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Electronic cigarettes and health outcomes: systematic review of global evidence

Report for the Australian Department of Health

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COMPETING INTEREST STATEMENT

The authors report no financial or non-financial competing interests with respect to e-cigarettes. One of the authors (MM) has previously worked in Tobacco Control in New Zealand and another (EB) has published research on the health effects of smoking.

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Abbreviations

AIHW	Australian Institute of Health and Welfare
ANU	Australian National University
CDC	Centers for Disease Control and Prevention
CSIRO	Commonwealth Scientific and Industrial Research Organisation
EC	E-cigarette, nicotine content not specified
ENDS	Electronic nicotine delivery system (nicotine e-cigarette)
ENNDS	Electronic non-nicotine delivery system (non-nicotine e-cigarette)
EU	European Union
EVALI	E-cigarette or vaping product use-associated lung injury
JBI	Joanna Briggs Institute
NASEM	National Academies of Sciences, Engineering and Medicine
NDSHS	National Drug Strategy Household Survey
NHIS	National Health Interview Survey
NHMRC	National Health and Medical Research Council of Australia
NRT	Nicotine replacement therapy
PATH	Population Assessment of Tobacco and Health
PHE	Public Health England
SCHEER	European Union Scientific Committee on Health, Environmental and Emerging Risks
THC	Tetrahydrocannabinol
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

Executive Summary

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Background

Electronic cigarettes (e-cigarettes) are a diverse group of battery-powered devices that aerosolise a liquid – often referred to as an 'e-liquid' – for inhalation. First manufactured commercially in 2003, e-cigarettes entered broader global markets around 2006-2007. Ensuring appropriate evidence-based policy and practice relating to e-cigarettes requires integration of large-scale contemporary evidence on their safety, including both their likely direct effects on health, as well as their indirect effects, through influencing smoking behaviour.

There are a number of major independent reviews of evidence on the health effects of e-cigarettes including: the 2018 United States (US) National Academies of Sciences, Engineering and Medicine (NASEM) review; the 2018 Public Health England review with an evidence update in 2020; the literature review by the Commonwealth Scientific and Industrial Research Organisation (CSIRO) of Australia; the 2020 Irish Health Research Board literature map; the European Union Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) 2021 Opinion on electronic cigarettes; and the US Preventive Services Task Force (USPSTF) 2021 recommendations and evidence synthesis on interventions for tobacco cessation.

However, no systematic reviews of the health effects of e-cigarettes were located; nor were there any reports incorporating systematic quality assessment. The conclusions and limitations of the reviews to date, and the rapid evolution of evidence on e-cigarettes, highlight a need for a comprehensive and critical systematic review of the available global evidence to inform the public, practitioners, policymakers and other stakeholders about the health effects of e-cigarettes at the individual and population level.

Aims

This report aims to provide a systematic overview of the contemporary evidence on the health effects of nicotine and non-nicotine e-cigarette use, excluding where possible use of tetrahydrocannabinol (THC) and other illicit substances. The primary health outcomes of interest include, but are not limited to: dependence; cardiovascular disease; cancer; respiratory disease; oral diseases; reproductive outcomes; injuries and poisonings; mental health conditions; and environmental hazards with human health implications. These findings are integrated with those from previous systematic reviews on smoking uptake and cessation.

Methods

The report commences with a narrative review of contextual information on the characteristics of e-cigarettes, nicotine and non-nicotine constituents, their national and international regulation and patterns of exposure. The main body of the report is a systematic review of the worldwide contemporary evidence on health outcomes in relation to e-cigarettes, which combines an umbrella review of evidence from major national and international independent reviews with a "top-up" systematic review of evidence published since the NASEM review. Results from previous systematic reviews by the report authors on e-cigarettes and smoking uptake and cessation are also integrated. All systematic reviews followed pre-specified, registered protocols. The report was informed by the National Health and Medical Research Council of Australia E-cigarettes Working Committee stakeholder consultations and underwent expert methodological review.

Summary of key findings

Context and exposure

E-cigarette devices and e-liquids vary widely, with many thousands of products on the market. Devices range from earlier lower power and nicotine dose products designed to resemble conventional cigarettes and larger "tank" devices with variable and highly powered heating coils; to more recent small and high concentration nicotine salt "pod" and disposable products. Standard e-liquids include water, propylene glycol and vegetable glycerine and often contain flavourings and nicotine in freebase or salt form. Use of e-cigarettes results in inhalation of a complex array of chemicals originating from the e-liquid, chemical reactions in the heating coil and the device itself. These include nicotine, solvent carriers (propylene glycol, ethylene glycol and glycerol), tobacco-specific nitrosamines, volatile organic compounds, phenolic compounds, flavourings, tobacco alkaloids, aldehydes, free radicals, reactive oxygen species, furans and

metals. Toxicological studies indicate that exposure to these substances can result in adverse health effects. Nicotine is highly addictive and there is evidence from basic human and animal studies that it adversely affects cardiovascular measures and brain development and functioning.

Overall, at least 32 countries ban the sale of nicotine e-cigarettes, 79 countries – including Australia – allow them to be sold while fully or partially regulating them and the remaining 84 countries do not regulate them at all. There are currently tens of millions of e-cigarette users worldwide, with enormous variation in the prevalence of use from country to country. Use is generally more common among youth, with ever-use among people aged 8-19 varying from 2% in Cambodia to 52% in France and current use varying from 1% in Hong Kong and Mexico to 33% in Guam. In Australia, data from 2019 indicate that 11% of people aged 14 and over have ever used e-cigarettes and 2% report current at least monthly use. Use is also more common among, youth, males and smokers and the majority is not for the purposes of smoking cessation; 53.0% of current e-cigarette use is dual-use in people who also smoke, 31.5% is in past smokers and 15.5% is in never smokers.

Systematic review

The systematic umbrella and top-up review identified a total of 18,992 potentially eligible studies; 12,434 duplicates were removed and 6,558 underwent title and abstract screening. There were 227 identified in the systematic literature database search, 10 from forward and backward searching and one from grey literature consistent with the inclusion criteria on health outcomes associated with e-cigarette use. Of these 238 studies, 152 were included in the evidence synthesis and 86 were excluded from evidence synthesis as they were rated as not providing evidence suitable for assessing the causal relationship between e-cigarette use and the outcome specified. In addition to the 152 studies, 37 studies from the two previous reviews on smoking uptake and cessation were included in evidence synthesis. Therefore, a total of 189 studies were included in evidence synthesis. While data on whether e-cigarettes were nicotine- or not nicotine-delivering were generally not reported, the vast bulk of use is nicotine e-cigarettes and the health effects observed were considered to apply to nicotine e-cigarettes, unless specified otherwise.

Evidence regarding the health impacts of e-cigarettes is very limited. The current worldwide evidence indicates that use of nicotine e-cigarettes increases the risk of certain adverse health outcomes (Table i). There is conclusive evidence that e-cigarettes and their constituents cause poisoning, injuries and burns and immediate toxicity through inhalation, including seizures, and that their use leads to addiction and that they cause less serious adverse events, such as throat irritation and nausea. There is conclusive evidence that e-cigarettes cause acute lung injury, largely linked to e-liquids containing THC and vitamin E acetate, although around 1 in 8 cases in the largest study to date were from reported use of nicotine-only products. Their environmental impacts include waste, fires and indoor airborne particulate matter, which, in turn, are likely to have adverse health impacts, the extent of which cannot be determined. There is insufficient evidence regarding ceasing smoking and switching completely to e-cigarettes with respect to exacerbations of respiratory disease or changes in respiratory symptoms, lung function and other respiratory measures. There is limited evidence that use of e-cigarettes in non-smokers leads to acute reductions in lung function and other respiratory measures. Among smokers, there is moderate evidence that use of e-cigarettes increases heart rate, systolic blood pressure, diastolic blood pressure and arterial stiffness acutely after use.

There is strong evidence that e-cigarettes increase combustible smoking uptake in non-smokers, particularly youth, and limited evidence that in the clinical setting freebase nicotine e-cigarettes are efficacious as an aid to smoking cessation. There is limited evidence that ex-smokers who use e-cigarettes have around double the likelihood of relapse to resuming smoking than ex-smokers who do not use e-cigarettes.

A central finding of this systematic review is the paucity of evidence regarding e-cigarettes and clinical health outcomes. While certain more immediate risks can be identified from the current evidence, the impact of nicotine and non-nicotine e-cigarettes on important clinical health outcomes – including those related to cardiovascular disease, cancer, mental health, development in children and adolescents, reproduction, sleep, wound healing, neurological disease and endocrine, olfactory, optical, allergic and haematological conditions – is not known, as reliable evidence is lacking. The health impacts of dual smoking and e-cigarette use are not known. The evidence that is available relates largely to common health outcomes discernible within months or years of commencing use – such as addiction and effects on smoking behaviour – and acute outcomes where causality between exposure to e-cigarettes and the health event is apparent at the individual or group level – such as poisonings, burns, nicotine toxicity and lung injury.

Table i: Overview of study papers identified in the systematic review, by health outcome category and study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Dependence and abuse liability		13 7 / 6	1 0 / 1	17 9 / 8			20 11 / 9		
Cardiovascular health outcomes	1 0 / 1	11 3 / 8	1 0 / 1	6 5 / 1			8 1 / 7		1 0 / 1
Cancer			1 1 / 0				2 1 / 1		3 2 / 1
Respiratory health outcomes*		9 5 / 4	5 2 / 3	5 1 / 4		18 0 / 18	21 4 / 17	11 0 / 11	26 0 / 26
Oral health			2 1 / 1	2 2 / 0			19 1 / 18		1 0 / 1
Developmental and reproductive effects			2 0 / 2				1 0 / 1		
Burns and injuries						7 1 / 6		24 14 / 10	16 5 / 11
Poisoning						25 13 / 12		4 2 / 2	23 14 / 9
Mental health effects			1 0 / 1				8 0 / 8		
Environmental hazards with health implications**				17 9 / 8		2 0 / 2		5 0 / 5	
Neurological outcomes						3 0 / 3		2 0 / 2	7 1 / 6
Sleep outcomes							4 0 / 4		
Less serious adverse events		11 3 / 8	3 1 / 2	2 2 / 0		1 0 / 1	3 0 / 3		
Optical health				1 0 / 1			1 0 / 1		
Wound healing									2 0 / 2
Olfactory outcomes							1 0 / 1		
Endocrine outcomes							2 0 / 2		
Allergic diseases							2 0 / 2	1 0 / 1	3 2 / 1
Haematological outcomes									2 0 / 2

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first bottom small number is the count of studies from the NASEM review; the second bottom small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

* Numbers in case series and case reports represent all evidence (both studies included in the evidence synthesis and those omitted from evidence synthesis due to issues with assessment of causality).

** Characterisation of studies in environmental outcomes differs from other outcomes. Those included in non-randomised intervention studies are controlled experimental studies and those included in case series are natural experiments.

Table ii: Summary of evidence synthesis on the effects of nicotine e-cigarettes on health outcomes

Health outcome group	Summary conclusions from evidence review
Dependence and abuse liability	• Among non-smokers, there is substantial evidence that e-cigarette use results in dependence on e-cigarettes. • Among smokers, there is limited evidence that e-cigarette use results in dependence on e-cigarettes. There is limited evidence that e-cigarettes have lower abuse liability than combustible cigarettes and limited evidence that e-cigarettes have a higher abuse liability than nicotine replacement therapy products among smokers. • Among smokers, there is insufficient evidence whether abuse liability risk is influenced by flavour and nicotine concentration variations.
Cardiovascular health outcomes	• There is no available evidence on the effect of e-cigarette use on the risk of clinical cardiovascular disease outcomes, such as myocardial infarction, stroke or cardiovascular mortality. • There is no available evidence on e-cigarette use and the risk of subclinical atherosclerosis-related outcomes such as carotid intima-media thickness and coronary artery calcification. • Among non-smokers, there is insufficient evidence that e-cigarette use is related to other cardiovascular outcomes, including: increased blood pressure, heart rate, autonomic control and arterial stiffness; reduced endothelial function, hand microcirculation and cardiac function/geometry; and cardiac device interference. • Among smokers, there is moderate evidence that use of e-cigarettes increases heart rate, systolic blood pressure, diastolic blood pressure and arterial stiffness acutely after use; and limited evidence that use increases endothelial dysfunction, and that long term use after switching from combustible cigarette smoking decreases blood pressure.
Cancer	• There is no available evidence on the relationship of e-cigarette use to invasive cancer risk. • There is no available evidence on the relationship of e-cigarette use to the risk of precancer/subclinical cancer outcomes.
Respiratory health outcomes	• There is conclusive evidence that the use of e-cigarettes can cause respiratory disease (EVALI) among smokers and non-smokers. Current evidence from the largest study to date is that this lung injury is chiefly related to e-cigarettes delivering THC, with half of cases related to THC in conjunction with vitamin E acetate, and 14% in patients reporting the use of nicotine-delivering products only, indicating that the latter products can cause EVALI. • There is insufficient evidence on the relationship of e-cigarette use to other clinical respiratory outcomes, including asthma, bronchitis and COPD in smokers and no available evidence in non-smokers. • There is insufficient evidence for a reduction in respiratory exacerbations and disease progression among adult healthy, asthmatic and COPD smokers who switch to exclusive or dual-use of e-cigarettes. • There is limited evidence in non-smokers and insufficient evidence in smokers that e-cigarettes have acute (up to two hours post-exposure) effects on spirometry parameters. • There is limited evidence that e-cigarette use increases respiratory resistance and impedance in healthy and asthmatic smokers up to 30 minutes post-exposure. • There is insufficient evidence on the effect of e-cigarettes on exhaled breath outcomes among smokers and non-smokers (healthy and asthmatic). • There is insufficient evidence on the relationship of e-cigarette use to other respiratory measures (sinonasal symptoms, airway hyperresponsiveness) in smokers and no available evidence in non-smokers.
Oral health	• There is no available evidence on the relationship of e-cigarette use to clinical or intermediate/subclinical oral health outcomes in exclusive e-cigarette users, independent of the effect of smoking. • There is insufficient evidence of reduced plaque, gingival and papillary bleeding in smokers switching to e-cigarette use.

Health outcome group	Summary conclusions from evidence review
	• In populations including exclusive e-cigarette users, dual users, and non-smokers (never and former smokers), there is insufficient evidence as to the relationship of e-cigarette use to increased gum disease, bone loss around the teeth and any periodontal disease.
Developmental and reproductive effects	• There is no available evidence as to how use of e-cigarettes affects the development of children or adolescents. • There is insufficient evidence as to how e-cigarette use relates to pregnancy and foetal outcomes, such as low birthweight, preterm birth, Apgar score and small-for-gestational-age birth, among exclusive e-cigarette users and dual users. • There is no available evidence as to how use of e-cigarettes affects other reproductive outcomes.
Burns and injuries	• There is conclusive evidence that e-cigarettes can cause burns and injuries, which can be severe and can result in death.
Poisoning	• There is conclusive evidence that intentional or accidental exposure to nicotine e-liquids can lead to poisoning, which can be severe and can result in death. A significant number of accidental poisonings occur in children under the age of six. • There is conclusive evidence that use of e-cigarettes can result in nicotine toxicity.
Mental health effects	• There is no available evidence as to how e-cigarette use affects clinical mental health outcomes. • There is insufficient evidence as to the relationship of e-cigarette use to depressive symptoms and no available evidence regarding their effects on alternative subclinical mental health measures.
Environmental hazards with health implications	• There is conclusive evidence that e-cigarette use results in increased airborne particulate matter in indoor environments. • There is limited evidence that e-cigarette use results in increased concentrations of airborne nicotine and of nicotine and cotinine on indoor surfaces. • There is insufficient evidence that e-cigarette use results in increased air levels of carbon dioxide, carbon monoxide, propylene glycol, volatile organic compounds and carbonyls. • There is substantial evidence that e-cigarettes can cause fires and environmental waste and insufficient evidence as to the extent that these present a hazard to human health.
Neurological outcomes	• There is conclusive evidence that the use of e-cigarettes can lead to seizures. • There is limited evidence that injuries due to e-cigarette explosions can lead to nerve damage. • There is no available evidence as to how the use of e-cigarettes affects the risk of other clinical neurological outcomes.
Sleep outcomes	• There is no available evidence as to the effect of e-cigarettes on clinical sleep outcomes.
Less serious adverse events	• There is moderate evidence that less serious adverse events – such as throat irritation, cough, dizziness, headache and nausea – occur with use of nicotine e-cigarettes.
Optical health	• There is no available evidence on the relation of e-cigarette use to clinical optical outcomes. • There is insufficient evidence on the relation of e-cigarette use to corneal epithelial thickness or pre-corneal tear film stability and no evidence on other optical outcomes.
Wound healing	• There is no available evidence as to the effect of e-cigarette use on clinical or subclinical wound healing outcomes.
Olfactory outcomes	• There is no available evidence on the effect of e-cigarette use on clinical olfactory outcomes. • There is insufficient evidence on the relationship between use of e-cigarettes and subclinical olfactory measures.

Health outcome group	Summary conclusions from evidence review
Endocrine outcomes	• There is no available evidence on the relationship of e-cigarette use to clinical endocrine outcomes and insufficient evidence regarding subclinical endocrine outcomes of prediabetes and insulin resistance.
Allergic diseases	• There is limited evidence that e-cigarette use can lead to contact dermatitis and no available evidence on other clinical allergy outcomes.
Haematological outcomes	• There is no available evidence on the relationship of e-cigarette use to haematological outcomes.
Smoking uptake	• There is strong evidence that never smokers who use e-cigarettes are on average around three times as likely than those who do not use e-cigarettes to initiate cigarette smoking. • There is strong evidence that non-smokers who use e-cigarettes are also around three times as likely as those who do not use e-cigarettes to become current cigarette smokers. • There is limited evidence that former smokers who use e-cigarettes are more likely to relapse and resume current smoking than former smokers who have not used e-cigarettes.
Smoking and nicotine cessation	• There is limited evidence that, in the clinical context, freebase nicotine e-cigarettes may be more efficacious for smoking cessation than existing NRT, and that nicotine e-cigarettes may be more efficacious than no intervention or usual care. • Trials demonstrating efficacy were limited to products with freebase nicotine concentrations ≤20mg/mL. There is no evidence that nicotine salt products are efficacious for smoking cessation. • There is insufficient evidence that freebase nicotine e-cigarettes are efficacious for smoking cessation, compared to non-nicotine e-cigarettes or that non-nicotine e-cigarettes are efficacious for smoking cessation compared to counselling or approved NRT. • There is insufficient evidence that freebase nicotine e-cigarettes are efficacious outside the clinical setting. • No evidence on nicotine salt products was located and their efficacy for smoking cessation is unknown. • There is limited evidence that use of nicotine e-cigarettes for smoking cessation results in greater ongoing exposure to nicotine than approved NRT, through ongoing exclusive e-cigarette use or dual use if smoking continues.

Discussion

Among non-smokers, there is currently strong evidence that use of e-cigarettes is harmful to health overall, with multiple health harms and no health benefits identified in this population. Given the evidence regarding the direct health risks of e-cigarette use, the evidence that they generate new tobacco smokers – with established high levels of harm – the uncertainty about major health outcomes, and the importance of low smoking uptake as a driver of progress against tobacco, use of e-cigarettes in non-smokers, especially youth, represents a serious public health risk. In this context, high and increasing use among youth, including in Australia, is concerning. Health impacts in ex-smokers will be reduced if use is avoided, compared to using e-cigarettes, and limited evidence indicates increased risk of resumption of smoking with use of e-cigarettes.

The most common pattern of e-cigarette use in many countries, including Australia, is dual tobacco smoking and e-cigarette use. The direct health impacts of dual use are unclear and prolongation of smoking is likely to increase risks. Smokers are vulnerable to the identified adverse health consequences of e-cigarettes. While some of the risks of e-cigarette use will accrue to the smokers themselves, others – such as poisoning, environmental impacts, use by non-smokers and increased smoking uptake in non-smokers – affect other community and family members. Given the extreme harms of smoking, the balance of probabilities may be that e-cigarettes are beneficial in some smokers who use them to quit smoking completely and promptly. However, since evidence on efficacy for smoking cessation is limited, multiple risks of nicotine e-cigarettes have been identified, most users continue to smoke, and their long-term effects are unknown, the ultimate balance of safety and efficacy of the use of e-cigarettes for smoking cessation is unclear. The majority of smokers who quit do so unaided and a range of first-line approved smoking cessation aids with established safety, quality and efficacy are available. Hence, for current smokers, there continues to be insufficient evidence that the benefits of e-cigarettes outweigh their harms. This is consistent with the fact that, internationally, they are not registered as therapeutic goods and, as such, their quality, safety and efficacy for smoking cessation have not been established. It is also consistent with the World Health Organization (WHO) position that e-cigarettes should be strictly regulated for maximum protection of public health.

The identified risks of e-cigarettes are likely to be increased with: high nicotine concentrations; high e-liquid volumes; “at home” dilution and other preparation; open systems; high concentration nicotine salt products; flavourings and products likely to appeal to children, adolescents and non-smokers; adulteration; inadequate or inaccurate labelling; and non-child-resistant packaging. Nicotine e-cigarette use in the broader community, including among youth and non-smokers, and e-cigarette related risks will also increase with factors such as: availability; advertising and promotion; low cost; lack of enforcement of legislation; tobacco/nicotine industry influence; misinformation about health impacts; and high concentration nicotine salt products.

Conclusions

There is strong or conclusive evidence that nicotine e-cigarettes can be harmful to health and uncertainty regarding their impacts on a range of important health and disease outcomes. Based on the current worldwide evidence, use of nicotine e-cigarettes increases the risk of a range of adverse health outcomes, including: poisoning; toxicity from inhalation (such as seizures); addiction; trauma and burns; lung injury; and smoking uptake, particularly in youth. Their effects on most other clinical outcomes are unknown, including those related to cardiovascular disease, cancer, respiratory conditions other than lung injury, mental health, development in children and adolescents, reproduction, sleep, wound healing, neurological conditions other than seizures, and endocrine, olfactory, optical, allergic and haematological conditions. Nicotine e-cigarettes are highly addictive, underpinning increasing and widespread use among children and adolescents in many settings. Less direct evidence indicates adverse effects of e-cigarettes on cardiovascular health markers, including blood pressure and heart rate, lung function and adolescent brain development and function. Environmental impacts include indoor air pollution, waste and fires. The commonest pattern of e-cigarette use is dual e-cigarette use and tobacco smoking, which is generally considered an adverse outcome. There is limited evidence of efficacy of freebase nicotine e-cigarettes as an aid to smoking cessation in the clinical setting. E-cigarettes may be beneficial in some smokers who use them to quit smoking completely and promptly, with uncertainty about their overall balance of risks and benefits for cessation. Current evidence supports national and international efforts to avoid e-cigarette use in the general population, particularly in non-smokers and youth. Better evidence is needed on health impacts, the overall balance of quality, safety and efficacy of e-cigarettes as potential aids for smoking cessation, and effective regulatory options.

1 Introduction

1.1 Purpose and scope

This document presents a review of the health effects of electronic cigarettes (e-cigarettes). It was commissioned by the Australian Department of Health and was undertaken independently by researchers from the National Centre for Epidemiology and Population Health, The Australian National University.

1.2 Background

E-cigarettes are a diverse group of battery-powered devices that aerosolise a liquid (often referred to as an 'e-liquid') for inhalation.[1,2] The composition of e-liquids varies widely. Standard e-liquids include water, propylene glycol and vegetable glycerine and often contain flavourings and nicotine. Nicotine is in either freebase or, more recently, in salt form.[3] First manufactured commercially in China in 2003, e-cigarettes entered the European and United States (US) marketplaces around 2006-2007. They now include many thousands of devices and liquids.[4,5,6]

There are currently tens of millions of e-cigarette users worldwide, with enormous variation in the prevalence of use from country to country, reflecting diverse approaches to regulation and other factors (see Chapter 3 for more detail).[7] Ensuring appropriate evidence-based policy and practice relating to e-cigarettes requires large-scale integration of contemporary evidence on their likely effects on health, including their safety. This requires consideration of evidence regarding their direct effects on health, as well as their indirect effects – through influencing smoking behaviour. Evidence regarding the latter – in terms of effects of e-cigarettes on smoking uptake and efficacy for smoking cessation – has been reviewed in previous reports, which are summarised in Chapter 5 of this review.[8-10]

There are a number of major independent reviews of evidence on the health effects of e-cigarettes including: the 2018 US National Academies of Sciences, Engineering and Medicine (NASEM) review;[3] the 2018 Public Health England review[11] with evidence updates in 2020[12] and 2021;[13] the literature review by the Commonwealth Scientific and Industrial Research Organisation of Australia (CSIRO);[14] the 2020 Irish Health Research Board literature map;[15] the European Union Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) 2021 Opinion on electronic cigarettes[4]; and the US Preventive Services Task Force (USPSTF) 2021 recommendations and evidence synthesis on interventions for tobacco cessation.[16] The 2018 NASEM review on the human health effects of e-cigarettes reported the health outcomes associated with e-cigarette use, comparing smokers, ex-smokers and never smokers where evidence was available.[3] The review made 26 conclusions about the effects of e-cigarette use on human health, including 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*".

The review also identified evidence on health impacts of e-cigarettes as a major need, with knowledge gaps identified in the NASEM review including:

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).
2. There is no available evidence whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for e-cigarette use compared with use of combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products.
3. There is no available evidence whether or not e-cigarette use causes respiratory diseases in humans.
4. There is no available evidence whether or not e-cigarette use affects pregnancy outcomes.
5. There are no epidemiological studies examining the associations between e-cigarette use and incidence or progression of periodontal disease.
6. There are no epidemiological studies about injuries and poisonings, but the literature does contain numerous case reports, case series, and reports from passive surveillance systems, such as poison control centres.

The NASEM review identified the need for cohort studies to compare clinical and subclinical health outcomes among e-cigarette users versus combustible tobacco users.

Similar to the NASEM review,[3] the 2018 Public Health England[11] and CSIRO reviews[14] also identified a lack of evidence for long-term health outcomes and the need for further research to identify health outcomes associated with use of e-cigarettes.[11,14] These reviews note a lack of robust independent evidence on the health effects of e-cigarette use because of potential confounding by combustible tobacco smoking.[3,11,14]

The 2018 Public Health England review[11] updated a Public Health England report published in 2015 and included peer-reviewed primary research, systematic reviews, meta-analyses, repeated cross-sectional surveys and longitudinal studies published between 1 January 2015 and 18 August 2017.[11] The review focused on evidence from the United Kingdom (UK). It also included evidence on heat-not-burn products. The review only included evidence related to nicotine e-cigarettes and excluded studies on non-nicotine e-cigarettes. An update released in March 2020[12] reviewed studies of e-cigarette use among people with mental health conditions and those in pregnancy and postpartum, that were published between 5 November 2018 and 18 October 2019. An update released in February 2021 updated evidence on e-cigarettes for smoking cessation.[13]

The CSIRO review was also restricted to nicotine e-cigarettes.[14] A limitation of this review was that only Scopus and Web of Science were searched, compared to six databases searched in the NASEM and Public Health England reviews. The review included peer-reviewed primary research, systematic reviews and meta-analyses published from 1 January 2015 to 11 May 2018. The CSIRO review found likely adverse health consequences among regular users of e-cigarettes.[14] However, they found a lack of clarity about the magnitude of adverse health effects, and the quantity of e-cigarette use required to trigger adverse health effects. They also revealed lack of an independent effect of e-cigarette use on lung function, because of potential confounding by combustible tobacco smoking.

The Irish Health Research Board literature map[15] was published during the early stages of this review in June 2020. The Irish Health Research Board document stated that "long-term longitudinal cohort studies with detailed measures of exposure, specifically frequency of use and the chemical nature of the product used, are required in order to better understand if changes in the use of smoking-related products, such as the use of e-cigarettes, have a positive or negative impact on later life health outcomes." The review highlighted four main research gap areas including:

1. The comparison populations regarding smoking-related behaviours must be clearly defined.
2. The current variety of e-cigarette devices and the chemical composition of the various e-liquids available on the market needs to be documented and evaluated in order to determine the safety of these products, including the use of flavourings to entice non-smokers to initiate e-cigarette use and the issue of flavourings approved for ingestion, but not for inhalation.
3. A better understanding of the direct, mechanistic, and parallel effects of these toxins is required before assertions can be made that lower levels of exposure translate into reductions in the incidence of specific or overall disease outcomes.
4. A dearth of longitudinal information on specific populations where evidence on the impact of e-cigarettes could clearly contribute to public health policy formation. These populations include: adolescents, pregnant and lactating women and pregnancy itself (embryos and newborns), people with mental health problems, as well as patients with cancer, cardiovascular disease, or diabetes.

The Irish Health Research Board[15] noted several limitations with their literature map, which included the lack of depth with which health outcomes were explored, the limitations of the available epidemiological data in establishing causality, the lack of quality assessment and critical appraisal, and the array of e-cigarette products and difficulties generalising beyond the specific products tested.

The SCHEER review noted a range of likely health impacts of e-cigarettes and a lack of evidence, particularly on long-term health effects.[4] The USPSTF 2021 recommendations and evidence synthesis on interventions for tobacco cessation[16] noted the limited evidence on the benefits and harms of e-cigarettes.

No contemporary comprehensive systematic reviews of the current evidence on the health effects of e-cigarettes were located; nor were there any reports incorporating systematic quality assessment. The conclusions and limitations of the reviews to date, and the rapid evolution of evidence on e-cigarettes, highlight a need for a comprehensive and critical systematic review of the available evidence to inform the public, practitioners, policymakers and other stakeholders about the health effects of e-cigarettes at the individual and the population level.

2 Aims and methods

2.1 Aims

This systematic review aims to provide an overview of the contemporary evidence on the health outcomes directly related to e-cigarette use, and addresses the review question "What is the contemporary evidence on the health outcomes of nicotine and non-nicotine e-cigarette use?" It relates largely to outcomes in relation to e-cigarettes as whole products, rather than the effects of their individual constituent parts. The primary health outcomes of interest include, but are not limited to: dependence; cardiovascular disease; cancer; respiratory disease; oral diseases; reproductive outcomes; injuries and poisonings; mental health conditions; and environmental hazards with human health implications. These findings are integrated with those from previous systematic reviews on smoking uptake and cessation.

2.2 Methods

This report commences with contextual information on the characteristics of e-cigarettes, their national and international regulation, exposure to e-cigarettes and background information on nicotine and non-nicotine components. This brief section draws broadly on the methods used for the "exposure" sections in the Monographs of the International Agency for Research on Cancer, World Health Organization.[17] It presents narratives of information largely derived from national and international independent reviews to provide background to the systematic review.

The main body of the report is a systematic review of the worldwide contemporary evidence on health outcomes in relation to e-cigarettes, which combines an umbrella review of evidence from major national and international independent reviews – including NASEM, Public Health England, CSIRO, SCHEER and USPSTF reviews, and the Irish Health Research Board literature map – with a "top-up" systematic review of evidence published since the NASEM review.

In addition to the direct effects of e-cigarettes on health outcomes, e-cigarettes have the ability to indirectly impact health via influencing smoking behaviour, more specifically, smoking initiation and smoking cessation. These results are also presented and have been sourced from previous systematic reviews conducted by the report authors.[8,10] Details of the methods are presented in Appendix 1 and in the published reports.

2.3 Methodological considerations

As well as the standard issues related to establishing and excluding the effects of exposures of interests on outcomes, reliably ascertaining the health impacts of e-cigarettes presents specific challenges, including:

1. The wide range of e-liquid constituents, concentrations and devices, uncertainties about exposure and introduction of new products over time. E-cigarette use results in exposure to many thousands of different chemical combinations, with varying doses of these chemicals.[4] There are also many thousands of e-cigarette devices, capable of delivering varying doses of e-liquid constituents. New devices and e-liquids are also being introduced to the market. Hence, the combinations of chemicals delivered by e-cigarettes will vary between individuals in a given study, between studies and over time. In addition, it is often difficult to know with accuracy what the components of an e-liquid are, as labelling is variable and can be inaccurate. The components that are generally used are propylene glycol and vegetable glycerine, and most e-cigarettes are used to deliver nicotine. Health outcomes are likely to differ according to e-liquid composition and dose, including that attributable to use of different devices.

2. The wide range of health outcomes. To understand the potential health impacts of e-cigarettes, it is necessary to review the evidence on a very broad range of outcomes, including dependence on e-cigarettes, cardiovascular disease, cancer, respiratory diseases, oral diseases, maternal and foetal outcomes, injuries, burns and poisonings, mental health, human health risks from environmental impact, and other health outcomes as arise in the systematic search process. Data related to injuries, burns and poisoning and environmental impact are often not published in peer-reviewed journals, and calculating the incidence of these outcomes is challenging.[11,14]

3. The relatively recent introduction of e-cigarettes as a population exposure. Many of the adverse health impacts of new exposures take decades to become apparent. Population exposure to use of e-cigarettes has only become substantial since around 2010. It will therefore be some time before it is possible to reliably ascertain their long-term effects on health.

4. The evidence requirements for establishing and excluding causal relationships between e-cigarette exposure and disease outcomes. This review is concerned with evidence on the causal relationship of e-cigarette use to health outcomes. Evidence regarding the likely indirect health impacts of e-cigarettes via their effects on tobacco smoking behaviour has been reviewed separately.[8,9,18] From a safety perspective, the review is also concerned with the extent to which adverse effects can be excluded, including the statistical limits around estimates of risk. Given the potential for widespread exposure to e-cigarettes in the general population, relatively modest elevations in risk – of the order of 20 to 30% – are important for public health and therefore evidence is required to both detect and exclude such elevations in risk. These considerations necessitate the focus on study designs able to provide evidence relevant to causality, which are of sufficient size and quality to provide statistically reliable evidence.

4a. Study design: Broadly speaking, this includes studies where exposure to e-cigarettes can be demonstrated to precede the outcome and which are capable of contributing other evidence regarding causality.[19] These include randomised controlled trials, other intervention studies, prospective cohort studies and case-control studies, of sufficient quality and size, and suitable study design to support causal inferences. For certain outcomes when no other causal agent is likely – such as poisonings, burns and fires – case reports and evidence from surveillance systems are also informative. Cross-sectional surveys, case reports and case series generally do not permit assessment of likely causality for most outcomes.

4b. Clinical outcomes: The emphasis of this review is on clinically important health outcomes: disease endpoints such as the diagnosis of invasive cancer, cardiovascular diseases including myocardial infarction, stroke and peripheral vascular disease, respiratory diseases including asthma, infections and chronic obstructive pulmonary disease and dependency outcomes. While evidence on so-called "intermediate" outcomes (such as the thickness of artery walls) and pathophysiological parameters (e.g. heart rate, blood pressure) is presented, this is not a substitute for evidence relating to clinical outcomes and there are multiple examples of the inadequacy of, and risks relating to, use of this type of evidence for decision-making on safety (e.g. hormonal therapy for menopause).

4c. Bias and confounding, particularly in relation to tobacco smoking: A central consideration is being able to differentiate the likely effects of e-cigarette exposure from those of other factors, particularly combustible tobacco smoking. Smoking substantially increases the risk of over 30 health conditions including cancer, cardiovascular disease and respiratory disease. Contemporary Australian data show that the risk of lung cancer in current smokers is 18 times that of never smokers and in ex-smokers is 6 times (1800% and 600% increases, respectively).[20] The risk of cardiovascular disease – myocardial infarction, stroke, peripheral vascular disease, heart failure – in current smokers is around two- to three-fold that of never smokers[21] and the risk of dying of chronic obstructive pulmonary disease is more than 30-fold.[22] Moreover, among smokers the risk increases substantively with increasing duration and increasing intensity of smoking; the latter measured as number of cigarettes per day smoked. Differences in risk according to smoking intensity are large - for example, contemporary Australian data show that, compared to never smokers, the hazard ratio for lung cancer is 9.22 (95% CI 5.14-16.55) for current smokers of 1-5 cigarettes per day, increasing to 38.61 (95% CI 25.65-58.13) with >35 cigarettes per day.[20] Among ex-smokers, disease risk also varies according to age at or time since quitting.[22,23] Increased quitting among smokers diagnosed with illnesses (the "sick quitter" effect) is well-established and further complicates the picture.[24]

This is a well-recognised issue when examining the effects of exposures and outcomes known to vary according to smoking status. Where smoking has a large effect on risk and an exposure relates closely to smoking behaviour, it is virtually impossible to reliably quantify the effect of that exposure independent of smoking, if smokers are included in the analyses. Because risk varies not only according to smoking status, but also according to duration, intensity and recency, the most – and often the only – reliable evidence comes from restricting analyses to people who have never smoked. This well-established method is commonly used in analyses such as those quantifying the impacts of environmental tobacco smoke[25,26] and risk factors for lung cancer other than smoking.[27] Adjustment of analyses for smoking often only accounts for current, past and never smoking and not intensity and other smoking attributes, leading to issues with residual confounding.[28] Sometimes the adjustment or stratification required to be assured of effects independent of smoking is not possible, as disease events will tend to occur in smokers, leaving limited power to detect effects in never smokers, even in large studies.[29]

A substantial proportion of e-cigarette users are current or ex-smokers, and dual current use of both e-cigarettes and tobacco cigarettes is the most common pattern of exposure in Australia and much of the world. The smoking behaviour of e-cigarette users and non-users differ in a complex way, including according to smoking intensity, duration and recency, as well as other factors. Furthermore, smokers

diagnosed with illnesses may take up e-cigarette use with the aim of reducing or quitting combustible smoking (termed here "sick switching").

