	Teacher administered paper questionnaire in classroom. Sealed and coded by Optimal Software	Susceptibility to smoking based on collection of questions Ever e-cigarette use Current e-cigarette use Socio-demographics
Azagba, Wolfson	The objective of the present study was to examine the association between current e-cigarette use and quantity of cigarette smoking.	2014-2015 Canadian Student Tobacco, Alcohol and Drugs Survey	Canada	October 2014 and May 2015	n=1,411 for this analysis; Current smokers only 53% male	Stratified, single stage cluster design with strata based on health region smoking rates and type of school	NR	Quantity of cigarette smoking Demographics
Balogh, Faubl et al 2018	Explore cigarette, waterpipe and e-cigarette use among an international sample of medical students.	Researcher's survey (based on selected items from validated instruments eg 36-item short form survey instrument	Hungary and Germany	2014	2,935, 22.5(SE3.3), 39% male	All registered medical students were invited to participate in survey	Self-administered questionnaire	Demographics self-reported health status data on risk behaviours incl tobacco consumption
Berry, Burton, Howlett	This research examines cigarette smokers' and e-cigarette users' product-related health-risk beliefs across tobacco products and considers the effects of addiction warnings on consumers' responses to persuasion attempts.	Investigator developed		NR	Study 1 195 Study 2 265 Ages: Study 1 36.7 (NR); Study 2 34.0 (NR) % male: Study 1 49.0%; Study 2 54.1%	Amazon's Mechanical Turk (MTurk) was used to recruit participants	Unclear - presuming online	Study 1: health-risk beliefs associated with tobacco use and e-cigarette use Study 2: Health-risk belief and willingness to try the e-cigarette.
Boo, Inche Mat, P'ng et al	To explore adult's perceptions of risks and benefits to e-cigarettes.	Investigator developed based on Chaffee et al	Malaysia	NR	247 27% male	Students in a course at Serdang Hospital approached	Written, self-administered	Demographics Tobacco-related perceptions e-cigarette awareness Ever use e-cigarettes Recent use

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
								e-cigarettes Likelihood of 19 health and social outcomes from using e-cigarettes
Browne, Todd	This study investigated characteristics of nicotine dependence and consumption in a sample of vapers who formerly smoked cigarettes.		Internet UK, Australia, Finland, Ireland, US	NR	436 Mean age: 41.4(13.1) 80% male	Current vape users recruited via posts in social media	Online via Survey Monkey	Retrospective Fagerstrom Test for Nicotine Dependence Plus modified version for vaping
Brozek, Jankowski, Zejda et al	The objectives of this study were to assess the prevalence of e-cigarette and tobacco cigarette use; to compare the patterns of smoking; to assess the attitudes and motivations for e-cigarette use.	Investigator developed and piloted with 54 students	Katowice, Poland	2016	1,318 Mean age: 22.1(2.2) 34% male	Students in Faculty of Medicine	NR	Frequency and attitudes toward use of traditional and e-cigarettes Safety concerns Smoking in public places Attitudes to addiction Presence of respiratory symptoms motivations behind e-smoking
Cavalcante, Szklo, Perez et al.	This study sought to analyse: (1) awareness of electronic cigarettes, ever-use and recent use; (2) perception of harmfulness of electronic cigarettes when compared with conventional cigarettes; and (3) correlates of awareness and perception of harmfulness.	Brazilian International Tobacco Control Policy Evaluation Survey	Brazil	2012	721 respondents Mean age: 50.8 33% male	Random digit dialling	The interviews were administered in Portuguese by telephone between October 2012 and February 2013.	Demographics Smoking freq Awareness of e-cigarettes Ever use e-cigarettes Harm of e-cigarette relative to cigarettes
Chang, Tsai, Shiu et al.	This study investigated the prevalence and correlates of electronic cigarettes (e-cigarettes) use in Taiwan.	2015 Taiwan Adult Smoking Behaviour Survey	Taiwan	2015	26,021 Ages: 25–64 years (67.7%) 49% male	Random digit dialling	Computer-assisted telephone interviewing system	Ever use e-cigarettes Smoking status Demographics
Cheng, Chang, Hsu et al	We investigated the use of electronic cigarettes (e-cigarettes) with traditional cigarettes among adolescents during 2014 to 2016 to identify risk factors for	Taiwan Global Youth Tobacco Survey	Taiwan	2014-2016	20,434- 21,731 junior high school students; 22,978- 23,466 senior high school students	Conducted in different school selected at random	The survey was conducted in classrooms by three to six staff members from local health bureaus after undergoing a 1-day training program on the presentation of questionnaire	Smoking behaviour (cigarette and e-cigarette use past 30 days) Demographics

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
	using e-cigarettes only, traditional cigarettes only, or both products.				52% male		surveys by the HPA. Self-administered paper-based	
Chesaniuk, Marie, Sokolovsky et al	Examined motives associated with ENDS use and cessation outcomes.	NR	NR	NR	304 Mean age: 22.4 72% male	Amazon Mturk Platform	Online	14-item Wisonsin Inventory for Smoking Dependency Motives Smoking Consequences Questionnaire Smoking patterns Demographics
De Genna, Goldschmidt, Richardson et al	Parental exposures to maternal cigarette and cannabis use associated with cig use and tobacco dependence.	NR	NR	NR	413 Mean age: 29.7(3.4) 40% male	3 prenatal cohorts (unnamed)	Telephone interview	Offspring use of e-cigarettes
Etter	We assessed change in vaping and smoking behaviours over 12 months in regular vapers.	France (39%), US (18%), Switzerland (12%), UK (4%), and other countries (27%) Researchers in Switzerland	Internet	2012-2016	3,868 Mean age: 41 (baseline) 58% male (baseline)	Posted to smoking cessation website Stop-Tabac.ch We contacted discussion forums and websites informing about e-cigarettes or selling them, and asked them to publish links to the survey	Online	Use of e-cigarettes, Smoking status, Cigarette Dependence Scale, Demographics, Reasons to vape, vaping equipment, Minnesota Withdrawal Scale, Perceived addiction and ability to stop vaping, Mood and Physical Symptoms Scale (MPSS)
Farsalinos, Poulas, Voudris, Le Houezec	The study purpose was to analyse current daily and current daily nicotine-containing electronic cigarette (e-cigarette) use in the European Union (EU).	Special Eurobarometer 429	European Union (28 states)	2014	27,801 in full sample	TNS Opinion & Social at the request of the Directorate-General for Health and Food Safety. A number of sampling points were drawn in each country, with probability proportional to population size (for a total coverage of the country) and to population density.	Face-to-face interviews in homes	Smoking status e-cigarette use and frequency e-cigarette use to help stop smoking

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Farsalinos, Slakas et al 2018	Purpose was to assess prevalence and correlates of electronic cigarette (e-cigarette) use.	Investigator developed	Greece (Attica region)	2017	4,058, no other details reported	sample drawn from all registered landlines	Telephone interview	Demographics Smoking and e-cigarette use
Ferreira, Bordalo, de Melo et al	Analyse e-cigarette experimentation in adolescents and determinate risk factors associated with its experimentation.	Investigator developed	Portugal	2015	360 Mean age: 16.4(1.2) 51% male	All the students of the 10th, 11th and 12th years of a Portuguese public school in the municipality of Famalicão were included	Self-report, delivered by teachers in the classroom.	Demographics Ever use e-cigarettes, tobacco and cannabinoids, age and why Current use e-cigarettes, tobacco and cannabinoids Knowledge of e-cigarettes
Filippidis, Laverty, Gerovasili et al	This study assessed changes in levels of ever use, perceptions of harm from e-cigarettes and sociodemographic correlates of use among European Union (EU) adults during 2012-2014, as well as determinants of current use in 2014.	Special Eurobarometer for Tobacco survey	EU	2012-2014	26,751 (2012) 26,792 (2014 ex Croatia)	Probability sampling design was followed in each EU member state in both waves	NR	E-cigarette use ever, current, regular Reasons for e-cigarette use (categorical) Perceived harmfulness Current tobacco use Demographics
Goh, Dujaili, Blebil, Ahmed	This paper is the first in Malaysia to assess sociodemographic and behavioural characteristics associated with ENDS awareness, perceptions and use among students enrolled in health science programmes.	Investigator developed	Malaysia	2016	404 28% male	Undergraduates at International Medical University	Internet survey	Demographics e-cigarette awareness e-cigarette perceptions cig smoking behaviours health-risk behaviours
Kinnunen, Minkkinen, Ollila, Rimpela	We present preliminary results on adolescent e-cigarette use from the age of 16 to the age of 18 according to the type of liquid (nicotine/non-nicotine) used in them.	School Health Survey	Helsinki, Finland	2014 and 2016	3,474 adolescents Age: 16 to 18 years	NR	NR	NR
Kong, Idrisov, Galimov et al	We examined prevalence of and factors associated with youth e-cigarette use in the Russian Federation.	Investigator developed	Republic of Bashkortostan, Russian Federation	2015	716 adolescents Ages: 35.8% 16yo 49% male	9 high schools selected as a convenience sample	NR	E-cigarette use demographics antisocial behaviors stress coping strategies

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
								lifetime cigarette, hookah, alcohol, and marijuana use
Koprivnikar, Zupanic	The purpose of this paper is to present the latest data on the use of different tobacco and related products, with or without flavours, among 15-year old students in Slovenia.	Health Behaviour in School-Aged Children	Slovenia	2014	4,997 adolescents 11, 13, 15 yo 49% male	The survey sample was selected with stratified two-stage sampling method	Self-administered web-based	Use of different tobacco and related products, flavoured products, the number of cigarettes smoked in the last 30 days, and age at first cigarette smoking were answered only by 15-year-old students Use of different tobacco products in last 30 days Use of flavoured products
Kusiak, Wojtaszek-Słom ińska, Chomyszyn-Gaj ewska et al	The paper reports an analysis of electronic cigarette use among Polish dental students, particularly concerning the reasons for using e-cigarettes.	Investigator developed	Poland	2015-2016	581 Ages: 20-25 years 28% male	3 medical universities	NR	Use of e-cigarettes, smoking habits and motivation to use e-cigarettes
Lee, Lee, Cho	This study aims to determine the relation between the frequency of e-cigarette use and the frequency and intensity of cigarette smoking. Additionally, the study evaluates the association between the reasons for e-cigarette use and the frequency of its use.	Korean Youth Risk Behaviour Web-Based Survey	South Korea	2015	6,655 had e-cigarette experience total 70,362 students Ages: 13-18 52% male	Multistage, stratified, cluster-sampling method	Web	Cigarette and e-cigarette use Reasons for use of e-cigarettes Demographics
Lehmann, Kuhn, Reimer	The aim of the study was to characterize e-cigarette users in terms of their consumption patterns, motives, and the perceived health benefits they experience from using e-cigarettes.	Investigator developed with 133 questions	Germany	2015	3,320 Mean age: 40.8(11.0) 81% male	Online banner and flyer distributed to producers and traders	Lime Survey (online)	Demographics Vaping status, device and liquids Smoking behaviour Risk of dependency Reasons for e-cigarette use Perceived health changes Smoking/vaping

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
								cessation Opinion about e-cig
Leung, Ho, Chen et al	We investigated favourable perceptions of electronic cigarettes (e-cigarettes) relative to cigarettes and their associations with e-cigarette use susceptibility in adolescents.	Investigator developed based on Global Youth Tobacco Survey	Hong Kong	2014/2015	40,202 adolescents Mean age: 14.9(1.8) 52% male	92 schools randomly selected from all the 18 districts in Hong Kong were invited to complete an anonymous questionnaire	The survey was conducted in classrooms, and completed answer sheets were collected and sealed in an opaque envelope by research staff in front of students.	Cigarette smoking status e-cigarette status including susceptibility Favourable perceptions of e-cigarettes Demographics
Lindstrom, Rosvall	The aim was to investigate associations between e-cigarette use and social and psychosocial factors and cigarette smoking, alcohol consumption, and narcotics use among adolescents attending 9th grade in primary school and 2nd grade in secondary school.	No name	Scania, Sweden	2016	13,835 adolescents	The study was conducted among pupils in the 6th and 9th grades of the primary school (grundskolan) and the 2nd grade in secondary school (gymnasieskolan)	Questionnaires were either distributed by the teachers in the class room, answered by the respondents, and gathered in the class room during scheduled time in school or distributed and answered digitally during class	e-cigarette ever use and 30-day use Narcotic use Happiness in school Difficulties in school Stressed by school Generalised trust
Milicic, Leatherdale	This study examines the associations between e-cigarette use and tobacco, marijuana, and alcohol use among a large sample of Canadian youth.	COMPASS study	Canada	2014-2015	39,837 (year 3) adolescents Grade 9-12 students 27.2% 15 years 50% male	Purposefully sampled secondary schools	NR	E-cigarette use past 30 days Demographics Cig smoking Binge drinking Marijuana use
Montreuil, MacDonald, Asbridge et al	The aims of this study were to describe the prevalence of e-cigarette use among youth in Canada, by province, across sociodemographic variables and smoking-related correlates; and to examine associations among e-cigarette use, sociodemographic variables and smoking-related correlates, with adjustment for other factors.	Canadian Student Tobacco, Alcohol and Drugs Survey	Canada	2014/2015	42,094 adolescents Grades 6-12 60% male	Stratified, single-stage cluster design, with strata based on health-region smoking rate and type of school. In each province, 2 or 3 health-region smoking rate strata and 2 school-level strata were defined. Random selection of schools within each stratum ensured a generalizable sample within each province	paper-and-pencil school-based survey administered	Ever 30-day use e-cigarettes Ever use tobacco products Smoking status Perceived harm from e-cigarettes Ease of access to e-cigarettes Demographics
Morgenstern, Nies et al 2018	Explore the "gateway" hypothesis, according to which the use of e-cigarettes can motivate adolescents to start smoking conventional cigarettes.	Investigator developed (cohort)	Germany	2015 to 2016	2,186, 15.5(SD0.65) years, 48% males, 10th grade students	Not reported	Not reported	Socioeconomic status, various personality traits (sensation-seeking, impulsivity, anxiety,

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
								hopelessness, extraversion, agreeableness, conscientiousness, neuroticism, openness), and the use of alcohol, cannabis, and other illicit drugs
Nahin, Bispo, Llabre, Sokolovsky	The purpose of this study was to evaluate dimensions of dependency within the young adult ENDS user population.	Second phase of an ongoing three phase study (unnamed)	NR	NR	304 61.5% male	Amazon Mechanical TurK	Online	Wisconsin Inventory for Smoking Dependency Motives (WISDM)
Park S, Lee H et al 2017	Aimed to investigate (a) rates of e-cigarette use and (b) significant factors associated with e-cigarette use among current cigarette users in adolescence.	10th Korea Youth Risk Behaviour Web based Survey	Korea	2014	6,307 current smokers adolescents (grades 7 -12) 79% male	Nationally representative sample of Korean adolescents (no further info)	Online	E-cigarette use; demographics; perceived stress, parental and friends smoking; health risk behaviours
Robertson L, Hoek J et al 2018	To explore the of dual use of electronic nicotine delivery systems (ENDS) and smoked tobacco.	Researcher developed in-depth, semi-structured interviews	New Zealand	NR	20 Ages: 19-65 7 women, 13 men	Participants were recruited from three urban areas in New Zealand—Dunedin, Wellington and Auckland— using social media and community advertising. We also drew on whanaungatanga (kinship) and professional networks to purposefully recruit Māori (New Zealand's indigenous peoples) and Pacific participants	Face-to-face interview; flexible, allowing probing where necessary	Smoking history and current smoking, then probed their trial, uptake and patterns of ENDS use, and smoking and vaping intentions
Ruokolainen O, Ollila H et al 2017	Explore the prevalence of e-cigarette use among the Finnish adult population and to examine correlates of ever use and current use of e-cigarettes prior to some changes in the Finnish regulatory scheme.	Researcher developed survey	Finland	2014	3,485 50% male	A representative random sample (N=7000) of Finnish people aged 15–69 years was drawn from the Finnish Population Information System	Self-administered anonymous online/postal questionnaire	E-cigarette use.
Shaddock E 2017 ABSTRACT ONLY	To explore electronic Cigarette And Tobacco Product Use in school going adolescents.	Researcher developed survey	South Africa (Johannesburg)	NR	229 adolescents Ages: 14-18 21% male	Questionnaire administered to 2 schools		

Study reference	Purpose	Name of survey	Country or location	Year data collected	Participants	Recruitment/ selection method	Admin Method	Measures
Truman P, Glover M et al 2018	To understand practices of vaping and reasons for use.	Electronic survey of vapers	New Zealand	January – April 2016	218 31-35 median age 77% male	Aimed to recruit 150 vapers via e-cigarette retailers, vaper groups and social media, and via links provided on the End Smoking NZ (www.endsmoking.org.nz) and Tobacco Control Research Tūranga (www.turanga.org.nz) websites	Online questionnaire	Vaping patterns, vaping and smoking history, vaping context, demographics. Questionnaires 2 and 3 at monthly intervals measured use patterns
Urrutia-Pereira M et al 2016	Prevalence and factors associated with smoking among adolescents.	Researcher designed questionnaire	Brazil (Uruguaina)	March – June 2015	798 adolescents Ages: 12 to 19 yrs 50% male	Via schools	Self-administered questionnaire in classroom (pen and paper)	Use of tobacco; thoughts and knowledge of tobacco/e-cigarettes

Table 47: Results from studies of other countries

Study reference	Purpose	Results	Author conclusion
Adriaens, van Gucht, Baeyens	To discover elements to be included in an intervention aiming at dual users who want to quit smoking completely in the future.	18% dual users, 81% switchers. E-cigarette use not different between dual users and switch users: both highly dependent Puffing freq not different but dual users used sig less e-liquid than switchers Both groups used as an aid to reduce smoking but switcher saw important to avoid relapse to smoking. E-cigarette versus regular cigs used in different environments No differences in smoking behaviours. 82% reduction in smoking for dual users Main reasons to start vaping: because smoking is unhealthy, because vaping has other advantages, to quit smoking completely. All perceived e-cigarette to be less harmful than cigarettes	Differences between dual users and switchers centre around variables proximal to the vaping behaviour and its experienced effects rather than hinging on more general vaping-related beliefs and attitudes
Ajjandaleh, Bolze, Khoury, Melchior, Mary-Krause.	Understand factors associated with e-cigarette use in young adults in France.	28.2% reported using e-cigarette at least once Positive perception, low SES, and asthma associated for ever-use of e-cigarettes Compared to non-smokers traditional smoking is associated with e-cigarette use	In young adults, e-cigarette is used among former but also current traditional cigarettes smokers.
Alexander, Williams	Reasons for initiation and current use qualitatively explored among users of e-cigarettes.	Most interested in trying due to flavours and friends using them Most reported this was their first experience of using a nicotine product. Older youth liked to use to show off talents (smoke rings) Continued use in social settings. E-cigarette use did not change how they felt about cigarettes. Seen as less negative health consequences and less stigmatised	Summary of results
Ayers, Leas, Allem et al.	We demonstrate the feasibility of a data-driven protocol that allows the public to describe why they vape in their own words by passively monitoring public tweets.	During 2012 quitting combustibles was the most cited reason for using ENDS with 43% (95%CI 39–48) of all reason-related tweets cited quitting combustibles, e.g., "I couldn't quit till I tried e-cigs," eclipsing the second most cited reason by more than double. Other frequently cited reasons in 2012 included ENDS's social image (21%; 95%CI 18–25), use indoors (14%; 95%CI 11–17), flavours (14%; 95%CI 11–17), safety relative to combustibles (9%; 95%CI 7–11), cost (3%; 95%CI 2–5) and favourable odour (2%; 95%CI 1–3). By 2015 the reasons for using ENDS cited on Twitter had shifted. Both quitting combustibles and use indoors significantly declined in mentions to 29% (95%CI 24–33) and 12% (95%CI 9–16), respectively. At the same time, social image increased to 37% (95%CI 32–43) and lack of odour increased to 5% (95%CI 2–5), the former leading all cited reasons in 2015.	Our data suggest the reasons people vape are shifting away from cessation and toward social image
Azagba	The current study examined associations between e-cigarette use, dual use of e-cigarettes and tobacco cigarettes, and frequency of cannabis use.	E-cigarette and cigarette use status: E-cigarette only use 4.2%; Cigarette only use 5.4%; Dual use 3.8%; Non-use 86.7% Those who used only e-cigarettes, cigarettes only, and both products were significantly more likely to use cannabis, and at a higher frequency of use relative to the non-use group. At lower frequencies of cannabis use, the cigarette-only and e-cigarette-only groups were not significantly different	Youth who reported use of e-cigarettes, tobacco cigarettes, and both products showed a heightened risk of using cannabis more frequently.
Azagba, Baskerville, Foley	This study examined the association between e-cigarette use and future intention to smoke cigarettes among middle and high school students who had never smoked cigarette.	80% never tried a cigarette About 10% of the students had ever tried an e-cigarette. There were higher rates of ever e-cigarette use among students in grades 10-12 (12.5%) than those in grades 7-9 (7.3%). Students who had ever tried an e-cigarette had higher odds of susceptibility to cigarette smoking (adjusted odds ratio=2.16, 95% confidence interval=1.80-2.58) compared to those that had never tried an e-cigarette.	Our findings suggest that a potential increase in harmful cigarette use may follow as e-cigarette use continues to rise amongst adolescent populations.