As noted above, establishing safety requires studies able to detect and exclude risk increases from exposure to e-cigarettes of the order of 20-30%. However, as also noted above, this magnitude of variation in disease risk is much smaller than that observed with relatively minor variations in the number of cigarettes per day, among smokers. This means that residual confounding with tobacco smoking could overwhelm the ability to detect – and exclude – any direct effects of e-cigarettes. Hence, users of e-cigarettes who are never smokers, and remain so without ever proceeding to combustible smoking, are the most appropriate population to reliably quantify the health effects of e-cigarette use.[3,14]

An additional potential source of bias relates to competing interests, particularly from tobacco and e-cigarette company influence.[30,31]

4d. Effect modification/statistical interaction: Factors influencing disease risk will tend to have different magnitudes of relative effect across subgroups which vary in their baseline risks of disease. For example, the absolute rates of cardiovascular disease mortality vary by age. Blood pressure lowering treatments reduce risk across all age groups and this effect varies with age, with greater relative risk reductions in younger age groups and greater absolute risk reductions in older age groups. Current, past and never smokers have very different baseline risks of disease. Even in the event that relatively risks could be ascertained reliably in populations including smokers (see above), it is likely that the relative effect of e-cigarettes would differ between them. The general solution for this situation is to stratify analyses, meaning that the effects of e-cigarettes should be examined separately in current, past and never smokers.

4e. Statistical power: Reliable quantification of the relationship of an exposure to an outcome requires sufficient numbers of outcome events among those exposed and not exposed to the factor of interest, taking account of issues relating to confounding and bias, to detect the required magnitude of effect. All of the issues raised above have a bearing on statistical power. For exposures that are or may become common, particularly in the general population, detection of moderate elevations in relative risk – of the order of 20% – is important to establish safety.

Most of the disease outcomes of interest for e-cigarettes – such as cancer, cardiovascular disease and chronic obstructive pulmonary disease – tend to occur at older ages. Some outcomes, such as mental health issues and asthma also occur in younger populations. Use of e-cigarettes at older ages is chiefly among current or ex-smokers; there is very little use among older people (e.g. those aged >40 years) who have never smoked. Use among never smokers is more common at younger ages and, since smoking habits are generally not considered to be established until people are in their mid-20s, use below this age is generally not regarded as being for the purpose of smoking cessation.

A central issue for reliably establishing and quantifying the effect of e-cigarettes on disease outcomes is the fact that at the age where the vast majority of disease events occur, use is almost exclusively in smokers. This makes it very difficult to disentangle the effects of e-cigarettes from those of variations in smoking behaviour (see above). At the age where use among never smokers is more common, disease events – apart from those mentioned above – are generally rare. For example, in a major large-scale cohort study of e-cigarettes and respiratory outcomes, 99.4% of e-cigarette users were current or ex-smokers.[28] The fact that a certain proportion of never smokers who initiate e-cigarette use ultimately start combustible smoking further limits evidence about health outcomes attributable to prolonged use of e-cigarettes.[3,14]

Statistical power is also impacted by the other methodological issues including those mentioned above, such as: the wide variety of different exposures represented by use of e-cigarettes; the relatively short duration of population exposure to e-cigarettes; the need to account for confounding, bias and potential effect modification; missing data; and measurement error. If effect modification is likely to be present, statistical power is then determined by the numbers of events in the exposed and unexposed within the population subgroups of interest - among other considerations.

Taking all of these methodological challenges into consideration, this review emphasises sufficiently-powered evidence from randomised controlled trials, intervention studies, prospective studies and case-control studies of the likely impacts of the cigarettes on clinical outcomes, where it is possible to separate the likely effects of e-cigarette use from those of other factors such as differences in smoking behaviour. This means including and emphasising evidence from people who have never been regular tobacco smokers, as well as considering separately evidence from current, ex- and never smokers, where possible. In addition, evidence on outcomes that are able to be directly attributed to e-cigarettes – such as poisonings, burns and injuries – is reviewed in detail, including data from surveillance reports and case

reports. The potential influence of competing interests is also considered, where possible and appropriate.

2.4 Search strategy

2.4.1 Primary research article search

A systematic review was undertaken to examine the primary evidence on health outcomes associated with e-cigarette use, published since the NASEM review.[3]

Six databases (PubMed, Scopus, Web of Science, PsycINFO (Ovid), MEDLINE (Ovid), and Cochrane) were searched between July 2017 and July 2020. Searches were restricted to evidence published from July 2017 to July 2020, to capture evidence published since the NASEM review search dates commencing 1 February 2017, with continuing inclusion of studies up to 31 August 2017. Study authors were not contacted as part of this review.

The systematic review protocol was published on PROSPERO (CRD42020200673). Further details on search terms are located in Appendix 2.

2.4.2 Supplementary search for systematic reviews and meta-analyses

In addition to the systematic review of primary research, a search was undertaken to identify systematic reviews/meta-analyses of relevant health outcomes using the same search terms and limits as the primary evidence search. Papers were screened alongside the primary evidence. Systematic reviews/meta-analyses identified in this search, along with the NASEM review,[3] the Irish Health Research Board literature map,[15] the Public Health England reviews,[11,12] the CSIRO review,[14] the SCHEER review[4] and the USPSTF Evidence Synthesis[16] were used to identify studies that were not identified in the systematic review search.

Appendix 7 includes relevant literature published after the search date. Articles were identified non-systematically and were not included in evidence synthesis.

2.5 Inclusion and exclusion criteria

This review includes published, peer-reviewed original research into the health outcomes of e-cigarette use in humans. It focuses largely on nicotine e-cigarettes and, where possible, excludes e-cigarettes delivering tetrahydrocannabinol (THC), which were considered out of scope by the Australian Department of Health. No animal, *in vitro* or in vivo studies were included. Primary outcomes were clinical disease endpoints, such as myocardial infarction, stroke and cancer. Studies with primary evidence that had already been included in the NASEM review were excluded. The full inclusion and exclusion criteria can be found in Appendix 3.

2.6 Data screening

Papers were imported into an EndNote library, exported to Covidence[32] and duplicates were removed. Two authors of this review independently screened all titles and abstracts identified in the searches, followed by full text screening. Only studies with abstracts published in English were screened. After removing duplicates, titles, abstracts, and then full texts were screened for any studies fulfilling the inclusion and exclusion criteria by two review authors. Discrepancies were resolved through consensus or by a third review author. Forward and backward reference search was performed from the final included articles and identified systematic reviews using ANU Library, Web of Science and Scopus.

2.7 Data extraction

One review author independently extracted data from the primary research articles using a pre-specified, piloted data extraction Excel template. Extracted data was checked by a second review author. Discrepancies were resolved through consensus or by third review author. Missing data within studies was noted and reported in the results.

2.8 Quality assessment

The methodological quality (risk of bias) for each included study was independently assessed by two review authors using the Joanna Briggs Institute's (JBI) suite of critical appraisal tools.[33] Disagreements were resolved through consensus or by a third review author. Three studies were excluded based on their quality assessment scores. A PRISMA diagram showing the number of articles at each stage of the review, and reasons for exclusion is provided in Appendix 4.

The quality of the body of evidence for health outcomes was evaluated using the GRADE approach,[34] adopting the modification for the assessment of a public health intervention.[35] he body of evidence for each health outcome was given a preliminary rating based on the main study designs, and then reduced according to risk of bias, inconsistency, indirectness, imprecision and publication bias. The modification allowed for ratings to be increased where studies met certain conditions.

Table 2.8-1 Factors that can increase or decrease the quality rating of evidence in GRADE

Effect	Factor	Consequence
Reduce	Limitations in study design or execution (risk of bias)	↓ 1 or 2 levels
	Inconsistency of results	↓ 1 or 2 levels
	Indirectness of evidence	↓ 1 or 2 levels
	Imprecision	↓ 1 or 2 levels
	Publication bias	↓ 1 or 2 levels
Increase	Large magnitude of effect	↑ 1 or 2 levels
	All plausible confounding factors would reduce the demonstrated effect or increase the effect if no effect was observed	↑ 1 level
	Dose-response gradient	↑ 1 level

As this review aims to summarise the available high-quality, reliable evidence on the health outcomes of e-cigarettes, it is important to consider whether authors of the studies under review hold any conflicts of interest that could potentially bias their findings, or whether the research was funded by an organisation with a financial interest in the outcomes, as such information on the source of research sponsorship or external involvement was also extracted. Where authors or studies declared funding from the tobacco or e-cigarette industry, the risk of bias was noted in the GRADE assessment.

See Figure 2.10-1 for an outline of the evidence evaluation process.

2.9 Data synthesis

The highest quality data was prioritised, depending on the health outcome, in the following order:

- Randomised controlled trials (including randomised crossover trials)
- Prospective cohort studies
- Case-control studies
- Non-randomised intervention studies (with comparison group or compared to baseline).

For health outcomes where epidemiological studies were not available or were not relevant, and where these types of evidence were likely to be informative, other forms of evidence, listed below, were considered:

- Cross-sectional surveys
- Case reports and case series (particularly for exposure-dependent health outcomes, for example, burns and injuries)
- Evidence from surveillance systems (usually in grey literature/reports).

There were no restrictions in the effect measures reported and they were presented in the findings as reported in the original study. The plan for data synthesis included the potential for meta-analyses where more than one study presenting data on the same e-cigarette exposure parameter and outcome were available and capable of being summarised statistically. Statistical tests for heterogeneity, applying methods such as I^2 tests, would be applied to studies included in the meta-analysis.

Study characteristics and main findings were summarised in narrative synthesis for each health outcome from prior national and international reviews and from the top-up review, with top-up review studies tabulated. Findings from the previous reviews and the top-up review were then integrated to summarise the evidence and draw conclusions regarding the likely health effects of e-cigarettes. The methods for each study, including study design, exposure and outcome measures, were described, along with narrative consideration of clinical and methodological heterogeneity. See Figure 2.10-1 for an outline of the evidence evaluation process, including the framework for forming conclusions based on the evidence.

2.10 Engagement with experts and stakeholders

This review was conducted in response to the needs of the Australian Department of Health, the National Health and Medical Research Council of Australia (NHMRC) and other stakeholders. It was informed by their requirements, with regular consultation with the NHMRC Electronic Cigarettes Working Group and was subject to independent methodological review, in keeping with NHMRC practices.[36]

Figure 2.10-1 Tools and methods for evaluating the evidence

Assessing the evidence

Individual studies

Assess	Quality of studies
Tool	Joanna Briggs Institute (JBI) critical appraisal of study methodology

Possible ratings	Definition
High	80-100% criteria met
Moderate	50-79% criteria met
Low	<50% criteria met

Elements appraised vary by study design and include the following:

- Clear temporal relationship of variables
- Representativeness
- Comparator
- Group allocation
- Selection criteria
- Blinding
- Measurement of exposure/condition
- Management of confounding factors
- Assessment of outcomes
- Clinical detail
- Exposure/follow-up period
- Management of and accounting for follow-up
- Statistical analysis
- Trial design

Synthesised evidence

Assess	Certainty of evidence
Tool	GRADE appraisal for systematic reviews and evidence syntheses

Possible ratings	Definition
High	Confident in the evidence
Moderate	Moderately confident
Low	Limited confidence
Very low	Very little confidence

Initial certainty rated based on study design:

High (randomised controlled/crossover trial)
Moderate (case-control, cohort, NR intervention)
Low (case report/series, surveillance report)

Certainty rated down due to:

	Assessing	*Example*
Risk of bias	Methodological limitations	Low JBI ratings, conflicts of interest, small N studies
Inconsistency	Effect across studies	Contradicting outcomes
Indirectness	Addressing the research question	Lack of evidence on primary outcomes
Imprecision	Number of events	Small number of small studies
Publication bias	Evidence of bias	Only small positive studies

Assess	Conclusions based on evidence
Tool	NASEM framework for assessing levels of evidence for conclusions

Possible ratings	Definition
Conclusive evidence	High confidence, no limitations
Substantial evidence	High confidence, minor limitations
Moderate evidence	Moderate confidence, limitations
Limited evidence	Limited confidence, significant limitations
Insufficient evidence	Very little confidence, substantial uncertainty
No available evidence	No conclusion, no evidence

Rating	Supportive findings	Opposing findings	Type of studies
Conclusive	Many	None	Good-quality controlled
Substantial	Several	Few or none	Good-quality observational
			Controlled trials
Moderate	Several	Few or none	Fair-quality studies
Limited	Few	None	Fair-quality studies
	Most	Some	Any
Insufficient	Few	Some	Any
	One	NA	
No available	None	NA	NA

Notes: Joanna Briggs Institute's (JBI) critical appraisal checklists assessed methodological quality for individual studies identified in the top-up review only.
GRADE and the NASEM framework were applied to synthesised evidence from all sources (top-up, NASEM review and other).

3 E-cigarette characteristics, use and constituents

3.1 E-cigarette devices and e-liquids

E-cigarettes are battery powered rechargeable or disposable devices that heat an "e-liquid" to produce an aerosol, which is inhaled by the user. E-cigarette devices and e-liquids are extremely diverse, with hundreds of thousands of products registered worldwide.[4]

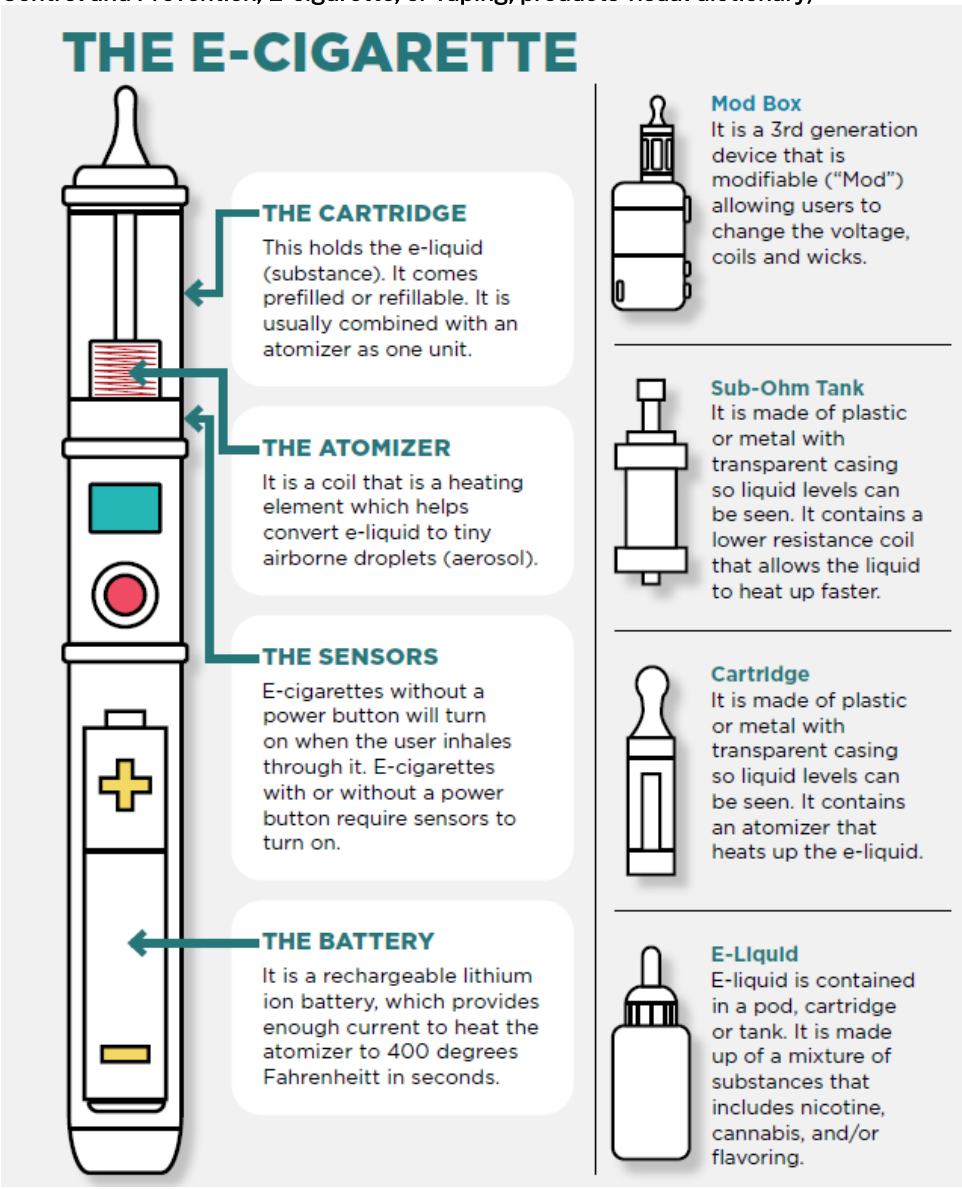
3.1.1 E-liquids

E-liquids consist of water and the organic solvents propylene glycol and glycerine. They commonly include nicotine in either freebase or salt form.[4,37] Flavours are often added. Propylene glycol and vegetable glycerine are humectants which produce aerosols that simulate tobacco smoke.[37] Additional details regarding e-liquid and aerosol chemical constituents are in Section 3.3 below.

3.1.2 Devices

E-cigarette devices comprise a mouthpiece, a tank or a cartridge for e-liquid, a battery, sensors and an atomiser (Figure 3.1-1).[4,37] While some, particularly earlier products, resemble conventional tobacco products such as cigarettes and pipes, most do not, with the diversity of products including those resembling USB memory sticks, pens, cylinders and boxes.[38]

Figure 3.1-1 Features of e-cigarettes (from US Department of Health and Human Services, Centers for Disease Control and Prevention, E-cigarette, or vaping, products visual dictionary)[37]



"Open" system e-cigarette devices are manually filled with e-liquid, while "closed" devices use cartridges or "pods" that are ready-filled with e-liquid that then attach to the rest of the device, or are prefilled, fully disposable devices.[4] Where e-liquids are added to the device by the user, they can be available either as "ready to vape" – with the liquid components already combined – or are mixed by the user. Such mixing can include the dilution of high-concentration liquid nicotine, requiring relatively complex calculations and processes.[39] In general, freebase nicotine e-liquid is used in open devices, although those using prefilled cartridges are available. Nicotine salts are more commonly used in closed pod or disposable devices.

The types of e-cigarettes available have changed over time, and there have also been developments within each type (Figure 3.1-2). Currently, the following main types are recognised:

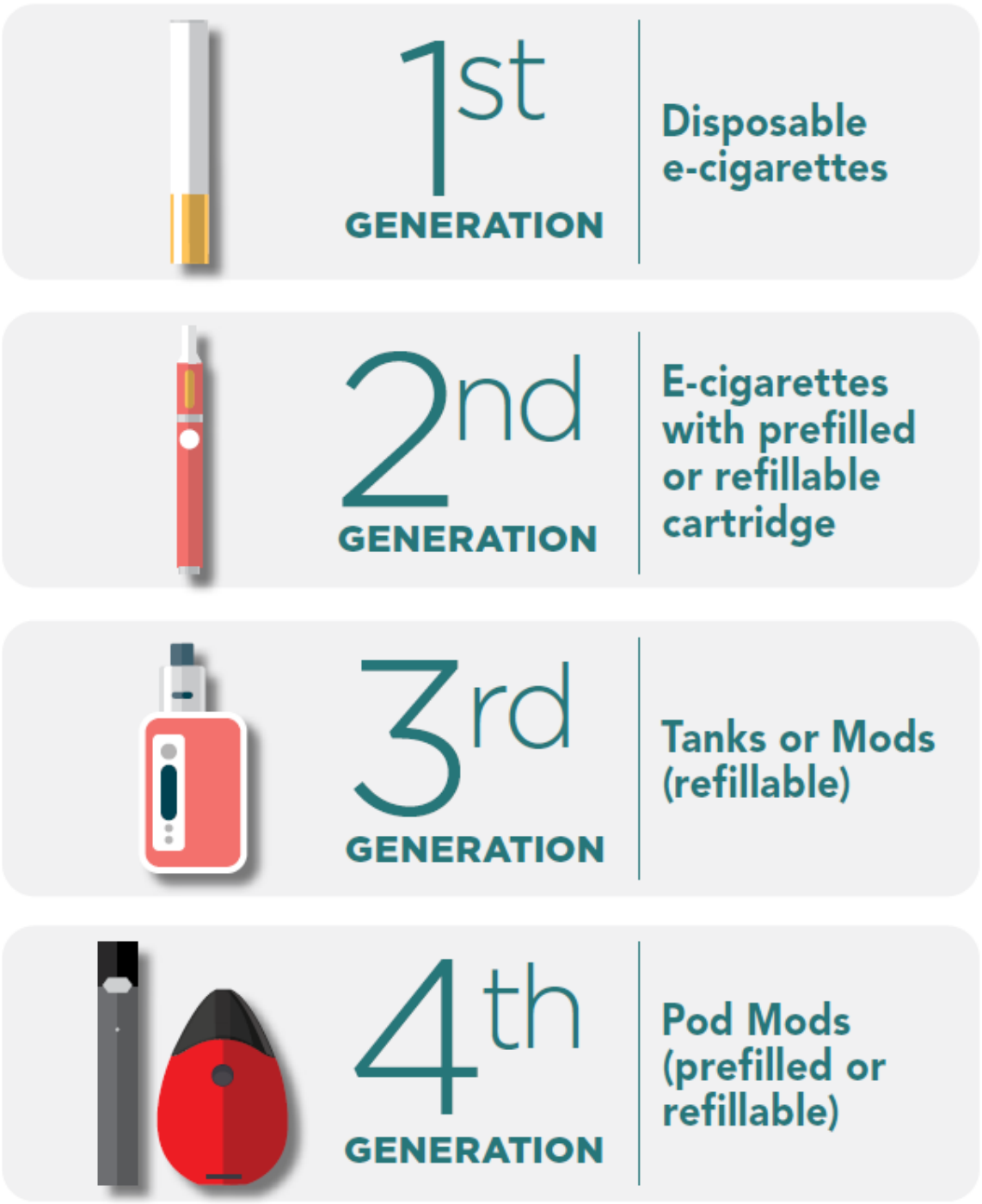
Cigalikes (first generation):
First generation e-cigarettes are designed to mimic the visual appearance and the smoking experience of combustible tobacco cigarettes. They are commonly referred to as "cigalikes" and come with fixed and low voltage batteries. They provide the least control over heating and other variables of the e-cigarette types, and have lower efficiency of nicotine delivery.[4] These devices are made of plastic or metal and consist of a battery, a reservoir that contains e-liquid with or without nicotine, and an atomiser (known as a heating element) that connects to the battery and converts the solution into an aerosol.[37] They are available as disposable or refillable devices.

Vape pens (second generation):
Second generation e-cigarettes include products that resemble pens and have larger variable voltage batteries compared to the previous generation of e-cigarettes.[4] They usually contain a prefilled or refillable cartridge which is referred to as a clearomiser.[3] The clearomisers are transparent and have a removable atomising unit that is attached to the fluid reservoir and the battery. Fluid reservoirs can be prefilled or refilled with any fluids that may include nicotine, cannabis (THC, cannabidiol), flavouring, solvents, or other substances.[37] These e-cigarette devices often come with a manual button which allows users to regulate the length and frequency of puffs.[40]

Tanks or mods (third generation):
Third generation e-cigarettes bear little to no resemblance to combustible cigarettes and come in many different sizes and shapes (such as square, rectangular or cylindrical). They are refillable and include a tank which holds larger amounts of liquid than earlier models[3,37] and users may modify or build their own devices from device components.[3] Most allow control over both voltage and wattage – and therefore the temperature of the heating coil of the device – allowing greater control of the dose received and other aspects of the user experience, and can be used at much higher power levels than earlier devices.[4] Some include tanks with low resistance heating coils (also known as a "sub-ohm tank"), designed to create large clouds of aerosol and deliver high doses of the e-liquid constituents (e.g. nicotine) for a given e-liquid concentration.[37]

Pods, pod mods and disposables (fourth generation):
These are small prefilled or refillable ''pod'' or pod cartridge systems that come in many shapes, sizes and colours. They often resemble USB drives. They can be single-use fully disposable devices or devices where a pod cartridge is replaced when it is empty.[37] They almost exclusively contain high concentration nicotine salt e-liquid.[4]

Figure 3.1-2 Major e-cigarette types (from US Department of Health and Human Services, Centers for Disease Control and Prevention, E-cigarette, or vaping, products visual dictionary)[37]



3.2 Nicotine delivery

On average, a smoker receives a dose of 0.5-1.5mg of nicotine per combustible cigarette.[41-43] Registered nicotine replacement therapies (NRTs) with demonstrated efficacy as aids to smoking cessation – such as nicotine patches and gums – deliver a bioavailable nicotine dose of around 0.3 to 1mg/hour.[44] This often achieves nicotine concentrations in the range of those experienced by smokers but with a slower onset and offset. The potentially lethal dose of nicotine is 5mg/kg.[45] The dose of nicotine received by users of e-cigarettes varies widely and is influenced by a range of factors including:

- The nicotine concentration in the e-liquid.
- The type of e-cigarette device used. More recently developed products generally deliver high doses.[46,47] "Cigalikes" and "vape pens" tend to deliver lower doses while tank devices, particularly those with highly powered heating coils, generally deliver higher doses. Nicotine salt pod and

disposable products use high nicotine concentrations (e.g. many are at concentrations of 5% or 59mg/mL) and deliver high doses.[4]
- User behaviour, including depth of inhalation and number of puffs.

While published evidence is limited, it is clear that the dose of nicotine delivered by e-cigarettes is highly variable. Recent data indicate greater variation in nicotine dose according to device than e-liquid concentration.[46] The main evidence reviewed in the US NASEM review[3] is from a paper published in 2013 which found a total level of nicotine in e-cigarette aerosol of 0.5-15.4mg from 15 puffs of 1.6-19mg cartridges,[48] while a 2016 publication found an average dose of 1.3mg with 15 puffs from e-cigarettes with measured nicotine concentrations of 5.0-15.3µg/mg[49] (nicotine concentrations on product labels 6-24mg/mL). The European Tobacco Products Directive[50] limits nicotine concentration in e-cigarettes to a maximum of 20mg/mL, with the rationale that this allows delivery of nicotine at a concentration comparable to the permitted dose of nicotine from a standard cigarette during the time taken to smoke a cigarette.[51]

Nicotine doses higher than conventional cigarettes have been reported, particularly for high concentration e-cigarette e-liquid and pod devices. For example, the level of nicotine exposure – as measured by urinary cotinine – in 38 adolescents attending a US children's hospital outpatient clinic using high concentration nicotine pod-based e-cigarettes (21.8-56.2mg/mL) was substantively higher (245µg/L) than levels detected in adolescent regular cigarette smokers (155µg/mL).[52,53] Under controlled conditions, with the same device and 10 puffs, average increases in plasma concentrations of nicotine with inhalation of 36mg/mL freebase nicotine e-liquid exceeded those of conventional cigarettes, among experienced e-cigarette users.[54]

Nicotine concentration is often inaccurate on product labels and it has been suggested by recent data that there is greater variation in nicotine dose according to the device used rather than the e-liquid concentration.[3,46] Large reductions in craving and other withdrawal-related symptoms have been observed with use of nicotine e-cigarettes, with the majority of data relating to nicotine concentrations <20mg/mL.[47,55,56] Commercial information targeting e-cigarette consumers[57-60] refers to freebase nicotine e-liquids with concentrations at or below 18mg/mL, none recommend use above this concentration, and many note the need to dilute products above this concentration.[39] The most common nicotine strengths available on the market for freebase liquid nicotine are: 0mg, 3mg, 6mg and 12mg,[57] with 12mg/mL generally reserved for heavy smokers. Such information generally recommends e-liquids for vape pens and less powerful devices with nicotine concentration for smoking cessation for light to moderate smokers of 3 - <12mg/mL and 12-18mg/mL for heavy smokers. Highly powered devices[57,61] require much lower nicotine concentrations than lower powered devices to achieve the same delivered dose of nicotine[3], and users of high powered devices are advised to avoid concentrations >12mg/mL.[57,61]

Nicotine salt products allow the delivery of high concentrations of nicotine with less throat irritation than freebase forms of liquid nicotine and deliver nicotine rapidly.[4] These newer products are available in very high concentrations and there is concern that innovations in e-cigarette liquid formulations are leading to a "nicotine arms race".[51] Nicotine salt products in the US were introduced in "pods" – which are small and easy to conceal – the most popular with a starting nicotine concentration of 59mg/mL (5% nicotine). They are one of the most common products used by children and adolescents,[4] including in the US and Canada, and evidence indicates that they enhance delivery of high doses of nicotine and have greater dependence potential than other products.[52]

3.3 Nicotine and non-nicotine constituents and toxicology

Use of e-cigarettes results in inhalation of a complex and highly variable array of chemicals,[4] which can be broadly categorised as:

(i) **Originating from e-liquids**: nicotine, solvent carriers (propylene glycol, ethylene glycol and glycerol), tobacco-specific nitrosamines, volatile organic compounds (including include toluene, phenols, xylenes, ethyl acetate, ethanol, methanol, pyridine, acetylpyrazine, 2,3,5-trimethylpyrazine, octamethylcyclo-tetrasiloxane, benzene, ethylbenzene, styrene),[3] phenolic compounds, flavourings as well as tobacco alkaloids.

(ii) **Formed by chemical reactions in the heating element**: aldehydes (predominantly acetaldehyde and formaldehyde, with others detected such as acrolein (propenal), propionaldehyde (propanal), (methyl)benzaldehyde and isobutyraldehyde), free radicals and reactive oxygen species and furans.[4]

(iii) **Originating from the device**: metals, with the following having been reported in aerosols: aluminium, antimony, arsenic, boron, cadmium, chromium, copper, iron, lanthanum, lead, nickel, potassium, silver, tin, titanium, zinc.[3]

The levels of the chemicals received by the user vary greatly, according to the e-liquid contents, puffing rate, type of device, and the battery voltage or heating power.[3,4]

Nicotine is a parasympathomimetic drug that binds to nicotinic acetylcholine receptors in the central nervous system, resulting in the release of major neurotransmitters. It also binds to nicotinic acetylcholine receptors in other parts of the body comprising parts of the parasympathetic nervous system. It has both stimulatory and relaxant properties. Tobacco smoking is known to harm virtually every organ in the body[62] and nicotine is considered a potential contributor to many of these effects. Evidence on the effects of nicotine on many outcomes is mostly derived from smoker populations and the presence of other constituents in tobacco cigarette smoke make the discrimination of the role of individual potential causative agents difficult.

Nicotine is one of the most addictive substances known to humanity.[63] It is the primary agent responsible for addiction in tobacco.[45] The risk of nicotine addiction increases with the rate of delivery, the rate of absorption and the blood concentration of nicotine attained.[62]

Acute nicotine toxicity is a well-recognised effect of nicotine exposure and is dependent on dose, dose duration and frequency, route of exposure, formulation of the nicotine product, and interpersonal variability.[62] Widespread nicotinic acetylcholine receptors in the body means that their activation leads to a broad range of physiological effects. Mild acute toxicity symptoms can include nausea and vomiting. Greater exposure can lead to cholinergic syndrome, which includes diarrhoea, increased salivation, increased respiratory secretions, and bradycardia. Severe poisonings can progress further to seizures and respiratory depression, which can be fatal.[62] Repeated exposure leads relatively rapidly to tolerance, making smokers much less prone to toxicity than people who are not habitually exposed, such as children.[62]

The current evidence indicates that nicotine increases heart rate, blood pressure, myocardial contractility and vascular resistance, and reduces insulin sensitivity, which are likely to contribute to elevated cardiovascular risk in smokers.[3,62] Furthermore, evidence suggests nicotine also adversely affects myocardial remodelling, arrhythmogenesis, thrombogenesis, endothelial functioning, and angiogenesis.[3]

The foetus undergoes rapid and extensive development while in utero. During this critical phase of human development, a foetus is vulnerable to compounds that cross the maternal placenta barrier, such as nicotine.[3] Nicotine, via exposure from passive or active smoker mothers, crosses both the placental barrier and the blood brain barrier and can be found at concentrations 15% higher than in non-exposed mothers depending on dose and time of exposure.[64] In utero exposure to nicotine is associated with foetal growth restriction, preterm delivery and stillbirth.[62] Evidence also indicates in utero nicotine exposure negatively effects foetal lung structure and functions.[3,62] Maternal smoking during pregnancy, including exposure to nicotine, has been linked to sudden infant death syndrome (SIDS),[65] cognitive, attentional and auditory processing deficits,[66-69] disruptive behaviours[70,71] and smoking initiation in offspring.[2,72,73]

Another critical period of brain development occurs during adolescence during which the brain undergoes major reorganisation of neurochemical systems and structure and leads to a window of vulnerability.[74,75] Exposure to nicotine at these critical developmental stages has been shown to adversely affect the structure and function of the brain. Smoking during adolescence can impact brain development and is associated with comorbid substance abuse and addiction,[76] impairments in memory,[65,77] anxiety disorders,[78,79] depression and disruptive disorders,[80,81] which may persist long term.[62,82-84] Many of these effects have been attributed to nicotine.[82,85] Adolescence is a life stage when many risk-related behaviours are defined and commence.[86] A significant concern of nicotine exposure during this life stage is the implications for long-term nicotine and tobacco dependence. Evidence from both human studies and animal models indicate an age-dependent susceptibility to nicotine, with greater susceptibility from exposure at younger ages.[2] Patterns of addiction to tobacco smoking, primarily driven by addiction to nicotine, demonstrate that smokers almost always commence during childhood, when aged less than 18, and smoking and addiction then persist into adult life.[62] This is supported by animal data: in adolescent rats, nicotine enhances neuronal activity in several reward-related brain regions leading to the strengthening of the behavioural reward responses to nicotinic stimuli.[87,88] This effect occurs more robustly in adolescent than adult rats and persists even at low doses.[89,90] The US Surgeon General concludes that *"given the existing evidence from human and animal studies of the detrimental impact of nicotine exposure on adolescent brain development, the use of e-cigarettes by youth should be avoided and actively discouraged".*[2]

As noted above, the non-nicotine constituents of e-cigarettes include solvents – water, propylene glycol and vegetable glycerine – and flavourings, as well as multiple other chemicals. There are many thousands of e-liquids on the market and over 15,000 flavours were identified for sale online in 2017.[4,91]

The main substances in e-cigarettes aerosol that raise health concern are metals (such as chromium, nickel, and lead), carbonyls (such as formaldehyde, acetaldehyde, acrolein and glyoxal), and particulate matter and some flavourings. Exposure to some metals may cause serious health effects, including diseases of the nervous, cardiovascular and respiratory systems.[4,92] Carbonyl compounds are potentially hazardous to users. Formaldehyde is a human carcinogen, acetaldehyde is possibly carcinogenic to humans, acrolein is a strong irritant of the respiratory system and glyoxal shows mutagenicity.

Under typical conditions of use, the number and concentrations of potentially toxic substances emitted from unadulterated e-cigarettes are lower than in tobacco smoke, except for some metals, which may be found in higher levels in e-cigarette aerosol than tobacco smoke.[92]

In the 2019 National Industrial Chemicals Notification and Assessment Scheme (NICNAS) report,[93] 243 unique chemicals found from e-liquid ingredients or from e-cigarette emissions were identified from the published scientific evidence, the majority of which (235) were flavourings. There were 156 chemicals identified in e-liquids only, 19 in emissions only and 60 in both e-liquids and emissions. All e-liquids were found to contain glycerol, propylene glycol or a mixture of both as solvents. Flavouring compounds were found at high concentrations (1% or more).[93] The US Food and Drug Administration considers some flavourings identified as 'Generally Recognised as Safe' for use as food additives only, however, this does not extend to the inhalation of the flavours. Thirty-eight chemicals from the published evidence are listed as poisons on the Australian Poisons standard. One chemical identified is not permitted in e-cigarette liquids, and three chemicals exceeded cut-off levels for the relevant standard.[93]

In addition to the chemicals identified from e-liquids and emissions, 27 chemical reaction products, most commonly carbonyl compounds, were identified. Carbonyls such as acetaldehyde, acetone, acrolein and formaldehyde are associated with adverse health outcomes in humans.[93]

3.4 Regulation of e-cigarettes

There is wide variation in the regulation of nicotine and non-nicotine e-cigarettes internationally. In their recent report, the World Health Organization (WHO) notes that 111 countries worldwide have adopted some measure to regulate nicotine e-cigarettes.[38] These regulations including those relating to product classification, sale, minimum age restrictions, nicotine concentration, flavours, use in public places, advertising and promotion and packaging.

Sale: The sale of all types of e-cigarettes is banned in 30 countries (Argentina, Brazil, Brunei Darussalam, Cambodia, Colombia, Egypt, Gambia, India, Iran, Kuwait, Lao People's Democratic Republic, Lebanon, Mauritius, Mexico, Nepal, Nicaragua, Oman, Panama, Qatar, Seychelles, Singapore, Sri Lanka, Suriname, Syrian Arab Republic, Thailand, Timor-Leste, Turkey, Turkmenistan, Uganda, and Uruguay).[7] Jamaica, Japan and Switzerland ban the sale of nicotine e-cigarettes but not non-nicotine cigarettes.[7] A further 79 countries, including Australia, fully or partially regulate e-cigarettes while allowing them to be sold. The remaining 84 countries do not regulate e-cigarettes at all.[38]

Australia is unique in permitting use of nicotine e-cigarettes only on prescription from a registered medical practitioner for the purpose of smoking cessation. Consumers with a prescription can purchase these products legally from an Australian pharmacy or import a limited quantity for personal use. It is illegal for local retailers other than pharmacies to sell nicotine e-cigarettes.[94] Non-nicotine e-cigarettes can be sold in all Australian states and territories, with the exception of Western Australia.[95] The importation of e-cigarettes that do not contain nicotine is unrestricted in Australia.[95]

Age restrictions: Sixty-nine countries have minimum age restrictions on the sale of nicotine e-cigarettes. The mandated minimum age varies from 18 years, 19 years to 21 years of age.[38] In Australia, the sale of e-cigarettes to children and young people is prohibited across all states and territories, predominantly to those under 18 years of age.

E-liquid product regulation: Overall, 36 countries, including Australia, regulate the concentration and volume of nicotine in e-cigarettes.[7] Thirty-four of these countries – including Canada, Israel, Saudi Arabia, England, Scotland, Wales, Northern Ireland and countries in the European Union (EU) – stipulate an upper limit of 20mg/mL nicotine concentration in e-liquids and Iceland stipulates an upper limit of 20mg/mL for use in consumer products with higher concentrations regulated as medicinal products. EU regulations limit e-cigarette refill containers sizes to 10mL and device tank and cartridge sizes to 2mL.[96] The quality of e-liquids, nicotine and other ingredients, require compliance with safety and quality regulations in 33 countries. Australia has an upper limit of 100mg/mL on nicotine concentration in e-liquids.[97] There is no limit on the volume of e-liquid that can be prescribed in Australia, although personal importation is limited to three months' supply at a time.[97]

Flavours: Three countries – Finland, Hungary and Montenegro – have adopted a ban on all flavours other than tobacco in nicotine e-cigarettes and selected flavours are banned in six other countries.[38] In Australia, flavours for nicotine e-cigarettes are prohibited if they contain an ingredient that is considered to be a significant health risk.[98] There is currently no regulation around flavours for non-nicotine e-cigarettes.

Use in public places: In addition to the countries that ban sale of nicotine e-cigarettes, their use in public places, workplaces and public transport is banned or restricted in 30 countries. Forty-five countries have implemented partial bans on their use in these places.[38] In Australia, the use of nicotine and non-nicotine e-cigarettes is banned in smoke-free places (places where a traditional tobacco smoking is banned) in most states and territories. All states and territories prohibit the use of e-cigarettes in vehicles when a child is present.[7]

Marketing: There are a number of avenues through which e-cigarettes are promoted, offering widespread reach. These include newspapers and magazines, retail stores, e-cigarette vaping conventions, online advertising, banner and video advertisements, through social media platforms with the use of celebrities and influencers to promote products, through product placement in films, television shows and music videos, through giveaways, promotions and discounts, and marketing at the point of sale.[99]

Advertising, promotion and sponsorship of nicotine e-cigarettes is banned in 22 countries.[38] Partial regulations have been adopted by 53 countries.[38] Specific regulations vary from country to country, with approaches including minimising misleading advertising, banning distinctive branding elements on packaging, focusing on regulating aspects that appeal to young people such as flavours and the use of cartoon images on packaging.[51] In Australia, restrictions around the advertising and promotion of e-cigarettes vary for each state and territory.

Packaging: Child safety packaging regulations for e-cigarettes are in place in 32 countries and 40 countries require health warnings to be displayed on e-cigarette packaging. Israel is the only country that mandates plain packaging for all e-liquids.[7] Graphic health warnings on packaging of nicotine e-cigarettes are mandated in eight countries. Partial regulations are in place for forty-five countries.[38]

Measures around packaging and labelling practices and design and safety features introduced by a number of jurisdictions, including Canada, the European Union, the United Kingdom and the United States include:

- Safety mechanisms (such as childproof fastening and opening) for e-liquid containers, cartridges and tanks;
- Health warnings on packaging such as information on addictiveness and toxicity;
- Inclusion of consumer information such as instructions for use, storage, and advice to keep out of reach of children;
- A full list of ingredients, including information on nicotine content;
- Inclusion of a prescribed warning statement regarding the presence of nicotine;
- Information on emissions, health hazards and health effects; and
- Advice on overdose management.[96]

Requirements around packaging and labelling for nicotine e-cigarettes supplied in Australia include an ingredient list, nicotine concentration (mg/mL), warning statements and child-resistant packaging.[98] These do not apply to products sourced through personal importation. Australia currently has no regulations regarding packaging for non-nicotine e-cigarettes.

3.5 E-cigarette use

E-cigarette use is changing rapidly and varies substantively according to a range of factors, including age. Reliably ascertaining the prevalence of use of e-cigarettes requires high-quality representative population surveys of sufficient size and frequency to quantify contemporary use according to age. Although monitoring of tobacco smoking and use of related products is a cornerstone of the WHO Framework Convention on Tobacco Control, many countries do not have suitable data relevant to e-cigarettes.[38]

3.5.1 International prevalences and trends

The available data indicate that the prevalence of use of e-cigarettes varies markedly between countries internationally and has increased substantially in many countries over the past decade, with use being more common among young people and smokers.[4]

According to the WHO, the US and Europe are the two main world markets for e-cigarettes.[92] From 2020 Eurobarometer data, an average of 14% of respondents from European member states reported having

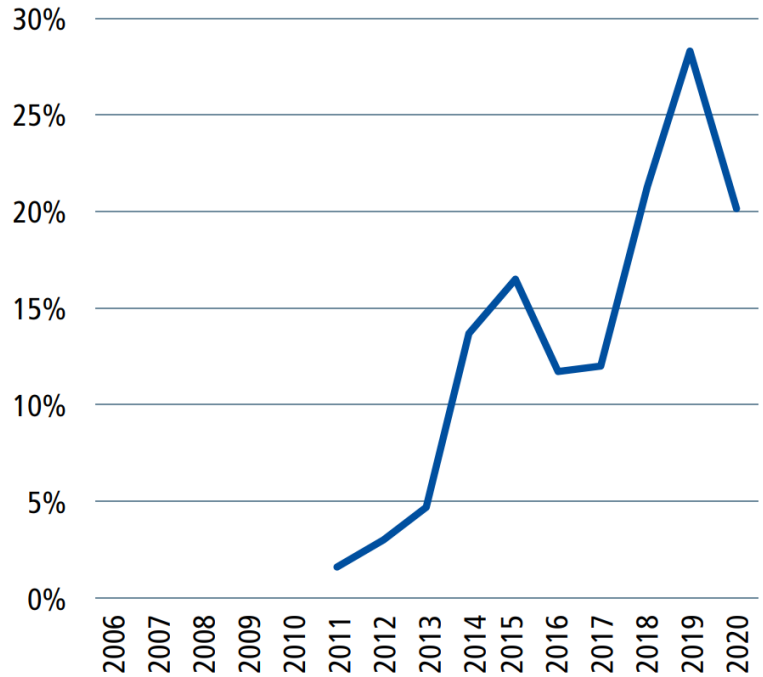
ever used e-cigarettes.[4,100] More than 20% of respondents reported ever having used e-cigarettes in Ireland (29%), Estonia (25%), France and the United Kingdom (both 22%), Luxembourg and Latvia (both 21%) and Belgium (20%); less than 10% reported such use in Poland (6%), Malta, Portugal and Romania (all 7%) and Hungary (9%). Overall, 2% reported current use.[100] Use was more common among males than females and the younger the respondents, the more likely they were to be users, with around a quarter of respondents aged 15-24 reporting ever having used e-cigarettes compared with 8% of those aged 55 and over.

In the 2019 US National Health Interview Survey, ever-use of e-cigarettes amongst adults was reported to be 14.9%, an increase from 12.6% in 2014.[101,102] Current use of e-cigarettes, as defined by use "every day" or "some days", was 4.5% in adults in 2019.[102] This was an increase from 3.7% in 2014. Use was more common in young people with 9.3% of people aged 18-24 reporting current use in 2019 and was also more common in males than females.[102] Among current e-cigarette users, 36.9% were current cigarette smokers, 39.5% were ex-smokers, and 23.6% had never smoked.[102] From the New Zealand Health Survey, ever-use of e-cigarettes was 23.9% amongst individuals 18 and over in 2019/2020, which was an increase from 16.2% in 2015/2016.[103] The proportion of individuals that reported current use in the past 30 days was 5.2% in 2019/2020 which also represented a significant increase from 1.4% in 2015/2016.[103]

The most recent systematic review and meta-analysis of e-cigarette use in young people internationally found that, on average, 17% of youth aged 8-19 surveyed across 51 countries in 2016-2019 had ever used nicotine or non-nicotine e-cigarettes.[104] Use varied more than 10-fold from country to country, ranging from estimates of ≤10% ever-use in Australia, Cambodia, Denmark, Ghana, Hong Kong, Japan, Kosovo, Laos, Mexico, Panama, Samoa, Tunisia, Vanuatu and Wales to >20% in most high income countries, including 34% in Canada, 37% in New Zealand, 43% in Poland, 42% in the US and 52% in France.[104] Prevalence estimates for use among children and adolescents aged 11-20 within the last 30 days ranged from 1% for Hong Kong, Japan, and Mexico, to 20% in Canada, 23% in the US, 25% in Poland and 33% for Guam, with an average of 8%.[104] In general, use was more common in males than females.

In 2018, the US Surgeon General declared youth use of e-cigarettes to be an "epidemic" and identified high concentration nicotine salt products as a key driver (Figure 3.5-1).[75] Health Canada noted a doubling in current/recent e-cigarette use among schools student from 2016/17 to 2018/19, to around 20% of 12-17 year-olds, with high concentration nicotine salt products introduced around 2018 and capturing 62% of the market share in 2019.[104-107] This evidence was a key justification for the July 2021 reduction in the maximum nicotine concentration in e-cigarettes to 20mg/mL in Canada.

Figure 3.5-1 Current e-cigarette use (past 30 days) among high school students in the US (from WHO report on the global tobacco epidemic, 2021)[38]



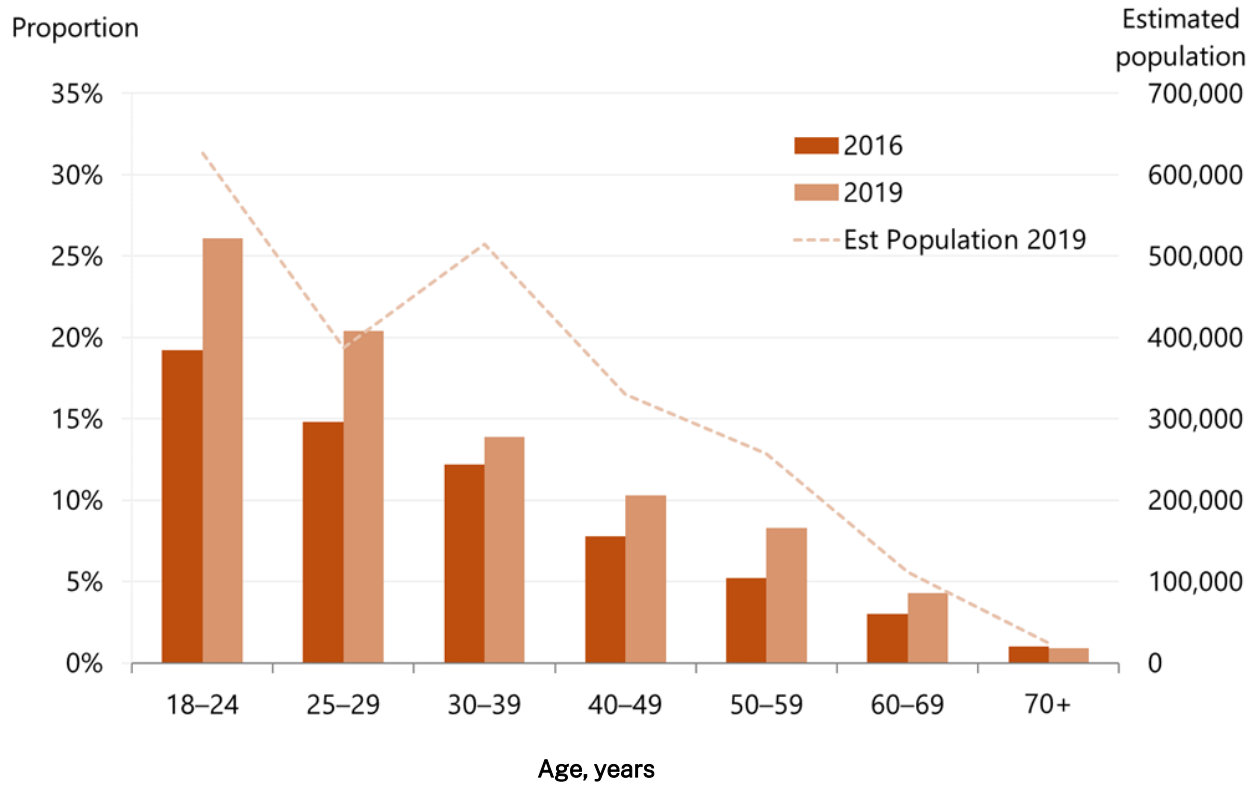
3.5.2 Prevalence and trends in use in Australia

The most recent national data on e-cigarette use in Australia are from 2019 and indicate that use is increasing rapidly, is most common among young people and, although use is more common in smokers, it is generally not for the purpose of smoking cessation.[108] Over half of all current use is in combination with tobacco smoking (i.e. dual use) and 16% is in people who have never smoked.[108]

Lifetime and current use of e-cigarettes in the general population

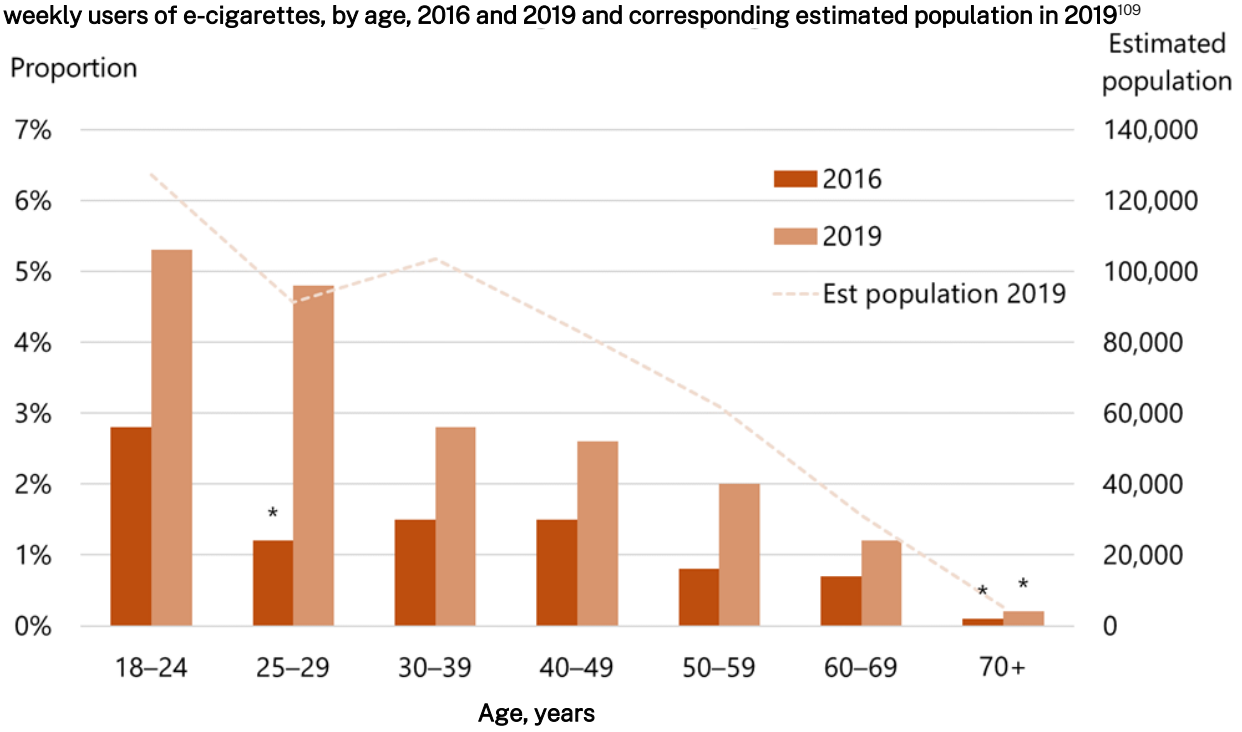
Data from the 2019 National Drug Strategy Household Survey (NDSHS) indicate that an estimated 11.3% of people aged 14 and over in Australia (approximately 2.4 million people) reported ever having used e-cigarettes, up from 8.8% in 2016 and 4.5% in 2013.[108] In 2019, around 60% of ever-users reported having tried them once or twice only. Among adults, ever-use was greater in younger age groups, such that 26.1% of people aged 18-24 and 4.3% of those aged 60-69 reported ever-use of e-cigarettes in 2019[108] (Figure 3.5-2). It was also more common in males than females, particularly in younger people, with 2019 NDSHS data provided by the Australian Institute of Health and Welfare (AIHW) to the review team showing that 26.8% of males aged 15-24 had ever used e-cigarettes compared to 17.2% of females.[109]

Figure 3.5-2 Proportion of the Australian population reporting that they have ever used e-cigarettes, by age, 2016 and 2019 and corresponding estimated population in 2019[109]



Overall, 1.1% of people aged 14 and older in Australia (approximately 230,000 people) reported daily e-cigarette use and 2.0% (approximately 418,000 people) reported current at least monthly e-cigarette use in 2019.[108] These represent statistically significant approximate doublings in use from 0.5% daily use and 1.2% current use in 2016. Current use was more common in younger age groups, with 5.3% of 18-24 year-olds reporting current daily, weekly or less than weekly use[108] (Figure 3.5-3). The prevalence of current use was also more common in males than females, particularly in younger people, with 2019 NDSHS data provided by the AIHW indicating that 6.3% of males aged 15-24 reported current daily, weekly or less than weekly use of e-cigarettes compared to 2.4% of females.[109]

Figure 3.5-3 Proportion of the Australian population reporting that they were current daily, weekly or less than weekly users of e-cigarettes, by age, 2016 and 2019 and corresponding estimated population in 2019[109]



* Estimate has a relative standard error of 25% to 50% and should be used with caution.

Use of e-cigarettes among people aged under 18 years

From the 2017 Australian Secondary Students' Alcohol and Drug Survey results, around 14% of 12-17-year-old students indicated they had ever used e-cigarettes at least once, and among these ever-users, 32% had used e-cigarettes in the past month, indicating that about 4.5% of all 12-17 year old students were current (at least monthly) users.[110] Although these findings are from some time ago, self-reported data on use for individuals aged under 18 are more reliable than those reported in the NDSHS, which were largely based on reporting by children under 18 with a parent or caregiver present or were based on parental reports of their e-cigarette use; this method has been shown to substantively underestimate use.[111]

Among students aged 12-17, ever-use increased with age (4% of 12 year-olds, up to 21% of 17 year-olds) and male students were more likely to have ever used e-cigarettes than female students. Of the students who had ever used an e-cigarette (n=2,403), 48% reported that they had never smoked a tobacco cigarette before using e-cigarettes.[110]

Use of e-cigarettes according to smoking status

In 2019, data from the Australian NDSHS show that among people who had ever used e-cigarettes, 42.7% were current smokers at initiation of e-cigarette use, 26.2% were occasional or social smokers, 7.9% were ex-smokers and 23.2% had never smoked.[108] The proportion of e-cigarette users who were never smokers varied markedly with age, with 64.5% of those aged 14-17 being never smokers at initiation.[108]

From the same 2019 survey, among people aged 14 and over reporting current use of e-cigarettes (i.e., those reporting daily, weekly or at least monthly use of e-cigarettes): 53.0% reported being current smokers (daily, weekly or less than weekly)(approximately 222,000 people); 31.5% reported being ex-smokers (132,000) and 15.5% reported never having smoked (65,000).[108]

The percentage of current smokers in Australia aged 14 years and over who had ever used an e-cigarette was 38.7% in 2019, having increased significantly from 18.8% in 2013 to 31.0% in 2016.[108] Among non-smokers, 6.9% reported ever-use of e-cigarettes in 2019, compared to 1.8% and 4.9% in 2016.[108] The percentage of current smokers in Australia aged 14 years and over who were current daily, weekly or less than weekly users of e-cigarettes increased significantly between 2016 (4.4%) and 2019 (9.7%); and among non-smokers between 2016 (0.6%) and 2019 (1.4%).[108]

An estimated 3.2% of current (daily, weekly or less than weekly) smokers were daily e-cigarette users in 2019 and 7.8% of current smokers used e-cigarettes at least monthly.[108] This translates into 0.45% of the Australian population aged 14 and over (approximately 94,000 people) being dual daily e-cigarette users

and current smokers and 1.1% being dual at least monthly e-cigarette users and current smokers (approximately 226,000 people).[108]

In 2019, 0.2% of never smokers aged 14 and over reported current daily use of e-cigarettes (approximately 26,000 people) and 0.5% reported at least monthly use (approximately 66,000 people).[108] At age 15-24, around half of all current e-cigarette use was in non-smokers.[108]

Reasons for use

The reported reasons for using e-cigarettes varies according to smoking status. Among never smokers at initiation of e-cigarette use, using data from the 2019 NDSHS, the commonest reasons given were: out of curiosity (85.4%); I think they are less harmful than regular cigarettes (9.5%); I think they taste better than regular cigarettes (7.4%); and they seem more acceptable than regular cigarettes (5.8%).[108]

Among current smokers at e-cigarette initiation, the reasons reported for use were: out of curiosity (43.7%); to help me quit smoking (43.7%); to cut down on the number of cigarettes smoked (31.9%); I think they are less harmful than regular cigarettes (27.3%); they are cheaper than regular cigarettes (23.7%); to try to stop me going back to smoking regular cigarettes (23.3%); I think they taste better than regular cigarettes (18.5%); they seem more acceptable than regular cigarettes (11.8%); and you can use them in places where regular cigarettes are banned (8.9%).[108] For this measure, respondents could select more than one response.

While current smokers who also use e-cigarettes include some who are attempting to quit, the substantial proportions of e-cigarette users who continue to smoke, including in randomised controlled trials (see Section 4), and who report reasons for use other than quitting, indicates ongoing dual use is a significant issue. Data on duration of e-cigarette use is required for clarification.

4 Systematic and umbrella review findings

4.1 Search outcomes and study characteristics

The systematic umbrella and top-up review identified a total of 18,992 potentially eligible studies; 12,434 duplicates were removed and 6,558 underwent title and abstract screening. There were 227 studies identified in the systematic literature database search, 10 from forward and backward searching and one from grey literature consistent with the inclusion criteria on health outcomes associated with e-cigarette use. Of these 238 studies, 152 were included in the evidence synthesis and 86 were excluded from evidence synthesis as they were rated as not providing evidence suitable for assessing the causal relation between e-cigarette use and the outcome specified. In addition to the 152 studies, 37 studies from the two previous reviews on smoking uptake and cessation were included in evidence synthesis. Therefore, a total of 189 studies were included in evidence synthesis. No ongoing studies were identified. No meta-analyses were conducted for direct health outcomes as there were insufficient suitable studies relating to clinical outcomes identified; meta-analyses were conducted as part of previous reviews of e-cigarettes in relation to smoking uptake[8,9] and smoking cessation.[10]

Table 4.1-1. Overview of study papers identified in the systematic review, by health outcome category and study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Dependence and abuse liability		13 7 / 6	1 0 / 1	17 9 / 8			20 11 / 9		
Cardiovascular health outcomes	1 0 / 1	11 3 / 8	1 0 / 1	6 5 / 1			8 1 / 7		1 0 / 1
Cancer			1 1 / 0				2 1 / 1		3 2 / 1
Respiratory health outcomes*		9 5 / 4	5 2 / 3	5 1 / 4		18 0 / 18	21 4 / 17	11 0 / 11	26 0 / 26
Oral health			2 1 / 1	2 2 / 0			19 1 / 18		1 0 / 1
Developmental and reproductive effects			2 0 / 2				1 0 / 1		
Burns and injuries						7 1 / 6		24 14 / 10	16 5 / 11
Poisoning						25 13 / 12		4 2 / 2	23 14 / 9
Mental health effects			1 0 / 1				8 0 / 8		
Environmental hazards with health implications**				17 9 / 8		2 0 / 2		5 0 / 5	
Neurological outcomes						3 0 / 3		2 0 / 2	7 1 / 6
Sleep outcomes							4 0 / 4		
Less serious adverse events		11 3 / 8	3 1 / 2	2 2 / 0		1 0 / 1	3 0 / 3		
Optical health				1 0 / 1			1 0 / 1		
Wound healing									2 0 / 2
Olfactory outcomes							1 0 / 1		
Endocrine outcomes							2 0 / 2		
Allergic diseases							2 0 / 2	1 0 / 1	3 2 / 1
Haematological outcomes									2 0 / 2

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first bottom small number is the count of studies from the NASEM review; the second bottom small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.
* Numbers in case series and case reports represent all evidence (both studies included in evidence synthesis and those omitted from evidence synthesis due to issues with assessment of causality).
** Characterisation of studies in environmental outcomes differs from other outcomes. Those included in non-randomised intervention studies are controlled experimental studies and those included in case series are natural experiments.

4.2 Evidence synthesis

The evidence synthesis for this review relates to nicotine and non-nicotine e-cigarettes; e-cigarettes delivering THC were excluded, where possible. This is a point of difference between this review and previous reviews. Few studies presented data allowing the distinction between nicotine and non-nicotine e-cigarettes. However, since the vast majority of e-cigarettes used are nicotine-delivering – for example, research by the Centers for Disease Control and Prevention (CDC) found that 99% of 2015 sales in US supermarkets, convenience stores, mass merchandisers, drug, club, and dollar stores, and Department of Defense commissaries were for nicotine e-cigarettes[112] – the results presented are assumed to relate chiefly to nicotine e-cigarettes.

Where it was not possible to separate completely the health effects of e-cigarettes delivering substances such as THC from nicotine or non-nicotine e-cigarettes, study results have been included and this issue noted.

In addition, the evidence synthesis focused on study designs likely to be most informative for the assessment of the causal effect of e-cigarettes on the health outcomes of interest. The study designs included in determining conclusions for the health outcomes need to be appropriate to establishing a likely causal relationship between e-cigarette use and resultant health outcome. All other things being equal, the best evidence comes from studies where the health outcome occurs after e-cigarette exposure (temporal relationship) and the link between the e-cigarette use and the health outcome is likely to be free from serious confounding (specificity of the relationship).

To establish a temporal relationship, prospective cohort studies, randomised controlled trials and non-randomised intervention studies provide the strongest evidence. To establish specificity of the relationship, the best evidence would come from randomised controlled trials, followed by crossover trials. Non-randomised intervention studies and cohort studies can increase the specificity of the relationship reported if study designs account appropriately for potential confounding factors.

Cross-sectional surveys cannot generally be used to establish temporal relationships and consequently are excluded from the evidence synthesis for most outcomes, except for those relating to dependence/abuse liability, reproduction, olfactory and endocrine.

Case reports and case series present difficulties in establishing specificity of the relationship, with the exception of that the observed outcome is a consequence of e-cigarette exposure. These outcomes are generally limited to burns and injuries from e-cigarette explosion, poisonings from e-cigarette use or e-liquid exposure, and e-cigarette or vaping product use-associated lung injury (EVALI). Studies reporting surveillance data, where identified, were also included for these outcomes. A major additional shortcoming of studies of cases, whether report, series, or surveillance, is that there is no way to determine the extent of the issue and the incidence of the health outcome among users of e-cigarettes, and this is taken into account when drawing conclusions from this type of evidence.

Consequently, the study designs mainly intended for inclusion in evidence synthesis were randomised controlled trials, cohort studies, non-randomised intervention studies, and case-control studies. Case reports, case series and surveillance reports were included for selected outcomes only.

All studies identified in the systematic search, including all study designs, are included in Table 4.1.1. Only those included in synthesis for establishing conclusions are discussed in detail in the findings chapters below. The process of study selection for the top-up systematic review is shown in the PRISMA flowchart in Appendix 4.

4.3 Dependence and abuse liability

Main conclusions from the synthesised evidence on dependence and abuse liability in relation to e-cigarette use

- Among non-smokers, there is substantial evidence that e-cigarette use results in dependence on e-cigarettes.
- Among smokers, there is limited evidence that e-cigarette use results in dependence on e-cigarettes. There is limited evidence that e-cigarettes have lower abuse liability than combustible cigarettes and limited evidence that e-cigarettes have a higher abuse liability than nicotine replacement therapy products among smokers.
- Among smokers, there is insufficient evidence whether abuse liability risk is influenced by flavour and nicotine concentration variations.

Table 4.3-1 Overview of studies of dependence and abuse liability health outcomes identified in the systematic review, by study design

Health outcome	Meta-analysis	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Dependence and abuse liability		13 7* / 6	1 0 / 1	17 9 / 8			20 11 / 9		

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our protocol, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.
* One article described two separate randomised controlled trials.

Outcomes

- **Clinical outcomes**: Measures of dependence, including compulsion to use e-cigarettes, intensity of e-cigarette use (e.g., sessions per day), withdrawal symptoms, time to first use after waking, and craving.
- **Subclinical outcomes**: Measures of abuse liability, including subjective effects of mood enhancement or drug liking, or behavioural choices indicating the motivational value of the drug.

4.3.1 Findings from previous reviews

For the purpose of this review, epidemiological studies on dependence were considered under clinical outcomes and abuse liability studies, often human laboratory-controlled experiments, were considered informative for subclinical outcomes. Since assessment of dependence includes evaluation of measures among current users, cross-sectional evidence on dependence measures and symptoms (such as craving for e-cigarettes, short time to first e-cigarette after awakening, difficulty refraining from e-cigarette use when use is prohibited) was considered relevant.[3] Reports relating to frequency of use in isolation were not considered indicative of dependence.[3]

Abuse liability testing involves assessing the immediate effects of an exposure (drug) with proxy measures that reflect the likelihood that the exposure will cause dependence.[3] Outcomes include subjective and rewarding effects, such as mood enhancement, subjective euphoria, drug liking, sensory satisfaction, and intention to use, or behavioural choices paradigms that indicate the motivational value of the drug, such as the amount of money willing to spend for the drug and willingness to work to receive the drug.[3] The effects of e-cigarettes in smokers acutely deprived of nicotine (abstinent) on nicotine withdrawal symptoms, combustible tobacco cigarette craving, and other factors believed to maintain smoking behaviour are not generally considered evidence of abuse liability or dependence. Other products, such as approved smoking cessation products, are known to be effective at suppressing nicotine withdrawal and cigarette craving and have little to no abuse liability.[3] Consequently, measures on suppression of withdrawal symptoms on the alleviation of smoking have been excluded. Participants included in abuse liability studies involve either naïve or inexperienced e-cigarette tobacco smokers or experienced e-cigarette users as it is unethical to expose non-tobacco-product users to e-cigarettes.[3] As much of e-cigarette dose is dependent of user behaviour, inexperience with the device is likely to impact abuse liability outcomes. Furthermore, it is not possible to ascertain abuse liability risk in non-users.

The NASEM review identified 15 epidemiological studies on dependence, 11 cross-sectional surveys and four non-randomised laboratory-based studies.

Of the 11 cross-sectional surveys[113-121] included in the NASEM review, three used nationally representative data.[119-121] Rostron et al.[120] used data from the 2012–2013 National Adult Tobacco Survey (NATS) in the US to measure dependence symptoms in the past 30-days among exclusive daily e-cigarette users (n=124) and cigarette smokers (n=3,963). Prevalence of dependence symptoms ranged from 23%-46% among exclusive e-cigarette users. Among exclusive e-cigarette users, 46.1% (95% CI 35.1–57.4) reported use 30 minutes after waking, 46.2% (95% CI 35.2–57.5) reported strong cravings, 46.2% (95% CI 35.2–57.5) reported need to use and 22.8% (95% CI 14.8–33.4) reported withdrawal symptoms upon abstinence. Dependence symptoms were significantly less prevalent among exclusive daily e-cigarette users than smokers. Using Wave 1 of the US Population Assessment of Tobacco and Health (PATH) survey, Liu et al.[121] compared dependence in the past 30-days between exclusive e-cigarette users (n=156) and smokers (n=3,340). Considering yourself addicted to tobacco was highly prevalent in both exclusive e-cigarette users (77.2%) and smokers (94.0%) as was strong cravings (72.8% e-cigarettes and 86.9% smokers) and need to use (71.5% e-cigarettes and 88.5% smokers). Difficulty refraining where prohibited affected 5.6% of e-cigarette users and 28.6% of smokers. Average time to first use after waking was 23.5 minutes in e-cigarette users and 19.25 minutes in tobacco smokers. Also using the US PATH survey, Strong et al.[119] used four dependence tools to measure 24 tobacco dependence symptoms. Setting mean tobacco smoking dependence as 0.0 (SD=1.0) for comparisons, mean tobacco dependence in exclusive e-cigarette users (n=437) was 1.37 standard deviations below that of smokers (n=8,689) while dual smokers and e-cigarette users had mean dependency slightly higher than smokers (0.35 higher). Among exclusive e-cigarette users, higher levels of dependence were reported for daily users compared to non-daily users ($p<0.002$).

The NASEM review[3] identified eight studies using non-representative sampling.[119-126] Johnson et al.[116] reported dependence in 177 e-cigarette users (including 10 dual users) at an e-cigarette convention in the US. By categorising scores from modified questions of the Fagerström Test for Cigarette Dependence (FTCD), 17% had low, 22% had low-moderate, 45% moderate, and 15% high dependence. Length of e-cigarette use and use of nicotine e-cigarettes were positively associated with e-cigarette dependence category. In the Spanish survey by González-Roz et al.,[115] e-cigarette users (n=39) were dependent on nicotine e-liquids and were less nicotine dependent than current cigarette smokers (n=42).

The Penn State Electronic Cigarette Dependence Index (PSECDI) was used to measure dependence among 3,609 exclusive e-cigarette users that responded to an online survey between 2012-2014 in the study by Foulds et al.[117] Participants were all former smokers but had not smoked cigarettes in the past 30-days. E-cigarette users had between low and medium dependence (average score: 8.1; SD: 3.5). PSECDI was significantly higher by certain e-cigarette characteristics such as length of use, large device, trialling multiple models and more advanced models. Using the same dataset as in Foulds et al.,[117] Yingst et al.[127] compared e-cigarette dependence between first and fourth generation past 30-day e-cigarette users who were ever-tobacco smokers. Compared to first generation users, fourth generation users had a higher means PSECDI score (mean (SD) = 8.3 (3.3) vs. 7.1 (4.0); both considered low dependence) and short time to first e-cigarette after waking (mean (SD) = 38.7 (60.0) vs. 67.3 (116.1) minutes) despite using lower nicotine concentrations. Dawkins et al.[118] used an online survey to measure dependence among current e-cigarette uses who were former smokers (n=1,123) and current dual users (n=218). The mean FTCD score was higher for former smokers (6.2; SD: 2.30) than dual users (4.93; SD: 2.66).

The studies by Etter (2015),[113] Etter (2016)[122] and Etter and Eissenberg[114] used an overlapping sample from online surveys from 2004-2007 (nicotine gum sample) and 2012-2014. Etter and Eisenberg[114] reported dependence in 1,284 daily e-cigarette users. For long-term use (three months or more) among former smokers, e-cigarette users were less dependent on e-cigarettes than those who had used nicotine gum. Nicotine e-cigarettes users had higher dependence ratings than non-nicotine e-cigarettes users. In Etter (2015),[113] e-cigarette dependence among exclusive e-cigarette users (n=374) who were former smokers (quit in the previous two months) was positively associated with increasing satisfaction with e-cigarettes to alleviate the desire to smoke. Etter (2016)[122] looked at dependence by self-reported throat hit – which is generally greater with higher nicotine doses – among 1,672 current e-cigarette users. Time to first e-cigarette was generally shorter among stronger throat hit respondents (suggestive of greater dependence), and the median time ranged from 15 to 30 minutes across all throat hit categories (five categories ranging from very weak to very strong), indicating medium levels of dependence. Abuse liability measures investigating subjective reward (e.g., liking, feels good) were prevalent at high levels in the sample and generally most prevalent in the stronger throat hit group.[122]

Four non-randomised intervention studies incidentally reported dependence outcomes as part of their sample characteristics description. All were small laboratory studies, with samples ranging from 7 to 20 participants and one was conducted in the UK[124] and three in the US.[125-127] The study populations were of young and middle-age adult current e-cigarette users, with mean age ranging from 26.3 to 41.6 years. One study was conducted using a smoker population.[127] Gender distributions were varied among the studies, with males ranging between 28.6% to 100%. The mean score of modified Fagerström Test for Nicotine Dependence (FTND) for e-cigarettes was 4.73 (SD=1.35, range=2-7) in one study.[124] PSECDI scores across three studies were low to moderate, ranging from 3.2 to 8.4, out of a possible score range of 0 to 20.[125-127] The results indicated moderate levels of nicotine dependence in e-cigarette users and a harmful effect of e-cigarette use on dependence.[3]

Of the 11 articles (describing 12 trials) reporting the relation of e-cigarette use to abuse liability outcomes, two also included dependence outcomes.[124,127] There were five randomised controlled trials[128-131] (Rosbrook and Green described two separate trials in one article[131]) and seven non-randomised intervention studies.[124,127,132-136] Five studies[127,131,132,135] compared various e-liquid flavours on abuse liability. Six studies[124,127,131,133,134] compared differing nicotine concentrations on abuse liability and four studies[128-130,136] compared the effects of e-cigarettes with tobacco cigarettes on abuse liability among smokers.

In the double-blinded non-randomised US intervention study by Goldenson et al.,[127] 20 young adults (aged 19-34 years) with past 30-day e-cigarette use, trialled 10 different e-liquid flavours with 6mg/mL and 0mg/mL nicotine concentrations to measure liking, willingness to use again and monetary value. Participants inhaled 20 standardised two-puff doses (10-second preparation, 4-second inhalation, 1-second hold, and 2-second exhale) and flavours were grouped into sweet, non-sweet and flavourless. Compared to non-sweet flavours, sweet flavours produced significantly higher abuse liability ratings for each of the three measures ($p<0.0001$). Perceived sweetness of flavour was also positively associated with abuse liability. There was no significant effect of nicotine concentration on flavour effects.