Study reference	Purpose	Results	Author conclusion
		Current use of an e-cigarette was associated with higher odds of smoking susceptibility (adjusted odds ratio=2.02, 95% confidence interval=1.43-2.84).	
Azagba, Wolfson	The objective of the present study was to examine the association between current e-cigarette use and quantity of cigarette smoking.	Sig differences in the association between current e-cigarette use and the number of cigarettes smoked for light and heavy smokers. Current e-cigarette use was significantly associated with the number of cigarettes smoked among light smokers and no significant association was found for heavy smokers. Additional analyses were performed to examine whether the association between e-cigarette use and quantity of cigarettes smoked varied by individual smoking pattern.	Our results showed that e-cigarette use was associated with the quantity of cigarettes smoked by light smokers. However, additional analyses suggest that the association between e-cigarette use and quantity of cigarettes smoked varied by individual smoking pattern. Among beginner/experimental cigarette smokers, e-cigarette users were likely to smoke a greater quantity of cigarettes compared to non-e-cigarette users
Balogh, Faubl et al 2018	Explore cigarette, waterpipe and e-cigarette use among an international sample of medical students.	Prevalence of e-cigarette use was 0.9% (95% CI 0.5–1. 2%) with only 12 daily users (0.4%). More students in the multinational group used e-cigarettes as compared to the German and Hungarian groups. E-cigarette use was not related to age, gender, study year, religiosity or financial situation. Waterpipe and e-cigarette use were more common among cigarette smokers than non-smokers.	Prevalence of e-cigarette use was low, whereas waterpipe tobacco smoking was popular in our sample.
Berry, Burton, Howlett	This research examines cigarette smokers' and e-cigarette users' product-related health-risk beliefs across tobacco products and considers the effects of addiction warnings on consumers' responses to persuasion attempts.	Study 1: For cigarettes, health-risk beliefs are extremely high and approach the scale ceiling. In contrast, for e-cigarettes, health-risk beliefs are much lower and vary substantially; beliefs related to addiction and harm to an unborn baby are greater than beliefs about other risks. Study 2: An e-cigarette addiction warning increases the strength of beliefs about the health risks associated with e-cigarette use; these risk beliefs, in turn, negatively influence willingness to try the promoted product. In contrast, the cigarette addiction warning did not influence the strength of health-risk beliefs.	Findings indicate that the addition of an addiction warning may be effective in changing consumers' risk beliefs associated with e-cigarettes and consumers' responses to e-cigarette persuasion attempts.
Boo, Inche Mat, P'ng et al	To explore adult's perceptions of risks and benefits to e-cigarettes.	Ever use 2.4%; current use 0%, Intention to try 1.6% Upset family and lung cancer had highest % agreements (67% strongly agree) Positive outcomes seen as unlikely - look cool (54% strongly disagree), feel alert (50.8%), Increased athletic performance (50.4%)	This study provides fundamental information on their risk and benefit perception to enable appropriate measures to be carried out in tackling young adults engaging with e-cigarettes
Browne, Todd	This study investigated characteristics of nicotine dependence and consumption in a sample of vapers who formerly smoked cigarettes.	Reasons (non-exclusive) given for vaping included: health benefits (74.1%), other NRTs ineffective (45.2%), more enjoyable (35.1%) and for pleasure (22.7%), less offensive to others (31.8%), and being easier than quitting nicotine completely (35.1%). The vast majority of our sample of vapers was ex-smokers, who generally used vaping as a safer alternative to cigarettes. Overall, nicotine concentration tended to increase over time, although this effect was moderated by users' intentions to reduce their intake. Indicators of smoking addiction do not appear to be applicable to vaping, with respect to both internal consistency and relationship to consumption	First, we found that the large majority of vapers were ex-smokers who had either ceased or dramatically reduced their cigarette consumption. Second, there was a marked decrease in dependence among vapers compared to their retrospective prior cigarette dependence. Finally, we also observed decoupling: a large attenuation of the relationship between dependence and consumption for vapers as compared to their retrospective prior smoking.
Brozek, Jankowski, Zejda et al	The objectives of this study were to assess the prevalence of e-cigarette and tobacco cigarette use; to compare the patterns of smoking; to assess the attitudes and motivations for e-cigarette use.	78.4% non-smokers; 3.5% used e-cig. High frequency of smoking (all types) in men than women. 1.29% e-cigarette smokers; 2.2% dual smokers. An attempt to quit tobacco smoking was the most frequently reported factor leading to e-smoking (58.7%), followed by the perceived less harmful impact on health (43.5%), and the price (34.8%). Only 11.3% of e-smokers indicated that they would recommend the use of e-cigarettes to others, while almost half of e-smokers (48.7%) would not recommend the use of e-cigarettes to others.	Among students of medicine, e-smoking is not a frequent habit and it is apparently less popular than smoking tobacco cigarettes. An analysis of the pattern of e-cigarette use indicates that the percentage of smokers smoking daily is definitely higher among e-smokers as compared to people smoking normal cigarettes

Study reference	Purpose	Results	Author conclusion
Cavalcante, Szklo, Perez et al.	This study sought to analyse: (1) awareness of electronic cigarettes, ever-use and recent use; (2) perception of harmfulness of electronic cigarettes when compared with conventional cigarettes; and (3) correlates of awareness and perception of harmfulness.	37.4% (n=249) of current smokers were aware of e-cigs, 9.3% (n=48) reported having ever tried or used e-cigarettes and 4.6% (n=24) reported having used them in the previous six months. Among those who were aware of e-cigs, 44.4% (n=103) believed they were less harmful than regular cigarettes (low perception of harmfulness). "Low perception of harmfulness" was associated with a higher educational level and with having recently tried/used e-cigarettes. Among smokers who were aware of e-cigarettes in Brazil, 44.4% believed they were less harmful compared to regular cigarettes	This study describes e-cigarette awareness, perceptions of harmfulness, and correlates of these measures in Brazil, a middle-income country with strong tobacco control policies (for the past 20 years) and with strict e-cigarette regulations (since 2009). It is the first study to examine the correlates of e-cigarette perceptions in Brazil.
Chang, Tsai, Shiu et al.	This study investigated the prevalence and correlates of electronic cigarettes (e-cigarettes) use in Taiwan.	2.7% ever use of e-cigarettes; 14.2% in current smokers Males, those between 18-24, highest monthly income all had higher prevalence of e-cigarette use.	This national representative study in Taiwan suggests that people with higher education level and income are more likely to use e-cigarettes. Among smokers, women have a prevalence of using e-cigarettes similar to or even greater than that of men. The overall rate of ever having used e-cigarettes in Taiwan is lower than that in western countries; however, adolescents and young adults have the highest prevalence of ever using e-cigarettes
Cheng, Chang, Hsu et al	We investigated the use of electronic cigarettes (e-cigarettes) with traditional cigarettes among adolescents during 2014 to 2016 to identify risk factors for using e-cigarettes only, traditional cigarettes only, or both products.	The rates averaged over three years were as follows: non-smoking (91.6%), traditional cigarettes only (5.4%), e-cigarettes only (1.5%), and dual usage (1.6%). Among adolescents in Taiwan, the following were risk factors for dual use: male, older, high monthly allowance, smoking parents, smoking friends, use of other tobacco products, contact with cigarette advertisements, and access to free cigarettes	Our results revealed an increase in the number of adolescents using e-cigarettes with traditional cigarettes.
Chesaniuk, Marie, Sokolovsky et al	Examined motives associated with ENDS use and cessation outcomes.	Less loss of control predicted ENDS use (UNCLEAR without data)	Nil
De Genna, Goldschmidt, Richardson et al	Parental exposures to maternal cigarette and cannabis use associated with cig use and tobacco dependence.	Gestational exposures on adult e-cig. Indirect effect of prenatal exposure to tobacco and cannabis on e-cigarette use	There is a pathway from prenatal exposures to combustible tobacco and cannabis on adult e-cigarette use
Etter	We assessed change in vaping and smoking behaviours over 12 months in regular vapers.	During the course of 12 months, patterns of e-cigarette use were relatively stable in this sample of regular vapers enrolled on the Internet Permanent vapers gradually decreased the nicotine concentration in their e-liquids Over 12 months, we observed low rates (9% of 687) of relapse to smoking in former smokers and high rates (28% of 64) of smoking cessation among current smokers (dual users). We observed high rates of hazardous drinking, cannabis use, overweight and depression in this sample.	After 12 months, enjoyment and relapse prevention were the most important reasons to vape. Rates of relapse to smoking were low in former smokers and quit rates were high in current smokers. Stopping vaping was associated with relapsing to smoking.
Farsalinos, Poulas, Voudris, Le Houezec	The study purpose was to analyse current daily and current daily nicotine-containing electronic cigarette (e-cigarette) use in the European Union (EU).	Daily use of e-cigarette 1.08%. Current former smokers have highest prevalence 2.31% Smoking status is the strongest correlate, with current and former smokers having higher odds of being current daily and current daily nicotine-containing e-cigarette users compared to never smokers. Age groups\55 years, male gender, higher social class and marital status (divorced, widowed or other) also positively correlate with both current and daily use, while no association with education is observed. Finally, frequency of seeing	The strongest correlates of daily e-cigarette use were being current and former smokers. In the EU in late 2014, current daily e-cigarette use was predominantly observed in current and former smokers and was associated with high self-reported rates of smoking cessation and reduction. Current daily e-cigarette use by never smokers was extremely infrequent.

Study reference	Purpose	Results	Author conclusion
		e-cigarette advertisements and perceptions that e-cigarette are not harmful are associated with higher odds of both current daily and current daily nicotine e-cigarette use.	
Farsalinos, Slakas et al 2018	Purpose was to assess prevalence and correlates of electronic cigarette (e-cigarette) use .	Current smoking was reported by 32.6% of participants. Ever e-cigarette use was reported by 54.1% (51.4–56.8%) of current smokers, 24.1% (21.7–26.5%) of former smokers and 6.5% (5.3–7.7%) of never smokers. Past experimentation was the most prevalent pattern of e-cigarette use among ever users (p<0.001). Almost 80% of ever and 90% of current e-cigarette users were using nicotine. Extrapolated to the whole Attica population (3.1 million), there were 1 million current smokers, 848,000 ever e-cigarette users and 155,000 current e-cigarette users. The majority of current e-cigarette users (62.2%) were former smokers. Only 0.2% of never smokers were current e-cigarette users. One out of 20 participants considered e-cigarettes a lot less harmful than smoking. Being current or former smoker were the strongest correlates current e-cigarette use (OR 30.82, 95%CI 10.21–69.33 and OR 69.33, 95%CI 23.12–207.90 respectively).	E-cigarette use in Greece is largely confined to current or former smokers, while current use and nicotine use by never smokers is extremely rare. The majority of current e-cigarette users were former smokers. Most participants overestimate the harmfulness of e-cigarettes relative to smoking.
Ferreira, Bordalo, de Melo et al	Analyse e-cigarette experimentation in adolescents and determinate risk factors associated with its experimentation.	The experimentation of e-cigarette, tobacco and cannabinoids was 35%, 57.5% and 24.2%, respectively. The main reason cited for this experimentation was curiosity. In the analysis of adolescent characteristics associated with e-cigarette experimentation, it was found that being male (p. 000), attending professional education (p 0.002), self-perceived precocious puberty (p .01) and practicing activities (p 0.008) were associated with e-cigarette experimentation. Having a rebellious spirit (0.002) and adventurer (p. 000), being impulsive (p. 0.002) and having less facility in making friends (p. 0.006) were behavioural characteristics associated with further experimentation.	About one-third of adolescents tried e-cigarettes. Being male, current tobacco or cannabinoid smoker were the major risk factors associated with e-cigarette experimentation.
Filippidis, Laverty, Gerovasili et al	This study assessed changes in levels of ever use, perceptions of harm from e-cigarettes and sociodemographic correlates of use among European Union (EU) adults during 2012-2014, as well as determinants of current use in 2014.	Ever use e-cigarette increased for 7.2% (2012) to 11.6% (2014). Highest use in France 21.3% Being a current or a former smoker significantly increased the likelihood of having ever tried an e-cigarette (aOR=23.36; 95% CI 20.86 to 26.17, and OR=6.54; 95% CI 5.74 to 7.45, respectively). Also, younger age (especially being 18–24 years old), living in urban areas and higher educational level, were associated with higher likelihood of having ever tried an e-cigarette. Among those who had ever tried an e-cigarette, those defining themselves as current e-cigarette users were more likely to be older. Current e-cigarette users were more likely to have started using e-cigarettes because they thought e-cigarettes could help them quit smoking (aOR=2.82; 95% CI 1.99 to 3.99), as well as to circumvent smoking bans (aOR=1.54; 95% CI 1.19 to 2.00).	Ever use of e-cigarettes increased during 2012-2014. People who started using e-cigarettes to quit smoking tobacco were more likely to be current users, but the trends vary by country.
Goh, Dujaili, Blebil, Ahmed	This paper is the first in Malaysia to assess sociodemographic and behavioural characteristics associated with ENDS awareness, perceptions and use among students enrolled in health science programmes.	95% awareness of e-cigarettes 13.8% ever use e-cig; 55% fruit flavoured Female students were less likely to report e-cigarette use (adjusted odds ratio [aOR]=0.199, 95% CI=0.102–0.387; p<0.001). Students who had a father with a college degree or higher were about four times more likely to use e-cigarettes (aOR=3.872, 95% CI=1.763–8.504; p=0.001). Furthermore, ever use of e-cigarettes was not predicted by nationality, race and mother's educational level after controlling for the effects of other sociodemographic factors. The strongest predictor of reporting ever use of e-cigarettes was hookah use, with an odds ratio (OR) of 8.511. Respondents who reported the ever use of a hookah were over eight times more likely to report the ever use of e-cigarettes than those who had not used a hookah, controlling for all other factors in the model. The OR of 0.196 for cigarette	In this sample of young adults, e-cigarette awareness was high and ever-use was evident especially among ever cigarette smokers. Nearly half of ever-users had not used an e-cigarette in the past 30 days of the survey and mostly reported flavoured over unflavoured e-cigarette use.

Study reference	Purpose	Results	Author conclusion
		smoking of parents was less than 1, indicating that respondents who had a mother or a father or both who smoked cigarette were 0.196 times less likely to report ever use of e-cigarette, controlling for other factors in the model.	
Kinnunen, Minkkinen, Ollila, Rimpela	We present preliminary results on adolescent e-cigarette use from the age of 16 to the age of 18 according to the type of liquid (nicotine/non-nicotine) used in them.	24.9% and 4.5% had used for nicotine and non-nicotine e-cigarettes 2.1% used e-cigarette daily at FU Of those who had not tried e-cigarettes at the baseline, 18.4% tried nicotine containing and 5.7% non-nicotine e-cigarettes during the follow-up	Experimenting e-cigarettes is common among youth but daily use is rare. E-cigarette experimentation with nicotine containing liquids leads to daily conventional cigarette smoking more often than experimentation with non-nicotine products or having no experimentation.
Kong, Idrisov, Galimov et al	We examined prevalence of and factors associated with youth e-cigarette use in the Russian Federation.	28.6% ever use of e-cigarettes; 2.2% past 30-day use Compared to never users, ever users were older, had more educated fathers, higher lifetime cig, hookah, alcohol and marijuana use, reported getting suspended from school, and being arrested or having a family member arrested. Anger coping was higher and social-support and decision making coping were lower. Belonging to Tatar/Bashkir ethnicity relative to Russian ethnicity (odds ratio [OR]=1.60) and lifetime use of cigarettes (OR=21.64), hookah (OR=4.21), and alcohol (OR=1.90) were associated with greater odds of lifetime use of e-cigarette. Greater social-support coping strategies was associated with lower odds of lifetime use of e-cigarettes (OR=0.94).	Despite high lifetime e-cigarette use, past-30-day use was low. Greater knowledge of the reasons for e-cigarette discontinuation through continued surveillance is needed in the Russian Federation. Social coping strategies involving parents may inform e-cigarette use prevention.
Koprivnikar, Zupanic	The purpose of this paper is to present the latest data on the use of different tobacco and related products, with or without flavours, among 15-year old students in Slovenia.	E-cigarette use past 30 days 0.9% (1.5% for boys; 0.4% for girls) The most frequent combinations used were cigarettes with waterpipe or e-cigarette. Only one 15-year-old student used solely e-cigarettes, others used e-cigarettes and other products (12 of 14 e-cigarette users also smoked cigarettes).	15-year-old students in Slovenia currently use mostly conventional products, very often they use products with flavours and mostly they use only one product
Kusiak, Wojtaszek-Słomińska, Chomyszyn-Gajewska et al	The paper reports an analysis of electronic cigarette use among Polish dental students, particularly concerning the reasons for using e-cigarettes.	10 students (1.72%) were smoking e-cigarettes only 20.14% (51) dual users For 28 students (45.9%), e-smoking was associated with a trend. Next, 18 people (35.29%) believed that electronic cigarettes would help them quit smoking.	The main reason for taking up electronic cigarettes was the increasing trend.
Lee, Lee, Cho	This study aims to determine the relation between the frequency of e-cigarette use and the frequency and intensity of cigarette smoking. Additionally, the study evaluates the association between the reasons for e-cigarette use and the frequency of its use.	The prevalence of ever and current e-cigarette use was 10.1% and 3.9%, respectively. Out of the total participants, 6.0% were ever e-cigarette users but had not used e-cigarettes within a month, while 1.3% had used them for only 1–2 days per month. Daily e-cigarette users were 0.7%. Compared with e-cigarette users for 0–2 per month, frequent users were older (16.2 years vs. 15.8 years) and were more prevalent among 12th graders than 7th graders (21.9% vs. 9.7%). A positive correlation was observed between the frequency of conventional cigarette smoking and the frequency of e-cigarette use. Percentage of frequent e-cigarette use was 9 times greater among daily smokers than among conventional cigarette users for <1 per month (28.7% vs. 3.5%). Smoking amount was also positively correlated to the frequency of e-cigarette use. Among ever e-cigarette users, the most common reason for e-cigarette use was curiosity (22.9%), followed by the belief that they were less harmful than conventional cigarettes (18.9%), the desire to quit smoking (13.1%), and the desire to smoke indoors (10.7%).	Results showed a positive relation between frequency or intensity of conventional cigarette smoking and the frequency of e-cigarette use among Korean adolescents, and frequency of e-cigarette use differed according to the reason for the use of e-cigarettes.