Audrain-McGovern et al.[132] conducted a non-randomised intervention study in 32 young US adult smokers who were inexperienced with e-cigarettes, comparing flavoured and sweet flavoured nicotine e-liquid on satisfaction and taste ratings and willingness to work. On a scale of 1-7, subjective reward ratings were significantly higher for sweet flavours compared to unflavoured and participants were more willing to work for flavoured e-liquids than unflavoured ($p<0.0001$).

The publication by Rosbrook and Green[131] detailed two separate US randomised controlled trials investigating the effect of menthol flavouring and nicotine on abuse liability. Both trials involved 32 adult smokers (aged 18-45 years), the majority of whom were self-reported menthol smokers. The trials included both experienced and inexperienced e-cigarette users and six participants partook in both trials. In the first experiment, participants used 15 different e-liquids (five different nicotine concentrations and three different menthol concentrations). In the second trial, participants used 12 different e-liquids (0mg/mL or 24mg/mL nicotine e-liquid with two menthol flavours, two menthol-mint flavours and two unflavoured). Combined results from the two studies found e-liquids were on average only 'slighted liked'. In the first trial, there was no difference in the degree of liking by nicotine or menthol concentration. In the second trial, both the menthol and menthol-mint flavours had significantly higher liking ratings than unflavoured e-liquids ($p<0.001$) and there was no significant nicotine or nicotine-flavour interaction.

In the US non-randomised crossover trial by St Helen et al.,[135] 14 exclusive e-cigarette or dual users (11 men and three women) compared abuse liability risk between their own usual e-cigarette flavours and two other flavours (strawberry and tobacco, 18mg/mL nicotine concentration). The evening prior to laboratory sessions, participants could acclimate to their assigned flavour between 4-10pm but then had to abstain from use overnight. The following morning, participants used the device for 15 puffs (30 seconds between puffs) then completed a four-hour period of abstinence before being allowed 90 minutes of ad lib use. For the standardised session, there was no differences in mood enhancement or any subjective satisfaction measure between tobacco and strawberry e-liquids. Mean change in mood and satisfaction was higher for own e-liquid, although no statistical tests were conducted. For the ad lib session, usual flavour was rated significantly higher for 'tastes good' than both strawberry and tobacco flavours ($p<0.001$) and there was no difference between strawberry and tobacco. Average satisfaction ratings were significantly lower for strawberry ($p=0.002$) and tobacco ($p<0.001$) e-liquids compared to usual brand e-liquids, as were ratings of enjoyment of sensations in chest and throat (strawberry: $p=0.022$; tobacco: $p=0.019$).

In the non-randomised intervention study by Dawkins et al.,[124] the effects of low (6mg/mL) and high (24mg/mL) nicotine concentrations were compared among 11 male experienced e-cigarette users from the UK. There was no statistical difference between the high and low nicotine concentrations for hit and satisfaction ratings. Perkins et al.[134] compared the abuse liability of 36mg/mL nicotine e-liquid and

placebo (0mg/mL) in 28 adult US smokers diagnosed with nicotine- dependence who were inexperienced with e-cigarettes in their non-randomised intervention study. Both liking and satisfaction were significantly higher for the nicotine e-cigarette than the placebo. Although the Italian non-randomised intervention study by Baldassarri et al.[133] was not specifically designed to investigate abuse liability, self-reported product liking was collected in their study on nicotine receptor occupancy. However, due to limitations with study size, the NASEM review found no conclusions regarding the evidence could be made.

Strasser et al.[130] compared the abuse liability of e-cigarettes to tobacco cigarettes among 28 e-cigarette naïve current smokers from the US. The within-subject randomised controlled trial consisted of a 10-minute cigarette session on day 1 and then ad lib exclusive e-cigarette use for the following nine days and testing occurred on day 1, 5 and 10. Participants were randomised to use one of five different e-cigarette brands with various nicotine concentrations. Liking of product was significantly lower for e-cigarettes (both at day 5 and 10) than tobacco cigarettes. There was no difference in abuse liability between e-cigarette devices.

Stiles et al.[128] compared three different nicotine e-cigarettes (14, 29, or 36mg/mL) to products with established high (usual brand cigarettes) or low (nicotine gum) abuse liability among 45 e-cigarette naïve smokers from the US. Participants were assigned to use each product for seven days in a randomised order and then return to the laboratory for testing. Product liking of e-cigarettes was significantly lower than combustible cigarettes ($p<0.001$) but higher than nicotine gum ($p<0.05$). Intent to use again was similarly patterned.

In the US randomised controlled trial by Vansickel et al. (2012)[129] subjective reward and behavioural choice abuse liability measures were compared between usual cigarette and 18mg/mL e-cigarette exposure among 20 e-cigarette naïve current smokers. Participants undertook four sessions. The first involved controlled e-cigarette use, whilst in the remaining three sessions participants preferenced a specific quantity of either e-cigarettes, cigarettes or money compared to a different quantity of an alternate option. This design enabled the calculation of the point at which participants chose to receive (1) money over 10 puffs from the e-cigarette; (2) money over 10 puffs of their own-brand combustible tobacco cigarette; or (3) own-brand puffs over 10 puffs from the e-cigarette. The average point at which participants would prefer money over product was much lower for e-cigarettes ($1.06; SD=$0.16) than cigarettes ($1.50; SD=$0.26) suggesting greater reinforcing effects of cigarettes. Comparing the value of puffs, 10 e-cigarette puffs were found to be the equivalent to three own-brand cigarette puffs. It was concluded that e-cigarettes possessed some abuse liability which was lower than combustible cigarettes.

In an earlier US non-randomised intervention study by Vansickel et al. (2010),[136] 32 e-cigarette naïve daily smokers compared the effects of their usual cigarettes, two e-cigarettes (16mg/mL and 18mg/mL) and an unlit cigarette (sham) on product liking at 5-, 15-, 30- and 45-minutes post-use. Significant condition-by-time interactions for ratings of "satisfying," "pleasant," and "taste good" were reported, and ratings were significantly higher for combustible cigarettes than both e-cigarettes.

Two additional clinical studies, both from the US, were reported by the NASEM review but were found to provide little addition weight to conclusions as they described secondary outcomes based on recall of user experience. In the randomised controlled trial by Steinberg et al.,[137] e-cigarettes had a higher total satisfaction and reward score than a nicotine inhaler, but no difference compared to cigarettes among 38 current smokers that trialled each product for three days. In the second study, the randomised controlled trial by Meier et al.[138] found no difference between nicotine e-cigarettes (16mg/mL nicotine) and non-nicotine e-cigarettes in satisfaction or rewarding effects among 24 smokers that trialled each product for a week with ad lib use and cigarette smoking.

The Irish Health Research Board literature map[15] identified 26 intervention studies (nine randomised controlled trials, 17 non-randomised intervention studies), 10 cohort studies, 21 cross-sectional surveys, two case reports[139,140] and one surveillance report[141] on the relationship of e-cigarette use to dependence and abuse liability outcomes. The case reports and surveillance report were not included as they examined the use of e-cigarettes for smoking cessation and reducing smoking dependence rather than e-cigarette dependence. Of the 10 cohort studies, one[142] was included in the dependence chapter of the top-up review, four[143-146] were considered in the mental health chapter of the top-up review and five[147-151] did not meet eligibility for inclusion. Of the 26 intervention studies, 10[55,152-156] were included in the top-up review, five[125,128,129,133,136] were included in the NASEM review, and 11[147,157-162] did not meet inclusion criteria.

Of the 21 cross-sectional surveys, three[163-165] were included in the dependence chapter of the top-up review, nine were considered in other chapters of the top-up review (three[166-168] in sleep and six[169-174] in mental health), two[114,116] were included in the NASEM review, one[175] was published before the top-up

review and not included in the NASEM review, and six[176-181] did not meet inclusion criteria. In the cross-sectional survey by Farsalinos et al.,[175] the authors measured e-cigarette dependence in 111 experienced e-cigarette users who has previously quit tobacco cigarettes by completely substituting cigarettes with e-cigarettes for at least one month. The average age of the sample was 37 years (SD=6 years) and 84% were male. For both measures of dependence (how soon after waking did you smoke your first cigarette/do you use the e-cigarette; How would you rate your past dependence on smoking/current dependence on e-cigarettes?), e-cigarette dependence was significantly lower than former smoking dependence ($p<0.001$).

The Public Health England review[11] included four cross-sectional surveys[114,119-121] reporting on the relationship of e-cigarette use to dependence and no original studies reporting on the relationship of e-cigarette use to abuse liability. All studies were included in the NASEM review.

The CSIRO review[14] included two cross-sectional surveys and one cohort study reporting on the relationship of e-cigarette use to dependence and no studies reporting on the relationship of e-cigarette use to abuse liability. One study[115] was included in the NASEM review, one[182] was included in the top-review and one did not meet eligibility criteria.[183]

No studies on dependence or abuse liability were identified in the SCHEER[4] and USPSTF[16] reviews.

4.3.2 Summary of conclusions from previous reviews

The NASEM review,[3] incorporating evidence from epidemiological studies, laboratory studies on the effects of nicotine concentration and flavours, and clinical trials in smoker populations, concluded that:

- There is substantial evidence that e-cigarette use results in symptoms of dependence on e-cigarettes.
- There is moderate evidence that risk and severity of dependence are lower for e-cigarettes than combustible tobacco cigarettes.
- 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.

The Irish Health Research Board review,[15] incorporating evidence from cross-sectional surveys, clinical intervention and cohort studies, concluded that:

- There was a mixture of possible e-cigarette-related harms (abuse liability, lower nicotine uptake in vapers than in smokers) and benefits (satisfaction, state of stable dependence, reduced cravings or withdrawal symptoms).

The Public Health England review,[11] incorporating evidence from cross-sectional surveys, concluded that:

- Nicotine addictiveness depends on a number of factors including presence of other chemicals, speed of delivery, pH, rate of absorption, the dose, and other aspects of the nicotine delivery system, environment and behaviour.

The CSIRO review[14] did not provide any summative conclusions on dependence.

4.3.3 Top-up review

Search results

Overall, 24 articles were located in the top-up systematic literature search reporting on the relationship of e-cigarette use and dependence and abuse liability (Table 4.3-1).

Dependence measures: clinical outcomes

Fifteen articles reporting on the association between e-cigarette use and dependence were identified, one randomised controlled trial,[153] one cohort,[142] nine cross-sectional[163,164,182,184-189] and four non-randomised intervention studies.[156,190-192] One cross-sectional survey,[185] one randomised controlled trial[153] and four non-randomised intervention studies[156,190-192] also provided findings on abuse liability. In this context, cross-sectional surveys are considered suitable evidence and have been included in evidence synthesis.

Meta-analyses

No meta-analyses of e-cigarette related dependence were located.

Randomised controlled trials

One randomised controlled trial reporting on e-cigarette dependence outcomes was located in the literature search.

The US study by Hiler et al.[153] compared 31 e-cigarette naïve smokers with 33 e-cigarette experienced individuals who smoked fewer than five cigarettes per day (70% male; mean age 30.6 years) to investigate the effect of various nicotine concentrations on abuse liability outcomes. As part of the sample characteristics, dependence for each group was assessed using modified versions of the Penn State Dependence Index (PSDI) and the Fagerström Test for Nicotine Dependence (FTND). There was no statistical difference in FTND scores between groups, however, e-cigarette naïve smokers were significantly more dependent on cigarettes than e-cigarette experienced users were on e-cigarettes using the PSDI ($p<0.05$). Both groups were considered to have medium dependence using the PSDI and low to moderate dependence using the FTND.

This study was of moderate methodological quality using the Joanna Briggs Institute's critical appraisal checklist and some of the study authors had been paid consultants in litigation against the tobacco industry.

Cohort studies

One moderately sized cohort study,[142] reporting on the relationship of e-cigarette use to e-cigarette dependence outcomes was located (Table 4.3-2). A total of 412 exclusive e-cigarette users from the US completed the Penn State Electronic Cigarette Dependence Index (PSECDI) at baseline and at approximately four years' follow-up. The mean age at baseline was 41.2 years and 67.5% of the group were male. Out of a possible score of 20, the mean PSECDI score was 8.5 (SD=3.4) at baseline and 8.4 (SD=3.8) at follow-up. This did not differ significantly for the poly user group, which was smaller (n=59) and younger (mean age 36.5 years). The authors concluded that there was evidence of e-cigarette–related dependence at baseline and no evidence of increased dependence over time.

The study was rated low methodological quality using the Joanna Briggs Institute's critical appraisal checklist and a potential conflict of interest, consultant and grants from pharmaceutical companies, was noted.

Non-randomised intervention studies

Four non-randomised intervention studies,[156,190-192] two published by the same authors, reporting on the relationship of e-cigarette use to dependence, were located (Table 4.3-2).

Both studies by Hughes et al. were small and were conducted in the US. One study included 30 never smokers[190] and there were 109 former smokers included in the second study;[156] participants were current daily e-cigarette users. There was a higher percentage of males in both studies (61% and 81%) and the average age was 21-22 and 32 years. Apart from the population, the studies shared the same study design and protocol in which participants used their own e-cigarettes for seven days followed by six days of biologically confirmed abstinence. Dependence was assessed by an adapted Diagnostic and Statistical Manual, Fifth Edition (DSM-5) definition of cigarette use disorder assessing withdrawal on a 0-3 scale, with three control symptoms for comparison (0-3 scale). In both studies, 40% of participants in the study on never smokers and 46% in the study on ex-smokers could not maintain abstinence. Among the never smoker population, withdrawal symptoms were found to increase marginally with abstinence (mean increase 0.23, $p=0.003$). Control items showed no significant increase. The study among ex-smokers showed a significant increase in withdrawal after abstinence (mean increase 0.57, $p<0.001$), and a significant but marginal increase in one control item (tremors; mean increase 0.15, $p<0.01$).

In the German non-randomised intervention study by Ruther et al.,[191] dependence was assessed as part of their sample characteristics. The sample consisted of nine exclusive e-cigarette users (mean age 28.5 years) and 11 daily smokers (mean age 26.2 years) all of whom were male. Both groups had low dependence using the FTND. The mean FTND score for the e-cigarette group was 2.67 (SD 2.18, range 0–6), and the level of physical dependence was mild in three participants, moderate in five, and severe in one. The mean FTND score for smokers was 2.73 (SD 2.41, range 0–8), and the level of physical dependence was mild in six participants, moderate in four, and severe in one.

Spindle et al.[192] also reported e-cigarette dependence as part of their sample characteristics in the US non-randomised intervention study among 30 experienced e-cigarette users who smoked less than five cigarettes daily (97% male; mean age 26.9 years). The average score of dependence was 3.7 (SD=2.4; low to moderate dependence) and 8.8 (SD=4.8; low to medium dependence) using the FTND and PSDI measures respectively.

The three studies were of moderate[156,190,191] and one was of high[192] methodological quality using the Joanna Briggs Institute's critical appraisal checklist. Potential conflicts of interest were noted in three studies. In two studies,[156,190] authors has received consultant fees and grants from pharmaceutical and tobacco companies. One study[192] had authors that were paid consultants in litigation against the tobacco industry. One study[191] had no conflicts of interest to declare.

Case-control studies
No case-control studies of e-cigarette related dependence were located.

Other study types not considered in the assessment of likely causality
Nine cross-sectional surveys[163,164,182,184-189] on e-cigarette related dependence were identified.

The online cross-sectional survey of US JUUL users by Leavens et al.,[185] mean age (SD): 25.9 (3.1); males: 60%, used the Penn State Electronic Cigarette Dependence Index to assess dependence by smoking status (current/dual (n=232), former smoker (n=187) and never smoker (n=174)). All groups had low dependence (score between 4-8) and the mean score was 8.0 (SD=4.1) for dual users, 7.6 (SD=4.0) for former smokers, and 7.0 (SD=4.2) for never smokers. Across the three groups, there was a significant difference in mean dependence score (p=0.043) and using a pairwise comparison, only never smokers and dual users were significantly different.

Using Waves 1-3 of the US Population Assessment of Tobacco and Health (PATH) survey, Shiffman and Sembower[186] measured e-cigarette dependence in exclusive current e-cigarette users by e-cigarette consumption. Out of a score of five, mean e-cigarette dependence was 1.98 (SD=0.06) among all current e-cigarette users. Dividing by use, daily e-cigarette users had a higher dependence score (mean: 2.17; SD 0.08) than non-daily e-cigarette users (mean: 1.37; SD 0.04).

Hughes and Callas[184] also used the PATH survey but included only Wave 2 in their analysis of abstinence on withdrawal symptoms in exclusive e-cigarette users, smokers and dual users that attempted to quit either e-cigarettes, cigarettes or both. Of the 25 exclusive e-cigarette users that made a quit attempt, the average number of withdrawal symptoms was 1.7 (SD=2.3) with 40% reporting any withdrawal symptoms and 25% reporting four or more. Among smokers (n=2,528) who made a quit attempt, an average of 2.5 (SD=2.3) symptoms were reported, 71% reporting any symptoms and 33% reporting four or more. There was no statistical difference in withdrawal symptoms between dual users who quit e-cigarettes but not cigarettes (n=60), and exclusive e-cigarette users that quit indicating that smoking abated e-cigarette withdrawal. Dual users who quit smoking but continued e-cigarette use (n=242) reported significantly more withdrawal symptoms than smokers who quit cigarettes, indicating e-cigarettes did not relieve smoking withdrawal (p<0.001 for mean, any, and 4+ symptoms). Prevalence of the seven dependence items from the DSM-5 criteria for tobacco withdrawal ranged from 12%-40% among e-cigarette users, 19%-49% in smokers, 10%-21% in dual users that quit e-cigarettes and 24%-62% in dual users that quit cigarettes.

The study by Jankowski et al.[164] was a continuation of the YoUng People E-Smoking Study (YUPESS), a multi-centred international project in which students from universities in Katowice, Poland, were issued a survey to measure e-cigarette and cigarette dependence among exclusive e-cigarette users, smokers and dual users. Compared to dual users, e-cigarette dependence was significantly different for exclusive e-cigarette users in only two out of six items on the Fagerström Test for Nicotine Dependence (FTND). More dual users reported e-cigarette use more frequently in the morning than the rest of the day (p=0.05) and using an e-cigarette when ill (p=0.01). This was similar for cigarette dependence among smokers and dual users. The average FTND score was over twice as high among exclusive users compared to smokers (3.5 vs. 1.6; p=0.002). Among dual users, the mean nicotine dependence level from e-cigarettes (mean 4.7) was higher than that of cigarettes (4.7 vs. 3.2; p=0.03).

The online study by Browne and Todd[182] surveyed 436 current e-cigarette users who were former smokers, 80% male with an average age of 41.4 years (SD=13.1), to compare past smoking dependence and current e-cigarette dependence. Of the 436 respondents, 22 (5.0%) reported some degree of current dual use. Mean responses for all components of the FTND were significantly less for e-cigarettes than past smoking (p<0.001) with the greatest difference in response to the question "did/do you smoke/vape more during the first hours of the day after waking than during the rest of the day?"

Boykan et al.[163] compared e-cigarette dependence between adolescent and young adult current exclusive pod users (n=20) and non-pod users (n=22). Participants were recruited from a larger sample from three children outpatient offices in the US. Pod users were younger than non-pod users and no information on sex was reported. Affirmative responses to the five questions on e-cigarette dependence were reported in 2-6 participants. There was no significant difference between pod and non-pod users in four out of five questions and there were significantly more pod users then non-pod users that agreed with the statement "I need to vape when I awaken in the morning" (p=0.006).

In the Canadian study by Camara-Medeiros et al.,[189] self-reported addiction among 578 youth and young adult regular e-cigarette users (mean age 18.7 years; 76% male) was assessed. The sample included 20% current smokers (dual users), 18% former smokers and 62% never smokers. Overall, 13% reported being

very addicted, 41% somewhat addicted and 46% not addicted. Those that reported daily e-cigarette use compared to non-daily use were more than seven times more likely to report higher addiction than lower addition (odds ratio: 7.51; 95% CI 4.55-12.42; p<0.0001). Using an e-cigarette more than 10 times per weekday or weekend day did not significantly increase the likelihood of higher self-reported addiction (weekday odds ratio: 1.17; 95% CI 0.65-2.10; p=0.594 and weekend odds ratio: 0.64; 95% CI 0.35-1.18; p=0.157). Those that reported e-cigarette use for more than one year were significantly more likely to report higher addiction (odds ratio: 1.62; 95% CI 1.06-2.47). Compared to 0mg/mL nicotine, more than 9mg/mL nicotine concentrations and not 1-8mg/mL concentrations were associated with higher self-reported addiction (9+mg/mL odds ratio: 2.35; 95% CI 1.10-5.03; p=0.001 and 1-8mg/mL odds ratio: 0.94; 95% CI 0.47-1.85; p=0.0298).

Case et al.[187] compared e-cigarette dependence symptoms between 91 past 30-day exclusive e-cigarette users and 41 dual users from Wave 4 of the Texas Adolescent Tobacco and Marketing Surveillance System survey (48.5% female; average age 15.1 years). Among exclusive e-cigarette users, 53.3% wanted to quit and 45.7% had a quit attempt in the past 12 months. Five percent of exclusive e-cigarette users reported really needing e-cigarettes, 5.7% reported use ≤30 minutes after waking and 5.6% reported a strong urge to use. When they have not used their device, 1.6% find it difficult to concentrate, 4.7% find irritable and 2.8% feel anxious. Among dual e-cigarette users, 24.2% wanted to quit e-cigarettes and 22.9% had a quit attempt in the past 12 months. Of dual users, 32.7% reported really needing e-cigarettes, 16.4% reported use ≤30 minutes after waking and 35.7% reported a strong urge to use. When they have not used their device, 19.2% find it difficult to concentrate, 29.0% find irritable and 15.4% feel anxious. All measures were significantly different between exclusive and dual users expect for quit attempts and use ≤30 minutes after waking.

Morean et al.[188] surveyed 520 past-month e-cigarette users at a high school using their own e-cigarette dependence scale. In the sample, 50.5% were female and the average age was 16.22 years. 55.6% of all respondents reported some e-cigarette dependence and the total dependence score was 2.27 (scored out of four with score greater than zero indicative of dependence). Average scores across the four items ranged from 0.30-0.74. Stronger dependence was significantly associated with use at an earlier age, more frequent use, and using higher nicotine concentrations (p<0.01). Using nicotine e-liquid rather than non-nicotine e-liquid was also strongly associated with dependence (p<0.001).

Of the nine studies, seven were low[163,182,184-188] and two were moderate[164,189] methodological quality. Potential conflicts of interest were noted in two studies [184,186] as authors were consultants for or had received funds from the tobacco industry. One study, Shiftman and Sembower,[186] was also funded by Reynolds American Inc Services Company, a subsidiary of the tobacco company Reynolds American Inc. Authors in Morean et al.[188] had previously received donated study medication from pharmaceutical companies and authors in Boykan et al.[163] had received grants or fees from pharmaceutical companies. No conflicts of interest were declared in five studies.[164,182,185,187,189]

Abuse liability measure: subclinical outcomes

Fifteen articles reporting the association between e-cigarette use and abuse liability measures were identified.[55,152-156,185,190-197] Six studies[153,156,185,190-192] have also been described under dependence.

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to abuse liability measures were located.

Randomised controlled trials

Six randomised controlled trials reporting on the relationship of e-cigarette use to abuse liability measures including subjective effects and behaviour choices were located (Table 4.3-2).[55,152-154,193,194]

In a US study, Stiles et al.[194] compared the subjective effects of menthol flavoured nicotine e-cigarettes (14, 29 and 36mg/mL nicotine) to combustible cigarettes (known high abuse liability) and nicotine gum (known low abuse liability) among 71 daily smokers (62% male; mean age 34.3 years). Average liking and intent to use again were significantly higher for all ENDS compared to gum, and maximum effects were significantly higher than gum for measures of liking for the lowest nicotine concentration ENDS only, and intent to use again for the two lowest nicotine concentration ENDS. Averages and maximum effects were significantly lower than combustible cigarettes for liking, intent to use again, and liking of positive effects for all nicotine concentration ENDS. No significant results were reported for disliking of negative effects for any product. The authors noted the abuse liability of e-cigarettes was higher compared to gum, and lower compared to combustible cigarettes.

In the US randomised within-subject trial by De La Garza et al.,[152] 15 tobacco dependent e-cigarette naïve smokers trialled three different e-cigarettes (0mg/mL, 18mg/mL and 36mg/mL) to investigate the effects of nicotine concentration on abuse liability. There were 66% male participants and the average age was

50.6 years. Participants undertook a period of abstinence overnight before completing four sessions in which they inhaled 10 puffs of their exposure twice with a 30-minute washout period in-between. On a scale of 0-7, 0 being not at all and 7 being very much, average satisfaction for e-cigarettes compared to cigarettes ranged from 2.7-3.1 across the three e-cigarette devices (ENNDS: 3.1 (SD 1.9); ENDS 18mg/mL: 3.0 (SD 1.8); ENDS 36mg/mL: 2.7 (SD 1.7). Eleven participants reported that they would prefer their combustible cigarettes to e-cigarettes for each of the three nicotine concentrations.

Palmer and Brandon[193] studied the effects of nicotine delivery and outcome expectancies on the reduction of cravings for e-cigarettes among 128 current e-cigarette users in the US. The sample consisted of 76 former smokers and 52 current smokers (dual users) of which 62% were male with a mean age of 36.4 years. On average, former smokers reported higher mean daily e-cigarette use (43.9) than dual users (26.7). No main effects were observed; however, an interaction effect was found when the participants were correctly informed that the e-cigarettes contained nicotine ($F(1, 120) = 5.56$, $p=0.020$, $\eta^2 = 0.04$), suggesting a reduction in craving for an e-cigarette resulting from e-cigarette use, that may not transfer to a different nicotine-delivering product such as a combustible cigarette. Among smokers, but not among the full sample, higher nicotine dose estimates were associated with greater cigarette craving reduction ($r (50) = 0.37$, $p=0.007$). The authors noted that the craving reduction was driven by participants' expectancies about the effects of nicotine rather than the pharmacological properties of nicotine. Abuse liability of e-cigarettes was indicated.

In the study previously described study by Hiler et al.,[153] the effects of nicotine concentrations (0, 8, 18 and 36mg/mL) on abuse liability measures were compared between e-cigarette naïve smokers and e-cigarette experience individuals. Using the Hughes-Hatsukami Withdrawal Scale, there were significant differences between groups for anxious, depression, impatient, irritable and restless. There was a significant difference (all p values <0.01) by nicotine concentration for all items but hunger and sweets, as score generally decreased as nicotine concentration increased. Significant nicotine concentration by group interactions were found for craving, depression, drowsy and urge. Both intention to use and relief from withdrawal significantly differed by nicotine concentration ($p<0.01$). Only relief from withdrawal was significantly different by group ($p<0.01$) and there was a significantly nicotine concentration by group interaction for intention to use ($p<0.05$). There was a significant difference for all items measuring the direct effects of ENDS by nicotine concentration. Only 'right now' was significantly different between groups and there was a significant nicotine concentration by group interaction for awake, pleasant and satisfy.

O'Connell et al.[55] compared the subjective effects of five different e-cigarettes to their own conventional cigarettes among 15 e-cigarette naïve smokers, 60% male and average age of 42.3 years. Scores for enjoyment ranged from 4.9-3.2 (three being a little and four being modestly enjoyable) and there was no significant difference between all products.

In the Belgian study by Adriaens et al.,[154] 30 e-cigarette naïve daily smokers (67% male, mean age 22 years) compared a 18mg/mL nicotine e-cigarette and a heat-not-burn device with their own cigarettes to assess product evaluation using the modified Cigarette Evaluation Questionnaire (adapted for e-cigarettes). E-cigarettes were rated significantly lower than combustible cigarettes on subjective ratings of satisfaction, psychological rewards, enjoyment of respiratory tract sensations and craving reduction (all $p<0.001$). There was no difference in aversion ratings.

Studies were rated of low[154], moderate[55,152,153,194] and high[193] methodological quality. No conflicts of interests were declared in two studies.[152,193] Stiles et al.[194] had potential competing interests as some authors are full-time employees of Reynolds American Inc Services, a subsidiary of British American Tobacco who also funded the trial. Potential conflicts of interest were also noted in O'Connell et al., in which most authors were full time employees of Imperial Grands Group (formerly Imperial Tobacco Group).[55] Hiler et al.[153] had authors that were paid consultants in litigation against the tobacco industry and authors in Adriaens et al.[154] acknowledged that they are tobacco harm reduction advocates.

Cohort studies

No cohort studies reporting on the relationship of e-cigarette use to abuse liability outcomes were located.

Non-randomised intervention studies

Eight non-randomised intervention studies[155,156,190-192,195-197] were identified reporting on the relationship of e-cigarette use to abuse liability measures, including subjective effects and behaviour choices (Table 4.3.2). The two non-randomised intervention studies by Hughes et al.,[156,190] the study by Spindle et al.[192] and the study by Ruther et al.[191] have also been included under dependence.

Dowd and Tiffany[195] assessed behaviour choices under cued conditions, with choices of the participant's own ENDS, a combustible cigarette, or a glass of water. The non-randomised crossover study[195] conducted in a US smoker population, was small in size (54 participants), comprised of mostly males (81.5%) and had an average age of 27.8 years. Craving for ENDS was higher than for water when water and ENDS were available ($F_{1,53} = 43.1$, $p<0.0001$, $\eta p^2 = 0.43$), and lower than water when a combustible cigarette was available ($F_{1,52} = 15.1$, $p=0.0003$, $\eta p^2 = 0.22$). Craving for a combustible cigarette was higher than for water when a combustible cigarette was available ($F_{1,52} = 15.1$, $p=0.0003$, $\eta p^2 = 0.22$), and not significantly different when an ENDS was available ($p=0.70$). Significantly more money was spent on ENDS trials when compared to water trials ($F_{1,53} = 46.6$, $p<0.0001$, $\eta p^2 = 0.47$), and significantly less when compared to combustible cigarette trials ($F_{1,53} = 23.8$, $p<0.0001$, $\eta p^2 = 0.31$). Spending choice times were significantly longer on e-cigarette ($F_{1,53} = 19.8$, $p<0.0001$, $\eta p^2 = 0.27$) trials compared to water trials. The authors noted the presence of a motivational impact for using e-cigarettes across variables indicating abuse liability of e-cigarettes. They also noted that the presence of an e-cigarette did not reduce cravings for tobacco cigarettes.

In the study by Maloney et al.,[197] the abuse liability of a non-nicotine e-cigarette and a 36mg/mL nicotine e-cigarette were compared to a combustible cigarette (high abuse liability) and a nicotine inhaler (low abuse liability) among 24 smokers (25% female; average age 30.9 years). The mean multiple-choice procedure (to determine a crossover value for receiving money vs. 10 puffs of product) was $0.87 for the nicotine e-cigarette, and $0.96 for the non-nicotine cigarette, both of which were significantly higher ($p<0.025$) than the nicotine inhaler ($0.32). The nicotine e-cigarette crossover value was significantly lower ($p<0.01$) than own cigarette ($1.42) and there was no difference between the non-nicotine e-cigarette and own cigarette. The higher the crossover point, the greater reinforcing efficacy and abuse liability of the product, therefore it was concluded the e-cigarettes, both nicotine and non-nicotine had greater abuse liability than the nicotine inhaler.

St Helen et al.[196] compared abuse liability measures of nicotine e-cigarettes and cigarettes among 36 dual users (22.2% female, average age 35.4 years) from the US. Measures used included the modified Cigarette Evaluation Scale (mCES) and Questionnaire for Smoking Urges (QSU– Brief) modified for e-cigarettes. E-cigarette users were divided into three groups: cigalike/pod, fixed power and variable power users. Compared to cigarettes, e-cigarettes were significantly less satisfying (mean: 14.3 vs. 16.6; $p=0.001$), had lower enjoyment of sensation (mean): 4.1 vs. 4.6; $p=0.05$), craving reduction (mean: 4.2 vs. 5.6; $p<0.001$) and psychological reward (mean: 19.7 vs. 23.2; $p=0.006$). There was no difference in aversive effects (mean: 5.1 vs. 5.5, $p=0.44$). The urge to vape significantly differed by type of e-cigarette device for the negative reinforcing factors of e-cigarette use ($p=0.004$), primarily driven by lower scores for the variable tank device than cigalike and fixed power tank devices.

Cobb et al.[155] compared abuse liability outcomes by nicotine concentrations (0 and 36mg/mL) and flavour (cream, tropical fruit, tobacco and menthol) among 20 smokers with no regular e-cigarette use. The sample included 50% males with a mean age of 19.9 years. There was no difference between e-cigarette conditions for satisfaction, and e-cigarettes were significantly lower than combustible cigarettes ($p<0.05$). For scores of pleasantness, nicotine e-cigarettes were significantly lower than cigarettes while non-nicotine scores were higher (significance not reported). The cream 0mg e-cigarette score was significantly higher than the tobacco and menthol 38mg/mL e-cigarette. After e-cigarette use at baseline, there was a significant difference in satisfaction ($p=0.012$), taste good ($p<0.01$) and desire to use another ($p=0.003$) between flavours and a significant difference for all items except for satisfaction ($p=0.773$) by nicotine concentration. For drug effect, there was a significant difference in feeling a rush ($p=0.010$) and feeling negative drug effects ($p=0.022$) between flavours and a significant difference for feeling a rush ($p<0.001$), liking the effects ($p<0.001$), feeling good effects ($p<0.001$) and feeling negative effects ($p=0.004$) by nicotine concentration.

The two non-randomised intervention studies by Hughes et al., already described under dependence, also included measures of abuse liability.[156,190] Abuse liability was assessed using two urge questions of the Mood and Physical Symptoms Scale, which included frequency of cravings on a 0-4 scale and strength of cravings on a 0-5 scale. Both studies showed a significant increase in frequency and strength of craving for an e-cigarette with abstinence. Among the never smoker population, a mean increase of 0.64 ($p=0.01$) in frequency of craving for an e-cigarette and of 0.72 ($p=0.007$) in strength of craving was found. The study among ex-smokers showed a mean increase of 0.49 ($p<0.001$) for frequency of craving and of 0.68 ($p<0.001$) for strength of craving.

In the study by Ruther et al., already described in dependence, reduction in cravings for cigarettes/e-cigarettes were compared between three different cigalike model e-cigarettes, one tank model e-cigarette and combustible cigarettes using a modified version of the German version of the Questionnaire

on Smoking Urges (QSU-G). Among e-cigarette users, exposure to tank devices significantly reduced positive reinforcing effects (the intention to use and the anticipated positive effects from use) compared to baseline (p<0.001). Exposure to cigarettes among smokers followed a similar pattern and was not significantly different from tank devices. There was a significant difference between tank and cigalike devices after exposure, with greater reduction from tank devices (mean decrease cigalike: 1.05 vs. tank: 2.09; p=0.015). For reduction in craving (negative reinforcing effects), there was a significant reduction from baseline for tank (p<0.01) and cigarettes (p<0.05) and there was no difference between the two conditions. There was a significant difference between e-cigarette types with a greater reduction from tank exposure (p=0.044).

In the study by Spindle et al.,[192] already described, the effects of various propylene glycol (PG) and vegetable glycerine (VG) ratios on subjective abuse liability measures was reported among 30 experienced e-cigarette users (smokers <5 cigarettes per day). There was no significant difference in any item on the Hughes-Hatsukami scale by PG:VG ratio. There was a significant difference in negative reinforcing effects but not positive by PG:VG ratio. There was a significant difference in awake (p<0.01), calm (p<0.05), concentrating (p<0.01), pleasant (p<0.01), satisfaction (p<0.05) and taste good (p<0.05) by PG:VG ratio. Participants reported that the 100 PG liquid was significantly less "pleasant" and "satisfying" relative to the other liquids (all ps<0.05). Using a general label magnitude scale questionnaire (scored 0 (no sensation) to 100 (strongest sensation), there was a significant difference in throat hit and harshness scores but not flavour.

Three studies[192,195,196] were of high methodological quality and five studies[155,156,190,191,197] were rated of moderate methodological quality using the Joanna Briggs Institute's critical appraisal checklist (Table 4.3.2). Both studies by Hughes and colleague had potential conflicts of interests as consultant fees and grants had been received by pharmaceutical and tobacco companies. Four studies[155,192,196,197] had authors that were paid consultants in litigation against the tobacco industry and two[191,195] had no conflicts of interest to declare.

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to abuse liability outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to abuse liability risk

One cross-sectional survey reporting on the relationship of e-cigarette use to abuse liability was identified. This study was also included under dependence.[185]

The online cross-sectional survey of US JUUL users by Leavens et al.,[185] described above also, measured e-cigarette demands. There was a statistically significant difference across dual users, former smokers and never smokers in all three measures. Never users would spend significantly less time using JUUL on a single day (mean: 6.4; SD: 6.2) than former smokers (mean: 8.9; SD: 8.4) and dual users (mean: 9.6; SD: 10.8). For the maximum money spent on a single day's worth of JUUL, never smokers (mean 10.6; SD: 13.2) were not statistically different to former smokers (mean: 7.9; SD: 8.3) and dual users (mean: 11.7; SD: 12.3), however, there was a significant difference between dual users and former smokers. Similarly, never smokers (mean: 4.3; SD: 5.7) were not significantly different in the maximum money spent for 10 minutes of JUUL use than former smokers (mean: 2.9; SD: 4.6) or dual users (mean: 5.7; SD: 8.0). Former smokers and dual users were significantly different.