Study reference	Purpose	Results	Author conclusion
		The belief that e-cigarettes are less harmful was a common reason for use among both less (<3 per month) and more (≥10 per month) frequent users of e-cigarettes (19.3% and 17.9%, respectively).	
Lehmann, Kuhn, Reimer	The aim of the study was to characterize e-cigarette users in terms of their consumption patterns, motives, and the perceived health benefits they experience from using e-cigarettes.	93% Daily vaping E-cigarette users who have never smoked cigarettes represent 1% of participants in our study. They are 5 years younger on average than ex-smokers or dual users and only one person began smoking tobacco products after starting to use e-cigarettes. The main motivation for current e-cigarette use, especially for ex-smokers, is the health improvement they expected.	E-cigarettes were primarily used as an alternative to smoking and a substitute for nicotine. More dual users than ex-smokers used e-cigarettes in places where smoking is forbidden. Positive health changes were more pronounced in ex-smokers than dual users
Leung, Ho, Chen et al	We investigated favourable perceptions of electronic cigarettes (e-cigarettes) relative to cigarettes and their associations with e-cigarette use susceptibility in adolescents.	8.9% e-cigarette ever use Many students (47.2%) had at least 1 favourable perception of e-cigarettes relative to cigarettes, including 24.1% having 1–2, 13.6% having 3–4, and 9.5% having 5 or more favourable perceptions, while less than one-third (28.9%) did not know e-cigarettes. E-cigarette use susceptibility was identified in 16.7% of all students. E-cigarette use susceptibility was associated with each of the favourable perceptions, especially greater attractiveness (APR 2.84, 95% CI 2.53-3.19), and better parental (2.75, 2.41-3.15) and school acceptability (2.56, 2.15-3.05)	Our findings inform strategies to reduce unwarranted favourable perceptions and prevent adolescent e-cigarette use
Lindstrom, Rosvall	The aim was to investigate associations between e-cigarette use and social and psychosocial factors and cigarette smoking, alcohol consumption, and narcotics use among adolescents attending 9th grade in primary school and 2nd grade in secondary school.	In 9th grade, 32% of male pupils and 27% of female pupils had ever used e-cigarettes, and in 2nd grade, 43% of males and 31% of females had ever used e-cigarettes. E-cigarette use was significantly associated with current smoking, snus (a moist powder tobacco product originating in Sweden) use, water pipe use, intensive alcohol consumption, and narcotics and also with psychosocial conditions related to home and parents, peers, and school	The prevalence of ever e-cigarette use was high among adolescents attending both grades. E-cigarette use was most strongly associated with health-related lifestyles. It was also associated with psychosocial factors such as study difficulties, school stress, problems talking with parents, and generalized trust.
Milicic, Leatherdale	This study examines the associations between e-cigarette use and tobacco, marijuana, and alcohol use among a large sample of Canadian youth.	Overall, 9.75% of respondents were current e-cigarette users. As a student's age increases, the likelihood of using e-cigarettes decreased relative to those aged 14 years or younger. Males are almost twice as likely as females to use e-cigarettes. Relative to white respondents, Aboriginal respondents were less likely to use e-cigarettes. Students with more spending money are more likely to use e-cigarettes. Current smokers were more likely to report using e-cigarettes than non-smokers. Compared to students who have never used marijuana, current users and even noncurrent users are substantially more likely to report using e-cigarettes. Gender differences among males and females showed higher risk of e-cigarette use among female current marijuana users relative to males and female current smokers compared to males. Compared to non-binge drinkers, weekly, monthly, and occasional binge drinkers were more likely to use e-cigarettes. Similarly, students who consume energy drinks mixed with alcohol were more likely to use e-cigarettes compared to students who do not consume them.	This study provides new analysis related to the use of e-cigarettes and multiple other substances. It advances the field by providing information about the profile of e-cigarette users and more detailed information that can be used in prevention and programming efforts.

Study reference	Purpose	Results	Author conclusion
Montreuil, MacDonald, Asbridge et al	The aims of this study were to describe the prevalence of e-cigarette use among youth in Canada, by province, across sociodemographic variables and smoking-related correlates; and to examine associations among e-cigarette use, sociodemographic variables and smoking-related correlates, with adjustment for other factors.	17.7% (95% CI 16.4%–18.9%) of students in grades 6–12 reported ever using e-cigarettes; 5.7% 30-day use. Substantial variation was observed across provinces. Female students had decreased odds of past 30-day use relative to male students (odds ratio [OR] 0.71, 95% CI 0.59-0.86), whereas current smokers (OR 10.0, 95% CI 6.66-15.02) and experimental smokers (OR 3.61, 95% CI 2.40-5.42) had increased odds relative to never smokers. Students who perceived that access was easy also had increased odds of using e-cigarettes relative to students who perceived that access was difficult (OR 3.86, 95% CI 2.96-5.03). Students who believed that regular use entailed slight risk (OR 0.68, 95% CI 0.52-0.88) and those who did not know risk levels (OR 0.31, 95% CI 0.21-0.46) had decreased odds compared with those perceiving no risk.	Our data confirm that many youth used e-cigarettes in the 30 days preceding the survey, although rates were substantially higher among current and experimental smokers than among students who had never tried smoking
Morgenstern, Nies et al 2018	Explore the "gateway" hypothesis, according to which the use of e-cigarettes can motivate adolescents to start smoking conventional cigarettes.	Analysis revealed that the association between the use of e-cigarettes and the onset of conventional cigarette smoking was stronger among adolescents with low sensation-seeking scores and without any experience of alcohol intoxication.	The risk of beginning experimentation with smoking conventional cigs was 2.2 times higher among e-cigarette users. Among adolescents who have never smoked, experimentation with conventional cigarettes is more common in those who have used e-cigarettes. This effect seems to be stronger among adolescents who, in general, have a lower risk of starting to smoke.
Nahin, Bispo, Llabre, Sokolovsky	The purpose of this study was to evaluate dimensions of dependency within the young adult ENDS user population.	Automaticity, loss of control, craving, and tolerance loaded on the first factor and represent physiological 'drive.' Drive can be conceptualized as the desire to satisfy the urge to use ENDS. Affective and cognitive enhancement loaded onto the second factor and represent 'positive reinforcement.'	These data demonstrate that there may be two distinct clusters of factors driving dependence among ENDS users.
Park S, Lee H et al 2017	Aimed to investigate (a) rates of e-cigarette use and (b) significant factors associated with e-cigarette use among current cigarette users in adolescence.	Of current cigarette users, 20% smoked e-cigarettes in their lifetime but not within the past 30 days (former users), and 42% smoked e-cigarettes in their lifetime and within the past 30 days (current users). Both former and current e-cigarette use were significantly associated with male gender, higher grades, higher weekly allowance, residence in urban areas, friends' smoking, daily smoking, a higher number of cigarettes smoked, and quit attempts. In addition, current e-cigarette use was significantly associated with at-risk drinking, lifetime drug use, and lifetime sexual intercourse	E-cigarette use should be included in intervention strategies for smoking prevention and cessation. Strict regulations should be implemented in order to prohibit easy access to e-cigarettes and forbid advertising of e-cigarettes as well.
Robertson L, Hoek J et al 2018	To explore the dual use of electronic nicotine delivery systems (ENDS) and smoked tobacco.	Dual use practices among participants evolved in four ways. First, as an attempt to manage the 'inauthenticity' of vaping relative to smoking and to retain meaningful rituals. Second, as complex rationalisations that framed decreased tobacco use, rather than smoking cessation, as 'success'. Third, as a means of alleviating the financial burden smoking imposed and to circumvent smoke-free policies. Lastly, dual use reflected attempts to comply with social group norms and manage stigma.	Dual use reflects both social and physical cues. It assisted participants to navigate smoking restrictions and allowed them to manage divergent norms. Policies that discourage smoking, particularly excise tax increases on smoked tobacco and smoke-free space restrictions, appear important in prompting ENDS use.
Ruokolainen O, Ollila H et al 2017	Explore the prevalence of e-cigarette use among the Finnish adult population and to examine correlates of ever use and current use of e-cigarettes prior to some changes in the Finnish regulatory scheme.	2% were current and 12% were ever users of e-cigarettes. Younger age and current or previous tobacco use increased the odds for both current and ever use of e-cigarettes when compared with never users. Unemployment and lower education were associated with current e-cigarette use and being a student was associated with ever use of e-cigarettes	The current use of e-cigarettes in the adult population is low in Finland, having at least tried is more common. Both types of e-cigarette use are concentrated to groups considered to be more vulnerable, such as younger people and those with a lower socioeconomic position. Further monitoring of e-cigarette use is needed in view of Finland's aim to become nicotine and tobacco free by 2030.

Study reference	Purpose	Results	Author conclusion
Shaddock E 2017 ABSTRACT ONLY	To explore electronic Cigarette And Tobacco Product Use in school going adolescents.	11% of total admitted to smoking cigarettes. The median age at which students started smoking was 15 years (range 12-17 years). 23% had tried e-cigarettes, 9% of whom currently used. 25% of students of the lower income school had tried e-cigarettes compared to 20% of the higher income school (p=0.43). 25% of the grade 9 (14-16 year olds) had tried e-cigarettes compared to 20% of grade 11 (16-18 year olds) (p=0.87). 38% of students had tried hookah, 50% from the lower income school versus 17% from the higher income (p=0.0001).	Experimentation with tobacco products is common in secondary school goers, especially in those from the lower income school. Electronic cigarette use is as common as conventional tobacco use.
Truman P, Glover M et al 2018	To understand practices of vaping and reasons for use.	The overriding motivation to begin and continue vaping was to stop or to reduce smoking. The results were consistent with a progression from initially both vaping and smoking using less effective electronic cigarette types, then moving to more powerful devices, experimentation with flavours and nicotine strengths—all resulting in reducing or stopping tobacco use. Lack of access to nicotine and lack of support for their chosen cessation method were the main problems reported. Vaping had resulted in effective smoking cessation for the majority of participants.	This survey of committed vapers suggests that, in New Zealand, with its advanced and highly dissuasive tobacco control program, vaping is almost exclusively used as a cessation tool. For many, it appears to have been successful.
Urrutia-Pereira M et al 2016	Prevalence and factors associated with smoking among adolescents.	Knowing about the dangers of electronic cigarettes (OR: 0.88, 95% CI: 0.21-0.92) were identified as protection factors; use of e-cigarettes higher in those who had tried conventional smoking	The prevalence of smoking among adolescents in Uruguaiana is high. The implementation of measures to reduce/stop tobacco use and its new forms of consumption, such as electronic cigarettes and hookah, are urgent and imperative in schools.

Appendix A US Academies of Sciences Conclusions

This report is titled Public Health Consequences of e-Cigarettes (Stratton, Kwan et al. 2018).

In reviewing the literature about the constituents in and exposures from e-cigarettes, the committee made nine conclusions:

Conclusion 3-1. *There is **conclusive evidence** that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with background levels.*

Conclusion 3-2. *There is **limited evidence** that e-cigarette use increases levels of nicotine and other e-cigarette constituents on a variety of indoor surfaces compared with background levels.*

Conclusion 4-1. *There is **conclusive evidence** that exposure to nicotine from e-cigarettes is highly variable and depends on product characteristics (including device and e-liquid characteristics) and how the device is operated.*

Conclusion 4-2. *There is **substantial evidence** that nicotine intake from e-cigarette devices among experienced adult e-cigarette users can be comparable to that from combustible tobacco cigarettes.*

Conclusion 5-1. *There is **conclusive evidence** that in addition to nicotine, most e-cigarette products contain and emit numerous potentially toxic substances.*

Conclusion 5-2. *There is **conclusive evidence** that, other than nicotine, the number, quantity, and characteristics of potentially toxic substances emitted from e-cigarettes is highly variable and depends on product characteristics (including device and e-liquid characteristics) and how the device is operated.*

Conclusion 5-3. *There is **substantial evidence** that except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes.*

Conclusion 5-4. *There is **substantial evidence** that e-cigarette aerosol contains metals. The origin of the metals could be the metallic coil used to heat the e-liquid, other parts of the e-cigarette device, or e-liquids. Product characteristics and use-patterns may contribute to differences in the actual metals and metal concentrations measured in e-cigarette aerosol.*

Conclusion 5-5. *There is **limited evidence** that the number of metals in e-cigarette aerosol could be greater than the number of metals in combustible tobacco cigarettes, except for cadmium, which is markedly lower in e-cigarettes compared with combustible tobacco cigarettes.*

Taken together, the evidence in support of these conclusions suggests that e-cigarette aerosol contains fewer numbers and lower levels of toxicants than smoke from combustible tobacco cigarettes. Nicotine exposure can mimic that found with use of combustible tobacco cigarettes, but is highly variable. The exposure to nicotine and toxicants from the aerosolization of flavorings and humectants is dependent on user and device characteristics, however.

A.1   Human health effects

Combustible tobacco cigarettes pose serious risks to human health; these risks are well documented and well understood. Many of those health effects emerge only after decades of cigarette smoking. E-cigarettes have only been on the market in the United States since 2006, making scientific comparisons between e-cigarettes and combustible tobacco cigarettes about most health effects difficult. However, research on short-term exposures to e-cigarettes and effects on disease symptoms and intermediate outcomes exist. An important distinction when considering these data is whether the effects are seen in an e-cigarette user who had never used combustible tobacco cigarettes (usually children or youth) or in a combustible tobacco cigarette user, with and without pre-existing tobacco-related disease, usually adults.

The committee reviewed evidence on the effects of e-cigarettes in several health domains: dependence, cardiovascular, cancer, respiratory diseases, oral diseases, maternal and foetal outcomes, and injuries and poisonings. Although the amount of literature is relatively scant and complicated by the multiple types of e-cigarettes in use even within a given study, the committee made 26 conclusions about the effects of e-cigarettes on health.

*Conclusion 7-1. There is **substantial evidence** that e-cigarette aerosols can induce acute endothelial cell dysfunction, although the long-term consequences and outcomes on these parameters with long-term exposure to e-cigarette aerosol are uncertain.*

*Conclusion 7-2. There is **substantial evidence** that components of e-cigarette aerosols can promote formation of reactive oxygen species/oxidative stress. Although this supports the biological plausibility of tissue injury and disease from long-term exposure to e-cigarette aerosols, generation of reactive oxygen species and oxidative stress induction is generally lower from e-cigarettes than from combustible tobacco cigarette smoke.*

*Conclusion 8-1. There is **substantial evidence** that e-cigarette use results in symptoms of dependence on e-cigarettes.*

*Conclusion 8-2. There is **moderate evidence** that risk and severity of dependence are lower for e-cigarettes than combustible tobacco cigarettes.*

*Conclusion 8-3. There is **moderate evidence** that variability in e-cigarette product characteristics (nicotine concentration, flavouring, device type, and brand) is an important determinant of risk and severity of e-cigarette dependence.*

*Conclusion 9-1. There is **no available evidence** whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima media-thickness and coronary artery calcification).*

*Conclusion 9-2. There is **substantial evidence** that heart rate, increases after nicotine intake from e-cigarettes.*

*Conclusion 9-3. There is **moderate evidence** that diastolic blood pressure increases after nicotine intake from e-cigarettes.*

*Conclusion 9-4. There is **limited evidence** that e-cigarette use is associated with a short-term increase in systolic blood pressure, changes in biomarkers of oxidative stress, increased endothelial dysfunction and arterial stiffness, and autonomic control.*

*Conclusion 9-5. There is **insufficient evidence** that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function.*

*Conclusion 10-1. There is **no available evidence** whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for comparisons of e-cigarette use compared with combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products.*

*Conclusion 10-2. There is **limited evidence** from in vivo animal studies using intermediate biomarkers of cancer to support the hypothesis that long-term e-cigarette use could increase the risk of cancer; there is **no available evidence** from adequate long-term animal bioassays of e-cigarette aerosol exposures to inform cancer risk.*

*Conclusion 10-3. There is **limited evidence** that e-cigarette aerosol can be mutagenic or cause DNA damage in humans, animal models, and human cells in culture.*

*Conclusion 10-4. There is **substantial evidence** that some chemicals present in e-cigarette aerosols (e.g., formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis. This supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes. Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined.*

*Conclusion 11-1. There is **no available evidence** whether or not e-cigarettes cause respiratory diseases in humans.*

*Conclusion 11-2. There is **limited evidence** for improvement in lung function and respiratory symptoms among adult smokers with asthma who switch to e-cigarettes completely or in part (dual use).*

*Conclusion 11-3. There is **limited evidence** for reduction of chronic obstructive pulmonary disease (COPD) exacerbations among adult smokers with COPD who switch to e-cigarettes completely or in part (dual use).*

*Conclusion 11-4. There is **moderate evidence** for increased cough and wheeze in adolescents who use e-cigarettes and an association with e-cigarette use and an increase in asthma exacerbations.*

*Conclusion 11-5. There is **limited evidence** of adverse effects of e-cigarette exposure on the respiratory system from animal and in vitro studies.*

*Conclusion 12-1. There is **limited evidence** suggesting that switching to e-cigarettes will improve periodontal disease in smokers.*

*Conclusion 12-2. There is **limited evidence** suggesting that nicotine and non-nicotine containing e-cigarette aerosol can adversely affect cell viability and cause cell damage of oral tissue in non-smokers.*

*Conclusion 13-1. There is **no available evidence** whether or not e-cigarettes affect pregnancy outcomes.*

*Conclusion 13-2. There is **insufficient evidence** whether or not maternal e-cigarette use affects fetal development.*

*Conclusion 14-1. There is **conclusive evidence** that e-cigarette devices can explode and cause burns and projectile injuries. Such risk is significantly increased when batteries are of poor quality, stored improperly or are being modified by users.*

*Conclusion 14-2. There is **conclusive evidence** that intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects including but not limited to seizures, anoxic brain injury, vomiting, and lactic acidosis.*

*Conclusion 14-3. There is **conclusive evidence** that intentionally or unintentionally drinking or injecting e-liquids can be fatal.*

Taken together, the evidence reviewed by the committee suggests that e-cigarettes are not without physiological activity in humans, but the implications for long-term effects on morbidity and mortality are not yet clear. Use of e-cigarettes instead of combustible tobacco cigarettes by those with existing respiratory disease might be less harmful.

A.2   Initiation and cessation

The Family Smoking Prevention and Tobacco Control Act of 2009, which is the basis for FDA's regulatory authority of tobacco products, including e-cigarettes, defined a unique regulatory standard, the public health standard. This requires that tobacco products introduced on the market after 15 February 2007 be shown to have a net population health benefit to users and non-users of the product. Operationally, if a product caused more people to begin harmful tobacco use and fewer people to quit tobacco use, even if the product itself poses less risk to the user than other products, it could be determined that the product poses a public health burden and would be kept off the market. Thus, the tobacco control field must pay close attention to the effects of e-cigarette use on initiation and cessation of combustible tobacco use, regardless of the effects of e-cigarettes on health outcomes. Although the studies reviewed had limitations, the committee was able to make seven conclusions:

Conclusion 16-1. *There is **substantial evidence** that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults.*

Conclusion 16-2. *Among youth and young adult e-cigarette users who ever use combustible tobacco cigarettes, there is **moderate evidence** that e-cigarette use increases the frequency and intensity of subsequent combustible tobacco cigarette smoking.*

Conclusion 16-3. *Among youth and young adult e-cigarette users who ever use combustible tobacco cigarettes, there is **limited evidence** that e-cigarette use increases, in the near term, the duration of subsequent combustible tobacco cigarette smoking.*

Conclusion 17-1. *Overall, there is* **limited evidence** *that e-cigarettes may be effective aids to promote smoking cessation.*

Conclusion 17-2. *There is* **moderate evidence** *from randomized controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation.*

Conclusion 17-3. *There is* **insufficient evidence** *from randomized controlled trials about the effectiveness of e-cigarettes as cessation aids compared with no treatment or to Food and Drug Administration–approved smoking cessation treatments.*

Conclusion 17-4. While the overall evidence from observational trials is mixed, there is **moderate evidence** from observational studies that more frequent use of e-cigarettes is associated with increased likelihood of cessation.

Taken together the evidence suggests that while e-cigarettes might cause youth who use them to transition to use of combustible tobacco products, they might increase adult cessation of combustible tobacco cigarettes.

A.3   Harm reduction

The committee reviewed evidence from the sections discussed above to specifically look at what is known about e-cigarette exposures and health effects when compared with combustible tobacco cigarettes. The committee reached five conclusions.

Conclusion 18-1. *There is* **conclusive evidence** *that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes.*

Conclusion 18-2.*There is* **substantial evidence** *that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems.*

Conclusion 18-3. *There is* **no available evidence** *whether or not long-term e-cigarette use among smokers (dual use) changes morbidity or mortality compared with those who only smoke combustible tobacco cigarettes.*

Conclusion 18-4. *There is* **insufficient evidence** *that e-cigarette use changes short-term adverse health outcomes in several organ systems in smokers who continue to smoke combustible tobacco cigarettes (dual users).*

Conclusion 18-5. *There is* **moderate evidence** *that second-hand exposure to nicotine and particulates is lower from e-cigarettes compared with combustible tobacco cigarettes.*

The evidence about harm reduction suggests that across a range of studies and outcomes, e-cigarettes pose less risk to an individual than combustible tobacco cigarettes.

Levels of Evidence Framework for Conclusions

Conclusive evidence: There are many supportive findings from good-quality controlled studies (including randomized and non-randomized controlled trials) with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

Substantial evidence: There are several supportive findings from good-quality observational studies or controlled trials with few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

Moderate evidence: There are several supportive findings from fair-quality studies with few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

Limited evidence: There are supportive findings from fair-quality studies or mixed findings with most favouring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

Insufficient evidence: There are mixed findings or a single poor study. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

Appendix B Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England

The key findings from this report (McNeill A 2018) are:

B.1   The effect of e-cigarette use on smoking cessation and reduction

B.1.1   Key findings

- In the first half of 2017, quit success rates in England were at their highest rates so far observed and for the first time, parity across different socioeconomic groups was observed. It is plausible that e-cigarettes have contributed to this.