The study was of low methodological quality using the Joanna Briggs Institute's critical appraisal checklist and no conflicts of interest were declared.

4.3.4 Summary of findings from top-up review

There were 15 studies – one randomised controlled trial, one cohort study, four non-randomised intervention studies and nine cross-sectional surveys – on the effects of e-cigarettes on dependence (clinical outcomes), finding:

- Nicotine e-cigarette use resulted in dependence in exclusive users in all studies including those in youth and young adults. One cross-sectional survey in a young population reported higher e-cigarette dependence among exclusive e-cigarette users than cigarette dependence among cigarette users.
- E-cigarette dependence did not increase over time in one moderately sized cohort study.
- Cross-sectional evidence is suggestive that e-cigarette dependence may be associated with earlier age of initiation, daily use and later generation/more powerful devices.
- Hence, there was:

    - Substantial evidence that e-cigarette use results in dependence among non-smokers and limited evidence in smokers.
    - Insufficient evidence that the relation of e-cigarette use to dependence remains stable over time in both smokers and non-smokers.

There were 15 studies, six randomised controlled trials, eight non-randomised intervention studies and one cross-sectional survey, on the effects of e-cigarettes on abuse liability (subclinical outcomes), finding:

- The majority of studies were conducted in smokers due to the ethical implications of exposing non-users to e-cigarettes.
- E-cigarettes were found to have some abuse liability risk in most studies.
- The abuse liability of e-cigarettes was lower than combustible cigarettes but higher than nicotine gum.
- Abuse liability increased with nicotine concentration and differed by flavours.
- Hence, there was:
    - Insufficient evidence e-cigarette use is associated with abuse liability in non-smokers and limited evidence in smokers;
    - Insufficient evidence that dependence risk of e-cigarettes is higher than nicotine gum and lower than the risk for combustible cigarettes; and
    - Insufficient evidence that the relation of e-cigarette use to abuse liability is influenced by nicotine concentration.

4.3.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence on dependence (clinical outcomes) from the top-up systematic review with the evidence from the previous reviews:

- There was a total of 31 studies on the relationship of dependence to e-cigarette use: one randomised controlled trial, one cohort study, eight non-randomised intervention studies, and 21 cross-sectional surveys. All studies, both those in smokers and non-smokers indicated e-cigarette-related dependence and that e-cigarette abstinence was associated with withdrawal symptoms.
- Cross-sectional evidence is suggestive that e-cigarette dependence may be associated with earlier age of initiation, daily use and later generation/more powerful devices.
- All intervention studies were small in size, most were very small, and the cohort was moderate-sized. Few of the cross-sectional surveys were nationally representative.
- The GRADE rating was very low certainty for both randomised controlled trial evidence and non-randomised evidence (Appendix 6).
- Hence, there was:
    - Substantial evidence that use of e-cigarettes results in dependence on e-cigarettes among non-smokers and limited evidence for smokers.
    - Insufficient evidence that e-cigarette dependence was associated with earlier age of initiation, daily use and later generation devices.
    - Insufficient evidence that the relation of e-cigarette use to dependence remains stable over time among smokers and non-smokers.

Combining evidence on abuse liability (subclinical outcomes) from the top-up systematic review with the evidence from the previous reviews:

- There was a total of 29 studies on the relationship of abuse liability to e-cigarette use: 13 randomised controlled trials, 15 non-randomised intervention studies and one cross-sectional survey.
- The majority of studies were conducted in smokers due to the ethical implications of exposing non-users to e-cigarettes.
- E-cigarettes were found to have some abuse liability risk in most studies.
- The abuse liability of e-cigarettes was lower than combustible cigarettes in most studies, however, some found no difference in abuse liability between combustible cigarettes and e-cigarettes.
- The abuse liability of e-cigarettes was higher than nicotine gum or nicotine inhalers.
- Abuse liability increased with nicotine concentration in the majority of studies and differed by flavours.

- All intervention studies were small in size, and most were very small.
- The GRADE rating was very low certainty for both randomised controlled trial evidence and non-randomised study evidence (Appendix 6).
- Hence, there was:
    - Limited evidence that abuse liability is associated with e-cigarette use in non-smokers and limited evidence in smokers.
    - Insufficient evidence whether abuse liability of e-cigarettes is lower than the risk for combustible cigarettes among smokers and no available evidence for non-smokers.
    - Limited evidence whether abuse liability of e-cigarettes is higher than the risk for nicotine replacements therapy products among smokers.
    - Insufficient evidence whether abuse liability risk of e-cigarettes is influenced by e-cigarette characteristics including flavour and nicotine concentration.

4.3.6 Main conclusions from the synthesised evidence on dependence and abuse liability associated with e-cigarette use

- Among non-smokers, there is substantial evidence that e-cigarette use results in dependence on e-cigarettes.
- Among smokers, there is limited evidence that e-cigarette use results in dependence on e-cigarettes. There is limited evidence that e-cigarettes have lower abuse liability than combustible cigarettes and limited evidence that e-cigarettes have a higher abuse liability than nicotine replacement therapy products among smokers.
- Among smokers, there is insufficient evidence whether abuse liability risk is influenced by flavour and nicotine concentration variations.

Table 4.3-2. Study details: dependence and abuse liability – randomised controlled trials, cohort, non-randomised intervention studies and cross-sectional surveys

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Randomised controlled trials					
De La Garza et al., 2019[152] US Randomised, double-blinded, placebo-controlled experimental trial Study date not reported	Study size 15 participants Sample Tobacco dependent e-cigarette naïve smokers Gender (%) Male: 66 Female: 33 Age – mean (SD) years 50.6 (7.6)	Intervention 1 ENDS: 18mg/mL nicotine Intervention 2 ENDS: 36mg/mL nicotine Comparator ENNDS: 0mg/mL Materials eGo devices with a 3.3V e-cigarette battery attached to a 1.5Ω dual-coil cartomizer Virginia Pure tobacco flavoured, containing 0, 18, or 36mg/mL nicotine loaded with 1mL of a 70% propylene glycol/30% vegetable glycerin Pattern of exposure 4 sessions: 10 puffs, twice with 30-minute washout. Abstinent night before	E-cigarette perception questionnaire How rewarding (satisfying) is this E-Cig dose compared to own? (mean) Which would you rather smoke — This E-cig dose or own cig? (ratio)	E-cigarette perception questionnaire ENNDS / 18mg/mL ENDS / 36mg/mL ENDS How rewarding (satisfying) is this E-Cig dose compared to own? — 3.1 ±1.9 / 3.0 ±1.8 / 2.7 ±1.7 Which would you rather smoke — This E-cig dose or own cig? (ratio) — 3:11 / 4:11 / 4:11	Moderate methodological quality Very small study size Conflicts of interest None declared Funding Supported by National Cancer Institute

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
O'Connell et al., 2019[55] US Randomised, open-label, crossover clinical trial Study date not reported	Study size 15 e-cigarette naïve smokers Sample Smoke ≥10 cigarettes per day, no previous use of e-cigarettes Gender (%) Male: 60 Female: 40 Age – mean (SD) years 42.3 (12.41)	Materials (1) myblu pod-system: 25mg nicotine ('freebase') tobacco flavour (2) myblu pod-system: 16mg nicotine lactate tobacco flavour (3) myblu pod-system: 25mg nicotine lactate tobacco flavour (4) myblu pod-system: 40mg nicotine lactate tobacco flavour (5) blu PRO open system: 48mg nicotine lactate tobacco flavour Pattern of exposure 10 inhalations every 30s for 3s in duration	Subjective measures Did you enjoy it?	Did you enjoy it? – mean (SD) Mean (SD) Conventional cigarette 4.9 (1.44) Myblu 40mg 4.0 (1.36) Myblu 25mg 3.5 (1.98) Myblu 16mg 3.5 (1.46) Blu PRO 48mg 3.2 (1.81) Blu PRO 25mg (freebase) 3.5 (1.87) Scale: 1, not at all; 2, very little; 3, a little; 4, modestly; 5, a lot; 6, quite a lot; 7, extremely No significant difference between the six products	Moderate methodological quality Very small study size Conflicts of interest Full time employees of the Imperial Brands Group or Celerion. Celerion has received funding from several e-cigarette /tobacco manufacturers Funding Supported by Imperial Brands

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr>
<td>Adriaens et al., 2018[154]

Belgium

Randomised, crossover within-subjects trial

Study date not reported</td>
<td><u>Study size</u>
30 participants

<u>Sample</u>
Smokers for at least three years (at least 10 cigarettes per day), unwilling to quit, never used e-cigarettes or heat-not-burn tobacco products

<u>Gender (%)</u>
Male: 67
Female: 33

<u>Age – mean (SD) years</u>
22 (3.09)</td>
<td><u>Intervention</u>
ENDS: 18mg/mL nicotine, tobacco or menthol flavour

<u>Comparator</u>
Own combustible tobacco cigarette (TC) and IQOS™ (heat-not-burn product) regular flavour

<u>Materials</u>
Own tobacco cigarette (TC), e-cigarette, IQOS™ (heat-not-burn product)

<u>Pattern of use</u>
Laboratory sessions on three consecutive days, 70-80 minutes each session. Five minutes ad lib use for each product</td>
<td><u>Modified Cigarette Evaluation Questionnaire (mCEQ)</u>
Smoking satisfaction
Psychological reward
Aversion
Enjoyment of respiratory tract sensations
Craving reduction

<u>Additional questions (visual analogue scale and open-ended questions)</u>
Willing to use the product for another five minutes

Willing to keep trying or start using the product

Desire/intention to go and buy the product

Willing to consider using the product to (try to) quit smoking

<u>Aspects missed when using the e-cigarette compared to tobacco cigarettes</u></td>
<td><u>Modified Cigarette Evaluation Questionnaire (mCEQ)</u>
<table>
<tr><th></th><th>Highest rating</th><th></th><th>Lowest rating</th></tr>
<tr><td>Satisfaction</td><td>TC</td><td>IQOS™</td><td>ENDS</td></tr>
<tr><td>Psychological reward</td><td>TC</td><td>IQOS™</td><td>ENDS</td></tr>
<tr><td>Aversion</td><td>TC</td><td>ENDS</td><td>IQOS™</td></tr>
<tr><td>Enjoyment of respiratory tract sensations</td><td>TC</td><td>IQOS™</td><td>ENDS</td></tr>
<tr><td>Craving reduction</td><td>TC</td><td>IQOS™</td><td>ENDS</td></tr>
</table>
<u>Between-group comparisons (mCEQ)</u>
TC and ENDS
p<0.001: satisfaction, psychological reward, respiratory tract sensations, craving reduction

<u>Additional questions</u>
Significantly (p<0.05) higher willingness to use IQOS™ for another five minutes compared to the e-cigarette. No difference found for all other items.

<u>Reported aspects missed when using the e-cigarette compared to tobacco cigarettes (frequency %)</u>
<table>
<tr><th></th><th>ENDS</th></tr>
<tr><td>Taste, aroma, flavour, smell</td><td>63</td></tr>
<tr><td>Psychophysiological effects e.g. relaxing effects</td><td>43</td></tr>
<tr><td>Feeling/sensations of inhalation in throat and lungs</td><td>27</td></tr>
<tr><td>Nicotine and throat hit</td><td>23</td></tr>
<tr><td>Handling/gesture of smoking</td><td>17</td></tr>
</table>
Six participants (20%) reported no missing aspects for the e-cigarette</td>
<td>Low methodological quality

Very small study size

<u>Conflicts of interest</u>
None declared, but authors are Tobacco Harm Reduction (THR) advocates

<u>Funding</u>
No external funding received</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type, [data source, time frame])</th><th>Sample characteristics</th><th>Intervention/ exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflict of interest and funding</th></tr>
<tr>
<td>Palmer & Brandon, 2018[193]

US

Randomised, double-blinded, balanced-placebo experimental crossover trial

Study date not reported</td>
<td><u>Study size</u>
128 participants

<u>Sample</u>
Current daily ENDS users: daily nicotine solution use for ≥30 days. Includes dual users (n=52) and former smokers (n=76)

<u>Gender (%)</u>
Male: 62
Female: 38

<u>Age – mean (SD) years</u>
36.4 (13.79)</td>
<td><u>Intervention</u>
ENDS: 12mg/mL nicotine, 50% vegetable glycerin, 50% propylene glycol, tobacco, menthol, or fruit flavour

<u>Comparator</u>
ENNDS: 0mg/mL, 50% vegetable glycerin, 50% propylene glycol, tobacco, menthol, or fruit flavour

<u>Materials</u>
eGo-style 3.6–4.2 Volt, 1100 mAh battery, 2.8-Ohm, 510-style clearomiser

<u>Pattern of exposure</u>
At least 10 puffs in 10 minutes, survey re-administered</td>
<td><u>Craving to vape/smoke (mean)</u>
Questionnaire of Smoking Urges (smoking and modified e-cigarette version)</td>
<td><u>Condition means - drug content and instructional set (nicotine or non-nicotine)</u>
<table>
<tr><th></th><th>True Positive</th><th>False positive (placebo)</th><th>False negative (anti-placebo)</th><th>True Negative</th></tr>
<tr><td>Craving to smoke</td><td>7.75</td><td>8.08</td><td>3.93</td><td>4.57</td></tr>
<tr><td>Craving to vape</td><td>8.00[a,b]</td><td>3.68[a]</td><td>3.84[b]</td><td>4.82</td></tr>
</table>
<u>Marginal means</u>
<table>
<tr><th></th><th colspan="2">Drug Content Nicotine</th><th colspan="2">Instructional Set Told Nicotine</th><th></th><th></th><th></th></tr>
<tr><th></th><th>Yes</th><th>No</th><th>Yes</th><th>No</th><th>F (N)</th><th>F (I)</th><th>F (N X I)</th></tr>
<tr><td>Craving to smoke</td><td>5.69</td><td>6.19</td><td>7.92[a]</td><td>4.25[a]</td><td>0.15</td><td>4.21*</td><td>0.02</td></tr>
<tr><td>Craving to vape</td><td>5.92</td><td>4.26</td><td>5.87</td><td>4.34</td><td>1.73</td><td>1.31</td><td>5.56*</td></tr>
</table>
N=nicotine; I=instruction
Positive difference scores represent reductions in value from pre- to post-tests
*p<0.05
Shared superscripts indicate significant differences in cell means: a: p<0.05, b: p<0.01

<u>Nicotine Dosing Estimate</u>
Smokers: higher nicotine dose estimates were associated with greater cigarette craving reduction; r (50)=0.37, p=0.007
Full sample: nicotine dose estimate was not associated with e-cigarette craving reduction; r (126)=0.15, ns</td>
<td>High methodological quality

Small study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
University of South Florida, the National Institute on Drug Abuse, and Cancer Center & Research Institute</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type, [data source, time frame])</th><th>Sample characteristics</th><th>Intervention/ exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflict of interest and funding</th></tr>
<tr>
<td>Stiles et al., 2018[194]

US

Randomised, open-label, crossover trial

Study date not reported</td>
<td><u>Study size</u>
71 participants

<u>Sample</u>
E-cigarette naïve current combustible cigarette smokers (10+ menthol king size (83–85mm) or 100mm cigarettes (filtered) per day for at least last 6 months; usually smoke within 30 min of waking)

<u>Gender (%)</u>
Male: 62
Female: 38

<u>Age – mean (SD) years</u>
34.3 (10.2)</td>
<td><u>Intervention 1</u>
ENDS: 14mg, 29mg or 36mg, menthol flavour

<u>Intervention 2</u>
Cigarettes (high-abuse liability)

<u>Comparator</u>
Nicotine gum (low abuse liability)

<u>Materials</u>
ENDS: Vuse Solo
Cigarettes: own
Nicorette White Ice Mint 4mg nicotine polacrilex gum

<u>Patter of exposure</u>
Home use (approx. 10 to 30 minutes ad libitum) at least 6 out of 7 days prior to laboratory visit. 12 hours abstinence prior to laboratory visit. At visit, 10 min ab libitum ENDS or cigarette, 30 minutes gum, measured up to 6 hours post-exposure</td>
<td><u>Subjective effects (overall and maximum effect (E_{max}) – mean (95% CI))</u>
Product liking

Intent to use again

Liking of positive effects

Disliking of negative effects</td>
<td><u>Subjective effects - mean (95% CI)</u>
<table>
<tr><th></th><th colspan="3">ENDS</th><th></th><th></th></tr>
<tr><th></th><th>14mg</th><th>29mg</th><th>36mg</th><th>Cigarette</th><th>Gum</th></tr>
<tr><td>Product liking</td><td>1521.63†§ (1314.14, 1729.12)</td><td>1426.20†§ (1204.32, 1648.08)</td><td>1256.89†§ (1035.52, 1478.27)</td><td>3148.10 (2933.18, 3363.02)</td><td>907.29 (692.69, 1121.89)</td></tr>
<tr><td>E_{max}</td><td>5.08†§ (4.46, 5.70)</td><td>4.51† (3.86, 5.16)</td><td>4.53† (3.86, 5.19)</td><td>9.29 (8.65, 9.93)</td><td>3.25 (2.61, 3.89)</td></tr>
<tr><td>Intent to use again</td><td>1489.01†§ (1346.90, 1631.12)</td><td>1534.54†§ (1383.20, 1685.87)</td><td>1412.88†§ (1261.88, 1563.89)</td><td>2403.50 (2256.57, 2550.43)</td><td>1143.37 (996.69, 1290.05</td></tr>
<tr><td>E_{max}</td><td>4.40†§ (3.99, 4.80)</td><td>4.49†§ (4.06, 4.91)</td><td>4.25† (3.82, 4.68)</td><td>6.93 (6.52, 7.35)</td><td>3.32 (3.82, 4.68)</td></tr>
<tr><td>Liking of positive effects</td><td>766.72† (475.9, 1057.54)</td><td>1003.47† (709.08, 1297.87)</td><td>704.70† (400.05, 1009.36)</td><td>1388.31 (1102.92, 1673.70)</td><td>842.96 (542.72, 1143.21)</td></tr>
<tr><td>E_{max}</td><td>6.45† (5.79, 7.11)</td><td>6.44† (5.76, 7.12)</td><td>6.74† (6.01, 7.47)</td><td>8.63 (8.00, 9.27)</td><td>6.02 (5.32, 6.72)</td></tr>
<tr><td>Disliking of negative effects</td><td>596.25 (297.04, 895.46)</td><td>822.23 (512.69, 1131.77)</td><td>491.65 (207.8, 775.51)</td><td>787.93 (462.74, 1113.12)</td><td>771.89 (498.84 1044.94</td></tr>
<tr><td>E_{max}</td><td>5.16 (4.15, 6.17)</td><td>6.16 (5.10, 7.21)</td><td>5.17 (4.23, 6.11)</td><td>6.06 (4.94, 7.17)</td><td>6.24 (5.34, 7.13)</td></tr>
</table>
† Significantly different from cigarettes; p<0.05
§ Significantly different from gum; p<0.05</td>
<td>Moderate methodological quality

Very small study size

<u>Conflicts of interest</u>
Authors full time employees of tobacco company subsidiary. Consultant services for pharmaceutical and tobacco companies

<u>Funding</u>
RJ Reynolds Vapor Company through its affiliate RJ Reynolds Tobacco Company</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Hiler et al., 2017[153]

US

Randomised, double-blinded trial

Study date not reported

Study size
64 participants; 31 ENDS naïve smokers
33 ENDS experienced

Sample
ENDS experienced individuals: ≥3 months use, using ≥1mL of n≥8mg/mL nicotine e-liquid daily; ≤5 cigarettes daily.
ENDS naïve cigarette smokers: ≥10 conventional tobacco cigarettes daily, <5 ENDS lifetime use

Gender - n (%)
Male: 45 (70)
Female: 19 (30)

Age – mean (SD) years
30.6 (9.1)

Intervention
ENDS: 8, 18, 36mg/mL nicotine

Comparator
ENNDS: 0mg/mL nicotine

Materials
"eGo" 3.3-V, 1,000-mAh battery with a 1.5-Ω, dual-coil, 510-style "cartomizer"; tobacco or menthol flavoured e-liquid

Patter of exposure
Four sessions (order randomised), separated by 48 hours. 12 hours abstinence prior to session. Session was two 10 puffs bouts (30 second break in between puffs)

Fagerström Test for Nicotine Dependence (FTND)
Modified e-cigarette appearance for ENDS experienced individuals

Penn State Dependence Index
ENDS experienced: Electronic Cigarette Dependence Index
ENDS naïve: Cigarette Dependence Index

Subjective questionnaire
Modified version of Hughes-Hatsukami Withdrawal Scale, Tiffany-Drobes Questionnaire of Smoking Urges (factor 1: intention to use; factor 2: anticipation of relief from withdrawal symptoms); modified for ENDS experienced individuals such that whenever the word cigarette appeared in the original, the word e-cigarette appeared instead.

Dependence scores – Mean (SD)

	ENDS experienced	ENDS naïve	T statistic	p
FTND	4.3 (2.0)	4.7 (1.9)	-0.8	NS
PSDI	9.9 (3.4)	12.2 (4.0)	-2.0	<0.05

Subjective effects

	Condition		Group		Condition x Group	
	F	P	F	P	F	P
Hughes-Hatsukami						
Anxious	5.0	<0.01	10.5	<0.01	0.6	NS
Craving	19.0	<0.01	1.7	NS	3.6	<0.05
Depression	7.7	<0.01	6.0	<0.05	4.7	<0.01
Difficulty concentrating	8.6	<0.01	3.3	NS	1.7	NS
Drowsy	6.8	<0.01	0.8	NS	4.9	<0.01
Hunger	0.7	NS	1.4	NS	1.7	NS
Impatient	6.2	<0.01	8.4	<0.05	0.4	NS
Irritable	8.5	<0.01	12.1	<0.01	0.0	NS
Restless	5.6	<0.01	6.5	<0.05	0.2	NS
Sweets	0.4	NS	1.4	NS	1.8	NS
Urge	20.8	<0.01	1.7	NS	4.4	<0.01
Tiffany-Drobes QSU						
Factor 1	17.5	<0.01	0.74	NS	3.7	<0.05
Factor 2	12.4	<0.01	10.9	<0.01	0.8	NS
Direct effects						
Awake	6.2	<0.01	1.3	NS	3.0	<0.05
Calm	10.2	<0.01	1.9	NS	2.9	NS
Concentrate	5.9	<0.01	3.9	NS	1.7	NS
Dizzy	7.6	<0.01	0.3	NS	0.7	NS
Pleasant	4.0	<0.05	1.5	NS	3.7	<0.05
Reduced hunger	6.4	<0.01	1.0	NS	0.7	NS
Right now	8.9	<0.01	6.8	<0.01	2.4	NS
Satisfy	10.4	<0.01	1.1	NS	5.9	<0.01
Sick	3.6	<0.05	0.5	NS	0.3	NS
Taste good	4.0	<0.01	1.1	NS	1.4	NS

Moderate methodological quality

Small study size

Conflicts of interest
Paid consultants in litigation against tobacco industry

Funding
Supported by NIH

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type, [data source, time frame])</th><th>Sample characteristics</th><th>Intervention/ exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflict of interest and funding</th></tr>
<tr><td colspan="6">Cohort studies</td></tr>
<tr>
<td>Du et al., 2019[142]

US

Longitudinal cohort study

Online e-cigarette survey

2012-2017</td>
<td><u>Study size</u>
494 participants
Exclusive EC: 412
Poly users: 59

<u>Sample</u>
Exclusive EC: past 7-day use
Poly users: EC and any other tobacco product

<u>Gender (%)</u>
EC
Male: 67.5
Female: 32.5
Poly
Male: 64.4
Female: 35.6

<u>Mean age (SD) years</u>
EC: 41.2 (11.9)
Poly: 36.5 (11.9)</td>
<td><u>Exposure</u>
EC: any nicotine concentration

<u>Comparator</u>
Within participants, baseline and follow-up

<u>Materials</u>
Own brand EC

<u>Follow-up</u>
6 years
Baseline: 2012-2014
Follow-up: 2017-2018</td>
<td>PSECDI

E-cigarette use times per day

Time to first e-cigarette use after waking

Awaken at night to use e-cigarette

Nights per week awakened to use e-cigarette

Hard to quit e-cigarette

Strong cravings to use e-cigarette

Strong urges to use e-cigarette

Hard to keep from using e-cigarette

Felt irritable if couldn't use e-cigarette

Felt nervous, restless, or anxious</td>
<td><u>EC users</u>
<table>
<tr><th>Outcomes</th><th>Baseline</th><th>Follow-up</th><th>p</th></tr>
<tr><td>PSECDI-mean (SD)</td><td>8.5 (3.4)</td><td>8.4 (3.8)</td><td>0.33</td></tr>
<tr><td>Times per day-mean (SD)</td><td>23.9 (24.7)</td><td>21.8 (23.9)</td><td>0.14</td></tr>
<tr><td>Time to first EC, mins-mean (SD)</td><td>44.5 (77.5)</td><td>41.7 (73.3)</td><td>0.54</td></tr>
<tr><td>Awaken to use EC – n (%)</td><td>29 (7.1)</td><td>39 (9.5)</td><td>0.10</td></tr>
<tr><td>Nights per week awaken to use E-mean (SD)</td><td>0.3 (1.2)</td><td>0.4 (1.3)</td><td>0.22</td></tr>
<tr><td>Hard quit EC – n (%)</td><td>133 (32.4)</td><td>83 (20.2)</td><td><0.0001</td></tr>
<tr><td>Craving to use EC – n (%)</td><td>176 (42.8)</td><td>182 (44.3)</td><td>0.60</td></tr>
<tr><td>Urge to use EC – n (%)</td><td>59 (14.3)</td><td>59 (14.3)</td><td>1.00</td></tr>
<tr><td>Hard to keep from using EC – n (%)</td><td>44 (10.7)</td><td>61 (14.8)</td><td>0.04</td></tr>
<tr><td>Irritable if can't use EC – n (%)</td><td>131 (31.8)</td><td>120 (29.1)</td><td>0.34</td></tr>
<tr><td>Anxious if can't use EC – n (%)</td><td>137 (33.3)</td><td>130 (31.6)</td><td>0.53</td></tr>
</table>
<u>Poly users: EC and any tobacco product</u>
<table>
<tr><th>Outcomes</th><th>Baseline</th><th>Follow-up</th><th>p</th><th>P (EC vs. poly)</th></tr>
<tr><td>PSECDI-mean (SD)</td><td>7.5 (3.8)</td><td>8.0 (3.9)</td><td>0.46</td><td>0.46</td></tr>
<tr><td>Times per day-mean (SD)</td><td>16.2 (14.6)</td><td>15.9 (22.9)</td><td>0.95</td><td>0.08</td></tr>
<tr><td>Time to first EC, mins-mean (SD)</td><td>64.9 (105.4)</td><td>59.0 (109.3)</td><td>0.75</td><td>0.12</td></tr>
<tr><td>Awaken to use EC – n (%)</td><td>6 (10.2)</td><td>9 (15.3)</td><td>0.32</td><td>0.17</td></tr>
<tr><td>Nights per week awaken to use EC- mean (SD)</td><td>0.5 (1.5)</td><td>0.5 (1.5)</td><td>0.84</td><td>0.43</td></tr>
<tr><td>Hard quit EC – n (%)</td><td>20 (33.9)</td><td>13 (22.0)</td><td>0.14</td><td>0.74</td></tr>
</table>
</td>
<td>Low methodological quality

Moderate study size

<u>Conflicts of interest</u>
Consultant fees and grants from pharmaceutical companies

<u>Funding</u>
Supported by the National Institute on Drug Abuse of NIH and the Center for Tobacco Products of the U.S. Food and Drug Administration</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results					Quality assessment, study size, conflict of interest and funding
			if couldn't use e-cigarette	Craving to use EC – n (%)	21 (35.6)	33 (55.9)	0.003	0.09	
				Urge to use EC – n (%)	10 (17.0)	10 (17.0)	1.00	0.59	
				Hard to keep from using EC – n (%)	9 (15.3)	15 (25.4)	0.11	0.04	
				Irritable if can't use EC – n (%)	20 (33.9)	23 (39.0)	0.47	0.12	
				Anxious if can't use EC – n (%)	20 (33.9)	26 (44.1)	0.22	0.06	
Non-randomised intervention studies									

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Hughes et al., 2020[156] US Non-randomised, unblinded, within-participants pre-post clinical study Study date not reported	Study size 109 participants enrolled, 59 used in analysis (compliant) Sample Former smoker using ENDS daily: history of cigarette use for at least 1 year and <6 cigarettes in last month; daily ENDS use >2 months Gender – compliant (%) Male: 81 Female: 19 Age (compliant) — mean (SD) years 32 (10)	Intervention ENDS: high nicotine concentration, exact concentration unknown Comparator Pre- and post Materials Own ENDS Pattern of use 7 days continuous ENDS use, 6 days biologically confirmed abstinence	DSM-5 withdrawal criteria Overall and individual items: angry, anxious/nervous, increased appetite, difficulty concentrating, depressed/sad, insomnia and restlessness E-cigarette craving measures How much of the time felt urge, and now strong urge Potential withdrawal symptoms Impatient/impulsive, enjoy pleasant events less, less positive outlook, and mood swings Control symptoms Diarrhea, headache and, tremor	Vaping Mean / Abstinent Mean / Increase Mean / t Withdrawal - mean Overall 0.16 / 0.57 / 0.41 / 6.5*** Angry 0.21 / 0.88 / 0.67 / 6.1*** Anxious 0.14 / 0.59 / 0.45 / 4.1*** Increased appetite 0.13 / 0.62 / 0.49 / 5.1*** Difficulty concentrating 0.10 / 0.52 / 0.41 / 4.6*** Depressed 0.08 / 0.28 / 0.21 / 3.6*** Insomnia 0.26 / 0.38 / 0.12 / 2.1* Restlessness 0.17 / 0.71 / 0.53 / 5.1*** EC craving - mean How much of time felt urge 1.97 / 2.47 / 0.49 / 3.7*** How strong urge 1.94 / 2.62 / 0.68 / 4.9*** Potential withdrawal - mean Impatient, impulsive 0.10 / 0.57 / 0.47 / 4.5*** Enjoy pleasant events less 0.03 / 0.31 / 0.28 / 3.1** Less positive outlook 0.04 / 0.27 / 0.22 / 2.7** Mood swings 0.05 / 0.41 / 0.36 / 3.9*** Control - mean Diarrhea 0.04 / 0.07 / 0.03 / 0.6 Headache 0.19 / 0.33 / 0.14 / 1.9 Tremors 0.00 / 0.15 / 0.15 / 3.4** *p<0.05, **p<0.01, ***p<0.001 Symptoms interfered with functioning Vaping 12% / Abstinent 38%	Moderate methodological quality Small study size Conflicts of interest Consultant fees and grants from pharmaceutical companies and tobacco industry Funding National Cancer Institute

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr>
<td>Hughes et al., 2020[190]

US

Non-randomised, unblinded, within-participants pre-post clinical study

Study date not reported</td>
<td><u>Study size</u>
30 participants enrolled, 18 used in analysis (compliant)

<u>Sample</u>
Never smoker using ENDS daily: <100 life cigarette use and no current “regular” use of other nicotine/ tobacco products; daily ENDS use >2 months

<u>Gender – compliant (%)</u>
Male: 61
Female: 39

<u>Age (compliant)- mean (SD) years</u>
22 (4)</td>
<td><u>Intervention</u>
ENDS: nicotine concentration unknown

<u>Comparator</u>
Pre- and post

<u>Materials</u>
Own ENDS

<u>Pattern of use</u>
7 days continuous EC use, 6 days biologically confirmed abstinence</td>
<td><u>DSM-5 withdrawal criteria</u>
Overall and individual items: angry, anxious/nervous, increased appetite, difficulty concentrating, depressed/sad, insomnia and restlessness

<u>E-cigarette craving measures</u>
How much of the time felt urge, and now strong urge

<u>Potential withdrawal symptoms</u>
Impatient/impulsive, enjoy pleasant events less, less positive outlook, and mood swings

<u>Control symptoms</u>
Diarrhea, headache and, tremor</td>
<td>
<table>
<tr><th></th><th>Vaping</th><th>Abstinent</th><th>Increase</th><th></th><th></th></tr>
<tr><th></th><th>Mean</th><th>Mean</th><th>Mean</th><th>t</th><th>p</th></tr>
<tr><td><u>Withdrawal - mean</u></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Overall</td><td>0.10</td><td>0.33</td><td>0.23 (0.28)</td><td>3.4</td><td>0.003</td></tr>
<tr><td>Angry</td><td>0.06</td><td>0.44</td><td>0.39 (0.53)</td><td>3.1</td><td>0.006</td></tr>
<tr><td>Anxious</td><td>0.14</td><td>0.42</td><td>0.28 (0.65)</td><td>1.8</td><td>0.09</td></tr>
<tr><td>Increased appetite</td><td>0.06</td><td>0.33</td><td>0.28 (0.71)</td><td>1.7</td><td>0.12</td></tr>
<tr><td>Difficulty concentrating</td><td>0.06</td><td>0.33</td><td>0.28 (0.52)</td><td>2.3</td><td>0.04</td></tr>
<tr><td>Depressed</td><td>0.14</td><td>0.25</td><td>0.11 (0.63)</td><td>0.7</td><td>0.47</td></tr>
<tr><td>Insomnia</td><td>0.14</td><td>0.25</td><td>0.11 (0.27)</td><td>1.7</td><td>0.10</td></tr>
<tr><td>Restlessness</td><td>0.14</td><td>0.31</td><td>0.17 (0.34)</td><td>2.1</td><td>0.05</td></tr>
<tr><td><u>EC craving - mean</u></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>How much of time felt urge</td><td>1.44</td><td>2.08</td><td>0.64 (0.97)</td><td>2.8</td><td>0.01</td></tr>
<tr><td>How strong urge</td><td>1.47</td><td>2.19</td><td>0.72 (1.00)</td><td>3.1</td><td>0.007</td></tr>
<tr><td><u>Potential withdrawal - mean</u></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Impatient, impulsive</td><td>0.08</td><td>0.33</td><td>0.25 (0.39)</td><td>2.7</td><td>0.02</td></tr>
<tr><td>Enjoy pleasant events less</td><td>0.03</td><td>0.06</td><td>0.03 (0.27)</td><td>0.4</td><td>0.67</td></tr>
<tr><td>Less positive outlook</td><td>0.06</td><td>0.06</td><td>0.00 (0.17)</td><td>0.0</td><td>1.00</td></tr>
<tr><td>Mood swings</td><td>0.00</td><td>0.14</td><td>0.14 (0.29)</td><td>2.1</td><td>0.06</td></tr>
<tr><td><u>Control - mean</u></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Diarrhea</td><td>0.08</td><td>0.19</td><td>0.11 (0.61)</td><td>0.8</td><td>0.45</td></tr>
<tr><td>Headache</td><td>0.11</td><td>0.42</td><td>0.31 (0.82)</td><td>1.6</td><td>0.13</td></tr>
<tr><td>Tremors</td><td>0.00</td><td>0.03</td><td>0.03 (0.12)</td><td>1.0</td><td>0.33</td></tr>
</table>
*Based on paired t-test (17 df)

Symptoms interfered with functioning
<table>
<tr><th>Vaping</th><th>Abstinent</th></tr>
<tr><td>11%</td><td>33%</td></tr>
</table>
</td>
<td>Moderate methodological quality

Very small study size

<u>Conflicts of interest</u>
Consultant fees and grants from pharmaceutical companies and tobacco industry

<u>Funding</u>
National Cancer Institute</td>
</tr>
<tr>
<td>Cobb et al., 2019[155]

US</td>
<td><u>Study size</u>
20 participants

<u>Sample</u></td>
<td><u>Intervention 1</u>
ENDS: eGo device 36mg/mL nicotine</td>
<td><u>Drug Effects Scale (visual analogue scale)</u>
“Do you feel a rush?”</td>
<td><u>Drug Effects Scale</u>
<table>
<tr><th></th><th colspan="2">Condition (C)</th><th colspan="2">Bout (B)</th><th colspan="2">Time (T)</th></tr>
<tr><th></th><th>F</th><th>p</th><th>F</th><th>p</th><th>F</th><th>p</th></tr>
<tr><td>Rush</td><td>11.3</td><td><.0001</td><td>0.5</td><td>0.464</td><td>36.1</td><td><.0001</td></tr>
</table>
</td>
<td>Moderate methodological quality</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Non-randomised intervention study (7 Latin-square ordered conditions) Study date not reported	Healthy young adult (18-21 years) smokers (at least 5 cigarettes per day for past three months), unwilling to quit, have not regularly used e-cigarettes (using weekly or greater for one month or longer) Gender (%) Male: 50 Female: 50 Age – mean (SD) years 19.9 (1.1)	concentration, in one of three flavours Intervention 2 ENNDS: eGo device 0mg/mL nicotine concentration, in one of three flavours Comparator Own brand (OB) cigarette Materials ENDS, ENNDS and own brand cigarette Pattern of use 10-puff (30s interpuff interval) product administration at baseline (bout 1) and 60 minutes (bout 2)	"Do you like the drug effects?" "Do you dislike the drug effects?" "Do you feel any good drug effects?" "Do you feel any bad drug effects?" Direct Effects of Nicotine Scale (DENS) (visual analogue scale)	Like effects 5.8 <.0001 0.0 0.885 16.3 <.0001 Dislike effects 1.5 0.182 0.4 0.519 3.4 0.009 Feel good 9.5 <.0001 0.1 0.809 20.2 <.0001 Feel bad 3.5 0.002 0.2 0.621 3.6 0.006 Drug Effects Scale (e-cigarette conditions only and bout 1) Flavour (F) Nicotine (N) F p F p Rush 4.66 0.010 35.21 <.001 Like effects 2.34 0.097 16.07 <.001 Dislike effects 2.06 0.128 2.46 0.117 Feel good 0.73 0.484 24.76 <.001 Feel bad 3.86 0.022 8.15 0.004 Direct Effects of Tobacco Scale Condition (C) Bout (B) Time (T) F p F p F p Satisfy 42.6 <.0001 17.7 <.0001 26.8 <.0001 Pleasant 50.0 <.0001 29.8 <.0001 36.6 <.0001 Taste good 27.2 <.0001 24.1 <.0001 36.6 <.0001 Calm 12.0 <.0001 1.3 0.261 22.0 <.0001 Like to use another 5.3 <.0001 0.1 0.742 5.0 0.001 Direct Effects of Tobacco Scale (e-cigarette conditions only and bout 1) Flavour (F) Nicotine (N) F p F p Satisfy 4.46 0.012 0.08 0.773 Pleasant 2.69 0.069 49.72 <.001 Taste good 16.32 <.001 29.30 <.001 Calm 0.23 0.796 18.82 <.001 Like to use another 5.75 0.003 10.84 0.001	Very small study size Conflicts of interest Paid consultant in litigation against the tobacco industry Funding Virginia Foundation for Healthy Youth, National Cancer Institute, National Institute on Drug Abuse, Center for Tobacco Products of the US FDA