- Recent estimates of additional quitters resulting annually from the availability of e-cigarettes, using the same dataset but two different methods, resulted in similar figures within the range of 16,000-22,000. Varying the assumptions, and updating these estimates for 2016, resulted in an upper bound estimate of around 57,000 additional quitters annually resulting from e-cigarettes (lower bound around 22,000). While caution is needed with these figures, the evidence suggests that e-cigarettes have contributed tens of thousands of additional quitters in England.

- E-cigarette use, alone or in combination with licensed medication and behavioural support from a Stop Smoking Service, appear to be helpful in the short term. However, fewer smokers use an e-cigarette as part of a quit attempt with a Stop Smoking Service compared with licensed medication.

- We identified 14 systematic reviews of e-cigarettes for smoking cessation and /or reduction published since our last report, seven of which included a meta-analysis. The authors of the systematic reviews arrived at the same conclusion that further randomised controlled trials of e-cigarettes are needed. However, the reviews that included a meta-analysis produced different results; two found a positive effect on cessation for e-cigarette use, four found an inconclusive effect for cessation and one found a negative effect.

B.1.2   Implications

Research

- An important focus of future research is longer-term relapse trajectories of people who use e-cigarettes for quitting compared with other stop smoking treatments and also assess whether the uptake of e-cigarettes after quitting can prevent relapse back to smoking.

- Funders should consider that although randomised controlled trials (RCTs) may yield higher internal validity this is at the cost of lower generalisability. Future robust observational studies and RCTs should consider allowing for user experimentation (e.g. trial and error of different types of e-cigarette products), as well as the inclusion of study outcomes that are relevant and meaningful for e-cigarette users.

- Funders should commission research about the effect of e-cigarettes on smoking cessation in vulnerable populations (e.g. people who smoke who have a mental illness, substance misuse disorder, homeless or prison populations).

Policy and practice

- Stop smoking practitioners and health professionals should provide behavioural support to smokers who want to use an e-cigarette to help them quit smoking.

- Stop smoking service practitioners and health professionals supporting smokers to quit should receive education and training in use of e-cigarettes in quit attempts.

- Local authorities should continue to fund and provide Stop Smoking Services in accordance with the evidence base.

B.2   Health risks of e-cigarettes

B.2.1   Key findings

- One assessment of the published data on emissions from cigarettes and e-cigarettes calculated the lifetime cancer risks. It concluded that the cancer potencies of e-cigarettes were largely under 0.5% of the risk of smoking.

- Comparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of smoking. Among e-cigarette users, two studies of biomarker data for acrolein, a potent respiratory irritant, found levels consistent with non-smoking levels.

- There have been some studies with adolescents suggesting respiratory symptoms among e-cigarette experimenters. However, small scale or uncontrolled switching studies from smoking to vaping have demonstrated some respiratory improvements.

- E-cigarettes can release aldehydes if e-liquids are overheated, but the overheating generates an aversive taste.

- To date, there is no clear evidence that specific flavourings pose health risks but there are suggestions that inhalation of some could be a source of preventable risks.

- To date, the levels of metals identified in e-cigarette aerosol do not give rise to any significant safety concerns, but metal emissions, however small, are unnecessary.

- Biomarkers of exposure assessed to date are consistent with significant reductions in harmful constituents and for a few biomarkers assessed in this chapter, similar levels to smokers abstaining from smoking or non-smokers were observed.

- One study showed no reductions across a range of biomarkers for dual users (either for nicotine replacement therapy or e-cigarette dual users).

- To date, there have been no identified health risks of passive vaping to bystanders.

- Reporting of some academic studies has been misleading.

B.2.2   Implications

Research

- More research is needed with human users about biomarkers of exposure, risk and harm and health effects over time.

- More research with biomarkers across the range of different combinations of dual use is needed.

- Adverse effects of passive vaping should be monitored.

Policy

- Policy makers and regulators should ensure that e-cigarettes are manufactured in a way that minimises harm. An advantage of e-cigarettes is that particular constituents can be removed or minimised in a way that is not feasible with tobacco cigarettes.

- Regulations should therefore be flexible to ensure any emerging evidence of constituent harmfulness can be acted upon, such that products are modified to remove any components shown to pose avoidable risks.

- Consumers and health professionals should be encouraged to use the Yellow Card Scheme for reporting adverse reactions to e-cigarette use.

- Vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits over continued smoking. Based on current knowledge, stating that vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk unambiguously so that more smokers are encouraged to make the switch from smoking to vaping. It should be noted that this does not mean e-cigarettes are safe.

- The lack of difference in biomarkers between dual users and smokers found so far underlines the need to encourage and support dual users to stop smoking altogether.

B.3   Poisonings, fires and explosions

B.3.1   Key findings

Poisonings

- There are recorded cases of poisoning from e-liquid in the UK. These have predominantly involved accidental ingestion with fewer incidences of other routes (eg ocular or dermal) of exposure.

- Intentional poisoning using e-liquids has been reported in self-harm and suicide attempts.

- Toxic effects from e-cigarette poisoning are usually short in duration and of minimal severity; severe cases and fatalities, while very rare, have been recorded.

- E-cigarette poisonings reported to medical centres most commonly occur in children under five years old. Toxic effects for this age group are usually short in duration and non-severe. Fatalities, while very rare, have also been recorded in this age group.

- Incidents of poisoning in children are often preventable and have involved liquids stored non-securely, in unmarked containers or in containers without safety caps.

Fires

- E-cigarette fires are recorded at the discretion of individual fire rescue services in the UK. Information provided to us through a Freedom of Information request suggest that, where recorded, they occur in low numbers and are vastly outweighed by fires caused by smokers' materials. There were no fatalities from fires caused by e-cigarettes in the reporting period.

- E-cigarettes and/or their batteries are recorded as the cause of fires by UK fire rescue services. The root cause of e-cigarette fires is likely to be through a malfunctioning lithium-ion battery.

Explosions

- Exploding e-cigarettes can cause severe burns and injuries that require intensive and prolonged medical treatment especially when they explode in users' hands, pockets or mouths.

- Incidents are very rare. The cause is uncertain but appears to be related to malfunctioning lithium-ion batteries.

B.3.2   Implications

Research

- Research is required on the prevalence of e-liquid poisoning, fires and explosions caused by e-cigarettes in England. This will require some synthesis of existing datasets.

- Research on presence and effectiveness of safety features and instructions should be part of a future review of the EU Tobacco Products Directive.

Policy and practice

- Monitoring of fires caused by e-cigarettes should be recorded by Fire Rescue Services in a mandatory way (similar to "cooking appliances", "smokers' materials" and "other electrical appliances") and should not continue to rely on free text entry.

- E-cigarettes can trigger fire/smoke detectors and therefore consumers should be advised to move away from detectors when using them.

- It is too early to assess the impact of the EU Tobacco Products Directive in reducing poisonings, fires or explosions, or whether further regulations are needed. Therefore, continued monitoring is required to assess effectiveness of EU Tobacco Product Directive regulations (such as childproof containers), in reducing accidental ingestion of e-liquid.

- Regulations should require that labelling on e-liquid bottles advises customers to store products away from similar looking medicines such as eye drops, ear drops and children's medicine.

- Regulations should require that labelling reinforces advice on the safe storage and transportation of batteries used by e-cigarettes. For example, advice should be given that e-cigarettes should not be carried in pockets with coins, keys or other metallic objects, and that the correct charger should always be used.

- Use of e-cigarettes among young people.

B.4   Use of e-cigarettes among young people

B.4.1   Key findings

- E-cigarettes cannot be legally sold to young people under the age of 18 in most parts of the UK. Purchasing does occur including from sources rarely used for tobacco, such as online suppliers.

- Despite some experimentation with these devices among never smokers, e-cigarettes are attracting very few young people who have never smoked into regular use.

- E-cigarettes do not appear to be undermining the long-term decline in cigarette smoking in the UK among young people.

- Never smokers in the UK who try e-cigarettes are more likely to have tried smoking subsequently than those who have not tried e-cigarettes. A causal link has not been established and neither has progression to regular smoking. The 'common liability' hypothesis seems a plausible explanation for the relationship between e-cigarettes and smoking implementation.

B.4.2   Implications

- Trends in e-cigarette use and smoking among youth should continue to be monitored using standardised definitions of use. This should include the use of nicotine in e-cigarettes and checks on the understanding of survey questions.

- Patterns of e-cigarette purchasing by young people should be closely monitored, particularly internet sales. Age of sale regulations are in place for e-cigarettes and cigarettes and should be strongly enforced.

- Research is needed on trajectories of use – not just from e-cigarette experimentation to smoking, but also from smoking to e-cigarette use among young people.

B.5   Use of e-cigarettes in adults

B.5.1   Key findings

Prevalence

- In Great Britain (GB), prevalence of e-cigarette use in adults has plateaued at approximately 6% of the adult population.

- E-cigarette use among never smokers in GB remains very rare at less than 1%, similar to the level of use of nicotine replacement therapy. Among never smokers who have ever used e-cigarettes, a minority have used nicotine-containing liquids and the vast majority not progressed to regular use.

- Prevalence of e-cigarette use and trial among smokers has plateaued while use and trial among ex-smokers continue to increase.

- Socioeconomic differences in e-cigarette use by smokers and recent ex-smokers have become smaller with no clear gradient in prevalence by occupational grade.

- Prevalence of dual use (use and smoking) is similar for e-cigarette users and users of nicotine replacement therapy.

Characteristics of use

- Most e-cigarette trial does not become regular use.

- Most current e-cigarette users use daily and have used e-cigarettes for more than six months.

- Models with refillable tanks for liquids are the most widely used type.

- Since May 2017, nicotine concentration in liquids has been limited to a maximum of 20mg/mL. In March 2017, around 6% of e-cigarette users reported using higher nicotine concentrations; substantial proportions had difficulties reporting these figures so more may have been affected by the limit.

- The most popular groups of flavours among current e-cigarette users are fruit (29%), tobacco (27%) and menthol/mint (25%).

- Specialist vape shops (physical premises rather than online) are the most popular place of purchase (>40%).

- The most common reason for e-cigarette use continues to be in order to stop smoking, and smokers who use e-cigarettes on average have higher motivation to stop smoking than other smokers.

International

- Data can be outdated by the time of publication.

- Prevalence of current use in GB is at the higher end for countries in the EU where the average is 2% for current e-cigarette use. Prevalence estimates for current e-cigarette use in the US are around 4% to 6%, which is similar to GB.

- Across international surveys, a consistently low prevalence (<1%) of e-cigarette use has been reported among never-smokers; one exception is one Spanish survey at 1.2%.

- Prevalence figures found for smokers and ex-smokers vary more widely across surveys in different countries (4% to 22% among smokers and 0.1% to 5% among ex-smokers).

B.5.2   Implications

Research

- As recommended in the 2015 PHE report, trends in e-cigarette use among adults should continue to be monitored using standardised definitions of use. Measures should include frequency and type of device used including different types of tank models.

- E-cigarette use among ex-smokers needs monitoring and further evidence to understand when and why they take up e-cigarette use and whether this is associated with an increase or decrease of relapse to smoking.

- More research is needed into different patterns of e-cigarette use while smoking and their effect on subsequent smoking behaviour to understand how best to move dual users to stop smoking.

- More research is needed on the impact of e-cigarettes on health and economic inequalities associated with smoking; in particular on use of e-cigarettes in disadvantaged groups with high smoking prevalence and smoking-related morbidity and mortality, such as those with mental health problems or offenders. Data that have been gathered from the Adult Psychiatric Morbidity Survey should be released for analysis.

Policy

- As recommended in 2015 and as per existing NICE guidance, all smokers should be supported to stop smoking completely, including 'dual users' who smoke and use e-cigarettes.

- Access to e-cigarettes should be improved for smokers in disadvantaged groups.

B.6 Nicotine

B.6.1 Key findings

- The addictiveness of nicotine depends on the delivery system.

- It is possible that the addictiveness of tobacco cigarettes may be enhanced by compounds in the smoke other than nicotine.

- As e-cigarettes have evolved, their nicotine delivery has improved. This could mean that their addiction potential has increased, but this may also make them more attractive to smokers as a replacement for smoking. It is not yet clear how addictive e-cigarettes are, or could be, relative to tobacco cigarettes.

- While nicotine has effects on physiological systems that could theoretically lead to health harms, at systemic concentrations experienced by smokers and e-cigarette users, long-term use of nicotine by 'snus' (a low nitrosamine form of smokeless tobacco) users has not been found to increase the risk of serious health problems in adults, and use of nicotine replacement therapy by pregnant smokers has not been found to increase risk to the foetus.

- Adolescent nicotine use (separate from smoking) needs more research.

- The long-term impact of nicotine from e-cigarettes on lung tissue is not yet known and may be different from its impact systemically.

B.6.2   Implications

Research

- More research on nicotine in comparison to tobacco cigarette smoking is needed, and the popularity of e-cigarettes enables such research, albeit in the context of the other components in e-cigarette and e-cigarette aerosol.

- Further research is needed on the similarities and differences in addictiveness of e-cigarettes and tobacco cigarettes and the potential harms associated with inhaled nicotine.

Policy and practice

- Widespread misperceptions about the relative risks of nicotine and tobacco need to be addressed and corrected.

- Clear messages, based on current evidence about nicotine, its relationship with harms, and its addictiveness, compared with smoking, are necessary and could have a marked impact on public health.

- Policies on tobacco and e-cigarettes should have at their core the recognition that nicotine use per se presents minimal risk of serious harm to physical health and that its addictiveness depends on how it is administered

Glossary

Term	Definition
ad libitum	At one's pleasure/ as desired.
Adjusted geometric mean (GM)	The central tendency of a set of numbers (n) expressed as the nth root of the product of the n numbers.
Aortic stiffness	Stiffness of the aorta (a large artery located near the heart and lungs).
Arterial elasticity	Ability of the arteries to expand and contract.
Atomizer	Component in the e-cigarette that heats the e-liquid to the point of aerosolisation.
Between-countries	A comparison where the country is the unit of analysis – for example, an analysis of the mean population age compared to the Gross Domestic Product.
Bone resorption	The process of dissolving bones to release minerals.
Bronchoalveolar lavage	A medical procedure in which a bronchoscope is passed through the mouth or nose into the lungs and fluid is squirted into a small part of the lung and then collected for examination.
Candidiasis	Fungal infection.
Capillary	Small blood vessels.
Carbon monoxide (CO)	Toxic gas produced by cigarettes.
Carboxyhemoglobin (COHb)	Carbon monoxide and haemoglobin, formed in red blood cells after inhalation of carbon monoxide.
Cartomizer	A combined atomizer and cartridge. The cartomizer combines a heating element and an e-liquid delivery system into a single unit.
Causal relationship/ Causality	An effect occurring as a result of their being a sufficient cause.
Cell viability	An assessment of the number of alive and dead cells in a sample of cells.
Cigalike	Electronic cigarette designed to look like a cigarette, usually disposable. Also known as first generation e-cigarettes.
Coil/Heating coil	Most commonly, a piece of nichrome or kanthal wire (containing nickel and chromium) wrapped around a wick, which once heated, aerosolizes e-liquid. Cartomizers can come in a single coil, dual coil, or multiple coil configurations, with more coils associated with greater production of aerosol.
Confounder	An event or trait which influences both an exposure and outcome, and which may result in a mistaken assessment of the relationship between them.
Conventional cigarette	Tobacco cigarettes/ traditional cigarettes/ combustible tobacco.
Covariate	A variable/ event/ trait that possibly predicts an outcome.
Craniofacial	head, skull, face, neck, jaws and associated structures.
Cross-sectional study	An observational study where measurements are made at one point in time.
Deep blood flow	Blood flow in veins found in the muscles and along the bones.
Disability adjusted life years (DALYs)	A measure of burden of disease, defined as the cumulative number of years lost due to poor health across a population.
DNA adducts	Segment of DNA bound to cancer-causing chemicals.
DNA fragmentation	Breaking down DNA.
E-cigarette	Any device with a heating element that produces an aerosol from a liquid that users can inhale.

E-juice, e-liquid	The liquid that produces the aerosol in the e-cigarette; usually made up of nicotine, propylene glycol, glycerine and flavourings.
Electrocardiogram (ECG)	A device used to measure the electrical activity of the heart.
Emphysematous lung destruction	Increased air spaces in the lung leading to destruction of the lung surface area.
Epithelium	Tissues/ cells which line the outer surfaces of organs or blood vessels in the body.
'Ever-user'	A person who has used a device or object at least once – contrasted with 'never-user' e.g. an 'ever-user' of e-cigarettes.
F-fluorodeoxyglucose (FDG) positron emission tomography/computer tomography	PET scan; an imaging test using radioactive tracers.
First generation/second generation/third generation/fourth generation e-cigarettes	First generation e-cigarettes generally refer to cigalikes with similar appearance to combustible tobacco cigarettes. Second generation often appear as pen-like devices with batteries with a greater capacity than cigalikes. Third generation (Advanced Personal Vaporisers) come in various shapes and sizes and contain mods ('modification' devices with a fire button, battery compartment and connector) which may or may not enable regulation of the e-cigarette voltage/wattage output. Second, third and fourth generation devices contain refillable tanks for e-solutions. Fourth generation e-cigarettes include mods that enable regulation of voltage/wattage and temperature control.
Fractional exhaled nitric oxide	Measurement of airway inflammation tested via breath tests.
Gene expression	Protein resulting from information coded by a gene.
Gingival crevicular fluid	Inflammatory secretions from gums.
Gingival pain	Gum pain.
Hairy tongue	Tongue appears dark and furry.
Health indice	An indicator of health used to describe the health of a population, e.g. life expectancy.
Health parameter	A variable used to describe health, e.g. serum cholesterol.
Hookah	A smoking device which uses heated water to vaporise the substance to be inhaled. Also known as a waterpipe.
Hypoxia	Oxygen deficiency in cells or an organ.
In utero	Within the uterus.
Intracranial self-stimulation	Paradigm for quantifying brain reward.
IOS (Impulse Oscillometry System)	A system to measure lung function using sound waves.
Leukocyte	Cells which help to fight disease.
Longitudinal study	An observational study where measurements are made on the same individuals for at least two time points.
Macrophage	A cell responsible for detecting, engulfing and destroying foreign cells.
Meta analysis	A statistical and scientific process where the results of multiple studies are combined to determine an overall result.
Metabolites	Substances which are required for metabolism or are formed by metabolism.
Mucociliary clearance	Self-clearing mechanism of the lungs.

Nasopharyngeal pneumococcal colonisation	An infection in the nasopharynx (top of throat).
Nasopharyngitis	A common viral infection, also known as a 'cold'.
Natural killer (NK) cells	Cells which help to fight disease.
NET (neutrophil extracellular trap)	The immune system's first line of defence against infection.
Nicotine equivalents	A measurement of the nicotine content within a person or substance.
NNAL	A chemical produced in the body after exposure to NNK.
NNK	A chemical found in and produced by tobacco products.
Oral lesions	A sore in the mouth, usually located in the gums.
Oxidative stress	Propensity for reactive oxygen species to cause molecular damage in a living system.
Peak Expiratory Flow	Maximum speed of a person's breath exhalation.
Personal vaporiser	The entire e-cigarette device; usually refers to second and third-generation products.
Phagocytosis	The process by which cells ingest bacteria or other material.
Plaque index	A measurement of plaque accumulation.
Plasma	An extracellular component of human blood containing water, salts and proteins.
Pro-inflammatory cytokines	Molecules which trigger inflammation.
Puff topography	Term used to describe how an e-cigarette is used. Includes duration of puffs, volume of vapour inhaled per puff and period of time between puffs.
Pulmonary function	Respiratory tract function.
Quit ratio	The percentage of former smokers amongst ever smokers.
Randomised controlled trial (RCT)	An experimental study in which subjects are randomly assigned to receive different interventions.
Reactive hyperaemia index (RHI)	A measurement of the brief increase in blood to the organs which occurs after inadequate blood supply.
Representative data	Data from a sample which accurately represents a larger set of data.
Respiratory system	The system in the body responsible for breathing (e.g. lungs, nose, mouth).
Respiratory system resistance	Resistance found within the respiratory tract when breathing in and exhaling.
Secondary analysis	An analysis of data which was primarily collected for another purpose.
Selection bias	Bias occurring when participants are selected for a study in a way that is related to the study outcome measures.
Self-stigma	The internalisation of external stigma, i.e. internalising public opinions which negatively reflect on oneself.
Shisha	A waterpipe, or the molasses-based tobacco concoction smoked in a hookah.
Social 'normalisation'	When ideas and actions are seen as 'normal' by a population or group of people.
Splenocardiac Axis	an inflammatory signaling network characterized by sympathetic nerve stimulation of hematopoietic tissues, such as the bone marrow and spleen, which then release proinflammatory monocytes that populate atherosclerotic plaques, thereby promoting ischemic heart disease.