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Dowd & Tiffany, 2019[195] US Non-randomised, crossover study Study date not reported	Study size 54 participants Sample Dual users: 30+ cigarettes and at least 3mL nicotine e-liquid per week for past 3 months Gender (%) Male: 81.5 Female: 18.5 Age – mean (SD) years 27.8 (10.2)	Intervention 1/cue 1 ENDS: unknown nicotine concentration but not intentionally using non-nicotine e-liquid Intervention 2/cue 2 Combustible tobacco cigarette Comparator/control cue Water Materials Own ENDS and cigarettes Pattern of use Cue in box, 8 second delay, questionnaire, sampling or not of cue (box locked or unlocked depending on computer), questionnaire 36 trials (12 trials of each cue), 30 seconds between trials	Choice behaviours under cued conditions E-cigarette craving Tobacco cigarette craving Spending choice time Money spent Latency to access cue Puff duration Water consumed	Behaviours under cued conditions - mean (SD) ENDS / Cigarette / Water EC craving: 3.5 (1.4)* / 2.9 (1.3)* / 3.1 (1.4) Cigarette craving: 4.0 (1.3) / 4.5 (1.2)* / 4.0 (1.2) Spending choice time (msec): 4,309 (2484)*† / 4,243 (1763)* / 3,070 (1518) Money spent ($): 0.09 (0.06)*† / 0.13 (0.06)* / 0.04 (0.04) Latency to access cue (msec): 3,167.5 (2400.4) / 3,222.7 (2504.2) / 2,869.4 (1606.8) Puff duration (msec): 5,450.0 (5241.6) / 4,401.9 (3922.6) / – Water consumed (mL): – / – / 9.8 (8.8) * Significantly different compared to water trials (p<0.0001) † Significantly different compared to CC trials (p<0.0001)	High methodological quality Very small study size Conflicts of interest None declared Funding None received

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Maloney et al., 2019[197] US Non-randomised crossover study (Latin-square ordered) Study date not reported	Study size 24 participants Sample Smokers (10 or more cigarettes per day for at least a year) aged between 18 and 55 years, who were e-cigarette naïve (used <20 times in life) Gender (%) Male: 75 Female: 25 Age – mean (SD) years 30.9 (9.5)	Intervention 1 ENDS: eGo device 36mg/mL nicotine, in one of two flavours Intervention 2 ENNDS: eGo device 0mg/mL nicotine, in one of two flavours Comparator FDA-approved nicotine inhaler, own brand cigarette Materials ENDS, ENNDS, nicotine inhaler, own brand cigarette Pattern of use Four separate laboratory sessions of approx. five hours each, separated by a minimum of 48 hours. In each session, one of four study products was used	Direct Effects of Product Use Questionnaire (visual analogue scale) Multiple-Choice Procedure (MCP) Eleven choices between increasing amounts of money or 10 puffs from study product used in that session Crossover point	Outcome measure: Condition F = 9.75, p <.001, n^2_p .30; Time F = 1.96, p *ns*, n^2_p .08 Direct Effects of Product Use Calm: Condition F = 14.86, p <.001, n^2_p .41; Time F = 11.43, p <.001, n^2_p .35 Pleasant: Condition F = 34.26, p <.001, n^2_p .62; Time F = 4.59, p <.05, n^2_p .18 Satisfy: Condition F = 44.20, p <.001, n^2_p .68; Time F = 2.54, p *ns*, n^2_p .11 Taste good: Condition F = 40.48, p <.001, n^2_p .66; Time F = 3.87, p <.05, n^2_p .16 MCP crossover point Product: Crossover point (mean (SD)) ENDS: $0.87 (1.0) ENNDS: $0.96 (1.2) Nicotine inhaler: $0.32 (0.6) Own brand cigarette: $1.42 (1.4) The mean MCP crossover point for the cigarette condition was significantly higher than the mean of the ENDS condition [$t(23) = 3.27$, $p<0.01$]. No significant difference between the mean crossover point in the cigarette condition and the ENNDS condition. The mean MCP crossover point for the nicotine inhaler was significantly lower than means for the ENDS condition and the ENNDS condition [$ts(23) > 2.71$, $ps<0.025$; Bonferroni-corrected p-value].	Moderate methodological quality Very small study size Conflicts of interest Paid consultant in litigation against the tobacco industry Funding National Institute on Drug Abuse of the National Institutes of Health and the Center for Tobacco Products of the U.S. Food and Drug Administration

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
St Helen et al., 2019[196] US Non-randomised two-arm counterbalanced crossover study Study date not reported	Study size 36 participants Sample Healthy dual-users aged 21 or over, smoke at least 5 cigarettes per day over past 30 days, use the same e-cigarette device at least once daily on 15 of past 30 days, no intention to quit smoking or ENDS over next three months Gender (%) Male: 78 Female: 22 Age – mean (SD) years 35.4 (11.7)	Intervention ENDS: usual brand, ranging in concentration from labelled 6mg/mL to 50mg/mL (actual measured ranged from 4.5ug/mg to 52.2ug/mg) Comparator Tobacco cigarette: usual brand Materials Usual brand ENDS and cigarettes – provided by study Pattern of use Two sessions, one week apart. One puff every 30 seconds (15 puffs for cigalike, 10 for tanks), puff duration not controlled Cigarette arm – smoked until cigarette complete	Modified Cigarette Evaluation Scale (mCES) Satisfaction Reward Aversive effects Enjoyment of sensation at the back of the throat and chest Craving reduction Questionnaire for Smoking Urges (QSU-Brief) and QSU-Brief modified for e-cigarettes Factor 1 – positive reinforcement aspects of smoking or vaping Factor 2 – negative reinforcing aspects of smoking or vaping	mCES (mean (SD)) – administered five minutes after last puff ENDS / Tobacco cigarette / *p* Enjoyment of sensation: 4.1 (1.5) / 4.6 (1.6) / 0.05 Craving reduction: 4.2 (1.7) / 5.6 (1.7) / <0.001 Satisfaction: 14.3 (4.3) / 16.6 (3.3) / 0.001 Psychological reward: 19.7 (7.6) / 23.2 (6.7) / 0.006 Aversion: 5.1 (3.3) / 5.5 (2.9) / 0.44 Subjective effects QSU – ENDS types (ENDS arm) QSU Factor 1 (*p*) / QSU Factor 2 (*p*) Urge to smoke: 0.035 / 0.009 Urge to vape: Not reported / 0.004	High methodological quality Very small study size Conflicts of interest Consultant to pharmaceutical companies and has been paid expert witness in litigation against tobacco companies Funding Supported by grants from the National Institute on Drug Abuse, National Cancer Institute

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr>
<td>Ruther et al., 2018[191]

Germany

Non-randomised pre-post within-subjects and between-subjects study

Study date not reported</td>
<td><u>Study size</u>
20 participants (9 in ENDS groups, 11 in TC group)

<u>Sample</u>
Healthy males aged over 18 years

ENDS groups: routine ENDS users for three months, not smoked TC for more than one month

TC group: smoking TC for at least three years and at least 5 cigarettes per day

<u>Gender (%)</u>
Male: 100

<u>Age – mean (SD) years</u>
ENDS: 28.5 ± 8.9
TC: 26.2 ± 6.9</td>
<td><u>Intervention</u>
ENDS: Three cigalike (disposable) and one tank model ENDS, 18 ± 1 mg/mL nicotine, industrial brand

<u>Comparator</u>
Tobacco cigarette (TC)

<u>Materials</u>
3 Cigalike models
1 tank model
Marlboro Red cigarette

<u>Pattern of use</u>
ENDS groups: four study visits at one-week intervals- different type of ENDS at each visit (non-randomised order). Duration of inhalation was four seconds, 26s interpuff interval

TC group: one study visit, smoked TC. Duration of inhalation was two seconds, 28s interpuff interval</td>
<td><u>Craving for smoking – German version Questionnaire on Smoking Urges (QSU-G)</u>
Two factor-specific dimensions of subjective craving for smoking on seven-level rating scale. ‘Cigarette’ and ‘smoking’ replaced with ‘e-cigarette’ and ‘vaping’ for ENDS groups

Factor 1 – intention to smoke and anticipation of positive effects from smoking (positive reinforcement)

Factor 2 – craving for smoking and anticipation of relief from negative effects of nicotine withdrawal (negative reinforcement)

<u>Fagerström Test for Nicotine Dependence (FTND)</u></td>
<td><u>QSU-G (German version of the Questionnaire on Smoking Urges) before and after consumption</u>
<table>
<tr><td>Product</td><td colspan="2">Factor 1 (positive reinforcement)</td><td colspan="2">Factor 2 (negative reinforcement)</td></tr>
<tr><td></td><td>Before</td><td>After</td><td>Before</td><td>After</td></tr>
<tr><td>Tobacco cigarette</td><td>4.93</td><td>2.6**</td><td>2.68</td><td>1.74*</td></tr>
<tr><td>Cigalikes</td><td>5.54</td><td>4.51</td><td>3.34</td><td>2.79</td></tr>
<tr><td>Tank model</td><td>5.56</td><td>3.45**</td><td>3.21</td><td>1.98*</td></tr>
</table>
Within-group pre-post comparisons: * Significant (p<0.05) ** Highly significant (p<0.001)

<u>Between-group comparisons – cigalike compared to tank devices</u>
<table>
<tr><td></td><td>Cigalike vs. Tank</td><td>Tank vs. Cigarettes</td></tr>
<tr><td>Factor 1</td><td>p=0.015</td><td>Non-significant</td></tr>
<tr><td>Factor 2</td><td>p=0.044</td><td>Non-significant</td></tr>
</table>
<u>FTND</u>
<table>
<tr><td></td><td>ENDS</td><td>Smoker</td></tr>
<tr><td>Mean (SD; range)</td><td>2.67 (2.18; 0–6)</td><td>2.73 (2.41; 0–8)</td></tr>
<tr><td>Physical dependence (n)</td><td></td><td></td></tr>
<tr><td>Mild</td><td>3</td><td>6</td></tr>
<tr><td>Moderate</td><td>5</td><td>4</td></tr>
<tr><td>Severe</td><td>1</td><td>1</td></tr>
</table>
</td>
<td>Moderate methodological quality

Very small study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Not reported</td>
</tr>
<tr>
<td>Spindle et al., 2018[192]

US</td>
<td><u>Study size</u>
30 participants

<u>Sample</u></td>
<td><u>Intervention</u>
ENDS: 18mg/mL, PG:VG ratios: 100:0,</td>
<td><u>Fagerström Test for Nicotine Dependence (FTND)</u></td>
<td><u>Dependence scores – Mean (SD)</u>
FTND: 3.7 (2.4)
PSDI: 8.8 (4.8)</td>
<td>High methodological quality</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Non-randomised intervention study Study date not reported	Used <5 tobacco cigarettes daily, used ≥1mL of ECIG liquid daily, used ≥6mg/mL nicotine concentration, and had used their ECIG ≥3 months Gender - n (%) Male: 29 (97) Female: 1 (3) Age - mean (SD) years 26.9 (7.1)	70:30, 30:70, and 0:100 Materials "eGo" (3.3 V) battery with a 1.5 ohm (Ω), dual-coil, 510 "cartomizer"; Virginia Pure" tobacco flavour) 18mg/mL nicotine Pattern of use 12-hour abstinence, 4 sessions. Each session, 2 bouts (60 washout) consisting of 10 puffs with 30s inter-puff-interval each	Modified e-cigarette appearance for ENDS experienced individuals Penn State Dependence Index Subjective questionnaire Hughes-Hatsukami Withdrawal Scale Tiffany-Drobes Questionnaire of Smoking Urges (factor 1: intention to use; factor 2: anticipation of relief from withdrawal symptoms); general labeled magnitude scale	Subjective effects								Very small study size Conflicts of interest Paid consultant in litigation against the tobacco industry Funding Supported by National Institute on Drug Abuse of the National Institutes of Health and the Center for Tobacco Products of the U.S. Food and Drug Administration
					Condition		Time		Condition x Time			
					F	P	F	P	F	P		
				Hughes-Hatsukami								
				Anxious	0.28	NS	7.87	<0.01	1.18	NS		
				Craving	0.34	NS	16.15	<0.001	0.97	NS		
				Depression	0.69	NS	3.06	NS	0.96	NS		
				Concentrating	0.32	NS	8.12	<0.001	0.89	NS		
				Drowsy	0.52	NS	9.90	<0.001	1.32	NS		
				Hunger	2.73	NS	6.83	<0.01	0.68	NS		
				Impatient	0.59	NS	5.43	<0.01	1.04	NS		
				Irritable	0.42	NS	3.73	<0.05	0.85	NS		
				Restless	0.73	NS	2.89	<0.05	1.00	NS		
				Sweets	0.58	NS	1.88	NS	2.04	NS		
				Urge	0.70	NS	15.97	<0.001	0.71	NS		
				Tiffany-Drobes QSU								
				Factor 1	0.74	NS	19.65	<0.001	1.15	NS		
				Factor 2	3.04	<0.05	9.71	<0.001	1.11	NS		
				Direct effects								
				Awake	5.53	<0.01	3.77	<0.01	2.25	<0.05		
				Calm	3.26	<0.05	7.32	<0.001	1.09	NS		
				Concentrate	5.03	<0.01	1.49	NS	1.58	NS		
				Dizzy	2.90	NS	5.00	<0.01	1.00	NS		
				Pleasant	6.94	<0.01	2.80	<0.05	0.71	NS		
				Reduced hunger	2.09	NS	3.68	<0.01	0.66	NS		
				Right now	0.11	NS	14.65	<0.001	0.41	NS		
				Satisfy	3.98	<0.05	4.70	<0.01	0.56	NS		
				Sick	0.49	NS	0.16	NS	0.81	NS		
				Taste good	3.14	<0.05	0.93	NS	0.69	NS		
				General labeled magnitude								
				Flavour	1.86	NS	0.56	NS	0.02	NS		
				Harshness	4.74	<0.01	0.92	NS	0.03	NS		
				Throat hit	11.47	<0.001	1.53	NS	0.05	NS		

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Cross-sectional surveys					
Camara-Medeiros et al., 2020[189] Canada Online survey March 2018	Study size 578 participants Sample Regular e-cigarette users Never smokers: 62.0% Former smokers: 17.6% Current smokers (dual users): 20.4% Gender (%) Male: 75.9 Female: 24.1 Age - mean (SD) years 18.7 (2.23)	Exposure Length of time since starting vaping ≤ 1 year ago or > 1 year ago Daily vaping (reported currently vaping 'daily or almost daily', number of times vaped per weekday and weekend day (<10 times per day/≥ times per day) Comparator Various Materials Own brand EC	Self-perceived addiction "Would you say that you are 'very addicted to vaping,' 'somewhat addicted to vaping,' 'not at all addicted to vaping,' or 'I don't know'" Very addicted Somewhat addicted Not addicted	Daily vaping No: 1.00 Yes: 7.51 (4.55 to 12.42); P-value <0.0001 Nicotine Strength 0 mg/mL: 1.00 1-8 mg/mL: 0.94 (0.47 to 1.85); P-value 0.0298 9+ mg/mL: 2.35 (1.10 to 5.03); P-value 0.0011 Time since initiating vaping Less than 1 year: 1.00 More than 1 year: 1.62 (1.06 to 2.47); P-value 0.026 # Times vaped per weekday <10: 1.00 10+: 1.17 (0.65 to 2.10); P-value 0.594 # Times vaped per weekend day <10: 1.00 10+: 0.64 (0.35 to 1.18); P-value 0.157	Moderate methodological quality Moderate study size Conflicts of interest None declared Funding Funded by the Ontario Ministry of Health and Long-Term Care

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Leavens et al., 2020[185] US Online survey January-March 2019	Study size 593 ever JUUL users Sample Ever JUUL users (may also use other e-cigarette devices) Gender (%) Male: 60 Female: 40 Age - mean (SD) years 25.9 (3.1) Ethnicity (%) Caucasian: 76.6 African American: 8.4 Asian: 7.3 Other: 7.7	Exposure Never smokers: denied smoking in the past 3 months and smoked <100 cigarettes in their lifetime Comparator 1 Former smokers: denied smoking in the past 3 months and reported smoking at least 100 cigarettes in their lifetime Comparator 2 Dual users: reported smoking cigarettes at least five times per month for the past 3 months and smoking at least 100 cigarettes in their lifetime Materials Own brand EC	Penn State Electronic Cigarette Dependence Index – all e-cigarettes Score out of 20 0–3: not dependent 4–8: low dependence 9–12: medium dependence 13+: high dependence E-cigarette demand (abuse liability) - JUUL specific If JUUL were free, how many times would you use JUUL in a single day? (One "time" consists of 15 puffs or 10 min) What is the maximum amount you would be willing to spend for a single day's worth of JUULing (in dollars)? What is the max you would be willing to pay to use a JUUL for 10 minutes?	E-cigarette dependence and demand by group - Mean (SD) Dual (n=232) / Former (n=187) / Never (n=174) / F / P Penn State E-cigarette Dependence: 8.0 (4.1)* / 7.6 (4.0)*+ / 7.0 (4.2) + / 3.2 / 0.043 Time use if free: 9.6 (10.8)* / 8.9 (8.4)* / 6.4 (6.2)+ / 6.5 / 0.002 Max. for day of use ($): 11.7 (12.3)* / 7.9 (8.3)+ / 10.6 (13.2)*+ / 5.6 / 0.004 Max. spent for 10 minutes of use ($): 5.7 (8.0)* / 2.9 (4.6)+ / 4.3 (5.7)*+ / 9.4 / <0.001 Symbols within each row indicate significant pairwise comparisons. Bolded values indicate significant omnibus tests.	Low methodological quality Moderate study size Conflicts of interest Not reported Funding Supported Oklahoma State University and National Institute on Drug Abuse

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Shiffman & Sembower, 2020[186] US Nationally representative cross-sectional survey The Population Assessment of Tobacco and Health (PATH) Wave 1-3 2013-2016	<u>Study size</u> 1,144 ever e-cigarette users <u>Sample</u> Ever used e-cigarettes "fairly regularly" and now uses them every day or some days, no other tobacco product use No demographic information reported	<u>Exposure</u> Exclusive e-cigarette use <u>Comparator</u> Daily (n=720): Reports using at least 27 days in past 30 days Non-daily (n=431): Reports using less than 27 days in past 30 days <u>Materials</u> Own brand EC	<u>PATH dependence scale</u> Consists of 16 items (15 using a 1–5 scale ranging from "not at all true of me" to "extremely true of me"; one dichotomous item was scored 1 or 5)	E-cigarette only dependence – exclusive e-cigarette users Current Exclusive EC: Respondents 1,114; Observations 1,586; Mean 1.98; SE 0.06 Daily EC: Respondents 720; Observations 1,082; Mean 2.17; SE 0.08 Non-daily EC: Respondents 431; Observations 493; Mean 1.37; SE 0.04 Adjusted analyses control for PATH wave of data collection, age, sex, ethnicity, and education	Low methodological quality Moderate study size <u>Conflicts of interest</u> Consultants to tobacco industry <u>Funding</u> Supported by RAI Services Company

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type, [data source, time frame])</th><th>Sample characteristics</th><th>Intervention/ exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflict of interest and funding</th></tr>
<tr>
<td>Boykan et al., 2019[163]

US

Three Stony Brook Children's outpatient offices

April 2017-April 2018</td>
<td><u>Study size</u>
42 current e-cigarette users

<u>Sample</u>
Past week exclusive users of pod and non-pod devices

<u>Gender</u>
Not reported

<u>Age - (%) years</u>
<table>
<tr><th></th><th>Pod</th><th>Non-pod</th></tr>
<tr><td>12-14</td><td>60.0</td><td>40.0</td></tr>
<tr><td>15-17</td><td>56.3</td><td>44.0</td></tr>
<tr><td>18-21</td><td>22.2</td><td>77.8</td></tr>
</table>
</td>
<td><u>Exposure</u>
Exclusive e-cigarette pod users

<u>Comparator</u>
Non-pod users

<u>Materials</u>
Own brand EC</td>
<td>If I go too long without vaping, the desire to vape interrupts my thinking

If I go too long without vaping, the desire to vape is so great that I need to vape again

If I go too long without vaping, I get angry or irritable

If I go too long without vaping, I get stressed

I need to vape when I awaken in the morning</td>
<td><u>E-cigarette dependence (past-week users) - Affirmative response - n (%)</u>
<table>
<tr><th></th><th>Total (n=42)</th><th>Pod (n=20)</th><th>Non-pod (n=22)</th><th>p</th></tr>
<tr><td>Desire interrupts thinking</td><td>3 (7)</td><td>3 (15)</td><td>0 (0)</td><td>0.060</td></tr>
<tr><td>Desire so great, I need to use again</td><td>2 (5)</td><td>2 (10)</td><td>0 (0)</td><td>0.130</td></tr>
<tr><td>I get angry or irritable</td><td>5 (12)</td><td>4 (20)</td><td>1 (5)</td><td>0.122</td></tr>
<tr><td>I get stressed</td><td>6 (14)</td><td>4 (20)</td><td>2 (9)</td><td>0.320</td></tr>
<tr><td>Use upon waking</td><td>6 (14)</td><td>6 (29)</td><td>0 (0)</td><td>0.006</td></tr>
</table>
Not all respondents answered all questions.</td>
<td>Low methodological quality

Small sample size

<u>Conflict s of interest</u>
Consultant fees and grants from pharmaceutical companies

<u>Funding</u>
Stony Brook University</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Hughes & Callas, 2019[184]

US

The Population Assessment of Tobacco and Health (PATH) Wave 2

2014-2015

Study size
3,210 ENDS or TC abstainers

Sample
Current or past established daily or some-day ENDS or TCs that had a successful or unsuccessful attempt to stop vaping or smoking completely or an attempt to reduce ENDS or TC use

Gender - (% female)
ENDS: 33
TC: 53
Dual/ENDS: 65
Dual/TC: 59
Dual/both: 60

Age – (%) years

	18-24	25-54	55+
EC	13	73	14
TC	7	63	31
Dual /EC	6	70	24
Dual /TC	8	70	21
Dual / both	10	66	23

Exposure
ENDS abstinence in exclusive (ENDS) or dual users (Dual/EC)

Comparator
TC abstinence in exclusive smokers (TC) or dual users (Dual/TC)

Dual ENDS and TC who quit both (Dual/both)

Materials
Own brand EC

DSM-5 criteria for tobacco withdrawal Angry, anxious, depressed, difficulty concentrating (diff conc.), eating more, insomnia, and restlessness

Prevalence of withdrawal symptoms on most recent quit attempt

	ENDS only, quit ENDS (n=25)	TC only, quit TC (n=2,528)	Dual, quit ENDS not TC (n=60)	Dual, quit TC not ENDS (n=355)	Within Dual, quit ENDS & TC (n=242)	
					ENDS	TC
Any Sx (%)	40	71**	30	80***	50	74***
4+ Sx (%)	25	33	12	45***	12	43***
No. SX [M (SD)]	1.7 (2.3)	2.5 (2.3)*	0.9 (1.9)	3.1 (2.4)***	1.8 (2.2)	3.0 (2.4)***

Sx=symptoms; * <0.05, **<0.01, ***<0.001

Dual users who stopped ENDS and continued TC reported non-significantly less withdrawal than ENDS-only users who stopped ENDS (first vs. third columns) suggesting continuing TC use abated ENDS withdrawal. In contrast, dual users who stopped TC and continued ENDS reported more, not less, withdrawal than exclusive TC users who stopped TC (second vs. fourth columns, p<0.001 for all three withdrawal measures).

Prevalence of individual symptoms on most recent quit attempt — (%)

	ENDS only, quit ENDS (n=25)	TC only, quit TC (n=2528)	Dual, quit ENDS not TC (n=60)	Dual, quit TC not ENDS (n=355)	Within Dual, quit ENDS & TC (n=242)	
					ENDS	TC
Angry	30	49	21	62	34	61
Anxious	23	45	14	48	35	52
Depressed	22	19	11	24	10	19
Diff con	12	25	10	36	21	35
Eat more	40	43	12	49	28	49
Insomnia	13	26	10	33	18	35
Restless	25	43	16	51	30	53

Low methodological quality

Large sample size

Conflicts of interest
Consultant fees and grants from pharmaceutical companies and tobacco industry

Funding
National Cancer Institute

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr>
<td>Jankowski et al., 2019[164]

Poland

YoUng People E-Smoking Study (YUPESS)

January-March 2019</td>
<td><u>Sample size</u>
90 participants

<u>Sample</u>
Exclusive ENDS users, smokers and dual users

<u>Gender - % female</u>
39.8

<u>Age – mean (SD) years</u>
22.4 (2.2)</td>
<td><u>Exposure (n=30)</u>
Exclusive e-cigarette users, duration of e-cigarette use was 29.0 ± 24.1 months

<u>Comparator 1 (n=30)</u>
Smokers, mean smoking duration was 50.0 ± 32.0 months

<u>Comparator 2 (n=30)</u>
Dual users, mean smoking duration was 67.3 ± 30.5 months and duration of e-cigarette use was 27.7 ± 17.4 months among dual users

<u>Materials</u>
Own brand EC</td>
<td><u>Fagerström Test for Nicotine Dependence (FTND)</u>
Scored out of 10
1-2: low dependence
3-4: low/moderate dependence
5-7: moderate dependence
8+: high dependence</td>
<td><u>Aspects of cigarette and e-cigarette dependence based on FTND</u>
<table>
<tr><th></th><th>Smokers</th><th>Exclusive e-cigarette user</th><th>Dual user</th><th></th><th>P (TC vs. Dual</th><th>P (EC vs. Dual</th></tr>
<tr><th></th><th></th><th></th><th>E-cigarette</th><th>Smoking</th><th></th><th></th></tr>
<tr><td colspan="7">How soon after waking up do you reach for a (e-) cigarette?</td></tr>
<tr><td>Within 30 min</td><td>17.9 (7.9–35.6)</td><td>53.9 (35.5–71.2)</td><td>57.1 (39.1–73.5)</td><td>42.3 (25.5–61.1)</td><td rowspan="2">0.04</td><td rowspan="2">0.8</td></tr>
<tr><td>After 30 mins</td><td>82.1 (64.4–92.1)</td><td>46.1 (28.8–64.5)</td><td>42.9 (26.5–60.9)</td><td>57.7 (38.9–74.5)</td></tr>
<tr><td colspan="7">Do you find it difficult to refrain from smoking/vaping in places where it is forbidden?</td></tr>
<tr><td>Yes</td><td>10.7 (3.7–27.2)</td><td>34.6 (19.4–53.8)</td><td>42.9 (26.5–60.9)</td><td>19.2 (8.5–37.9)</td><td rowspan="2">0.4</td><td rowspan="2">0.5</td></tr>
<tr><td>No</td><td>89.3 (72.8–96.3)</td><td>65.4 (46.2–80.6)</td><td>57.1 (39.1–73.5)</td><td>80.8 (62.1–91.5)</td></tr>
<tr><td colspan="7">Which (e-)cigarette would you hate most to give up?</td></tr>
<tr><td>First one</td><td>57.1 (39.1–73.5)</td><td>30.8 (16.5–50.0)</td><td>35.7 (20.7–54.2)</td><td>73.1 (53.9–86.3)</td><td rowspan="2">0.2</td><td rowspan="2">0.7</td></tr>
<tr><td>Any other</td><td>42.9 (26.5–60.9)</td><td>69.2 (50.0–83.5)</td><td>64.3 (45.8–79.3)</td><td>26.9 (13.7–46.1)</td></tr>
<tr><td colspan="7">How many (e-)cigarettes per day do you smoke?</td></tr>
<tr><td>10 or less</td><td>85.7 (68.5–94.3)</td><td>38.5 (22.4–57.5)</td><td>32.1 (17.9–50.7)</td><td>69.2 (50.0–83.5)</td><td rowspan="3">0.2</td><td rowspan="3">0.8</td></tr>
<tr><td>11-20</td><td>14.3 (5.7–31.5)</td><td>38.5 (22.4–57.5)</td><td>35.7 (20.7–54.2)</td><td>23.1 (11.0–42.1)</td></tr>
<tr><td>21-30</td><td>0.0 (0.0–11.3)</td><td>11.5 (4.0–28.9)</td><td>10.7 (3.7–27.2)</td><td>7.7 (2.1–24.1)</td></tr>
<tr><td>31+</td><td>0.0 (0.0–11.3)</td><td>11.5 (4.0–28.9)</td><td>21.4 (10.2–39.5)</td><td>0.0 (0.0–11.3)</td><td></td><td></td></tr>
</table></td>
<td>Moderate methodological quality

Small sample size

<u>Conflict of interest</u>
None declared

<u>Funding</u>
Medical University Silesia</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
				Do you smoke/vape more frequently during the first hours after waking than during the rest of the day? Yes: 14.3 (5.7–31.5); 15.4 (6.2–33.5); 39.3 (23.6–57.6); 34.6 (19.4–53.8); 0.8; 0.05 No: 85.7 (68.5–94.3); 84.6 (28.8–64.5); 60.7 (42.4–76.4); 65.4 (46.2–80.6) Do you smoke/vape if you are so ill that you are in bed most of the day? Yes: 21.4 (10.2–39.5); 34.6 (19.4–53.8); 67.9 (49.3–82.1); 42.3 (25.5–61.1); 0.09; 0.01 No: 78.6 (60.5–89.8); 65.4 (46.2–80.6); 67.9 (49.3–82.1); 57.7 (40.0–74.5) FTND Mean (SD): 1.6 ± 1.6; 3.5 ± 2.6; 4.7 ± 2.6; 3.2 ± 2.2; 0.002; 0.03 The average FTND score among exclusive e-cigarette users was over twice as high (mean 3.5 vs. 1.6) as among traditional cigarette smokers (p=0.002). The mean nicotine dependence level from e-cigarettes (mean 4.7) was higher than that from traditional cigarettes (mean 3.2; p=0.03) among dual users.	

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Case et al., 2018[187] US Wave 4 Texas Adolescent Tobacco and Marketing Surveillance System (TATAMS) April-June 2016	Study size 132 participants Sample Past 30-day exclusive or dual users Gender (%) Female: 48.5 Age – mean (years) 15.1 Ethnicity (%) White: 34.3	Exposure (n=91) Exclusive e-cigarette users (EC) Comparator 1 (n=41) Dual users Materials Own e-cigarette	Adapted from Hooked on Nicotine Checklist Fagerström Tolerance Questionnaire Adapted Population Assessment of Tobacco and Health (PATH) Survey	Cessation-related items - % (95% CI) Dual user: Want to quit 24.2 (10.0, 48.0); Quit attempt 22.9 (9.1, 46.9) EC: Want to quit 53.3 (37.6, 68.4); Quit attempt 45.7 (30.2, 62.1) Symptoms of e-cigarette dependence - % (95% CI) Dual user: Really need 32.7 (16.9, 53.9); ≤30 mins 16.4 (7.3, 32.7); Strong urge 35.7 (18.3, 57.8) EC: Really need 5.0 (2.2, 10.9); ≤30 mins 5.7 (2.5, 11.9); Strong urge 5.6 (2.5, 11.9) When you have not used an e-cigarette, vape pen, or e-hookah for a while, do you….- % (95% CI) Dual user: Find it difficult to concentrate 19.2 (9.1, 36.0); Feel irritable 29.0 (12.8, 53.1); Feel anxious 15.4 (6.9, 30.9) EC: Find it difficult to concentrate 1.6 (0.4, 5.7); Feel irritable 4.7 (2.1, 10.3); Feel anxious 2.8 (1.1, 7.4) E-cigarette-specific symptoms of nicotine dependence EC: AOR (95% CI) Ref Dual user: 0.22 (0.07, 0.70)* Dependence symptoms: 0.61 (0.41, 0.92)* Past-year quit attempt EC: Ref Dual user: 0.25 (0.07, 0.91)* Dependence symptoms: 0.52 (0.30, 0.92)* *<0.05	Low methodological quality Small study size Conflicts of interest None declared Funding Supported by a grant from the National Cancer Institute and the FDA Center for Tobacco Products (CTP)

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Morean et al., 2018[188] US School-based survey, pencil and paper 2017	Study size 520 participants Sample High school current e-cigarette users, 21.8% were also using tobacco cigarettes Gender (%) Female: 50.5 Age - mean (SD) years 16.22 (1.19) Ethnicity (%) White: 84.8	Exposure Past-month e-cigarettes Comparator None Materials Own e-cigarette	E-cigarette dependence scale Response options included: 0 (never) 1 (rarely) 2 (sometimes) 3 (often) 4 (almost always)	E-cigarette dependence Total 2.27 (3.84) When I haven't been able to vape for a few hours, the craving gets intolerable. 0.50 (1.00) I drop everything to go out and get e-cigarettes or e-juice. 0.30 (0.93) I vape more before going into a situation where vaping is not allowed. 0.74 (1.22) I find myself reaching for e-cigarettes without thinking about it. 0.73 (1.22) Stronger nicotine dependence was associated with being in a higher grade (r=0.13), vaping at an earlier age (r=−0.31), vaping more frequently (r=0.47), and using higher nicotine concentrations (r=0.46), p-values <.01. E-cigarette nicotine dependence also was significantly associated with using nicotine e-liquid (nicotine 0.36[0.40], nicotine-free 0.07[0.19], t=9.90) and past-month cigarette smoking (smokers 0.51[0.41], non-smokers 0.24[0.36], t=6.00), p-values<.001 More than half of the sample (55.6%) endorsed experiencing some level of e-cigarette nicotine dependence	Low methodological quality Moderate study size Conflicts of interest Previously received donate study medication from pharmaceutical companies Funding Supported in part by the FDA Center for Tobacco Products.

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, [data source, time frame])	Sample characteristics	Intervention/ exposure and comparator	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Browne et al., 2017[182] Multiple countries Online survey Study date not reported	Sample size 436 respondents Sample Current e-cigarette users (no definition provided), 22 dual users Gender - % Male: 80 Age – mean (SD) years 41.4 (13.1)	Exposure Current e-cigarette use Comparator Former tobacco smoking Materials Own e-cigarette	Fagerström Test for Nicotine Dependence Retrospective smoking (FTND-R) or current vaping (FTND-V)	Wilcoxon non-parametric t-tests confirmed that mean responses on all FTND-V probes were significantly less than their FTND-R counterparts ($p<0.001$), with the largest effect size observed for 'did/do you smoke/vape more during the first hours after waking than during the rest of the day?"	Low methodological quality Moderate sample size Conflict of interest None declared Funding Supported by Central Queensland University

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.4 Cardiovascular health outcomes

Main conclusions from the synthesised evidence on the cardiovascular health effects of e-cigarette use

- There is no available evidence on the effect of e-cigarette use on the risk of clinical cardiovascular disease outcomes, such as myocardial infarction, stroke or cardiovascular mortality.
- There is no available evidence on e-cigarette use and the risk of subclinical atherosclerosis-related outcomes such as carotid intima-media thickness and coronary artery calcification.
- Among non-smokers, there is insufficient evidence that e-cigarette use is related to other cardiovascular outcomes, including: increased blood pressure, heart rate, autonomic control and arterial stiffness; reduced endothelial function, hand microcirculation and cardiac function/geometry; and cardiac device interference.
- Among smokers, there is: moderate evidence that use of e-cigarettes increases heart rate, systolic blood pressure, diastolic blood pressure and arterial stiffness acutely after use; and limited evidence that use increases endothelial dysfunction, and that long term use after switching from combustible cigarette smoking decreases blood pressure.

Table 4.4-1. Overview of studies of cardiovascular health outcomes identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Cardiovascular health outcomes	1 0 / 1	11 3 / 8	1 0 / 1	6 5 / 1			8 1 / 7		1 0 / 1

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Clinical cardiovascular disease, including coronary heart disease, myocardial infarction, stroke, peripheral vascular disease, heart failure and death from cardiovascular disease.
- **Subclinical outcomes related to atherosclerosis**: Carotid intima media thickness, coronary artery calcification.
- **Other cardiovascular measures:** Include heart rate, systolic blood pressure, diastolic blood pressure.