Sputum	Saliva.
Superficial blood flow	Blood flow in veins found immediately under the skin.
Systematic review	A review of published papers on a topic which addresses a research question by including all papers which match pre-defined inclusion and exclusion criteria.
Tank	Refillable part of an e-cigarette (from 2nd generation device) that holds the e-solution.
Tank-model e-cigarette	E-cigarettes which are generally larger than cigalikes with refillable liquid tanks. Also known as second and third generation e-cigarettes.
Temporality	How a relationship is dependent on time i.e. a cause and effect relationship must have the cause occurring before the effect.
Titration	The process of determining the concentration of the e-cigarette liquid (e.g. nicotine concentration, amount of e-liquid used).
To adjust for	A statistical method by which the relationship between two factors is examined while holding another variable constant. It may be used to nullify the impact of confounding variables.
Tonsilloliths	Tonsil stones.
Uncontrolled trial	A study where subjects are given a treatment but no comparison group (given no treatment) is investigated .
Vagal tone	Activity of the vagus nerve.
Vagus nerve	A nerve involved in control of the heart, lungs, and digestive tract.
Vaping	The process of using an e-cigarette i.e. inhaling the vaporised e-cigarette liquid.
Volatile Organic Toxicants/ Compounds (VOCs)	Organic molecules which become vapours or gases at low temperatures.
Waterpipe	A smoking device which uses heated water to vaporise the substance to be inhaled e.g. a hookah.

References

Abadi, S., E. T. Couch, B. W. Chaffee and M. M. Walsh (2017). "Perceptions Related to Use of Electronic Cigarettes among California College Students." J Dent Hyg **91**(1): 35-43.

Ackley, E., J. T. B. Williams, C. Kunrath, M. Monson, A. Ignatiuk and J. Gaensbauer (2018). "Too Hot to Handle? When Vaporizers Explode." J Pediatr.

Agarwal, D., A. Loukas and C. L. Perry (2017). "Examining College Students' Social Environment, Normative Beliefs, and Attitudes in Subsequent Initiation of Electronic Nicotine Delivery Systems." Health Educ Behav: 1090198117739672.

Agochukwu, N. and J. Y. Liau (2018). "Debunking the myth of e-cigarettes: A case of free flap compromise due to e-cigarette use within the first 24 hours." J Plast Reconstr Aesthet Surg **71**(3): 451-453.

Aherrera, A., P. Olmedo, M. Grau-Perez, S. Tanda, W. Goessler, S. Jarmul, R. Chen, J. E. Cohen, A. M. Rule and A. Navas-Acien (2017). "The association of e-cigarette use with exposure to nickel and chromium: A preliminary study of non-invasive biomarkers." Environ Res **159**: 313-320.

AIHW. (2017). "National Drug Strategy Household Survey 2016: detailed findings."   Retrieved May 2018

from https://www.aihw.gov.au/reports/illicit-use-of-drugs/ndshs-2016-detailed/data.

Alasmari, F., L. E. Crotty Alexander, J. A. Nelson, I. T. Schiefer, E. Breen, C. A. Drummond and Y. Sari (2017). "Effects of chronic inhalation of electronic cigarettes containing nicotine on glial glutamate transporters and alpha-7 nicotinic acetylcholine receptor in female CD-1 mice." Prog Neuropsychopharmacol Biol Psychiatry **77**: 1-8.

Alexander, J. P. and P. Williams (2017). "Understanding adolescent e-cigarette users: attitudes, beliefs, and social norms." Annals of Behavioral Medicine **51**: S2866-S2867.

Amato, M. S., R. G. Boyle and D. Levy (2017). "E-cigarette use 1 year later in a population-based prospective cohort." Tob Control **26**(e2): e92-e96.

Anderson, H., C. Richie and A. Bernard (2017). "A Surprisingly Volatile Smoking Alternative: Explosion and Burns as Risks of E-Cigarette Use." J Burn Care Res **38**(5): e884.

Andresen, N. S., D. J. Lee, C. E. Kowalski and R. Bayon (2018). "Fall With e-Cigarette in Mouth Resulting in Pharyngeal and Esophageal Burns." JAMA Otolaryngol Head Neck Surg.

Anic, G. M., E. Holder-Hayes, B. K. Ambrose, B. L. Rostron, B. Coleman, A. Jamal and B. J. Apelberg (2018). "E-cigarette and Smokeless Tobacco Use and Switching Among Smokers: Findings From the National Adult Tobacco Survey." Am J Prev Med.

Antherieu, S., A. Garat, N. Beauval, M. Soyez, D. Allorge, G. Garcon and J. M. Lo-Guidice (2017). "Comparison of cellular and transcriptomic effects between electronic cigarette vapor and cigarette smoke in human bronchial epithelial cells." Toxicol In Vitro 45(Pt 3): 417-425.

Ashford, K. B., N. R. Chavan, A. Wiggins, J. Barnett, A. McCubbin, L. Ducas and J. M. O'Brien (2018). "Prenatal electronic cigarette, dual use and nicotine dependency." American Journal of Obstetrics and Gynecology 218(1): S431-S432.

ATSDR. (2012). "Manganese." Toxic Substances Portal Retrieved 14.06, 2018, from https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=102&tid=23.

ATSDR. (2013). "Chromium Toxicity - What Are the Physiologic Effects of Chromium Exposure?" Retrieved 14.06, 2018, from https://www.atsdr.cdc.gov/csem/csem.asp?csem=10&po=10.

ATSDR. (2014). "Nickel." Toxic Substances Portal Retrieved 14.06, 2018, from https://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=244&tid=44.

Aufderheide, M. and M. Emura (2017). "Phenotypical changes in a differentiating immortalized bronchial epithelial cell line after exposure to mainstream cigarette smoke and e-cigarette vapor." Exp Toxicol Pathol 69(6): 393-401.

Ayers, J. W., E. C. Leas, J. P. Allem, A. Benton, M. Dredze, B. M. Althouse, T. B. Cruz and J. B. Unger (2017). "Why do people use electronic nicotine delivery systems (electronic cigarettes)? A content analysis of Twitter, 2012-2015." PLoS One 12(3): e0170702.

Baldassarri, S. R., S. L. Bernstein, G. L. Chupp, M. D. Slade, L. M. Fucito and B. A. Toll (2018). "Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study." Addict Behav 80: 1-5.

Ban, C., D. G. Krishnan and Y. Abdallah (2017). "Ballistic trauma from an exploding electronic cigarette: Case report." Oral and Maxillofacial Surgery Cases 3(3): 61-63.

Bandiera, F. C., A. Loukas, X. Li, A. V. Wilkinson and C. L. Perry (2017). "Depressive Symptoms Predict Current E-Cigarette Use Among College Students in Texas." Nicotine Tob Res 19(9): 1102-1106.

Barber, K. E., B. Ghebrehiwet, W. Yin and D. A. Rubenstein (2017). "Endothelial Cell Inflammatory Reactions Are Altered in the Presence of E-Cigarette Extracts of Variable Nicotine." Cellular and Molecular Bioengineering 10(1): 124-133.

Bardellini, E., F. Amadori, G. Conti and A. Majorana (2018). "Oral mucosal lesions in electronic cigarettes consumers versus former smokers." Acta Odontol Scand 76(3): 226-228.

Bauld, L., A. M. MacKintosh, B. Eastwood, A. Ford, G. Moore, M. Dockrell, D. Arnott, H. Cheeseman and A. McNeill (2017). "Young People's Use of E-Cigarettes across the United Kingdom: Findings from Five Surveys 2015-2017." Int J Environ Res Public Health **14**(9).

Bauman, Z. M., J. Roman, M. Singer and G. A. Vercruysse (2017). "Canary in the coal mine-Initial reports of thermal injury secondary to electronic cigarettes." Burns **43**(3): e38-e42.

Behar, R. Z., Y. Wang and P. Talbot (2017). "Comparing the cytotoxicity of electronic cigarette fluids, aerosols and solvents." Tob Control.

Bengalli, R., E. Ferri, M. Labra and P. Mantecca (2017). "Lung Toxicity of Condensed Aerosol from E-CIG Liquids: Influence of the Flavor and the In Vitro Model Used." Int J Environ Res Public Health **14**(10).

Berry, C., S. Burton and E. Howlett (2017). "Are Cigarette Smokers', E-Cigarette Users', and Dual Users' Health-Risk Beliefs and Responses to Advertising Influenced by Addiction Warnings and Product Type?" Nicotine Tob Res **19**(10): 1185-1191.

Berry, K. M., L. M. Reynolds, J. M. Collins, M. B. Siegel, J. L. Fetterman, N. M. Hamburg, A. Bhatnagar, E. J. Benjamin and A. Stokes (2018). "E-cigarette initiation and associated changes in smoking cessation and reduction: the Population Assessment of Tobacco and Health Study, 2013-2015." Tobacco control.

Bharadwaj, S., R. J. Mitchell, A. Qureshi and J. H. Niazi (2017). "Toxicity evaluation of e-juice and its soluble aerosols generated by electronic cigarettes using recombinant bioluminescent bacteria responsive to specific cellular damages." Biosens Bioelectron **90**: 53-60.

Bigman, C. A., S. Mello, A. Sanders-Jackson and A. S. L. Tan (2018). "Speaking up about Lighting up in Public: Examining Psychosocial Correlates of Smoking and Vaping Assertive Communication Intentions among U.S. Adults." Health Commun: 1-11.

Bishop, E., L. Haswell, J. Adamson, S. Costigan, D. Thorne and M. Gaca (2018). "TEMPORARY REMOVAL: An approach to testing undiluted e-cigarette aerosol in vitro using 3D reconstituted human airway epithelium." Toxicol In Vitro.

Boas, Z., P. Gupta, R. S. Moheimani, M. Bhetraratana, F. Yin, K. M. Peters, J. Gornbein, J. A. Araujo, J. Czernin and H. R. Middlekauff (2017). "Activation of the "Splenocardiac Axis" by electronic and tobacco cigarettes in otherwise healthy young adults." Physiol Rep **5**(17).

Bold, K. W., G. Kong, D. A. Cavallo, D. R. Camenga and S. Krishnan-Sarin (2017). "E-Cigarette Susceptibility as a Predictor of Youth Initiation of E-Cigarettes." Nicotine Tob Res **20**(1): 140-144.

Bold, K. W., M. E. Morean, G. Kong, P. Simon, D. R. Camenga, D. A. Cavallo and S. Krishnan-Sarin (2017). "Early age of e-cigarette use onset mediates the association between impulsivity and e-cigarette use frequency in youth." Drug Alcohol Depend **181**: 146-151.

Bold, K. W., S. Sussman, S. S. O'Malley, R. Grana, J. Foulds, H. Fishbein and S. Krishnan-Sarin (2018). "Measuring E-cigarette dependence: Initial guidance." Addict Behav **79**: 213-218.

Bonevski, B., A. Guillaumier, E. Skelton, A. Shakeshaft, M. Farrell, F. Tzelepis, A. J. Dunlop, C. Paul and C. D'Este (2017). "ALCOHOL AND OTHER DRUG TREATMENT CLIENT PERCEPTIONS OF ELECTRONIC CIGARETTE USE, SAFETY AND HARM REDUCTION." Drug and Alcohol Review **36**: 22-22.

Boulay, M. E., C. Henry, Y. Bosse, L. P. Boulet and M. C. Morissette (2017). "Acute effects of nicotine-free and flavour-free electronic cigarette use on lung functions in healthy and asthmatic individuals." Respir Res **18**(1): 33.

Breheny, D., J. Adamson, D. Azzopardi, A. Baxter, E. Bishop, T. Carr, I. Crooks, K. Hewitt, T. Jaunky, S. Larard, F. Lowe, O. Oke, M. Taylor, S. Santopietro, D. Thorne, B. Zainuddin, M. Gaca, C. Liu, J. Murphy and C. Proctor (2017). "A novel hybrid tobacco product that delivers a tobacco flavour note with vapour aerosol (Part 2): In vitro biological assessment and comparison with different tobacco-heating products." Food Chem Toxicol **106**(Pt A): 533-546.

Breheny, D., O. Oke, K. Pant and M. Gaca (2017). "Comparative Tumor Promotion Assessment of e-Cigarette and Cigarettes Using the In Vitro Bhas 42 Cell Transformation Assay." Environmental and Molecular Mutagenesis **58**(4): 190-198.

Brikmanis, K., A. Petersen and N. Doran (2017). "E-cigarette use, perceptions, and cigarette smoking intentions in a community sample of young adult nondaily cigarette smokers." Psychol Addict Behav **31**(3): 336-342.

Brooks, J. K., J. W. Kleinman, J. B. Brooks and M. A. Reynolds (2017). "Electronic cigarette explosion associated with extensive intraoral injuries." Dent Traumatol **33**(2): 149-152.

Brown, J. E. H. (2018). "'Doing Things Little by Little': Smoking and Vaping While Being Pharmaceutically Treated for Schizophrenia." Anthropological Forum: 1-13.

Browne, M. and D. G. Todd (2018). "Then and now: Consumption and dependence in e-cigarette users who formerly smoked cigarettes." Addict Behav **76**: 113-121.

Bunch, K., M. Fu, M. Ballbe, N. Matilla-Santader, C. Lidon-Moyano, J. C. Martin-Sanchez, E. Fernandez and J. M. Martinez-Sanchez (2018). "Motivation and main flavour of use, use with nicotine and dual use of electronic cigarettes in Barcelona, Spain: a cross-sectional study." BMJ open **8**(3): e018329-e018329.

Camenga, D. R., G. Kong, D. A. Cavallo and S. Krishnan-Sarin (2017). "Current and Former Smokers' Use of Electronic Cigarettes for Quitting Smoking: An Exploratory Study of Adolescents and Young Adults." Nicotine Tob Res **19**(12): 1531-1535.

Cancer Council Victoria. (2018). "Prevalence of smoking—adults." Tobacco in Australia- Facts and Issues Retrieved 13.06, 2018, from http://www.tobaccoinaustralia.org.au/chapter-1-prevalence/1-3-prevalence-of-smoking-adults.

Cancer Council Victoria. (2018). "Prevalence of tobacco use among Aboriginal peoples and Torres Strait Islanders." Tobacco in Australia- Facts and Issues Retrieved 13.06, 2018, from http://www.tobaccoinaustralia.org.au/chapter-1-prevalence/1-9-prevalence-of-tobacco-use-among-aboriginal-peo.

Canistro, D., F. Vivarelli, S. Cirillo, C. Babot Marquillas, A. Buschini, M. Lazzaretti, L. Marchi, V. Cardenia, M. T. Rodriguez-Estrada, M. Lodovici, C. Cipriani, A. Lorenzini, E. Croco, S. Marchionni, P. Franchi, M. Lucarini, V. Longo, C. M. Della Croce, A. Vornoli, A. Colacci, M. Vaccari, A. Sapone and M. Paolini (2017). "E-cigarettes induce toxicological effects that can raise the cancer risk." Sci Rep 7(1): 2028.

Cant, A., B. Collard and D. Cunliffe (2017). "Electronic cigarettes: Necrotic ulcer." Br Dent J 222(4): 226.

Caponnetto, P., M. Maglia, M. C. Cannella, L. Inguscio, M. Buonocore, C. Scoglio, R. Polosa and V. Vinci (2017). "Impact of Different e-Cigarette Generation and Models on Cognitive Performances, Craving and Gesture: A Randomized Cross-Over Trial (CogEcig)." Front Psychol 8: 127.

Caraballo, R. S., P. R. Shafer, D. Patel, K. C. Davis and T. A. McAfee (2017). "Quit Methods Used by US Adult Cigarette Smokers, 2014-2016." Prev Chronic Dis 14: E32.

Carpenter, M. J., B. W. Heckman, A. E. Wahlquist, T. L. Wagener, M. L. Goniewicz, K. M. Gray, B. Froeliger and K. M. Cummings (2017). "A Naturalistic, Randomized Pilot Trial of E-Cigarettes: Uptake, Exposure, and Behavioral Effects." Cancer Epidemiol Biomarkers Prev 26(12): 1795-1803.

Carson, J. L., L. Zhou, L. Brighton, K. H. Mills, H. Zhou, I. Jaspers and M. Hazucha (2017). "Temporal structure/function variation in cultured differentiated human nasal epithelium associated with acute single exposure to tobacco smoke or E-cigarette vapor." Inhal Toxicol 29(3): 137-144.

Case, K. R., M. B. Harrell, A. Perez, A. Loukas, A. V. Wilkinson, A. E. Springer, M. R. Creamer and C. L. Perry (2017). "The relationships between sensation seeking and a spectrum of e-cigarette use behaviors: Cross-sectional and longitudinal analyses specific to Texas adolescents." Addict Behav 73: 151-157.

Case, K. R., A. P. Loukas, M. B. Harrell, A. V. Wilkinson, A. E. Springer, A. Perez, M. R. Creamer and C. L. Perry (2017). "The association between sensation seeking and e-cigarette use in Texas young adults: A cross-sectional study." J Am Coll Health 65(4): 277-285.

Chaffee, B. W., E. T. Couch and S. A. Gansky (2017). "Trends in characteristics and multi-product use among adolescents who use electronic cigarettes, United States 2011-2015." PLoS One 12(5): e0177073.

Chaffee, B. W., S. L. Watkins and S. A. Glantz (2018). "Electronic Cigarette Use and Progression From Experimentation to Established Smoking." Pediatrics.

Chang, H. C., Y. W. Tsai, M. N. Shiu, Y. T. Wang and P. Y. Chang (2017). "Elucidating challenges that electronic cigarettes pose to tobacco control in Asia: a population-based national survey in Taiwan." BMJ Open **7**(3): e014263.

Chaumont, M., A. Bernard, S. Pochet, C. Melot, C. El Khattabi, F. Reye, K. Zouaoui Boudjeltia, P. Van Antwerpen, C. Delporte and P. van de Borne (2018). "High Wattage E-cigarettes Induce Tissue Hypoxia and Lower Airway Injury: A Randomized Trial." Am J Respir Crit Care Med.

Chen, H., G. Li, Y. L. Chan, D. G. Chapman, S. Sukjamnong, T. Nguyen, T. Annissa, K. C. McGrath, P. Sharma and B. G. Oliver (2018). "Maternal E-Cigarette Exposure in Mice Alters DNA Methylation and Lung Cytokine Expression in Offspring." Am J Respir Cell Mol Biol **58**(3): 366-377.

Chen, J. C. (2018). "Flavored E-cigarette Use and Cigarette Smoking Reduction and Cessation-A Large National Study among Young Adult Smokers." Substance use & misuse: 1-15.

Chen, X., B. Yu and Y. Wang (2017). "Initiation of Electronic Cigarette Use by Age Among Youth in the U.S." Am J Prev Med **53**(3): 396-399.

Cheney, M., M. Gowin and A. H. Clawson (2018). "Using the Ecological Model to Understand Influences on College Student Vaping." J Am Coll Health: 1-32.

Chesaniuk, M. and A. Sokolovsky (2017). "Young adult motives for electronic nicotine delivery system use." Annals of Behavioral Medicine **51**: S2312-S2312.

Chi, A. C., B. W. Neville and M. Ravenel (2018). "Electronic cigarette explosion: Case report of an emerging cause of orofacial trauma." Trauma (United Kingdom) **20**(1): 62-67.

Chin, J., M. B. Lustik and M. Pflipsen (2018). "Prevalence of Use and Perceptions of Electronic Smoking Devices in a US Army Infantry Division." Mil Med **183**(1-2): e127-e133.

Cho, J. H. (2017). "The association between electronic-cigarette use and self-reported oral symptoms including cracked or broken teeth and tongue and/or inside-cheek pain among adolescents: A cross-sectional study." PLoS One **12**(7): e0180506.

Choi, K., R. Grana and D. Bernat (2017). "Electronic Nicotine Delivery Systems and Acceptability of Adult Cigarette Smoking Among Florida Youth: Renormalization of Smoking?" J Adolesc Health **60**(5): 592-598.

Clapp, P. W., E. A. Pawlak, J. T. Lackey, J. E. Keating, S. L. Reeber, G. L. Glish and I. Jaspers (2017). "Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function." Am J Physiol Lung Cell Mol Physiol **313**(2): L278-l292.

Clarke, T. N. and J. M. Lusher (2017). "Willingness to Try Electronic Cigarettes Among UK Adolescents." Journal of Child and Adolescent Substance Abuse **26**(3): 175-182.

Cobb, E., J. Hall and D. L. Palazzolo (2018). "Induction of Metallothionein Expression After Exposure to Conventional Cigarette Smoke but Not Electronic Cigarette (ECIG)-Generated Aerosol in Caenorhabditis elegans." Frontiers in Physiology **9**.

Cockburn, N., C. Gartner and P. J. Ford (2018). "Smoking behaviour and preferences for cessation support among clients of an Indigenous community-controlled health service." Drug Alcohol Rev.

Coleman, B., B. Rostron, S. E. Johnson, A. Persoskie, J. Pearson, C. Stanton, K. Choi, G. Anic, M. L. Goniewicz, K. M. Cummings, K. A. Kasza, M. L. Silveira, C. Delnevo, R. Niaura, D. B. Abrams, H. L. Kimmel, N. Borek, W. M. Compton and A. Hyland (2018). "Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) Study, Waves 1 and 2 (2013-2015)." Tobacco control.

Coleman, B. N., B. Rostron, S. E. Johnson, B. K. Ambrose, J. Pearson, C. A. Stanton, B. Wang, C. Delnevo, M. Bansal-Travers, H. L. Kimmel, M. L. Goniewicz, R. Niaura, D. Abrams, K. P. Conway, N. Borek, W. M. Compton and A. Hyland (2017). "Electronic cigarette use among US adults in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2014." Tob Control **26**(e2): e117-e126.

Conner, M., S. Grogan, R. Simms-Ellis, K. Flett, B. Sykes-Muskett, L. Cowap, R. Lawton, C. J. Armitage, D. Meads, C. Torgerson, R. West and K. Siddiqi (2017). "Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study." Tob Control.

Copeland, A. L., M. R. Peltier and K. Waldo (2017). "Perceived risk and benefits of e-cigarette use among college students." Addict Behav **71**: 31-37.

Corey, C. G., J. T. Chang and B. L. Rostron (2018). "Electronic nicotine delivery system (ENDS) battery-related burns presenting to US emergency departments, 2016." Inj Epidemiol **5**(1): 4.

Coulter, R. W. S., M. Bersamin, S. T. Russell and C. Mair (2017). "The Effects of Gender- and Sexuality-Based Harassment on Lesbian, Gay, Bisexual, and Transgender Substance Use Disparities." J Adolesc Health.

Courtney, R. (2015). The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014Us Department of Health and Human Services Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 20141081 pp. Online (grey literature): http://www.surgeongeneral.gov/library/reports/50-years-of-progress. **34:** 694-695.

Creamer, M. R., J. Delk, K. Case, C. L. Perry and M. B. Harrell (2017). "Positive Outcome Expectations and Tobacco Product Use Behaviors in Youth." Subst Use Misuse: 1-4.

Creamer, M. R., A. Loukas, S. Clendennen, D. Mantey, K. E. Pasch, C. N. Marti and C. L. Perry (2018). "Longitudinal Predictors of Cigarette Use among Students from 24 Texas Colleges." J Am Coll Health: 0.

Crotty Alexander, L. E., C. A. Drummond, M. Hepokoski, D. P. Mathew, A. Moshensky, A. Willeford, S. Das, P. Singh, Z. Yong, J. H. Lee, K. Vega, A. Du, J. Shin, C. Javier, J. Tian, J. H. Brown and E. C. Breen (2018). "Chronic Inhalation of E-Cigarette Vapor Containing Nicotine Disrupts Airway Barrier Function and Induces Systemic Inflammation and Multi-Organ Fibrosis in Mice." Am J Physiol Regul Integr Comp Physiol.

Curry, E., J. M. Nemeth, A. Wermert, S. Conroy, A. Shoben, A. K. Ferketich and M. E. Wewers (2017). "A Descriptive Report of Electronic Cigarette Use After Participation in a Community-Based Tobacco Cessation Trial." Nicotine Tob Res 20(1): 135-139.

D'Ruiz, C. D., G. O'Connell, D. W. Graff and X. S. Yan (2017). "Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers." Regul Toxicol Pharmacol 87: 36-53.

Dai, H., D. Catley, K. P. Richter, K. Goggin and E. F. Ellerbeck (2018). "Electronic Cigarettes and Future Marijuana Use: A Longitudinal Study." Pediatrics 141(5).

Davies, M. J., J. W. Birkett, M. Kotwa, L. Tomlinson and R. Woldetinsae (2017). "The impact of cigarette/e-cigarette vapour on simulated pulmonary surfactant monolayers under physiologically relevant conditions." Surface and Interface Analysis 49(7): 654-665.

De Genna, N., L. Goldschmidt, G. Richardson, N. Day and M. Cornelius (2017). "Pathways from prenatal exposures to tobacco and cannabis to adult electronic cigarette use." Neurotoxicology and Teratology 61: 151-151.

de Lacy, E., A. Fletcher, G. Hewitt, S. Murphy and G. Moore (2017). "Cross-sectional study examining the prevalence, correlates and sequencing of electronic cigarette and tobacco use among 11-16-year olds in schools in Wales." BMJ Open 7(2): e012784.

Demissie, Z., S. Everett Jones, H. B. Clayton and B. A. King (2017). "Adolescent Risk Behaviors and Use of Electronic Vapor Products and Cigarettes." Pediatrics 139(2).

Deveci SE, D. F., Acik Y, Ozan AT (2004). "The measurement of exhaled carbon monoxide in healthy smokers and non-smokers." Respiratory Medicine 98: 551-556.

Dobbs, P. D., B. Hammig and L. J. Henry (2017). "E-cigarette use among US adolescents: Perceptions of relative addiction and harm." Health Education Journal 76(3): 293-301.

East, K., S. C. Hitchman, I. Bakolis, S. Williams, H. Cheeseman, D. Arnott and A. McNeill (2018). "The Association Between Smoking and Electronic Cigarette Use in a Cohort of Young People." J Adolesc Health.

Ekanem, U. S., V. M. Cardenas, R. Cen, W. Simon, I. P. Chedjieu, M. Woodward, R. R. Delongchamp and J. G. Wheeler (2017). "Electronic Nicotine Delivery Systems and Smoking Cessation in Arkansas, 2014." Public Health Rep 132(2): 210-219.

El-Khoury Lesueur, F., C. Bolze and M. Melchior (2018). "Factors associated with successful vs. unsuccessful smoking cessation: Data from a nationally representative study." Addict Behav **80**: 110-115.

Ernst & Young (2016). E-cigarettes: an emerging category. London, UK, Ernst & Young**:** 4.

Etter, J. F. (2017). "Electronic cigarette: a longitudinal study of regular vapers." Nicotine Tob Res.

European Commission. (2017). "Attitudes of Europeans towards tobacco and electronic cigarettes."   Retrieved 18.05.2018, 2018, from http://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/Survey/getSurveyDetail/instruments/SPECIAL/yearFrom/2016/yearTo/2018/surveyKy/2146.

Farsalinos, K. E., G. Siakas, K. Poulas, V. Voudris, K. Merakou and A. Barbouni (2018). "Electronic cigarette use in Greece: an analysis of a representative population sample in Attica prefecture." Harm Reduction Journal **15**.

Fat, L. N., S. Scholes and J. S. Mindell (2017). "Motivation to quit smoking and changes in cigarette consumption, among smokers who use e-cigarettes, findings from the health survey for england." Journal of Epidemiology and Community Health **71**: A33-A33.

Fite, P. J., C. C. Cushing, J. Poquiz and A. L. Frazer (2018). "Family influences on the use of e-cigarettes." Journal of Substance Use: 1-6.

Foran, I., N. R. Oak and M. J. Meunier (2017). "High-Pressure Injection Injury Caused by Electronic Cigarette Explosion: A Case Report." JBJS Case Connect **7**(2): e36.

Fracol, M., R. Dorfman, L. Janes, S. Kulkarni, K. Bethke, N. Hansen and J. Kim (2017). "The Surgical Impact of E-Cigarettes: A Case Report and Review of the Current Literature." Arch Plast Surg **44**(6): 477-481.

Franks, A. M., W. A. Hawes, K. R. McCain and N. Payakachat (2017). "Electronic cigarette use, knowledge, and perceptions among health professional students." Curr Pharm Teach Learn **9**(6): 1003-1009.

Fryar, C. D., Y. Ostchega, C. M. Hales, G. Zhang and D. Kruszon-Moran (2017). "Hypertension Prevalence and Control Among Adults: United States, 2015-2016." NCHS Data Brief(289): 1-8.

Fuller, T., A. Acharya, G. Bhaskar, M. Yu, S. Little and T. Tarin (2017). "Evaluation of e-cigarettes users urine for known bladder carcinogens." Journal of Urology **197**(4): E1179-E1179.

Ganapathy, V., J. Manyanga, L. Brame, D. McGuire, B. Sadhasivam, E. Floyd, D. A. Rubenstein, I. Ramachandran, T. Wagener and L. Queimado (2017). "Electronic cigarette aerosols suppress cellular antioxidant defenses and induce significant oxidative DNA damage." PLoS One **12**(5): e0177780.

Gee, J., K. Prasad, S. Slayford, A. Gray, K. Nother, A. Cunningham, E. Mavropoulou and C. Proctor (2018). "Assessment of tobacco heating product THP1.0. Part 8: Study to determine puffing topography, mouth level exposure and consumption among Japanese users." Regulatory Toxicology and Pharmacology **93**: 84-91.

Gerloff, J., I. K. Sundar, R. Freter, E. R. Sekera, A. E. Friedman, R. Robinson, T. Pagano and I. Rahman (2017). "Inflammatory Response and Barrier Dysfunction by Different e-Cigarette Flavoring Chemicals Identified by Gas Chromatography-Mass Spectrometry in e-Liquids and e-Vapors on Human Lung Epithelial Cells and Fibroblasts." Appl In Vitro Toxicol **3**(1): 28-40.

Giachello, A. L., V. Thanh-Huyen, T. J. Payne, R. M. Robertson, C. Rodriguez, A. Groom, K. Walker, J. Hart, S. Langdon, V. Okhomina, A. Kesh, S. R. Seale, E. Navas-Nacher, E. Murillo, M. Sims, P. Salazar-Mitchell, R. Landry and V. Bates-Ambrus (2017). "Use of Tobacco Products Among LGBTQ: Results From 2016 Surveys & Focus Groups." Circulation **135**.

Giovacchini, C. X., L. Pacek, F. J. McClernon and L. G. Que (2017). "Use and Perceived Risk of Electronic Cigarettes Among North Carolina Middle and High School Students." N C Med J **78**(1): 7-13.

Giovenco, D. P. and C. D. Delnevo (2018). "Prevalence of population smoking cessation by electronic cigarette use status in a national sample of recent smokers." Addict Behav **76**: 129-134.

Global Tobacco Control. (nd.). "Country Comparison Database."   Retrieved 12.06.2018, from www.globaltobaccocontrol.org/e-cigarette/country-comparison-database.

Goldbach, J. T., E. H. Mereish and C. Burgess (2017). "Sexual Orientation Disparities in the Use of Emerging Drugs." Subst Use Misuse **52**(2): 265-271.

Goldenson, N. I., A. M. Leventhal, M. D. Stone, R. S. McConnell and J. L. Barrington-Trimis (2017). "Associations of Electronic Cigarette Nicotine Concentration With Subsequent Cigarette Smoking and Vaping Levels in Adolescents." JAMA Pediatr **171**(12): 1192-1199.

Goniewicz, M. L., M. Gawron, D. M. Smith, M. Peng, P. Jacob, 3rd and N. L. Benowitz (2017). "Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study." Nicotine Tob Res **19**(2): 160-167.

Gonzalez Roz, A., R. Secades Villa and S. Weidberg (2017). "Evaluating nicotine dependence levels in e-cigarette users." Adicciones **29**(2): 136-138.

Gorini, G., G. Ferrante, E. Quarchioni, V. Minardi, M. Masocco, P. Fateh-Moghadam, S. Campostrini, P. D'Argenio and D. Galeone (2017). "Electronic cigarette use as an aid to quit smoking in the representative Italian population PASSI survey." Prev Med **102**: 1-5.

Gravely, S., G. T. Fong, K. M. Cummings, M. Yan, A. C. Quah, R. Borland, H. H. Yong, S. C. Hitchman, A. McNeill, D. Hammond, J. F. Thrasher, M. C. Willemsen, H. G. Seo, Y. Jiang, T. Cavalcante, C. Perez, M. Omar and K. Hummel (2014). "Awareness, trial, and current use of electronic cigarettes

in 10 countries: Findings from the ITC project." Int J Environ Res Public Health **11**(11): 11691-11704.

Gubner, N. R., A. Pagano, B. Tajima and J. Guydish (2017). "A comparison of daily versus weekly electronic cigarette users in treatment for substance abuse." Nicotine Tob Res.

Gucht, D. V., K. Adriaens and F. Baeyens (2017). "Online Vape Shop Customers Who Use E-Cigarettes Report Abstinence from Smoking and Improved Quality of Life, But a Substantial Minority Still Have Vaping-Related Health Concerns." Int J Environ Res Public Health **14**(7).

Hall, M. T., R. P. Austin, T. A. Do and A. McGlynn (2018). "Vape and Aviate: Electronic-Cigarette Use and Misuse in Naval Aviation." Mil Med **183**(3-4): e165-e170.

Hammig, B., P. Daniel-Dobbs and H. Blunt-Vinti (2017). "Electronic cigarette initiation among minority youth in the United States." Am J Drug Alcohol Abuse **43**(3): 306-310.

Hammond, D., J. L. Reid, A. G. Cole and S. T. Leatherdale (2017). "Electronic cigarette use and smoking initiation among youth: a longitudinal cohort study." Cmaj **189**(43): E1328-e1336.

Harrell, P. T., S. M. H. Naqvi, A. D. Plunk, M. Ji and S. S. Martins (2017). "Patterns of youth tobacco and polytobacco usage: The shift to alternative tobacco products." Am J Drug Alcohol Abuse **43**(6): 694-702.

Harris, A. C., P. Muelken, J. R. Smethells, K. Yershova, I. Stepanov, T. T. Olson, K. J. Kellar and M. G. LeSage (2018). "Effects of nicotine-containing and "nicotine-free" e-cigarette refill liquids on intracranial self-stimulation in rats." Drug Alcohol Depend **185**: 1-9.

Harrold, T. C., A. K. Maag, S. Thackway, J. Mitchell and L. K. Taylor (2015). "Prevalence of e-cigarette users in New South Wales." Medical Journal of Australia **203**(8): 326-+.

Harshman, J., M. Vojvodic and A. D. Rogers (2017). "Burns associated with e-cigarette batteries: A case series and literature review." Cjem: 1-9.

Harvanko, A. M., C. A. Martin, R. J. Kryscio, W. W. Stoops, J. A. Lile and T. H. Kelly (2017). "A Prototypical First-Generation Electronic Cigarette Does Not Reduce Reports of Tobacco Urges or Withdrawal Symptoms among Cigarette Smokers." J Addict **2017**: 6748948.

Haswell, L. E., A. Baxter, A. Banerjee, I. Verrastro, J. Mushonganono, J. Adamson, D. Thorne, M. Gaca and E. Minet (2017). "Reduced biological effect of e-cigarette aerosol compared to cigarette smoke evaluated in vitro using normalized nicotine dose and RNA-seq-based toxicogenomics." Sci Rep **7**(1): 888.

Henry, A. D., J. Gettens, J. A. Savageau, D. Cullen and A. Landau (2017). "Massachusetts Medicaid members that smoked in 2008: Characteristics associated with smoking status in 2014." PLoS One **12**(10): e0186144.

Hershberger, A., M. Connors, M. Um and M. A. Cyders (2017). "The Theory of Planned Behavior and E-cig Use: Impulsive Personality, E-cig Attitudes, and E-cig Use." International Journal of Mental Health and Addiction: 1-11.

Hickey, S., J. Goverman, J. Friedstat, R. Sheridan and J. Schulz (2018). "Thermal injuries from exploding electronic cigarettes." Burns.

Hiler, M., A. Breland, T. Spindle, S. Maloney, T. Lipato, N. Karaoghlanian, A. Shihadeh, A. Lopez, C. Ramoa and T. Eissenberg (2017). "Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience." Exp Clin Psychopharmacol 25(5): 380-392.

Hines, J. Z., S. C. Fiala and K. Hedberg (2017). "Electronic Cigarettes as an Introductory Tobacco Product Among Eighth and 11th Grade Tobacco Users - Oregon, 2015." MMWR Morb Mortal Wkly Rep 66(23): 604-606.

Hirano, T., T. Tabuchi, R. Nakahara, N. Kunugita and Y. Mochizuki-Kobayashi (2017). "Electronic Cigarette Use and Smoking Abstinence in Japan: A Cross-Sectional Study of Quitting Methods." Int J Environ Res Public Health 14(2).

Hong, H., J. Barrington-Trimis, F. Liu, R. Urman and R. McConnell (2017). "Reasons For Electronic Cigarette Use Among Southern California Young Adults." American Journal of Respiratory and Critical Care Medicine 195.

Ikonomidis, I., D. Vlastos, K. Kourea, G. Kostelli, M. Varoudi, G. Pavlidis, P. Efentakis, H. Triantafyllidi, J. Parissis, I. Andreadou, E. Iliodromitis and J. Lekakis (2018). "Electronic Cigarette Smoking Increases Arterial Stiffness and Oxidative Stress to a Lesser Extent Than a Single Conventional Cigarette: An Acute and Chronic Study." Circulation 137(3): 303-306.

Jain, R. B. (2018). "Concentrations of selected metals in blood, serum, and urine among US adult exclusive users of cigarettes, cigars, and electronic cigarettes." Toxicological and Environmental Chemistry 100(1): 134-142.

Jamal, A., E. Phillips, A. S. Gentzke, D. M. Homa, S. D. Babb, B. A. King and L. J. Neff (2018). "Current Cigarette Smoking Among Adults — United States, 2016." Morbidity and Mortality Weekly Report 67(2): 53-59.

Javed, F., T. Abduljabbar, F. Vohra, H. Malmstrom, I. Rahman and G. E. Romanos (2017). "Comparison of Periodontal Parameters and Self-Perceived Oral Symptoms Among Cigarette Smokers, Individuals Vaping Electronic Cigarettes, and Never-Smokers." J Periodontol 88(10): 1059-1065.

Jiang, N., J. Chen, M. P. Wang, S. M. McGhee, A. C. Kwong, V. W. Lai and T. H. Lam (2016). "Electronic cigarette awareness and use among adults in Hong Kong." Addict Behav 52: 34-38.

Jiwani, A. Z., J. F. Williams, J. A. Rizzo, K. K. Chung, B. T. King and L. C. Cancio (2017). "Thermal injury patterns associated with electronic cigarettes." Int J Burns Trauma 7(1): 1-5.

Johnson, A. C., D. Mays, K. B. Hawkins, M. Denzel and K. P. Tercyak (2017). "A qualitative study of adolescent perceptions of electronic cigarettes and their marketing: Implications for prevention and policy." Children's Health Care **46**(4): 379-392.

Jones, D. M., B. A. Majeed, S. R. Weaver, K. Sterling, T. F. Pechacek and M. P. Eriksen (2017). "Prevalence and Factors Associated with Smokeless Tobacco Use, 2014-2016." Am J Health Behav **41**(5): 608-617.

Jorenby, D. E., S. S. Smith, M. C. Fiore and T. B. Baker (2017). "Nicotine levels, withdrawal symptoms, and smoking reduction success in real world use: A comparison of cigarette smokers and dual users of both cigarettes and E-cigarettes." Drug Alcohol Depend **170**: 93-101.

Kaisar, M. A., H. Villalba, S. Prasad, T. Liles, A. E. Sifat, R. K. Sajja, T. J. Abbruscato and L. Cucullo (2017). "Offsetting the impact of smoking and e-cigarette vaping on the cerebrovascular system and stroke injury: Is Metformin a viable countermeasure?" Redox Biol **13**: 353-362.

Kalkhoran, S., N. Alvarado, M. Vijayaraghavan, P. J. Lum, P. Yuan and J. M. Satterfield (2017). "Patterns of and reasons for electronic cigarette use in primary care patients." J Gen Intern Med **32**(10): 1122-1129.

Kaufmann, N. and D. Currie (2017). "The Scottish adolescent e-cigarette user: profiling from the Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS)." Public Health **147**: 69-71.

Keane, H., M. Weier, D. Fraser and C. Gartner (2017). "'Anytime, anywhere': vaping as social practice." Critical Public Health **27**(4): 465-476.

Kennedy, A. E., S. Kandalam, R. Olivares-Navarrete and A. J. G. Dickinson (2017). "E-cigarette aerosol exposure can cause craniofacial defects in Xenopus laevis embryos and mammalian neural crest cells." PLoS One **12**(9): e0185729.

Kennedy, R. D., A. Awopegba, E. De Leon and J. E. Cohen (2017). "Global approaches to regulating electronic cigarettes." Tobacco Control **26**(4): 440-445.