4.4.1 Findings from previous reviews

There were no studies examining clinical cardiovascular disease outcomes or intermediate/subclinical outcomes related to atherosclerosis in relation to e-cigarette use identified as part of the NASEM systematic review.[3] The review identified 16 studies overall; seven randomised controlled trials [135,136,198-202] (one of which was also analysed as a cohort study),[198] seven non-randomised intervention studies,[49,160,203-207] one cohort study,[208] and one cross-sectional survey[209] on the relationship of e-cigarette use to other cardiovascular measures.[3] Of these, nine studies were included in the top-up review (three randomised controlled trials[199-201], five non-randomised intervention studies[203-206,210] and one cross-sectional survey[209]) and seven were excluded from this review due to non-eligible comparator or outcome (Table 4.4-1). Cross-sectional surveys were not considered suitable evidence for this outcome and were not included in evidence synthesis.

Eligible studies that included non-smokers were two randomised controlled trials[199,201] and two non-randomised intervention studies[203,205] - two conducted in the US[199,201] and one each in Italy[203] and Greece.[205] All were small in size, with samples ranging from 20 to 21 participants. The study populations

were approximately half female except for one study[205] with 11% females, and were of young adults in three studies, with average age between 23 and 28 years, and an average of 36 years for the other study.[205]

Outcome measures varied and included heart rate and blood pressure in two studies,[199,201] autonomic control and heart rate variability in one study,[201] endothelial function based on brachial artery flow-mediated dilation in one study,[203] and cardiac geometry and function in one study.[205] The NASEM review[3] considered that their findings indicated a harmful effect of nicotine e-cigarettes on cardiovascular health. The findings included evidence of a decrease in endothelial function,[203] and an increase in blood pressure[199,201] and heart rate[201] in participants using ENDS compared to placebo, and one of the studies found no change in heart rate and a decrease in systolic blood pressure.[199] The NASEM review considered that the non-randomised intervention study indicated no harmful effect, with the study noting no acute changes in cardiac geometry and function measures after using e-cigarettes compared to before use.[205]

Eligible studies in smoker populations included four non-randomised intervention studies [203,204,206,210] and one randomised controlled trial;[200] two were conducted in the US[200,206] and one each in Italy,[203] Spain[210] and Poland.[204] The number of participants ranged from 13 to 42, with average ages from 28 to 44 years, and the percentage of males from 48% to 76%. The outcomes measured were heart rate, blood pressure and endothelial function. A significant increase in heart rate was reported following ENDS use by three studies[200,206,210] and no significant change recorded for one study.[204] Blood pressure measures, both systolic and diastolic, were found to increase significantly following ENDS use in one study[206] while no significant change was observed in one study,[204] and one study found evidence of a decrease in endothelial function.[203]

The Irish Health Research Board literature map[15] identified a total of 32 studies; 13 randomised controlled trials,[198-202,211-218] eight non-randomised intervention studies,[192,203,205,207,219-222] three cohort studies,[208,223,224] five cross-sectional surveys,[225-229] one case series,[230] and two case reports[231,232] on the relationship of e-cigarette use to cardiovascular outcomes or measures.[15] Seven were included in the top-up review[211-213,215,216,220,223] and nine studies[198-203,205,207,208] were included in the NASEM review, either in the cardiovascular chapter or in another chapter. One study[221] published prior to the time frame used in the top-up review was not included in the NASEM review. Fifteen studies assessed did not meet the inclusion criteria for the top-up review due to study design,[225-232] or non-eligible exposure,[192,217,224] comparator or outcome.[214,218,219,222]

The small non-randomised intervention study not captured by the NASEM review[3] that was published prior to the time limit of the top-up review was conducted in Greece with a sample of 24 smokers, who had an average age of 30 years and unreported sex characteristics. The study found a significant increase in blood pressure after five minutes and 30 minutes of use compared to the sham condition, while heart rate increased significantly after a 30-minute e-cigarette use session but not a five-minute session.[221] Using an e-cigarette for 30-minutes had similar adverse effects on aortic stiffness to cigarettes, whilst the response was weaker for five-minutes of e-cigarette use.[221]

The Public Health England review did not report on specific studies investigating the relationship of e-cigarette use to cardiovascular outcomes or other measures.[11]

The CSIRO review[14] included a total of five studies reporting on the relationship of e-cigarette use to cardiovascular measures; two randomised controlled trials,[216,233] one cohort study,[223] and two cross-sectional surveys.[209,228] Of the five studies, three[216,223,233] were included in the top-up review and two were excluded due to study design.[209,228]

The SCHEER review[4] identified eight studies, two non-randomised intervention studies[221,234] and six randomised controlled trials on cardiovascular outcomes.[202,215,235-238] Of the eight studies, three were included in the NASEM review[202,234,237] one was published before the date limit for the top-up review but not included in NASEM[221], three were included in the top-up review[215,235,239] and one did not meet inclusion for the top-up review due to non-eligible outcomes[238]. The study[221] not captured by the NASEM review [3]has already been discussed under the Irish Health Research Board summary[15].

No studies on the effects of e-cigarettes on cardiovascular outcomes were identified in the USPSTF review.[16]

4.4.2 Summary of conclusions from previous reviews

The NASEM review[3] concluded that:

- 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).

- There is substantial evidence that heart rate increases shortly after nicotine intake from e-cigarettes.
- There is moderate evidence that diastolic blood pressure increases shortly after nicotine intake from e-cigarettes.
- 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.
- There is insufficient evidence that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function.

The Irish Health Research Board literature map[15] concluded that there was some early evidence of damage to cardiovascular and respiratory tissue, mainly due to metals and volatile organic compounds, however cardiovascular findings were not consistent across all studies.

The CSIRO review[14] concluded that:

- Because of the lack of long-term studies, there continues to be no evidence that e-cigarette use is associated with clinical cardiovascular disease.
- Due to the few studies and the limitations related to sample size, [the studies in the review] provide little additional evidence to the relationship between e-cigarette use and cardiovascular outcomes.

The SCHEER review[4] did not provide any summative conclusion on cardiovascular outcomes.

4.4.3 Top-up review

Search results

Overall, 19 articles were located in the top-up systematic literature search (Table 4.4.2). Seven articles were cross-sectional surveys and hence did not meet eligibility criteria. One case report was identified and included in evidence synthesis as it was considered directly causal in nature. Therefore, 11 articles were available for the evidence synthesis in the top-up review.

Four systematic reviews with findings on cardiovascular outcomes related to e-cigarette use were identified in the database search.[240-243] Kennedy et al. identified 18 studies, seven non-randomised intervention studies and 11 randomised controlled trials.[242] Of the 18 papers, 10 were included in the NASEM review,[136,160,198-203,205,207] five were included in the top-up review,[211,212,215,216,220] one was published before the top-up review date limit but not included in NASEM (described above)[221] and two did not meet inclusion criteria for the top-up review[217,219]. Glasser et al.[241] identified four non-randomised intervention studies and six randomised controlled trials, all of which were included in the NASEM review.[129,136,160,198,200,201,205,207,210,244] Garcia et al. identified 17 articles, one cross-sectional survey, two cohort studies, 11 randomised controlled trials and three non-randomised intervention studies.[240] Of the 17 studies, seven were included in the NASEM review,[136,198,200,205,208,209,234] seven were included in the top-up review,[211-213,215,216,223,235] one was published prior to the top-up review date limit but no included in the NASEM review (described above),[221] and two did not meet eligibility for inclusion in the top-up review.[236,238] Skotsimara et al.[243] included 19 studies, of which 16 were included in the NASEM review,[129,136,161,198-200,204-209,234,244-246] two were included in the top-up review[216,225] and one was published prior to the top-up review date limit and not published in the NASEM review[221] (described above). The review also conducted meta-analyses and is discussed below in more detail.

Cardiovascular disease: clinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to clinical cardiovascular disease outcomes were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to clinical cardiovascular disease outcomes were located.

Cohort studies

No cohort studies reporting on the relationship of e-cigarette use to clinical cardiovascular disease outcomes were located.

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarette use to clinical cardiovascular disease outcomes were located.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to clinical cardiovascular disease outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to cardiovascular risk
Five cross-sectional surveys reporting on the relationship of e-cigarette use to clinical cardiovascular disease outcomes were identified and are not described further.[225,227,229,247,248] Two studies also had findings on other cardiovascular outcomes.[227,248]

Cardiovascular disease: subclinical outcomes related to atherosclerosis
No studies examining subclinical outcomes related to atherosclerosis were identified.

Other measures related to cardiovascular disease
Meta-analyses
No meta-analyses of the relationship of e-cigarette use to other cardiovascular measures specifically in non-smokers were located. A single meta-analysis[243] on the relationship of e-cigarette use to other cardiovascular measures including heart rate and blood pressure was identified, largely among smokers (Table 4.4.2). Of the 14 non-randomised intervention studies[129,136,161,198,200,205-208,216,221,234,244,245] included in the meta-analyses, 11 studies were among smokers only, 11 studies examined the acute effects of e-cigarettes on the cardiovascular system, between five and 30 minutes after e-cigarette use, and three studies examined the long-term effects of switching to e-cigarettes from combustible cigarette smoking, between five days and one year. No demographic information for participants in the included studies was reported.

Data from studies of acute effects were on 268 largely smoker participants, with population sample sizes ranging from eight to 43 participants. Where the information was provided, the mean nicotine concentration in the e-cigarette intervention was 17.4mg/mL (range 10–24mg/mL).

Heart rate increased significantly (pooled weighted MD=2.27; 95% CI 1.64-2.89; p<0.0001) 5-30 minutes after e-cigarette use, and there was significant heterogeneity among analysed studies (I^2=70%, p<0.001). Significant increases were also identified for both systolic blood pressure (pooled weighted MD=2.02; 95% CI 0.07-3.97; p=0.042) and diastolic blood pressure (pooled weighted MD=2.01; 95% CI 0.62-3.39; p=0.004). There was no significant heterogeneity among analysed studies, either for systolic (I^2=0%, p=0.866) or for diastolic blood pressure (I^2=15.7%, p=0.310). The quality of the meta-analysis was rated as moderate.

For the effects of non-acute e-cigarette use in smokers, data were included from 173 participants, with study samples ranging from 24 to 100 participants and with five days to one-year follow-up. Nicotine concentration was 7.2mg/mL in one study, 24mg/mL in one study, and varied in the third study.

Among smokers there was no change in heart rate with chronic e-cigarette use (pooled weighted MD=-0.03; 95% CI -2.57--2.52; p=0.983), while significant reductions were observed for both systolic blood pressure (pooled weighted MD=-7.00; 95% CI -9.63--4.37; p<0.0001) and diastolic blood pressure (pooled weighted MD=-3.65; 95% CI -5.71--1.59; p=0.001). No significant heterogeneity was evident among studies for heart rate (I^2=60.7%, p=0.079), systolic blood pressure (I^2=0%, p=0.411) and diastolic blood pressure (I^2=0%, p=0.936).

The study was of moderate methodological quality using the Joanna Briggs Institute's critical appraisal checklist. No conflicts of interest were declared and GRADE was not applied.

Randomised controlled trials
Eight randomised controlled trials were identified for inclusion in the top-up review, three in non-smoker participants and five in smoker participants (Table 4.4.3)

In the US study by Moheimani et al., 39 non-current users of both tobacco and e-cigarettes underwent three exposure sessions in randomised order: 1.2% nicotine e-cigarettes (ENDS), 0% nicotine e-cigarettes (ENNDS) and sham (e-cigarette with no e-liquid).[216] Of the 39 enrolled, 33 completed the study. Thirty-nine percent were male and the average age was 26.3 years. There was no statistical difference in heart rate or heart rate variability – a measure of variation in the time interval between heartbeats and an indicator of autonomic control – between ENNDS users and the sham condition. There was a statistically significant increase in heart rate (p=0.01) and heart rate variability (p=0.02) for ENDS users compared to sham users. Compared to ENNDS, ENDS users had a statistically significant increase in heart rate (p=0.05), but no statistical difference in heart rate variability (p=0.6). There was no statistical difference between the three groups for systolic and diastolic blood pressure and mean arterial pressure.[216]

In random order, 16 participants who had never used tobacco products underwent three exposure conditions (5.4% nicotine ENDS, 0% ENNDS and combustible cigarettes) in the US study by Cossio et al. The participants were 56% male and had an average age of 24 years. Compared to baseline, there was no statistical difference in cardio-ankle vascular index or flow-mediated dilation (significance values not reported) for the ENDS and ENNDS groups immediately post-exposure and one and two hours post-exposure. The authors reported no change in systolic and diastolic pressure, however no statistical test was conducted.[213]

Also in the US, Staudt at al. randomised 10 biologically-confirmed non-smokers to ENDS (concentration unknown) or ENNDS. There were three participants in the ENNDS condition and seven in the ENDS condition. All participants were male and had an average age of 31.6 years. There was no statistical difference in heart rate or mean arterial pressure in both the ENDS and ENNDS groups for both the first and second inhalation compared to baseline (heart rate: first inhalation p=0.9 and second inhalation p=0.6; mean arterial pressure: first inhalation p=0.2 and second inhalation p=0.3).[233]

In a Swedish study by Antoniewicz et al., 15 occasional users of tobacco products underwent exposure to both 19mg ENDS and ENNDS in a randomised order.[211] The average age was 26 years and 40% were male. Compared to baseline, there was no statistically significant difference in systolic (p=0.227) and diastolic (p=0.062) blood pressure due to ENDS or ENNDS at all during four-hour follow-up. Compared to baseline, there was a statistically significant increase in pulse wave velocity (p=0.037), heart rate (p=0.001) and heart rate corrected augmentation index (p=0.006) due to ENDS but not ENNDS, all of which returned to baseline by four-hour follow-up or earlier.[211]

In the study by Chaumont et al., 25 healthy Belgian occasional smokers undertook three randomly ordered experimental conditions: 3.0mg/mL ENDS, ENNDS and sham (use while the device was turned off). The average age was 23 years and 72% were male. There was no statistically significant difference between the three conditions for heart rate (p>0.7), systolic (p>0.8) and diastolic (p>0.9) blood pressure. There was also no statistical difference between conditions for any measure of arterial stiffness: aortic systolic blood pressure (p>0.8), aortic diastolic blood pressure (p>0.6), aortic pulse pressure (p>0.9), augmentation index corrected for heart rate (p>0.6), carotid–femoral pulse wave velocity (p>0.06) and subendocardial viability ratio (p>0.3).[212]

Franzen et al. exposed 15 smokers from Germany to 24mg ENDS, ENNDS and conventional cigarettes (order randomised) to examine changes in various vascular outcomes. The average age was 22.9 years and 33% were male. There were statistically significant increases in systolic blood pressure (p<0.05), heart rate (p<0.05) and peripheral pulse pressure (p<0.05) for ENDS users until approximately 40 minutes after exposure after which these returned to baseline levels. There was no statistical change in diastolic blood pressure in ENDS users. In ENNDS users, there was no statistical change in systolic blood pressure and peripheral pulse pressure, but there were statistically significant decreases in diastolic blood pressure (p<0.05) and heart rate, and all measures returned to baseline 120 minutes post-exposure. For measures of arterial stiffness in ENDS users, there was no significant difference in central systolic and diastolic blood pressure and a significant increase in corrected heart rate (p<0.05 at 90 minutes post-exposure) and pulse wave velocity (p<0.05 15 minutes post-exposure) before measures returned to baseline levels. In ENNDS users, only central diastolic blood pressure was statistically different (decrease, p<0.05 30 minutes post-exposure) at any point during two-hour follow-up.[215]

In a study from the UK, 20 habitual tobacco smokers underwent two randomly ordered experimental conditions (18mg/mL ENDS and own cigarettes) to measures changes in cardiovascular outcomes before and after exposure.[235] All participants were male and the average age was 31.6 years. In the ENDS condition, there was no statistically significant difference in systolic (p=0.431) and diastolic (p=0.950) blood pressure, and the augmented index corrected for heart rate (p=0.131) pre- and post-exposure. There was a statistically significant increase in augmentation index (p=0.010) and heart rate (p<0.001) post-exposure and a statistically significant decrease in reactive hyperaemia index (p=0.006), and pulse wave amplitude in both the occluded arm (p<0.001) and the control arm (p=0.001).[235]

Ikonomidis et al. randomised 40 current smokers to either continue with their regular cigarettes or completely switch to 12mg/mL ENDS for four months. The average age was 44.8 years and 20% were males. After four months of biochemically confirmed smoking abstinence, there was no statistically significant difference in any cardiovascular measure in smokers that switched to ENDS (all p>0.05).[239]

Of the eight studies, one was of high methodological quality[211] and the others were of moderate methodological quality[212,213,215,216,233,235,239] using the Joanna Briggs Institute's critical appraisal checklist. All studies were very small in size (less than 33 participants). No conflicts of interest were noted for any study and GRADE was not applied for these outcomes.

Cohort studies
One Italian cohort study including non-smoker participants was identified (Table 4.4.3).[223] Thirty-one participants were enrolled, but 10 were lost to follow-up. Follow-up occurred at 12, 24, and 42 months. Of the 21 participants included in analysis, two-thirds of participants were male and had an average age of 29.7 years among e-cigarette users and 32.5 years among non-users. In the e-cigarette group three (out of nine) participants used 0% nicotine concentration e-liquid. There was no statistically significant difference in heart rate (p=0.15), systolic blood pressure (p=0.82) and diastolic blood pressure (p=0.50) between e-cigarette users and non-users across the follow-up period.

The study was of moderate methodological quality using the Joanna Briggs Institute's critical appraisal checklist, but it had a very small sample size of 21 participants. Potential conflicts of interest were noted as authors had received grants and consulting and/or speaking fees from pharmaceutical companies, and e-cigarette industry and trade associations. GRADE was not applied.

Non-randomised intervention studies
One non-randomised intervention study reporting on the relationship of e-cigarette use to a cardiovascular measure was located, in both smoker and non-smoker populations (Table 4.4.3).[220]

The UK study investigated changes in hand microcirculation following e-cigarette exposure. Eight non-smokers and seven smokers were exposed to both 24mg ENDS and ENNDS (0mg nicotine) after which their microcirculation was tested for up to 20 minutes after exposure. Participants had an average age of 26 years and gender was not reported.

In non-smokers, neither ENDS nor ENNDS produced a significant change in either superficial or deep microcirculation during or following e-cigarette use.

Among smokers, those using ENNDS had a significant increase in superficial blood flow during and at each five-minute interval to 20 minutes after e-cigarette use. No changes were observed for deep blood flow following ENNDS use. Following the use of ENDS among smokers, superficial blood flow was significantly decreased at zero to five minutes, five to 10 minutes, and 10 to 15 minutes after e-cigarette use, but not during nor 15 to 20 minutes after e-cigarette use. Deep blood flow was significantly reduced among smokers during and for all measurements to 20 minutes following use of ENDS.[220]

The study was of high methodological quality using the Joanna Briggs Institute's critical appraisal checklist but had a very small sample size of 15 participants. No conflicts of interest were reported and GRADE was not applied.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to other cardiovascular measures were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to cardiovascular risk
Four cross-sectional surveys reporting on the relationship of e-cigarette use to other cardiovascular measures were identified.[227,248-250] Two studies also had findings on clinical cardiovascular outcomes.[227 248] Cross-sectional surveys were not considered suitable evidence for this outcome and no further description of these studies has been included.

One case report[251] reporting on the relationship of e-cigarette use to a cardiovascular measure was located and included in evidence synthesis (Table 4.4.4). The case was of a 48-year-old male in the US who experienced asymptomatic interference with his implanted dual-chamber implantable cardioverter-defibrillator (ICD). The proximity of the ICD to the magnet in his e-cigarette, located in his breast pocket, lead to the ICD emitting a "beep" several times. The case report was rated as moderate methodological quality and a potential conflict of interest was noted as funding had previously been received from medical device manufacturers. GRADE was not applied.

4.4.4 Summary of findings from top-up review
No studies on the effects of e-cigrattes on clinical cardiovascular outcomes were identifed. Hence:

- There is no available evidence as to how the use of e-cigarettes affects the risk of clinical cardiovascular outcomes.

No studies on the effects of e-cigrattes on subclinical cardiovascular outcomes were identifed. Hence:

- There is no available evidence as to how the use of e-cigarettes affects the risk of subclinical cardiovascular outcomes.

There were 12 studies, one meta-analysis, eight randomised controlled trials, one cohort study, one non-randomised intervention study and one case report on the effects of e-cigarettes on other cardiovascular outcomes.

- Among smokers, nicotine e-cigarette use was related to an acute increase in heart rate, compared to before use, in four randomised controlled trials, one non-randomised intervention study, one meta-analysis and one very small randomised controlled trial in non-smokers. Heart rate variability also increased in the same trial of non-smokers. Hence:
    - There is insufficient evidence on the relation of e-cigarette use to acute increases in heart rate and heart rate variability in non-smokers and moderate evidence among smokers.
- Among non-smokers, there were no acute changes in blood pressure, arterial stiffness, mean arterial pressure or hand microcirculation after e-cigarette use in two randomised controlled trials and a cohort study. Among smokers, e-cigarette use was related to an acute increase in blood pressure in one randomised controlled trial and one meta-analysis and no effect in three randomised controlled trials. An acute increase in peripheral pulse pressure was reported in one very small randomised controlled trial, and no effect on arterial stiffness was reported in two very small randomised controlled trials. One very small non-randomised intervention study found e-cigarette use was related to an acute decrease in hand microcirculation.
- E-cigarette use was not related to long-term changes in heart rate or blood pressure compared to no use among non-smokers in one very small cohort study. Hence:
    - There is insufficient evidence on the relation of e-cigarette use to acute increases in blood pressure, arterial stiffness, mean arterial pressure or hand microcirculation in non-smokers.
    - There is limited evidence that e-cigarette use is related to an acute increase in blood pressure among smokers.
    - There is insufficient evidence on the relation of e-cigarette use to acute changes in peripheral pulse pressure, hand microcirculation, arterial stiffness and endothelial function among smokers.
- Evidence from one case report indicated that use of e-cigarettes may interfere with cardiac device operation. Hence:
    - There is the potential for cardiac device interference by e-cigarette devices.

4.4.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining clinical evidence from the top-up systematic review with the evidence from previous reviews:

- No studies on the relationship of e-cigarette use to clinical cardiovascular outcomes were identified. Hence:
    - There is no available evidence as to how use of e-cigarettes affects the risk of clinical cardiovascular outcomes.

Combining subclinical evidence from the top-up systematic review with the evidence from previous reviews:

- No studies on the relationship of e-cigarette use to subclinical cardiovascular outcomes were identified. Hence:
    - There is no available evidence as to how use of e-cigarettes affects the risk of subclinical cardiovascular outcomes.

Combining evidence on other cardiovascular outcomes from the top-up systematic review with the evidence from previous reviews:

- There was a total of nine studies, all with small sample sizes, in non-smokers (never smokers and ex-smokers) on cardiovascular-related outcomes in relation to e-cigarette use.
- Among non-smokers, there is:
    - Insufficient evidence on the relation of e-cigarette use to heart rate and endothelial function when compared with no e-cigarette use;
    - Insufficient evidence, mostly indicating no significant effect of e-cigarettes on blood pressure and autonomic control when compared with no e-cigarette use;
    - Limited evidence of no significant changes in arterial stiffness and mean arterial pressure comparing e-cigarette use with no e-cigarette use; and
    - The potential for cardiac device interference.
- There was a total of 12 studies, all including small samples sizes, in current smokers on cardiovascular-related outcomes in relation to e-cigarette use.
- Among smokers, there is:

    - Moderate evidence that nicotine-delivering e-cigarettes are related to acute increases in heart rate after use;
    - Mostly consistent evidence that nicotine-delivering e-cigarettes are related to acute increases in systolic blood pressure, diastolic blood pressure and arterial stiffness after use;
    - Limited evidence that e-cigarettes are related to long-term decreases in blood pressure and no change in heart rate after switching from combustible cigarette smoking; and
    - Limited evidence that e-cigarette use is associated with increased endothelial dysfunction.
- GRADE was not applied.

4.4.6 Main conclusions from the synthesised evidence on the cardiovascular health effects of e-cigarette use

- There is no available evidence on the effect of e-cigarette use on the risk of clinical cardiovascular disease outcomes, such as myocardial infarction, stroke or cardiovascular mortality.
- There is no available evidence on e-cigarette use and the risk of subclinical atherosclerosis-related outcomes such as carotid intima-media thickness and coronary artery calcification.
- Among non-smokers, there is insufficient evidence that e-cigarette use is related to other cardiovascular outcomes, including: increased blood pressure, heart rate, autonomic control and arterial stiffness; reduced endothelial function, hand microcirculation and cardiac function/geometry; and cardiac device interference.
- Among smokers, there is: moderate evidence that use of e-cigarettes increases heart rate, systolic blood pressure, diastolic blood pressure and arterial stiffness acutely after use; and limited evidence that use increases endothelial dysfunction, and that long term use after switching from combustible cigarette smoking decreases blood pressure.

Table 4.4-2. Study details: cardiovascular health outcomes – meta-analyses

Study details (author, year, study type)	Inclusion and exclusion criteria	Outcome measure	Results	Quality assessment, study size, conflict of interest and funding
Skotsimara et al., 2019[243] Systematic review and meta-analysis	Not reported	Acute effects of ENDS Heart rate (beats/min) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg) Effects of switching to ENDS Heart rate (beats/min) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg)	Acute effects of ENDS - 5-30 minutes follow-up Heart rate: 11 studies, 273 participants, 2.27 (1.64-2.89), 70% Systolic blood pressure: 7 studies, 175 participants, 2.02 (0.07-3.97), 0% Diastolic blood pressure: 7 studies, 175 participants, 2.01 (0.62-3.39), 15.7% Non-acute effects of ENDS - 5 days to 1 year follow-up Heart rate: 3 studies, 173 participants, -0.03 (-2.57 – 2.52), 60.7% Systolic blood pressure: 3 studies, 173 participants, -7.00 (-9.63 – -4.37), 0% Diastolic blood pressure: 3 studies, 173 participants, -3.65 (-5.71 – -1.59), 0%	Moderate methodological quality Moderate study size Conflict of interest None declared Funding No specific funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Table 4.4-3. Study details: cardiovascular health outcomes – randomised controlled trials, cohort and non-randomised intervention studies

<table>
<tr><th>Study details (author, year, location, study type time frame, [data source])</th><th>Sample characteristics</th><th>Intervention/exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size conflicts of interest, funding</th></tr>
<tr><td colspan="6">Randomised controlled trials</td></tr>
<tr><td>Cossio et al., 2020[213]

US

Randomised, single-blinded, crossover study

Study date not reported</td><td><u>Study size</u>
16 participants

<u>Sample</u>
Naïve to regular tobacco products

<u>Gender</u>
Male: 9 (56%)
Female: 7 (44%)

<u>Age - mean (SD) years</u>
24 (3)</td><td><u>Intervention 1</u>
ENDS: 5.4% nicotine

<u>Intervention 2</u>
ENNDS: 0% nicotine

<u>Comparator</u>
Menthol-flavoured cigarette-like pipe (Harmless Cigarette Quit Smoking Aid)

<u>Materials</u>
1. ENDS: battery (Cirrus 3, White Cloud Cigarette) and cartridge (Menthol Flavour Clear Draw Max)
2. ENNDS: battery (Cirrus 3) and cartridge (Menthol Flavour Clear Draw Max)

<u>Pattern of exposure</u>
6 minutes: 4-second inhalations every 20 seconds (18 puffs). >48-hour break between sessions. Order randomised.</td><td>Cardio-ankle vascular index

Flow-mediated dilation (%)

<u>Haemodynamics</u>
Systolic blood pressure (mm Hg)

Diastolic blood pressure (mm Hg)</td><td><u>Cardio-ankle vascular index</u>
<table><tr><th></th><th>Control</th><th>ENNDS</th><th>ENDS</th></tr><tr><td>Baseline</td><td>5.7 ± 0.6</td><td>5.9 ± 0.6</td><td>5.8 ± 0.7</td></tr><tr><td>Immediately post</td><td>5.9 ± 0.9</td><td>6.0 ± 0.7</td><td>6.2 ± 0.8</td></tr><tr><td>1 hour post</td><td>6.0 ± 0.8</td><td>6.0 ± 0.5</td><td>6.0 ± 0.9</td></tr><tr><td>2 hours post</td><td>6.0 ± 0.8</td><td>6.1 ± 0.7</td><td>5.9 ± 0.8</td></tr></table>No statistical difference in any condition

<u>Flow-mediated dilation</u>
<table><tr><th></th><th>Control</th><th>ENNDS</th><th>ENDS</th></tr><tr><td>Baseline</td><td>5.6 ± 2.5</td><td>5.7 ± 2.8</td><td>5.6 ± 1.8</td></tr><tr><td>Immediately post</td><td>5.6 ± 2.4</td><td>5.0 ± 2.0</td><td>5.3 ± 1.7</td></tr><tr><td>1 hour post</td><td>5.6 ± 2.0</td><td>5.0 ± 2.2</td><td>6.1 ± 2.1</td></tr><tr><td>2 hours post</td><td>5.2 ± 3.2</td><td>5.2 ± 2.5</td><td>5.6 ± 2.6</td></tr></table>No statistical difference in any condition

<u>Systolic blood pressure</u>
<table><tr><th></th><th>Control</th><th>ENNDS</th><th>ENDS</th></tr><tr><td>Baseline</td><td>117 ± 6</td><td>115 ± 8</td><td>119 ± 10</td></tr><tr><td>Immediately post</td><td>119 ± 8</td><td>118 ± 10</td><td>124 ± 10</td></tr><tr><td>1 hour post</td><td>120 ± 7</td><td>120 ± 8</td><td>121 ± 10</td></tr><tr><td>2 hours post</td><td>120 ± 7</td><td>119 ± 10</td><td>121 ± 9</td></tr></table>
<u>Diastolic blood pressure</u>
<table><tr><th></th><th>Control</th><th>ENNDS</th><th>ENDS</th></tr><tr><td>Baseline</td><td>68 ± 3</td><td>66 ± 4</td><td>69 ± 4</td></tr><tr><td>Immediately post</td><td>68 ± 6</td><td>68 ± 5</td><td>73 ± 5</td></tr><tr><td>1 hour post</td><td>71 ± 6</td><td>70 ± 5</td><td>71 ± 6</td></tr><tr><td>2 hours post</td><td>69 ± 5</td><td>68 ± 5</td><td>70 ± 5</td></tr></table></td><td>Moderate methodological quality

Very small study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Not reported</td></tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type time frame, [data source])</th><th>Sample characteristics</th><th>Intervention/exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size conflicts of interest, funding</th></tr>
<tr>
<td>Ikonodimis et al., 2020[239]

Greece

Randomised controlled trial, not blinded

Study date not reported</td>
<td><u>Study size</u>
40 participants

<u>Sample</u>
Current smokers without cardiovascular disease

<u>Gender – n (%)</u>
Male: 8 (20)
Female: 32 (80)

<u>Age – mean (SD) years</u>
44.8 ± 11.3</td>
<td><u>Intervention (n=20)</u>
ENDS: 12mg/mL nicotine

<u>Comparator (n=20)</u>
Conventional cigarette

<u>Materials</u>
ENDS: NOBACCO eGo Epsilon
BDC 1100, eGo battery, 1100 mAh, operating at 3.9V
Conventional cigarette: participant's own type

<u>Pattern of exposure</u>
Complete switch to ENDS (biochemically verified) for four months</td>
<td><u>Haemodynamics</u>
Systolic blood pressure (mm Hg)

Diastolic blood pressure (mm Hg)

<u>Arterial stiffness</u>
Pulse wave velocity (m/sec)

Systolic blood pressure assessed by Complior device (mm Hg)

Diastolic blood pressure assessed by Complior device (mm Hg)</td>
<td><u>Systolic blood pressure</u>
<table>
<tr><th></th><th>Pre</th><th>Post</th><th>P-value</th></tr>
<tr><td>ENDS</td><td>129.3 ± 19.1</td><td>128.7 ± 19.9</td><td>0.949</td></tr>
<tr><td>Cigarette</td><td>124.3 ± 19.8</td><td>123.5 ± 15.1</td><td>0.855</td></tr>
</table>
<u>Diastolic blood pressure</u>
<table>
<tr><th></th><th>Pre</th><th>Post</th><th>P-value</th></tr>
<tr><td>ENDS</td><td>80.5 ± 12.5</td><td>79.3 ± 12.5</td><td>0.641</td></tr>
<tr><td>Cigarette</td><td>75 ± 10.6</td><td>72.4 ± 10.6</td><td>0.267</td></tr>
</table>
<u>Pulse wave velocity</u>
<table>
<tr><th></th><th>Pre</th><th>Post</th><th>P-value</th></tr>
<tr><td>ENDS</td><td>10.9 ± 1.9</td><td>10.1 ± 1.7</td><td>0.047</td></tr>
<tr><td>Cigarette</td><td>9.5 ± 2.8</td><td>10.3 ± 2.9</td><td>0.028</td></tr>
</table>
<u>Systolic blood pressure assessed by Complior device</u>
<table>
<tr><th></th><th>Pre</th><th>Post</th><th>P-value</th></tr>
<tr><td>ENDS</td><td>119.2 ± 18.5</td><td>121.2 ± 20.6</td><td>0.517</td></tr>
<tr><td>Cigarette</td><td>117.5 ± 17.2</td><td>115.3 ± 14.5</td><td>0.484</td></tr>
</table>
<u>Diastolic blood pressure assessed by Complior device</u>
<table>
<tr><th></th><th>Pre</th><th>Post</th><th>P-value</th></tr>
<tr><td>ENDS</td><td>78.9 ± 12.5</td><td>79.3 ± 11.7</td><td>0.843</td></tr>
<tr><td>Cigarette</td><td>77.1 ± 13.9</td><td>73.3 ± 9.9</td><td>0.244</td></tr>
</table>
</td>
<td>Moderate methodological quality

Small study size

<u>Conflict of interest</u>
None declared

<u>Funding</u>
None received</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Antoniewicz et al., 2019[211]

Sweden

Randomised, double-blinded, crossover study

Study date not reported

Study size
15 participants

Sample
Occasional users of tobacco products (max 10 cigarettes/month), healthy

Gender
Male: 6 (40%)
Female: 9 (60%)

Age - mean (SD) years
26 (3)

Intervention 1
ENDS: 19mg/mL nicotine

Intervention 2
ENNDS: 0mg/mL nicotine

Comparator
Before and after

Materials
Variable mod third generation e-cigarette (eVic-VT, Shenzhen Joyetech Co., Ltd., China) with e-liquid base primarily 49.4% propylene glycol, 44.4% vegetable glycerin, 5% ethanol, without any added flavourings

Pattern of exposure
30 puffs from ENDS for 30 min, with each puff lasting approximately three seconds; measurements up to 6 hours following exposure

Haemodynamics
Heart rate (beats/min)

Blood pressure (mm Hg)

Arterial stiffness
Pulse wave velocity (m/sec)

Heart-rate corrected augmentation index (%)

Heart rate

	ENDS	ENNDS	P-value (time)	P-value (time x exposure)
Baseline	65.4 ± 8.5	63.8 ± 9.7		
0 mins	71.7 ± 11.3*	64 ± 10.7		
10 mins	70 ± 12.4*	63.3 ± 12.2		
20 mins	69.7 ± 12.9*	62.7 ± 8.4	0.015	0.001
30 mins	65.7 ± 10.7	62.3 ± 9.2		
2 hours	64 ± 9.9	61.5 ± 9.4		
4 hours	67.6 ± 10.9	64.1 ± 9.9		

Systolic blood pressure

	ENDS	ENNDS	P-value (time)	P-value (time x exposure)
Baseline	109.4 ± 9.5	109.3 ± 10.3		
0 mins	119.3 ± 9.5†	114.5 ± 13.2†		
10 mins	117.4 ± 13†	111.2 ± 16.1†		
20 mins	113.7 ± 10.3	109.3 ± 15.5	<0.001	0.227
30 mins	114.5 ± 12	108.8 ± 15.4		
2 hours	111.1 ± 10.1	109 ± 10.2		
4 hours	109.1 ± 9.5	108.8 ± 11.7		

Diastolic blood pressure

	ENDS	ENNDS	P-value (time)	P-value (time x exposure)
Baseline	70.3 ± 5.7	70.2 ± 5.8		
0 mins	78.9 ± 5.9†	74.5 ± 6.9†		
10 mins	77.7 ± 6.6†	72.7 ± 8.2†		
20 mins	76.5 ± 6.6†	71.1 ± 8.1†	<0.001	0.062
30 mins	74.9 ± 5.8†	72.2 ± 8†		
2 hours	72.6 ± 5.4	72 ± 6.5		
4 hours	70.5 ± 6.6	69.8 ± 6.6		

Pulse wave velocity

	ENDS	ENNDS	P-value (time)	P-value (time x exposure)
Baseline	5.8 ± 0.8	6.2 ± 0.9		
0 mins	6.4 ± 0.8*	6.4 ± 1	<0.001	0.037
10 mins	6.3 ± 0.9*	6.2 ± 0.9		

High methodological quality

Very small study size

Conflicts of interest
None declared

Funding
Supported by the Swedish Heart and Lung Association, the Swedish Society of Medicine, the Swedish Heart–Lung Foundation and Stockholm County Council