Kerr, D., R. Touyz and C. Delles (2017). "The immediate effects of electronic cigarette use and tobacco smoking on vascular and respiratory function in healthy volunteers: a crossover study." Journal of Human Hypertension **31**(10): 662-662.

Kilibarda, B., V. Mravcik and M. S. Martens (2016). "E-cigarette use among Serbian adults: prevalence and user characteristics." Int J Public Health **61**(2): 167-175.

Kim, S. Y., S. Sim and H. G. Choi (2017). "Active, passive, and electronic cigarette smoking is associated with asthma in adolescents." Sci Rep **7**(1): 17789.

King, J. L., B. A. Reboussin, J. Spangler, J. Cornacchione Ross and E. L. Sutfin (2018). "Tobacco product use and mental health status among young adults." Addict Behav **77**: 67-72.

Kinnunen, J. M., J. L. K. Minkkinen, H. Ollila and A. Rimpela (2017). "Follow-up of adolescent electronic cigarette use in Finland." <u>European Journal of Public Health</u> **27**.

Kinouani, S., E. Pereira and C. Tzourio (2017). "Electronic Cigarette Use in Students and Its Relation with Tobacco-Smoking: A Cross-Sectional Analysis of the i-Share Study." <u>Int J Environ Res Public Health</u> **14**(11).

Kong, G., B. Idrisov, A. Galimov, R. Masagutov and S. Sussman (2017). "Electronic Cigarette Use Among Adolescents in the Russian Federation." <u>Subst Use Misuse</u> **52**(3): 332-339.

Kotz, D., J. Brown and R. West (2013). "Predictive validity of the Motivation To Stop Scale (MTSS): A single-item measure of motivation to stop smoking." <u>Drug and Alcohol Dependence</u> **128**(1): 15-19.

Krishnan-Sarin, S., B. G. Green, G. Kong, D. A. Cavallo, P. Jatlow, R. Gueorguieva, E. Buta and S. S. O'Malley (2017). "Studying the interactive effects of menthol and nicotine among youth: An examination using e-cigarettes." <u>Drug Alcohol Depend</u> **180**: 193-199.

Kristjansson, A. L., M. J. Mann and M. L. Smith (2017). "Prevalence of substance use among middle school-aged e-cigarette users compared with cigarette smokers, nonusers, and dual users: Implications for primary prevention." <u>Subst Abus</u> **38**(4): 473-476.

Kristjansson, A. L., M. J. Mann, M. L. Smith and I. D. Sigfusdottir (2017). "Social Profile of Middle School-Aged Adolescents Who Use Electronic Cigarettes: Implications for Primary Prevention." <u>Prevention Science</u>: 1-8.

Kulik, M. C., N. E. Lisha and S. A. Glantz (2018). "E-cigarettes Associated With Depressed Smoking Cessation: A Cross-sectional Study of 28 European Union Countries." <u>Am J Prev Med</u>.

Kwon, E., D. C. Seo, H. C. Lin and Z. Chen (2018). "Predictors of youth e-cigarette use susceptibility in a U.S. nationally representative sample." <u>Addict Behav</u> **82**: 79-85.

Lam, R. P. K., M. H. Y. Tang, S. C. Leung, Y. K. Chong, M. S. H. Tsui and T. W. L. Mak (2017). "Supraventricular tachycardia and acute confusion following ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA: a case report with quantitative analysis of serum drug concentrations." <u>Clin Toxicol (Phila)</u> **55**(7): 662-667.

Lanza, H. I. and H. Teeter (2018). "Electronic Nicotine Delivery Systems (E-cigarette/Vape) use and Co-Occurring Health-Risk Behaviors Among an Ethnically Diverse Sample of Young Adults." <u>Subst Use Misuse</u> **53**(1): 154-161.

Lanza, S. T., M. A. Russell and J. L. Braymiller (2017). "Emergence of electronic cigarette use in US adolescents and the link to traditional cigarette use." <u>Addict Behav</u> **67**: 38-43.

Lappas, A. S., A. S. Tzortzi, E. M. Konstantinidi, S. I. Teloniatis, C. K. Tzavara, S. A. Gennimata, N. G. Koulouris and P. K. Behrakis (2018). "Short-term respiratory effects of e-cigarettes in healthy individuals and smokers with asthma." Respirology **23**(3): 291-297.

Laube, B. L., N. Afshar-Mohajer, K. Koehler, G. Chen, P. Lazarus, J. M. Collaco and S. A. McGrath-Morrow (2017). "Acute and chronic in vivo effects of exposure to nicotine and propylene glycol from an E-cigarette on mucociliary clearance in a murine model." Inhal Toxicol **29**(5): 197-205.

Lechner, W. V., T. Janssen, C. W. Kahler, J. Audrain-McGovern and A. M. Leventhal (2017). "Bi-directional associations of electronic and combustible cigarette use onset patterns with depressive symptoms in adolescents." Prev Med **96**: 73-78.

Lee, C., H. H. Yong, R. Borland, A. McNeill and S. C. Hitchman (2018). "Acceptance and patterns of personal vaporizer use in Australia and the United Kingdom: Results from the International Tobacco Control survey." Drug Alcohol Depend **185**: 142-148.

Lee, H. W., S. H. Park, M. W. Weng, H. T. Wang, W. C. Huang, H. Lepor, X. R. Wu, L. C. Chen and M. S. Tang (2018). "E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells." Proc Natl Acad Sci U S A **115**(7): E1560-e1569.

Lee, H. Y., H. C. Lin, D. C. Seo and D. K. Lohrmann (2017). "Determinants associated with E-cigarette adoption and use intention among college students." Addict Behav **65**: 102-110.

Lee, Y. O., J. M. Nonnemaker, B. Bradfield, E. C. Hensel and R. J. Robinson (2017). "Examining Daily Electronic Cigarette Puff Topography Among Established and Non-established Cigarette Smokers in their Natural Environment." Nicotine Tob Res.

Lee, Y. O., J. K. Pepper, A. J. MacMonegle, J. M. Nonnemaker, J. C. Duke and L. Porter (2018). "Examining Youth Dual and Polytobacco Use with E-Cigarettes." International journal of environmental research and public health **15**(4).

Leslie, L. J., P. Vasanthi Bathrinarayanan, P. Jackson, J. A. Mabiala Ma Muanda, R. Pallett, C. J. P. Stillman and L. J. Marshall (2017). "A comparative study of electronic cigarette vapor extracts on airway-related cell lines in vitro." Inhal Toxicol **29**(3): 126-136.

Levy, D. T., R. Borland, E. N. Lindblom, M. L. Goniewicz, R. Meza, T. R. Holford, Z. Yuan, Y. Luo, R. J. O'Connor, R. Niaura and D. B. Abrams (2018). "Potential deaths averted in USA by replacing cigarettes with e-cigarettes." Tob Control **27**(1): 18-25.

Levy, D. T., Z. Yuan and Y. Li (2017). "The Prevalence and Characteristics of E-Cigarette Users in the U.S." Int J Environ Res Public Health **14**(10).

Levy, D. T., Z. Yuan, Y. Luo and D. B. Abrams (2017). "The Relationship of E-Cigarette Use to Cigarette Quit Attempts and Cessation: Insights From a Large, Nationally Representative U.S. Survey." Nicotine Tob Res.

Loonat, K., R. Sagar and C. Selinger (2018). "Current smoking trends in British IBD patients in the age of e-cigarettes." Journal of Crohns & Colitis **12**: S473-S474.

Lopez AD, C. N., Piha T. (1994). "A descriptive model of the cigarette epidemic in developed countries." Tobacco Control **3**: 242-247.

Lozano, P., I. Barrientos-Gutierrez, E. Arillo-Santillan, P. Morello, R. Mejia, J. D. Sargent and J. F. Thrasher (2017). "A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents." Drug Alcohol Depend **180**: 427-430.

Masiero, M., C. Lucchiari, K. Mazzocco, G. Veronesi, P. Maisonneuve, C. Jemos, E. O. Sale, S. Spina, R. Bertolotti and G. Pravettoni (2018). "E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial." Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.

McConnell, R., J. L. Barrington-Trimis, K. Wang, R. Urman, H. Hong, J. Unger, J. Samet, A. Leventhal and K. Berhane (2017). "Electronic Cigarette Use and Respiratory Symptoms in Adolescents." Am J Respir Crit Care Med **195**(8): 1043-1049.

McKeganey, N., M. Barnard and C. Russell (2018). "Vapers and vaping: E-cigarettes users views of vaping and smoking." Drugs: Education, Prevention and Policy **25**(1): 13-20.

McNeill A, B. L., Calder R, Bauld L, Robson D. (2018). "Evidence Review of e-cigarettes and heated tobacco products 2018. A Report comissioned by Public Health England.".

McNeill A, B. L., Calder R, Bauld L, Robson D. (2018). Evidence Review of e-cigarettes and heated tobacco products 2018. A Report commissioned by Public Health England. London, Public Health England.

McNeill, A., L. S. Brose, R. Calder, L. Bauld and D. Robson (2018). Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England.

Mendy, V. L., R. Vargas, G. Cannon-Smith, M. Payton, E. Byambaa and L. Zhang (2017). "Electronic Cigarette Use among Mississippi Adults, 2015." J Addict **2017**: 5931736.

Merianos, A. L., R. A. Yockey, K. J. Wood, L. A. Nabors, K. A. King and R. A. Vidourek (2017). Friend and family influence on electronic cigarette use among hispanic adolescents nationwide. Advances in Health and Disease. Volume 1**:** 209-226.

Miler, J. A. and P. Hajek (2017). "Resolution of recurrent tonsillitis in a non-smoker who became a vaper. A case study and new hypothesis." Med Hypotheses **109**: 17-18.

Milicic, S. and S. T. Leatherdale (2017). "The Associations Between E-Cigarettes and Binge Drinking, Marijuana Use, and Energy Drinks Mixed With Alcohol." J Adolesc Health **60**(3): 320-327.

Ministry of Health of Ukraine. (2017). Global Adult Tobacco Survey: Ukraine 2017: Executive Summary. Ukraine, Ministry of Health of Ukraine, Kiev International Institute of Sociology, World Health Organization Regional Office for Europe, National Academy of Medical Sciences of Ukraine, & U.S. Centers for Disease Control and Prevention: 2.

Ministry of Health Viet Nam (2016). Global Adult Tobacco Fact Sheet: Viet Nam 2015. Ministry of Health Viet Nam, Vinacosh, World Health Organisation and Centers for Disease Control and Prevention. Ha Noi.

Ministry of Healthcare and Social Development of the Republic of Kazakhstan. (2014). Global Adult Tobacco Survey (GATS): The Republic of Kazakhstan, 2014: Country Report, Ministry of Healthcare and Social Development of the Republic of Kazakhstan, World Health Organisation, Centers for Disease Control and Prevention.: 22, 41.

Miyashita, L., R. Suri, E. Dearing, I. Mudway, R. E. Dove, D. R. Neill, R. Van Zyl-Smit, A. Kadioglu and J. Grigg (2018). "E-cigarette vapour enhances pneumococcal adherence to airway epithelial cells." Eur Respir J **51**(2).

Moheimani, R. S., M. Bhetraratana, K. M. Peters, B. K. Yang, F. Yin, J. Gornbein, J. A. Araujo and H. R. Middlekauff (2017). "Sympathomimetic Effects of Acute E-Cigarette Use: Role of Nicotine and Non-Nicotine Constituents." J Am Heart Assoc **6**(9).

Moheimani, R. S., M. Bhetraratana, F. Yin, K. M. Peters, J. Gornbein, J. A. Araujo and H. R. Middlekauff (2017). "Increased Cardiac Sympathetic Activity and Oxidative Stress in Habitual Electronic Cigarette Users: Implications for Cardiovascular Risk." JAMA Cardiol **2**(3): 278-284.

Morean, M. E. and A. L'Insalata (2018). "Electronic cigarette use among individuals with a self-reported eating disorder diagnosis." Int J Eat Disord **51**(1): 77-81.

Morean, M. E., N. Lipshie, M. Josephson and D. Foster (2017). "Predictors of Adult E-Cigarette Users Vaporizing Cannabis Using E-Cigarettes and Vape-Pens." Subst Use Misuse **52**(8): 974-981.

Morgenstern, M., A. Nies, M. Goecke and R. Hanewinkel (2018). "E-Cigarettes and the Use of Conventional Cigarettes." Deutsches Arzteblatt International **115**(14): 243-+.

Morley, S., J. Slaughter and P. R. Smith (2017). "Death from Ingestion of E-Liquid." Journal of Emergency Medicine **53**(6): 862-864.

Moses, E., T. Wang, S. Corbett, G. R. Jackson, E. Drizik, C. Perdomo, C. Perdomo, E. Kleerup, D. Brooks, G. O'Connor, S. Dubinett, P. Hayden, M. E. Lenburg and A. Spira (2017). "Molecular Impact of Electronic Cigarette Aerosol Exposure in Human Bronchial Epithelium." Toxicol Sci **155**(1): 248-257.

Musk, B., Hunter M, Larcombe A, Hui J, James A. (2018). "Electronic cigarette awareness, use and perception of harmfulness in middle-aged adults: the Bussleton Baby Boomer Study " Respirology **23**(Suppl 1): 171.

Muthumalage, T., M. Prinz, K. O. Ansah, J. Gerloff, I. K. Sundar and I. Rahman (2017). "Inflammatory and Oxidative Responses Induced by Exposure to Commonly Used e-Cigarette Flavoring Chemicals and Flavored e-Liquids without Nicotine." Front Physiol **8**: 1130.

Nahin, E. R., J. A. B. Bispo, M. M. Llabre and A. W. Sokolovsky (2017). "Discovering dimensions of dependency among young adult electronic nicotine delivery systems users." Annals of Behavioral Medicine **51**: S2296-S2296.

NHMRC. (2018). "Outcomes of funding rounds."   Retrieved 13.06, 2018, from https://www.nhmrc.gov.au/grants-funding/outcomes-funding-rounds.

Ni, H. and J. Xu (2016). "COPD-related Mortality by Sex and Race Among Adults Aged 25 and Over: United States, 2000-2014." NCHS Data Brief(256): 1-8.

Norii, T. and A. Plate (2017). "Electronic Cigarette Explosion Resulting in a C1 and C2 Fracture: A Case Report." J Emerg Med **52**(1): 86-88.

O'Connor, R. J., V. W. Rees, C. Rivard, D. K. Hatsukami and K. M. Cummings (2017). "Internalized smoking stigma in relation to quit intentions, quit attempts, and current e-cigarette use." Subst Abus **38**(3): 330-336.

O'Gara, E., E. Sharma, R. G. Boyle and K. A. Taylor (2017). "Exploring Exclusive and Poly-tobacco Use among Adult Cigarette Smokers in Minnesota." Am J Health Behav **41**(1): 84-91.

Oelsner, E., E. A. Hoffman, I. Barjaktarevic, E. Bleecker, C. B. Cooper, A. P. Comellas, D. Couper, G. J. Criner, M. Dransfield, M. B. Drummond, M. K. Han, R. E. Kanner, J. A. Krishnan, F. J. Martinez, R. Paine, P. G. Woodruff, R. Bowled, N. N. Hansel and R. G. Barr (2017). "E-Cigarette Use And Lung Density On Computed Tomography. Subpopulations And Intermediate Outcome Measures In COPD Study (spiromics)." American Journal of Respiratory and Critical Care Medicine **195**.

Otreba, M., L. Kosmider, J. Knysak, J. D. Warncke and A. Sobczak (2018). "E-cigarettes: voltage- and concentration-dependent loss in human lung adenocarcinoma viability." Journal of applied toxicology : JAT.

Owotomo, O. and J. Maslowsky (2017). "Marijuana and e-cigarette use in a US national sample of 8th and 10th grade never-smokers of conventional cigarettes." Journal of Applied Research on Children **8**(2).

Palazzolo, D. L., J. M. Nelson, E. A. Ely, A. P. Crow, J. Distin and S. C. Kunigelis (2017). "The Effects of Electronic Cigarette (ECIG)-Generated Aerosol and Conventional Cigarette Smoke on the Mucociliary Transport Velocity (MTV) Using the Bullfrog (R. catesbiana) Palate Paradigm." Front Physiol **8**: 1023.

Palipudi, K. M., L. Mbulo, J. Morton, L. Mbulo, R. Bunnell, G. Blutcher-Nelson, S. Kosen, G. H. Tee, A. M. Abdalla, K. A. Mutawa, A. Barbouni, E. Antoniadou, H. Fouad, R. N. Khoury, J. Rarick, D. N. Sinha and S. Asma (2016). "Awareness and Current Use of Electronic Cigarettes in Indonesia,

Malaysia, Qatar, and Greece: Findings From 2011-2013 Global Adult Tobacco Surveys." Nicotine Tob Res **18**(4): 501-507.

Palmer, A. M. and T. H. Brandon (2018). "How Do Electronic Cigarettes Affect Cravings to Smoke or Vape? Parsing the Influences of Nicotine and Expectancies Using the Balanced-Placebo Design." Journal of Consulting and Clinical Psychology **86**(5): 486-491.

Parikh, A. S. and N. Bhattacharyya (2018). "Patterns of concurrent cigarette, alcohol, and e-cigarette use: Off-setting or additive behaviors?" Laryngoscope.

Park, E. J. and Y. G. Min (2018). "The Emerging Method of Suicide by Electronic Cigarette Liquid: a Case Report." J Korean Med Sci **33**(11): e52.

Park, S., H. Lee and S. Min (2017). "Factors associated with electronic cigarette use among current cigarette-smoking adolescents in the Republic of Korea." Addict Behav **69**: 22-26.

Park, S. H., D. T. Duncan, O. E. Shahawy, L. Lee, J. A. Shearston, K. Tamura, S. E. Sherman and M. Weitzman (2017). "Characteristics of Adults Who Switched From Cigarette Smoking to E-cigarettes." Am J Prev Med **53**(5): 652-660.

Park, S. H., L. Lee, J. A. Shearston and M. Weitzman (2017). "Patterns of electronic cigarette use and level of psychological distress." PLoS One **12**(3): e0173625.

Parker, T. T. and J. Rayburn (2017). "A comparison of electronic and traditional cigarette butt leachate on the development of Xenopus laevis embryos." Toxicol Rep **4**: 77-82.

Pasquereau, A., R. Guignard, R. Andler and V. Nguyen-Thanh (2017). "Electronic cigarettes, quit attempts and smoking cessation: a 6-month follow-up." Addiction **112**(9): 1620-1628.

Patterson, S. B., A. R. Beckett, A. Lintner, C. Leahey, A. Greer, S. B. Brevard, J. D. Simmons and S. A. Kahn (2017). "A Novel Classification System for Injuries After Electronic Cigarette Explosions." Journal of Burn Care & Research **38**(1): E95-E100.

Pearce, J., C. Best, F. Haseen, D. Currie, A. M. MacKintosh, M. Stead, D. Eadie, A. MacGregor, A. Amos, J. Frank and S. Haw (2017). "Electronic cigarette use and smoking initiation in Scottish adolescents: a cohort study." European Journal of Public Health **27**: 38-38.

Penzes, M., K. L. Foley, V. Nadasan, E. Paulik, Z. Abram and R. Urban (2018). "Bidirectional associations of e-cigarette, conventional cigarette and waterpipe experimentation among adolescents: A cross-lagged model." Addict Behav **80**: 59-64.

Pepper, J. K., M. C. Farrelly and K. A. Watson (2018). "Adolescents' understanding and use of nicotine in e-cigarettes." Addictive Behaviors **82**: 109-113.

Pericot-Valverde, I., D. E. Gaalema, J. S. Priest and S. T. Higgins (2017). "E-cigarette awareness, perceived harmfulness, and ever use among U.S. adults." Prev Med **104**: 92-99.

Perkins, K. A., J. L. Karelitz and V. C. Michael (2017). "Effects of nicotine versus placebo e-cigarette use on symptom relief during initial tobacco abstinence." Exp Clin Psychopharmacol 25(4): 249-254.

Phillips, B., B. Titz, U. Kogel, D. Sharma, P. Leroy, Y. Xiang, G. Vuillaume, S. Lebrun, D. Sciuscio, J. Ho, C. Nury, E. Guedj, A. Elamin, M. Esposito, S. Krishnan, W. K. Schlage, E. Veljkovic, N. V. Ivanov, F. Martin, M. C. Peitsch, J. Hoeng and P. Vanscheeuwijck (2017). "Toxicity of the main electronic cigarette components, propylene glycol, glycerin, and nicotine, in Sprague-Dawley rats in a 90-day OECD inhalation study complemented by molecular endpoints." Food Chem Toxicol 109(Pt 1): 315-332.

Phung, A., L. Luo, N. Breik and S. Alessi-Severini (2017). "Use of smoking cessation products: A survey of patients in community pharmacies." Can Pharm J (Ott) 150(5): 326-333.

Polosa, R., F. Cibella, P. Caponnetto, M. Maglia, U. Prosperini, C. Russo and D. Tashkin (2017). "Health impact of E-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked." Sci Rep 7(1): 13825.

Polosa, R., F. Cibella, P. Caponnetto, M. Maglia and D. Tashkin (2017). "Health impact of e-cigarettes: a prospective 3.5-year study of regular users who have never smoked." Respirology 22: 22-23.

Przybyla, R. J., J. Wright, R. Parthiban, S. Nazemidashtarjandi, S. Kaya and A. M. Farnoud (2017). "Electronic cigarette vapor alters the lateral structure but not tensiometric properties of calf lung surfactant." Respir Res 18(1): 193.

Pulvers, K., A. S. Emami, N. L. Nollen, D. R. Romero, D. R. Strong, N. L. Benowitz and J. S. Ahluwalia (2018). "Tobacco Consumption and Toxicant Exposure of Cigarette Smokers Using Electronic Cigarettes." Nicotine Tob Res 20(2): 206-214.

Pywell, M. J., M. Wordsworth, R. M. Kwasnicki, P. Chadha, S. Hettiaratchy and T. Halsey (2018). "The Effect of Electronic Cigarettes on Hand Microcirculation." J Hand Surg Am.

Rahali, D., A. Jrad-Lamine, Y. Dallagi, Y. Bdiri, N. Ba, M. El May, S. El Fazaa and N. El Golli (2018). "Semen Parameter Alteration, Histological Changes and Role of Oxidative Stress in Adult Rat Epididymis on Exposure to Electronic Cigarette Refill Liquid." The Chinese journal of physiology 61(2): 75-84.

Ramirez, J. I., C. A. Ridgway, J. G. Lee, B. M. Potenza, S. Sen, T. L. Palmieri, D. G. Greenhalgh and P. Maguina (2017). "The Unrecognized Epidemic of Electronic Cigarette Burns." J Burn Care Res 38(4): 220-224.

Ramji, R., B. B. Arnetz, M. Nilsson, Y. Wiklund, H. Jamil, W. Maziak and J. Arnetz (2017). "Waterpipe use in adolescents in Northern Sweden: Association with mental well-being and risk and health behaviours." Scand J Public Health: 1403494817746534.

Rau, A. S., V. Reinikovaite, E. P. Schmidt, L. Tarasevicine-Stewart and F. W. Deleyiannis (2017). "Electronic Cigarettes Are as Toxic to Skin Flap Survival as Tobacco Cigarettes." Ann Plast Surg **79**(1): 86-91.

Reid JL, H. D., Rynard VL, Madill CL, Burkhalter R. . (2017). "E-cigarette prevalence by sex." Retrieved 11.04.2018, 2018, from https://uwaterloo.ca/tobacco-use-canada/e-cigarette-use-canada/prevalence-e-cigarette-use/e-cigarette-prevalence-sex.

Reidel, B., G. Radicioni, P. W. Clapp, A. A. Ford, S. Abdelwahab, M. E. Rebuli, P. Haridass, N. E. Alexis, I. Jaspers and M. Kesimer (2018). "E-Cigarette Use Causes a Unique Innate Immune Response in the Lung, Involving Increased Neutrophilic Activation and Altered Mucin Secretion." Am J Respir Crit Care Med **197**(4): 492-501.

Reinikovaite, V., I. E. Rodriguez, V. Karoor, A. Rau, B. B. Trinh, F. W. Deleyiannis and L. Tarasevicine-Stewart (2018). "The effects of electronic cigarette vapour on the lung: direct comparison to tobacco smoke." Eur Respir J.

Republic of the Philippines Department of Health (2017). Global Adult Tobacco Survey Fact Sheet: Philippines 2015. Republic of the Philippines Department of Health, Philippine Statistics Authority, World Health Organisation Pacific Region and Centers for Disease Control and Prevention, Republic of the Philippines Department of Health,.

Rigotti, N. A., Y. Chang, H. A. Tindle, S. M. Kalkhoran, D. E. Levy, S. Regan, J. H. K. Kelley, E. M. Davis and D. E. Singer (2018). "Association of E-Cigarette Use With Smoking Cessation Among Smokers Who Plan to Quit After a Hospitalization: A Prospective Study." Annals of internal medicine **168**(9): 613-620.

Robertson, L., J. Hoek, M. L. Blank, R. Richards, P. Ling and L. Popova (2018). "Dual use of electronic nicotine delivery systems (ENDS) and smoked tobacco: a qualitative analysis." Tob Control.

Rodu, B. and N. Plurphanswat (2017). "Quit Methods Used by American Smokers, 2013-2014." Int J Environ Res Public Health **14**(11).

Rohsenow, D. J., J. W. Tidey, R. A. Martin, S. M. Colby and T. Eissenberg (2018). "Effects of six weeks of electronic cigarette use on smoking rate, CO, cigarette dependence, and motivation to quit smoking: A pilot study." Addict Behav **80**: 65-70.

Rouabhia, M., H. J. Park, A. Semlali, A. Zakrzewski, W. Chmielewski and J. Chakir (2017). "E-Cigarette Vapor Induces an Apoptotic Response in Human Gingival Epithelial Cells Through the Caspase-3 Pathway." J Cell Physiol **232**(6): 1539-1547.

Rowell, T. R., S. L. Reeber, S. L. Lee, R. A. Harris, R. C. Nethery, A. H. Herring, G. L. Glish and R. Tarran (2017). "Flavored e-cigarette liquids reduce proliferation and viability in the CALU3 airway epithelial cell line." Am J Physiol Lung Cell Mol Physiol **313**(1): L52-l66.

Rubinstein, M. L., K. Delucchi, N. L. Benowitz and D. E. Ramo (2018). "Adolescent Exposure to Toxic Volatile Organic Chemicals From E-Cigarettes." Pediatrics.

Rudy, S. F. and E. L. Durmowicz (2017). "Electronic nicotine delivery systems: Overheating, fires and explosions." Tobacco Control 26(1): 10-18.

Russo, C., F. Cibella, E. Mondati, P. Caponnetto, E. Frazzetto, M. Caruso, G. Caci and R. Polosa (2018). "Lack of Substantial Post-Cessation Weight Increase in Electronic Cigarettes Users." International journal of environmental research and public health 15(4).

Ruther, T., D. Hagedorn, K. Schiela, T. Schettgen, H. Osiander-Fuchs and W. Schober (2018). "Nicotine delivery efficiency of first- and second-generation e-cigarettes and its impact on relief of craving during the acute phase of use." Int J Hyg Environ Health 221(2): 191-198.

Sancilio, S., M. Gallorini, A. Cataldi, L. Sancillo, R. A. Rana and V. di Giacomo (2017). "Modifications in Human Oral Fibroblast Ultrastructure, Collagen Production, and Lysosomal Compartment in Response to Electronic Cigarette Fluids." J Periodontol 88(7): 673-680.

Satteson, E. S., N. J. Walker, C. J. Tuohy and J. A. Molnar (2017). "Extensive Hand Thermal and Blast Injury From Electronic Cigarette Explosion: A Case Report." Hand (N Y): 1558944717744333.

Schoenborn, C. A. and T. C. Clarke (2017). "Percentage of Adults Who Ever Used an E-cigarette and Percentage Who Currently Use E-cigarettes, by Age Group - National Health Interview Survey, United States, 2016." Mmwr-Morbidity and Mortality Weekly Report 66(33): 892-892.

Schoenborn, C. A. and R. M. Gindi (2015). "Electronic Cigarette Use Among Adults: United States, 2014." NCHS Data Brief(217): 1-8.

Schweitzer, R. J., T. A. Wills, E. Tam, I. Pagano and K. Choi (2017). "E-cigarette use and asthma in a multiethnic sample of adolescents." Prev Med 105: 226-231.

Scungio, M., L. Stabile and G. Buonanno (2018). "Measurements of electronic cigarette-generated particles for the evaluation of lung cancer risk of active and passive users." Journal of Aerosol Science 115: 1-11.

Selya, A. S., L. Dierker, J. S. Rose, D. Hedeker and R. J. Mermelstein (2017). "The Role of Nicotine Dependence in E-Cigarettes' Potential for Smoking Reduction." Nicotine Tob Res.

Serpen, J., A. Gutierrez, K. Cushing and A. Chiplunker (2017). "The Impact of E-Cigarette Use in Inflammatory Bowel Disease." Inflammatory Bowel Diseases 23: S49-S49.

Serror, K., M. Chaouat, A. De Runz, M. Mimoun and D. Boccara (2017). "Thigh deep burns caused by electronic vaping devices (e-cigarettes): A new mechanism." Burns 43(5): 1133-1135.

Serror, K., M. Chaouat, M. M. Legrand, F. Depret, J. Haddad, N. Malca, M. Mimoun and D. Boccara (2017). "Burns caused by electronic vaping devices (e-cigarettes): A new classification proposal based on mechanisms." Burns.

Shah, A., Y. Paliwal and D. Holdford (2017). "Prevalence and characteristics of e-cigarette users among COPD patient population in the united states " Value in Health 20(5): A201-A201.

Shahab, L., M. L. Goniewicz, B. C. Blount, J. Brown, A. McNeill, K. U. Alwis, J. Feng, L. Wang and R. West (2017). "Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users A Cross-sectional Study." Annals of Internal Medicine 166(6): 390-+.

Sharapova, S. R., T. Singh, I. T. Agaku, S. M. Kennedy and B. A. King (2018). "Patterns of E-cigarette Use Frequency-National Adult Tobacco Survey, 2012-2014." Am J Prev Med 54(2): 284-288.

Sharma, R., B. Wigginton, C. Meurk, P. Ford and C. E. Gartner (2017). "Motivations and limitations associated with vaping among people with mental illness: A qualitative analysis of reddit discussions." International Journal of Environmental Research and Public Health 14(1).

Shim, T. N. and T. Kosztyuova (2018). "Allergic Contact Dermatitis to Electronic Cigarette." Dermatitis.

Simonavicius, E., A. McNeill, D. Arnott and L. S. Brose (2017). "What factors are associated with current smokers using or stopping e-cigarette use?" Drug Alcohol Depend 173: 139-143.

Smith, S. L., C. Smith, M. Cheatham and H. G. Smith (2017). "Electronic Cigarettes: A Burn Case Series." Journal for Nurse Practitioners 13(10): 693-699.

Solleti, S. K., S. Bhattacharya, A. Ahmad, Q. Wang, J. Mereness, T. Rangasamy and T. J. Mariani (2017). "MicroRNA expression profiling defines the impact of electronic cigarettes on human airway epithelial cells." Sci Rep 7(1): 1081.

Soneji, S., J. L. Barrington-Trimis, T. A. Wills, A. M. Leventhal, J. B. Unger, L. A. Gibson, J. Yang, B. A. Primack, J. A. Andrews, R. A. Miech, T. R. Spindle, D. M. Dick, T. Eissenberg, R. C. Hornik, R. Dang and J. D. Sargent (2017). "Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis." JAMA Pediatr 171(8): 788-797.

Soneji, S., Sung, H-Y, Primack, BA, Pierce, JP, Sargent, JD. (2018). "Quantifying population-level health benefits and harms of e-cigarette use in the United States." PLoS One 13(3): e0193328.

Spears, C. A., D. M. Jones, S. R. Weaver, T. F. Pechacek and M. P. Eriksen (2017). "Use of electronic nicotine delivery systems among adults with mental health conditions, 2015." International Journal of Environmental Research and Public Health 14(1).

Spears, C. A., D. M. Jones, S. R. Weaver, T. F. Pechacek and M. P. Eriksen (2018). "Motives and perceptions regarding electronic nicotine delivery systems (ENDS) use among adults with mental health conditions." Addict Behav **80**: 102-109.

Staudt, M. R., J. Salit, R. J. Kaner, C. Hollmann and R. G. Crystal (2018). "Altered lung biology of healthy never smokers following acute inhalation of E-cigarettes." Respiratory research **19**(1): 78-78.

Stewart, C. J., T. A. Auchtung, N. J. Ajami, K. Velasquez, D. P. Smith, R. De La Garza, II, R. Salas and J. F. Petrosino (2018). "Effects of tobacco smoke and electronic cigarette vapor exposure on the oral and gut microbiota in humans: a pilot study." Peerj **6**.

Stokes, A., J. M. Collins, K. M. Berry, L. M. Reynolds, J. L. Fetterman, C. J. Rodriguez, M. B. Siegel and E. J. Benjamin (2018). "Electronic Cigarette Prevalence and Patterns of Use in Adults with a History of Cardiovascular Disease in the United States." Journal of the American Heart Association **7**(9).

Stratton, K., L. Y. Kwan and D. L. Eaton (2018). Public Health Consequences of e-Cigarettes. Washington DC, Board on Population Health and Public Health Practice, Health and Medicine Division, The National Academies of Sciences, Engineering and Medicine.

Stratton, K., L. Y. Kwan and D. L. Eaton (2018). Public health consequences of e-cigarettes. Washington, DC, National Academies of Sciences, Engineering, and Medicine. .

Subialka Nowariak, E. N., R. K. Lien, R. G. Boyle, M. S. Amato and L. A. Beebe (2018). "E-cigarette use among treatment-seeking smokers: Moderation of abstinence by use frequency." Addict Behav **77**: 137-142.

Sung, B. (2017). "E-cigarette Use and Smoking Cessation Among South Korean Adult Smokers: A Propensity Score-Matching Approach." Asia Pac J Public Health: 1010539517740054.

Sussan, T. E., F. G. Shahzad, E. Tabassum, J. E. Cohen, R. A. Wise, M. J. Blaha, J. T. Holbrook and S. Biswal (2017). "Electronic cigarette use behaviors and motivations among smokers and non-smokers." BMC Public Health **17**(1): 686.

Taylor, M., T. Jaunky, K. Hewitt, D. Breheny, F. Lowe, I. M. Fearon and M. Gaca (2017). "A comparative assessment of e-cigarette aerosols and cigarette smoke on in vitro endothelial cell migration." Toxicol Lett **277**: 123-128.

Temple, J. R., R. C. Shorey, Y. Lu, E. Torres, G. L. Stuart and V. D. Le (2017). "E-cigarette use of young adults motivations and associations with combustible cigarette alcohol, marijuana, and other illicit drugs." Am J Addict **26**(4): 343-348.

Tommasi, S., S. E. Bates, R. Z. Behar, P. Talbot and A. Besaratinia (2017). "Limited mutagenicity of electronic cigarettes in mouse or human cells in vitro." Lung Cancer **112**: 41-46.

Toy, J., F. Dong, C. Lee, D. Zappa, T. Le, B. Archambeau, J. T. Culhane and M. M. Neeki (2017). "Alarming increase in electronic nicotine delivery systems-related burn injuries: A serious unregulated public health issue." Am J Emerg Med **35**(11): 1781-1782.

Treitl, D., R. Solomon, D. L. Davare, R. Sanchez and C. Kiffin (2017). "Full and Partial Thickness Burns from Spontaneous Combustion of E-Cigarette Lithium-Ion Batteries with Review of Literature." J Emerg Med **53**(1): 121-125.

Treur, J. L., A. D. Rozema, J. J. P. Mathijssen, H. van Oers and J. M. Vink (2017). "E-cigarette and waterpipe use in two adolescent cohorts: cross-sectional and longitudinal associations with conventional cigarette smoking." European Journal of Epidemiology: 1-12.

Truman, P., M. Glover and T. Fraser (2018). "An Online Survey of New Zealand Vapers." Int J Environ Res Public Health **15**(2).

Tsai, J., K. Walton, B. N. Coleman, S. R. Sharapova, S. E. Johnson, S. M. Kennedy and R. S. Caraballo (2018). "Reasons for Electronic Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2016." MMWR Morb Mortal Wkly Rep **67**(6): 196-200.

Tucker, M. R., M. Laugesen, C. Bullen and R. C. Grace (2017). "Predicting Short-Term Uptake of Electronic Cigarettes: Effects of Nicotine, Subjective Effects and Simulated Demand." Nicotine Tob Res.

UNICEF. (2015). "MODULE 1: What are the Social Ecological Model (SEM), Communication for Development (C4D)?" Communication for Development (C4D) Retrieved 13.06, 2018, from https://www.unicef.org/cbsc/index_65738.html.

Urman, R., R. McConnell, J. B. Unger, T. B. Cruz, J. M. Samet, K. Berhane and J. L. Barrington-Trimis (2018). "Electronic Cigarette and Cigarette Social Environments and Ever Use of Each Product: A Prospective Study of Young Adults in Southern California." Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.

US Dept of Health and Human Services (2016). "E-cigarette Use among Youth and Young Adults:A report of the Surgeon General."

Valentine, G. W., K. Hefner, P. I. Jatlow, R. A. Rosenheck, R. Gueorguieva and M. Sofuoglu (2017). "Impact of E-cigarettes on Smoking and Related Outcomes in Veteran Smokers With Psychiatric Comorbidity." J Dual Diagn: 1-12.

Van Der Meer, D. H., A. D. Pranger, I. Jansen, E. B. Wilms, H. Kieft and J. G. Maring (2017). "Fatal intoxication with nicotine for e-cigarette Background." Nederlands Tijdschrift voor Geneeskunde **161**(43).

Van Heel, M., D. Van Gucht, K. Vanbrabant and F. Baeyens (2017). "The Importance of Conditioned Stimuli in Cigarette and E-Cigarette Craving Reduction by E-Cigarettes." Int J Environ Res Public Health **14**(2).

Veliz, P., S. E. McCabe, V. V. McCabe and C. J. Boyd (2017). "Adolescent Sports Participation, E-cigarette Use, and Cigarette Smoking." Am J Prev Med **53**(5): e175-e183.

Vogel, E. A., D. E. Ramo and M. L. Rubinstein (2018). "Prevalence and correlates of adolescents' e-cigarette use frequency and dependence." Drug and alcohol dependence **188**: 109-112.

Walele, T., J. Bush, A. Koch, R. Savioz, C. Martin and G. O'Connell (2018). "Evaluation of the safety profile of an electronic vapour product used for two years by smokers in a real-life setting." Regul Toxicol Pharmacol **92**: 226-238.

Wang, X., X. Zhang, X. Xu and Y. Gao (2018). "Electronic cigarette use and smoking cessation behavior among adolescents in China." Addictive Behaviors **82**: 129-134.

Warner, K. E. and D. Mendez (2018). "E-cigarettes: Comparing the Possible Risks of Increasing Smoking Initiation with the Potential Benefits of Increasing Smoking Cessation." Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.

Ween, M. P., J. J. Whittall, R. Hamon, P. N. Reynolds and S. J. Hodge (2017). "Phagocytosis and Inflammation: Exploring the effects of the components of E-cigarette vapor on macrophages." Physiol Rep **5**(16).

Wei, B., M. L. Goniewicz, R. J. O'Connor, M. J. Travers and A. J. Hyland (2018). "Urinary metabolite levels of flame retardants in electronic cigarette users: A study using the data from NHANES 2013–2014." International Journal of Environmental Research and Public Health **15**(2).

Westling, E., J. C. Rusby, R. Crowley and J. M. Light (2017). "Electronic Cigarette Use by Youth: Prevalence, Correlates, and Use Trajectories From Middle to High School." J Adolesc Health **60**(6): 660-666.

Williams, T. and V. White (2018). "What Factors are Associated with Electronic Cigarette, Shisha-Tobacco and Conventional Cigarette Use? Findings from a Cross-Sectional Survey of Australian Adolescents?" Subst Use Misuse: 1-11.

World Health Organization (2016). "Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS)."

Yao, T., W. Max, H. Y. Sung, S. A. Glantz, R. L. Goldberg, J. B. Wang, Y. Wang, J. Lightwood and J. Cataldo (2017). "Relationship between spending on electronic cigarettes, 30-day use, and disease symptoms among current adult cigarette smokers in the U.S." PLoS One **12**(11): e0187399.

Yong-da Wu, S., M. P. Wang, W. H. Li, A. C. Kwong, V. W. Lai and T. H. Lam (2018). "Does Electronic Cigarette Use Predict Abstinence from Conventional Cigarettes among Smokers in Hong Kong?" International Journal of Environmental Research and Public Health **15**(3).

Yuke, K., P. Ford, W. Foley, A. Mutch, L. Fitzgerald and C. Gartner (2018). "Australian urban Indigenous smokers' perspectives on nicotine products and tobacco harm reduction." Drug Alcohol Rev **37**(1): 87-96.

Zhu, S. H., Y. L. Zhuang, S. S. Wong, S. E. Cummins and G. J. Tedeschi (2017). "E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys." Bmj-British Medical Journal **358**.