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type time frame, [data source])</th><th>Sample characteristics</th><th>Intervention/exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size conflicts of interest, funding</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>20 mins</td><td>6.1 ± 0.9*</td><td>6.1 ± 0.8</td></tr>
<tr><td>30 mins</td><td>6 ± 0.8</td><td>6.1 ± 0.9</td></tr>
<tr><td>2 hours</td><td>5.8 ± 0.8</td><td>6.1 ± 0.8</td></tr>
<tr><td>4 hours</td><td>5.8 ± 0.9</td><td>6 ± 0.8</td></tr>
</table>
<u>Heart-rate corrected augmentation index</u>
<table>
<tr><th></th><th>ENDS</th><th>ENNDS</th><th>P-value (time)</th><th>P-value (time x exposure)</th></tr>
<tr><td>Baseline</td><td>− 5.1 ± 9.5</td><td>− 2 ± 9.2</td><td rowspan="8"><0.001</td><td rowspan="8">0.006</td></tr>
<tr><td>0 mins</td><td>5.7 ± 11*</td><td>0.6 ± 12.8</td></tr>
<tr><td>10 mins</td><td>3.9 ± 13.2*</td><td>0 ± 10.7</td></tr>
<tr><td>20 mins</td><td>2 ± 11.1*</td><td>− 0.7 ± 12.9</td></tr>
<tr><td>30 mins</td><td>1.9 ± 10.1</td><td>− 0.3 ± 10.7</td></tr>
<tr><td>2 hours</td><td>− 2.6 ± 11*</td><td>− 3.9 ± 10.7</td></tr>
<tr><td>4 hours</td><td>− 3.8 ± 10.4</td><td>− 2 ± 9.5</td></tr>
</table>
*Denotes significant change from baseline due to exposure (contrast for ‘time × exposure’)
†Denotes significant change from baseline, not influenced by exposure (contrast for ‘time’)
</td><td></td></tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Kerr et al., 2019[235]

UK

Single-centre, prospective, randomised crossover study

June-December 2016

Study size
20 participants

Sample
Habitual tobacco smoker of one or more tobacco cigarettes per day

Gender
Male: 100%

Age – mean (SD) years
31.6 ± 10.5

Intervention 1
ENDS: 18mg/mL nicotine, tobacco flavoured

Intervention 2
Conventional cigarette

Comparator
Before session

Materials
ENDS: SmokeMax, second generation; 1300mAh variable voltage rechargeable battery
Conventional cigarette: participant's own type

Pattern of exposure
15 puffs

Haemodynamic parameters
Heart rate (beats/min)

Systolic blood pressure (mm Hg)

Diastolic blood pressure (mm Hg)

Reactive hyperaemia index (RHI)

Pulse wave amplitude (PWA)- occluded and control arms

Arterial stiffness
Augmentation index (%)

Augmentation index corrected for heart rate (AIx75) (%)

Heart rate

	Pre	Post	Change	P-value
ENDS	65±9	73±8	8±5	<0.001
Cigarette	64±8	86±13	23±12	<0.001

Systolic blood pressure

	Pre	Post	Change	P-value
ENDS	124±12	123±11	-1±6	0.431
Cigarette	121±14	125±14	4±9	0.058

Diastolic blood pressure

	Pre	Post	Change	P-value
ENDS	80±11	80±10	0±5	0.950
Cigarette	75±11	77±10	2±5	0.167

Reactive hyperaemia index

	Pre	Post	Change	P-value
ENDS	1.68±0.33	1.96±0.44	0.28±0.38	0.006
Cigarette	1.86±0.47	1.96±0.51	0.10±0.44	0.156

Pulse wave amplitude - occluded arm

	Pre	Post	Change	P-value
ENDS	860±397	465±359	-395±310	<0.001
Cigarette	895±392	437±387	-458±324	<0.001

Pulse wave amplitude - control arm

	Pre	Post	Change	P-value
ENDS	906±434	5070±399	-399±353	0.001
Cigarette	966±451	475±396	-492±340	<0.001

Augmentation index

	Pre	Post	Change	P-value
ENDS	-10.5±13.2	-6.9±13.5	3.7±5.7	0.010
Cigarette	-9.0±10.0	-10.9±13.5	-1.9±7.4	0.265

Augmentation index corrected for heart rate

	Pre	Post	Change	P-value
ENDS	-16.6±14.5	-14.3±14.6	2.3±6.5	0.131
Cigarette	-15.6±10.4	-16.2±13.9	0.7±7.8	0.709

Moderate methodological quality

Very small study size

Conflicts of interest
None declared

Funding
Authors supported by British Heart Foundation Centre of Research Excellence

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr>
<td>Chaumont et al., 2018[212]

Belgium

Randomised, single-blinded, placebo controlled, three period crossover study

2017</td>
<td><u>Study size</u>
25 participants

<u>Sample</u>
Healthy occasional tobacco smokers

<u>Gender – n (%)</u>
Male: 18 (72)
Female: 7 (28)

<u>Age - mean (SD) years</u>
23 (0.4)</td>
<td><u>Intervention 1</u>
ENDS: 3.0mg/mL nicotine

<u>Intervention 2</u>
ENNDS: 0mg/mL nicotine

<u>Comparator</u>
Sham vaping (device with power off)

<u>Materials</u>
Last generation high-power vaping device, 60 watts (0.4Ω dual coils)

<u>Pattern of exposure</u>
4 second puffs at 30 second intervals, 25 times, order randomised</td>
<td><u>Haemodynamics</u>
Heart rate (beats/min)

Humeral systolic blood pressure (mm Hg)

Humeral diastolic blood pressure (mm Hg)

<u>Arterial stiffness</u>
Aortic systolic blood pressure (mm Hg)

Aortic diastolic blood pressure (mm Hg)

Aortic pulse pressure (mm Hg)

Augmentation index corrected for heart rate (AIx75) (%)

Carotid–femoral Pulse Wave Velocity (m/s)

Subendocardial viability ratio (SEVR)</td>
<td><u>Haemodynamic parameters - mean ± SEM</u>
<table><tr><th></th><th>ENNDS</th><th>ENDS</th><th>Sham</th><th>P-value</th></tr><tr><td>Heart rate</td><td>60 ± 2</td><td>59 ± 2</td><td>60 ± 2</td><td>>0.7</td></tr><tr><td>Systolic blood pressure</td><td>110 ± 2</td><td>109 ± 1</td><td>110 ± 2</td><td>>0.8</td></tr><tr><td>Diastolic blood pressure</td><td>68 ± 2</td><td>68 ± 1</td><td>68 ± 1</td><td>>0.9</td></tr></table>
<u>Arterial stiffness indices - mean ± SEM</u>
<table><tr><th></th><th>ENDS</th><th>ENDS</th><th>Sham</th><th>P-value</th></tr><tr><td>Aortic systolic blood pressure</td><td>95 ± 2</td><td>94 ± 1</td><td>94 ± 2</td><td>>0.8</td></tr><tr><td>Aortic diastolic blood pressure</td><td>69 ± 1</td><td>69 ± 1</td><td>68 ± 1</td><td>>0.6</td></tr><tr><td>Aortic pulse pressure</td><td>26 ± 1</td><td>26 ± 1</td><td>26 ± 1</td><td>>0.9</td></tr><tr><td>AIx75</td><td>−4,5 ± 1.9</td><td>−3.5 ± 1.5</td><td>−3,4 ± 2.1</td><td>>0.6</td></tr><tr><td>Carotid–femoral PWV</td><td>4.9 ± 0.1</td><td>4.9 ± 0.1</td><td>5 ± 0.1</td><td>>0.6</td></tr><tr><td>SEVR</td><td>184 ± 8</td><td>193 ± 7</td><td>184 ± 8</td><td>>0.3</td></tr></table></td>
<td>Moderate methodological quality

Very small study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Supported by the “Fonds Erasme pour la Recherche Médicale”; “Fondation pour la Chirurgie Cardiaque”; “Fondation Emile Saucez-René Van Poucke”; “Prix Docteur & Mrs Rene Tagnon”; “Fondation IRIS”; the “Prix de l’Association André Vésale”; Astra Zeneca; “Fonds Fruit de Deux Vies’; “Fond David and Alice Van Buuren”</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Franzen et al., 2018[215] Germany Single-centre pilot, randomised, double-blinded, crossover study Study date not reported	Study size 15 participants Sample Active traditional cigarette smokers; average pack years 2.9 ± 1.5 Gender – n (%) Male: 5 (33) Female: 10 (67) Age – mean (SD) years 22.9 ± 3.5	Intervention 1 ENDS: 24mg/mL nicotine, 55% propylene glycol and 35% glycerin, tobacco flavour Intervention 2 ENNDS: 0mg/mL nicotine, 55% propylene glycol and 35% glycerin, tobacco flavour Intervention 3 Conventional cigarette Comparator Before session Materials Tobacco cigarette: Philip & Morris ENDS and ENNDS: DIPSE, eGo-T CE4 vaporizer (third generation), 3.3 volts, 1.5 ohms and 7.26 watts Pattern of exposure Minimum one puff every 30 seconds for 10 puffs. Puff had to last 4 seconds. Order randomised.	Haemodynamic parameters Heart rate (beats/min) Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg) Peripheral pulse pressure (mm Hg) Arterial stiffness Central systolic blood pressure (mm Hg) Central diastolic blood pressure (mm Hg) Augmentation index corrected for heart rate (AIx75) (%) Pulse wave velocity (m/s)	Heart Rate ENDS: significant increase (>12%; p<0.05) 45-minute follow-up ENNDS: significant decrease (p<0.05) 110-minute follow-up Systolic Blood Pressure ENDS: significant increase (>3%; p<0.05) 40-minute follow-up ENNDS: no change from baseline (p>0.05) Diastolic Blood Pressure ENDS: no change from baseline (p>0.05) ENNDS: decreased (>4%, p<0.05) 30-minute follow-up Peripheral Pulse Pressure ENDS: significant increase (p<0.05) 30-minute follow-up ENNDS: no change from baseline (p>0.05) Central Systolic Blood Pressure ENDS: no change from baseline (p>0.05) ENNDS: no change from baseline (p>0.05) Central Diastolic Blood Pressure ENDS: no change from baseline (p>0.05) ENNDS: significantly decreased (p<0.05) 30-minute follow-up Augmentation index corrected for heart rate ENDS: significantly increase (p<0.05) 90-minute follow-up ENNDS: no change from baseline (p>0.05) Pulse Wave Velocity ENDS: significant increase (p<0.05) 15-minute follow-up ENNDS: no change from baseline (p>0.05)	Moderate methodological quality Very small study size Conflicts of interest None declared Funding Medizinische Klinik III of the Universitaetsklinikum Schleswig-Holstein

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type time frame, [data source])</th><th>Sample characteristics</th><th>Intervention/exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size conflicts of interest, funding</th></tr>
<tr>
<td>Staudt et al., 2018[233]

US

Randomised (unequal), before-and-after study

Study date not reported</td>
<td><u>Study size</u>
10 participants

<u>Sample</u>
Never smokers, self-reported history and confirmed by absence of tobacco metabolites in urine

<u>Gender</u>
Male: 100%

<u>Age – mean (SD) years</u>
31.6 ± 10.5</td>
<td><u>Intervention 1 (n=7)</u>
ENDS: nicotine concentration unknown

<u>Intervention 2 (n=3)</u>
ENNDS

<u>Comparator</u>
Before session

<u>Materials</u>
Blu branded ENDS and ENNDS

<u>Pattern of exposure</u>
10 puffs, 30 minutes rest, 10 puffs</td>
<td><u>Haemodynamics</u>
Heart rate (beats/min)

Mean Arterial Pressure (MAP) (mm Hg)</td>
<td><u>Heart Rate</u>
<table>
<tr><th></th><th>1st inhalation - baseline</th><th>2nd inhalation - baseline</th></tr>
<tr><td>ENDS</td><td>-0.1±4.0</td><td>0.1±7.8</td></tr>
<tr><td>ENNDS</td><td>-0.3±2.5</td><td>-3.7±10.4</td></tr>
<tr><td>P-value</td><td>0.9</td><td>0.6</td></tr>
</table>
<u>Mean Arterial Pressure (MAP)</u>
<table>
<tr><th></th><th>1st inhalation - baseline</th><th>2nd inhalation - baseline</th></tr>
<tr><td>ENDS</td><td>1.3±4.7</td><td>4.6±5.1</td></tr>
<tr><td>ENNDS</td><td>1.6±3.7</td><td>5.6±4.5</td></tr>
<tr><td>P-value</td><td>0.2</td><td>0.3</td></tr>
</table>
</td>
<td>Moderate methodological quality

Very small study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Supported by NIH and the Family Smoking Prevention and Tobacco Control Act</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type time frame, [data source])</th><th>Sample characteristics</th><th>Intervention/exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size conflicts of interest, funding</th></tr>
<tr>
<td>Moheimani et al., 2017[216]

US

Randomised, open-label, crossover study

Study date not reported</td>
<td><u>Study size</u>
39 participants enrolled, 33 included, 4 lost to follow-up

<u>Sample</u>
No current (within 1 year) e-cigarette or combustible cigarette use

<u>Gender – n (%)</u>
Male: 13 (39)
Female: 20 (61)

<u>Age - mean (SD) years</u>
26.3 (0.9)</td>
<td><u>Intervention 1</u>
ENDS: 1.2% nicotine

<u>Intervention 2</u>
ENNDS: 0% nicotine

<u>Comparator</u>
E-cigarette without e-liquid (sham)

<u>Materials</u>
Greensmoke cigalike with tobacco-flavoured liquid or 1.0 Ω eGo-One by Joyetech with strawberry flavouring

<u>Pattern of exposure</u>
Three x 30 minute (60 puffs) sessions separated by a 4-week washout. Order randomised.</td>
<td><u>Heart rate variability</u>
Heart rate (HR) (beats/min)

High frequency component (HF)

Low frequency component (LF)

<u>Haemodynamics</u>
Systolic Blood Pressure (SBP) (mm Hg)

Diastolic Blood Pressure (DBP) (mm Hg)

Mean Arterial Pressure (MAP) (mm Hg)</td>
<td><u>Heart rate variability after use</u>
<table>
<tr><th></th><th>ENDS vs. Sham</th><th>ENDS vs. ENNDS</th><th>ENNDS vs. Sham</th></tr>
<tr><td>Δ HR</td><td>Increase (p=0.01)</td><td>Increase (p=0.05)</td><td>No difference (p=0.54)</td></tr>
<tr><td>Δ HF, nu</td><td>Decrease (p=0.02)</td><td>Decrease (p=0.03)</td><td>No difference (p=0.9)</td></tr>
<tr><td>Δ LF, nu</td><td>Increase (p=0.003)</td><td>No difference (p=0.08)</td><td>No difference (p=0.17)</td></tr>
<tr><td>Δ LF/HF</td><td>Increase (p=0.02)</td><td>No difference (p=0.06)</td><td>No difference (p=0.6)</td></tr>
</table>
<u>Acute changes in haemodynamics (mean ± SEM)</u>
<table>
<tr><th></th><th>Δ SBP</th><th>Δ DBP</th><th>Δ MAP</th></tr>
<tr><td>ENDS</td><td>1.2 ± 2.0</td><td>1.3 ± 1.1</td><td>1.3 ± 1.2</td></tr>
<tr><td>ENNDS</td><td>-0.8 ± 1.9</td><td>-1.0 ± 1.1</td><td>-1.0 ± 1.2</td></tr>
<tr><td>Sham</td><td>-1.7 ± 2.0</td><td>-1.1 ± 1.1</td><td>-0.8 ± 1.2</td></tr>
<tr><td>P-value</td><td>0.59</td><td>0.23</td><td>0.37</td></tr>
</table></td>
<td>Moderate methodological quality

Very small study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Supported by the Tobacco-Related Disease Research Program, American Heart Association, the National Institute of Environmental Health Sciences, National Institutes of Health, and the UCLA Clinical and Translational Science Institute.</td>
</tr>
<tr><td colspan="6">Cohort studies</td></tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type time frame, [data source])	Sample characteristics	Intervention/exposure and comparator	Outcome measure	Results	Quality assessment, study size conflicts of interest, funding
Polosa et al., 2017[223] Italy Prospective cohort study 2013-2017 Online survey of regular vape shop customers	Study size 31 never smoker regular vape shop customers enrolled, 21 included in analysis Sample Never smokers or <100 cigarettes smoked in lifetime, daily EC users for ≥3 months Gender (%) Male: 67.8% Female: 32.2% Age - mean (SD) years ENDS: 29.7 (6.1) Control: 32.5 (7.0)	Exposure (n=9) Daily e-liquid consumption- median (SD): 4.0mL (2-5) Comparator (n=12) Non-smoker and non-EC user Materials - device type Advanced refillable: 44% Standard refillable: 56% Materials - nicotine concentration 0%: 33% 0.9%: 22% 1.2%: 22% 1.6%: 11% 1.8%: 11% Follow-up Follow-up at 12, 24 and 42 months	Systolic blood pressure (mm Hg) Diastolic blood pressure (mm Hg) Heart rate (beats/min)	Systolic blood pressure - Mean ± SD Baseline / 12 months / 24 months / 42 months EC: 115±9 / 116±5 / 114±9 / 118±10 Control: 117±9 / 117±10 / 116±10 / 116±9 p-value: 0.82 Diastolic blood pressure - Mean ± SD Baseline / 12 months / 24 months / 42 months EC: 79±6 / 78±4 / 73±9 / 76±8 Control: 74±9 / 76±6 / 75±9 / 73±9 p-value: 0.50 Heart rate - Mean ± SD Baseline / 12 months / 24 months / 42 months EC: 72±7 / 71±9 / 71±9 / 71±7 Control: 79±9 / 78±8 / 76±8 / 78±9 p-value: 0.15 p-value: EC vs. control	Moderate methodological quality Very small study size Conflicts of interest Grants and consulting/speaking fees from pharmaceutical companies, and electronic cigarette industry and trade associations Funding Supported by Catania University
Non-randomised intervention studies					

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type time frame, [data source])	Sample characteristics	Intervention/exposure and comparator	Outcome measure	Results	Quality assessment, study size conflicts of interest, funding
Pywell et al., 2018[220] UK Non-randomised before-and-after pilot crossover study Study date not reported	Study size 15 participants Participants Smokers (n=7): average cigarette consumption as 1.5 packs per week. Non-smokers (n=8) Gender Not reported Age – mean (range) years 26 (25-27)	Intervention 1 ENDS: 24mg nicotine Intervention 2 ENNDS: 0mg nicotine Comparator Before session Materials - device type Not specified Pattern of exposure Baseline (5 mins), ENNDS one puff every 30 secs for 10 inhalations. Same protocol for ENDS	Hand microcirculation (superficial and deep)	Superficial blood flow - Average % change in flow (SE) During / 0-5 / 5-10 / 10-15 / 15-20 Non-smokers ENNDS: -11.37 (16.28) / -4.76 (16.68) / -8.24 (16.92) / -11.47 (17.56) / -16.93 (23.60) p-value: 0.74 / 0.86 / 0.83 / 0.74 / 0.74 ENDS: -23.12 (16.28) / -3.05 (16.68) / 7.42 (16.92) / -2.71 (17.56) / 20.37 (23.63) p-value: 0.32 / 0.88 / 0.83 / 0.88 / 0.71 Smokers ENNDS: 37.15 (11.18) / 56.07 (11.86) / 49.81 (13.32) / 39.27 (14.73) / 69.70 (16.98) p-value: <0.05 / <0.05 / <0.05 / <0.05 / <0.05 ENDS: -4.27 (14.90) / -52.99 (16.79) / -66.37 (14.97) / -76.92 (13.74) / -4.73 (21.50) p-value: 0.86 / < 0.05 / < 0.05 / < 0.05 / 0.09 Deep blood flow - Average % change in flow (SE) During / 0-5 / 5-10 / 10-15 / 15-20 Non-smokers ENNDS: 1.98 (5.94) / -7.26 (6.31) / -8.46 (6.18) / -7.46 (6.82) / -0.21 (6.66) p-value: 0.82 / 0.61 / 0.58 / 0.61 / 0.97 ENDS: -4.73 (5.94) / -7.25 (6.31) / -3.64 (6.18) / -6.26 (6.82) / -1.84 (6.67) p-value: 0.75 / 0.61 / 0.75 / 0.72 / 0.82 Smokers ENNDS: -3.42 (6.00) / 3.02 (6.29) / 2.88 (6.08) / 3.33 (6.67) / 3.86 (6.68) p-value: 0.75 / 0.75 / 0.75 / 0.75 / 0.75 ENDS: -19.31 (6.13) / -26.68 (6.05) / -27.83 (5.79) / -28.43 (6.51) / -24.01 (6.43) p-value: <0.05 / <0.05 / <0.05 / <0.05 / <0.05 p-value: value compared to baseline	High methodological quality Very small study size Conflicts of interest Not reported Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Table 4.4-4. Study details: cardiovascular health outcomes – case reports

Study details (author, year, location, data source)	Demographics and medical history	Exposure	Presentation	Outcome	Quality assessment
Shea et al., 2020[251] US Hospital record	Male 48 years <u>Medical history</u> History of cardiac sarcoidosis and symptomatic non-sustained ventricular tachycardia, underwent implantation of a primary-prevention implantable cardioverter-defibrillator (ICD), later upgraded to a dual-chamber ICD	E-cigarette (JUUL device with a magnetic USB charging dock) was frequently stored in his left breast pocket overlying the device	Reported "beep" several times from device. The JUUL device was held up to his ICD, which elicited the steady magnet tone There were no symptoms associated with these episodes and the patient denied any clinical ICD shock. There had been no recent reprogramming of his device. A remote transmission demonstrated normal device function without any alert notifications	Educated about the importance of keeping any type of magnet at least 6 inches from the device	Moderate methodological quality <u>Conflicts of interest</u> Educational and research funding from medical device manufacturers <u>Funding</u> No specific funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.5 Cancer

Main conclusions from the synthesised evidence on cancer outcomes in relation to e-cigarette use

- There is no available evidence on the relationship of e-cigarette use to invasive cancer risk.
- There is no available evidence on the relationship of e-cigarette use to the risk of precancer/subclinical cancer outcomes.

Table 4.5-1. Overview of studies of cancer outcomes identified in the systematic review, by study design

Health outcome	Meta-analysis	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Cancer			1 1 / 0				2 1 / 1		3 2 / 1

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Invasive carcinoma.
- **Precancerous/subclinical outcomes:** Carcinoma in situ, dysplasia, other cancer-related risk markers.

4.5.1 Findings from previous reviews

Cancers can take years to develop, often leading to long time delays between exposure to certain carcinogens and disease onset. Evidence on invasive carcinoma is likely to be impacted by this time lag given the relatively recent introduction of e-cigarettes to the market.

The NASEM review[3] identified four studies on the relationship of e-cigarettes and cancer, one cohort study,[148] one cross-sectional survey[252] and two case reports.[253,254] Cross-sectional surveys and case reports were not considered suitable evidence for this outcome and no further description of these studies has been included.

The cohort study by Manzoli et al. reported the number of cancer events in combustible cigarette smokers (n=363), e-cigarette users (n=97) and dual users of combustible cigarettes and e-cigarettes (n=37) over 24 months.[148] At follow-up, 0.8% (3/363) of smokers, 2.1% (2/97) of e-cigarettes users, and no dual users (0/37) self-reported any cancer.[148] The NASEM review calculated the risk ratios for this study and found no significant difference in cancer risk between e-cigarette users and combustible cigarette smokers (risk ratio 2.49, 95% CI 0.42-14.72). The risk ratio for dual users was 0 (95% CI not estimable).[3] The study was limited by a small sample size, self-reported measures and confounding, and the data was considered low quality by the NASEM review.[3]

The Irish Health Research Board literature map[15] identified seven studies on cancer, one case series,[255] one case-control study[256] and five cross-sectional surveys.[252,257-260] In this context, cross-sectional surveys and case series are not considered informative and no further description of these studies has been included. The case-control study assessed bladder carcinogenic risk via a range of biomarkers and found that e-cigarette users had higher levels of two carcinogenic compounds than non-smoker controls.[256] This study did not meet inclusion criteria for the top-up review since studies of biomarkers were not eligible, and was not included.

The review conducted by Public Health England[11] did not report any findings on e-cigarettes and cancer.

The CSIRO review[14] found four studies on the relationship of e-cigarettes to cancer, one case-control study[256] also included in the Irish Health Research Board literature map,[15] and three cross-sectional surveys.[261-263]

The SCHEER[4] review identified one systematic review[264] on cancers related to e-cigarette use which was also identified in the top-up review. No studies on cancer were identified in the USPSTF[16] review.

4.5.2 Summary of conclusions from previous reviews

The NASEM review,[3] including case reports, a cohort study and a cross-sectional survey, concluded that:

- There are no available epidemiological studies on the potential association between e-cigarette use and cancer in humans to make any conclusions. 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 no available evidence whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for e-cigarette use compared with use of combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products.

The Irish Health Research Board literature map[15] did not provide any summative conclusions regarding cancer and e-cigarettes.

The CSIRO review,[14] using a case-control study and cross-sectional surveys, concluded 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.

4.5.3 Top-up review

Search results

Overall, two articles were located in the top-up systematic literature search. One was a case report[265] and the other a cross-sectional survey[266] and both did not meet eligibility criteria, hence, no articles were available for the top-up synthesis of evidence (Table 4.5-1).

Three systematic reviews with findings on e-cigarettes and cancer were identified in the database search.[241,264,267] Of the four papers included in the review of head and neck cancers by Flach et al.,[264] three were cross-sectional[252,257,266] and one was a case series.[255] Both Glasser et al.[241] and Tzortzi et al.[267] identified one case report,[253] also included in the NASEM review. In this context, cross-sectional surveys and case series are not considered informative and have not been included in evidence synthesis.

Cancer: clinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to cancer were located.

Randomised controlled and trials

No randomised controlled trials reporting on the relationship of e-cigarette use to cancer were located.

Cohort studies

No cohort studies reporting on the relationship of e-cigarette use to cancer were located.

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarette use to cancer were located.

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to cancer were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to cancer risk

One case report, Shields et al.,[265] was identified in the top-up review. In this context, case reports are not considered suitable evidence and no further description of the study has been included.

Cancer: subclinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to cancer were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to cancer were located.

Cohort studies
No cohort studies reporting on the relationship of e-cigarette use to cancer were located.

Non-randomised intervention studies
No non-randomised intervention studies reporting on the relationship of e-cigarette use to cancer were located.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to cancer were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to cancer risk
One cross-sectional survey, Bardellini et al.[266] was identified in the top-up review. In this context, cross-sectional surveys are not considered suitable evidence and no further description of the study has been included.

4.5.4 Summary of findings from top-up review

No studies on the relationship of e-cigarette use to clinical and subclinical cancer outcomes were identified.

4.5.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence from the top-up systematic review with the evidence from previous reviews:

- There was one cohort study identified (from the NASEM review) which included all cancer types, included self-reported cancer and was of too small a size to reliably quantify the relationship of e-cigarette use to cancer risk.
- The GRADE rating was very low certainty and the assessment was that this did not constitute informative evidence.
- There is no available evidence on the relationship of e-cigarette use to the risk of precancer/subclinical cancer outcomes.

4.5.6 Main conclusions from the synthesised evidence on effects of e-cigarette use on cancer

- There is no available evidence on the relationship of e-cigarette use to invasive cancer risk.
- There is no available evidence on the relationship of e-cigarette use to the risk of precancer/subclinical cancer outcomes.

4.6 Respiratory health outcomes

Main conclusions from the synthesised evidence on the respiratory health effects of e-cigarette use

- There is conclusive evidence that the use of e-cigarettes can cause respiratory disease (EVALI) among smokers and non-smokers. Current evidence is that this lung injury is largely related to e-cigarettes delivering THC, with half of cases related to THC in conjunction with vitamin E acetate, and 14% of cases were in patients reporting the use of nicotine-delivering products only, indicating that these products can cause EVALI.
- There is insufficient evidence on the relationship of e-cigarette use to other clinical respiratory outcomes, including asthma, bronchitis and COPD in smokers and no available evidence in non-smokers.
- There is insufficient evidence for a reduction in respiratory exacerbations and disease progression among adult healthy, asthmatic and COPD smokers who switch to exclusive or dual-use of e-cigarettes.
- There is limited evidence in non-smokers and insufficient evidence in smokers that e-cigarettes have acute (up to two hours post-exposure) effects on spirometry parameters.
- There is limited evidence that e-cigarette use increases respiratory resistance and impedance in healthy and asthmatic smokers up to 30 minutes post-exposure.
- There is insufficient evidence on the effect of e-cigarettes on exhaled breath outcomes among smokers and non-smokers (healthy and asthmatic).
- There is insufficient evidence on the relationship of e-cigarette use to other respiratory measures (sinonasal symptoms, airway hyperresponsiveness) in smokers and no available evidence in non-smokers.

Table 4.6-1. Overview of studies of respiratory health outcomes identified in the systematic review, by study design

Health outcome	Meta-analysis	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Respiratory health outcomes*		9 5 / 4	5 2 / 3	5 1 / 4		18 0 / 18	21 4 / 17	11 0 / 11	26 0 / 26

Notes:
* Numbers in case series and case reports represent all evidence (both studies included in the evidence synthesis and those omitted from evidence synthesis due to issues with causality).
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Clinical respiratory diseases (chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma, and e-cigarette, or vaping, product use-associated lung injury (EVALI)), exacerbation and/or progression of existing clinical respiratory diseases.
- **Subclinical outcomes**: Lung function (spirometry including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory ratio (FEV_1/FVC), peak expiratory flow (PEF), forced expiratory flow (FEF); impulse oscillometry including impedance, resistance, reactance), lung structure (assessed via CT or MRI), exhaled breath analysis (fraction of exhaled nitric oxide (FeNO), fraction of exhaled carbon monoxide (FeCO)).
- **Other respiratory measures**: Includes nasal mucociliary clearance (MCC), voice performance, airway hyperresponsiveness.

4.6.1 Findings from previous reviews

Clinical, subclinical and other respiratory measures have been included in this respiratory disease section. Clinical outcomes include the onset and diagnosis of a range of respiratory diseases as well as the exacerbation and/or progression of existing disease. Progression of disease refers to a change in disease stage (either more or less severe), measured through a validated tool, such as the Global Initiative for Obstructive Lung Disease (GOLD) criteria for COPD. Disease exacerbations, defined as an increase in respiratory symptoms requiring a short course of treatment and/or hospital admission for treatment, were also considered under clinical outcomes.

Subclinical outcomes include the assessment of pulmonary function, which allow for the diagnosis and management of many respiratory conditions.[268] Spirometry is one aspect of pulmonary function testing, and includes measurement of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory ratio (FEV_1/FVC), forced expiratory flow (FEF), and peak expiratory flow (PEF), among other measures.[268] These measurements are particularly useful for evaluating the presence and/or progression of obstructive airway disorders, such as asthma and COPD, but are less helpful for assessing restrictive respiratory diseases.[268] Carbon monoxide (CO) and nitric oxide (NO) are small gas molecules that are endogenously produced in the human body.[269] Measuring the fractional concentration of these molecules in exhaled breath (FeNO and FeCO) has been proposed as a quantitative and non-invasive method of assessing airway inflammation, complementing other tests for respiratory disease.[269,270] The US Food and Drug Administration (FDA) has recommended the use of FeNO as a measure of airway inflammation in individuals with asthma.[270] However, when analysing empirical evidence it becomes evident that there is great variability in FeNO levels depending on the population being studied. For example, some studies have demonstrated reduced levels in smokers (compared with non-smokers)[271,272], increased levels in individuals with eosinophilic-induced asthma[272], and reduced levels in subjects with other respiratory conditions such as cystic fibrosis[273]. Respiratory outcomes such as cough, shortness of breath and wheezing are considered in the adverse event chapter.

Case reports, which are ranked as a lower form of evidence on the hierarchy of research designs, typically provide limited evidence of causality. However, the highly specific EVALI criteria developed by the CDC addresses issues surrounding causality and enables reliable and consistent measurement of this novel respiratory outcome. Consequently, only case reports where the patients fulfilled the CDC criteria for a probable or confirmed case of EVALI[274] were included in the evidence synthesis. Case reports which made explicit mention of the criteria, and those which incidentally included the criteria (confirmed after being scrutinised by the authors of this review) were both included. EVALI is a relatively novel syndrome, with the criteria being published by the CDC in August 2019.[274] Only including articles with an explicit mention of EVALI would therefore restrict inclusion to studies published after this date. It is also possible that a lack of awareness about EVALI among researchers and authors may lead to an underreporting of cases. For these reasons, all case reports were carefully scrutinised by the review authors, to ensure that no articles were missed.

The NASEM review identified 17 publications on the effect of e-cigarette use on respiratory function and clinical disease. There were two instances of two publications being from the same group of authors and population and following the same procedures. In one instance, two cohort studies measured the same respiratory outcomes over different follow-up lengths.[275,276] In the other instance, involving two randomised controlled trials, different respiratory outcomes were assessed over the same follow-up period, and there were 130 participants in one study and 134 in the other (difference due to missing data).[277,278] Therefore, for the purposes of this review, the two separate occurrences of duplications have been merged such that the four studies are counted as two although both references are provided. In this context, cross-sectional surveys are not considered suitable evidence and no further description of the four cross-sectional surveys[279-282] has been included. Two non-randomised intervention studies and one cohort study are discussed in the chapter on acute adverse events.[162,283,284] Therefore eight studies, five randomised controlled trials[234,237,277,278,285,286], two cohort studies[275,276,287] and one non-randomised intervention study[288] on respiratory outcomes from the NASEM review have been included.

Of the eight studies in smoker populations, four were based in Italy[275-278,286], and one each in the United Kingdom[237], the United States[234], Turkey[285] and Greece[288]. Sample sizes ranged from 16 to 419, with a mean of 99 participants. The proportion of males ranged from 46.7% to 85.4%. All studies were carried out in adults, with a mean age range of 33.9 years to 66.9 years. Most study interventions required smokers to switch to e-cigarettes. Cognitive behavioural treatment[285], continuing tobacco use[237] and dual-use[234] were the other study interventions, identified in one study each.

Two cohort studies examined asthma and chronic obstructive pulmonary disease (COPD) exacerbations. One study[275,276] in 16 asthmatic smokers who switched to exclusive e-cigarette or dual use reported no significant difference in the frequency of respiratory exacerbations before switching and six, 12, and 24 months after switching. In one study,[287] annual COPD exacerbations and symptoms were significantly reduced at two-year follow-up among 24 smokers with COPD who non-exclusively switched to e-cigarettes, and several patients had their COPD severity downgraded. There was little change in COPD symptoms and disease status during follow-up among sustained smokers (control).[287]

One study, Ferrari et al.,[286] an Italian laboratory-based randomised crossover trial, examined subclinical respiratory function parameters in both smokers and non-smokers. Ten smokers and 10 non-smokers (55.0% males and mean age 39.3 ± 12.6 (SD) years) trialled both ENNDS and combustible cigarettes in a randomly assigned order and had pulmonary function measured immediately after use. FEV_1 and FEF_{25} were significantly reduced in smokers after five minutes of ENNDS use, but all other lung function parameters showed no statistically significant change. In non-smokers, no statistically significant changes were reported.[286]

Six studies (three randomised controlled trials[234,237,278], one non-randomised intervention study[288], two cohort studies[275,276,287]) reported on lung function parameters in smokers who completely or partially switched to e-cigarettes. One cohort study[275,276] found significant improvements in lung function (FEV_1, FVC and $FEF_{25-75\%}$) for 16 asthmatic ENDS users (exclusive and dual users) at 12- and 24-month follow-up, but not at six-month follow-up. For exclusive ENDS users (n=10) the only significant change was in $FEF_{25-75\%}$, increasing at both 12- and 24-month follow-up. In one randomised controlled trial, 130 smokers were invited to quit or reduce their cigarette consumption by switching to e-cigarettes.[278] The three study arms included 12 weeks use of 2.4% ENDS, 2.4% ENDS for six weeks and 1.8% ENDS for six weeks, and 12 weeks of ENNDS. Despite this randomisation process, results were grouped and analysed by smoking phenotype classification (quitters: complete self-reported and biochemically-verified abstinence from tobacco smoking; reducers: sustained self-reported ≥50% reduction in the number of cigarettes per day, also biochemically verified; and failures: not categorised in either of the above categories) at one-year follow-up. The study found a statistically significant increase in $FEF_{25-75\%}$ among smoking 'quitters' at one-year follow-up compared to baseline.[278] Four[234,237,287,288] studies found no statistically significant changes, and one demonstrated an increase in airway impedance and lung impedance associated with the use of ENDS.[288]

In the NASEM review, three studies (two randomised controlled trials[234,277], one non-randomised intervention study[288]) measured FeNO and/or FeCO in the exhaled breath of smokers who switched to using e-cigarettes. Compared to baseline, there was a statistically significant decrease in FeNO after five minutes in one study[288] (n=30), and a statistically significant decrease in FeCO at five days in another study[234] (n=105). The third study[277] (n=134) reported a significant between-subjects effect ($p<0.0001$) between failures, reducers, and quitters of tobacco smoking, for both FeCO and FeNO at one-year follow-up.

One cohort study[275,276] and one randomised controlled trial[285] reported on other respiratory symptoms in relation to the use of e-cigarettes in smoker populations. The cohort study found statistically significant improvements in Asthma Control Questionnaire scores for all participants using e-cigarettes (exclusive and dual users) at all follow-up visits (six months, 12 months).[275,276] There were also statistically significant improvements in airway hyperresponsiveness – assessed via methacholine challenge – for all patients using ENDS.[275] One randomised controlled trial in healthy smokers (n=98 randomised) reported that sinonasal symptoms significantly reduced after three months use of ENDS, with a greater reduction in participants also receiving cognitive behaviour treatment.[285] For mucociliary clearance, a significant reduction was reported only in the e-cigarette plus cognitive behaviour group.[285]

The Irish Health Research Board literature map[15] identified a total of 78 studies (nine randomised controlled trials[233-235,277,278,285,286,289,290], seven non-randomised intervention studies[214,284,288,291-294], five cohort studies[275,276,287,295,296], one case-control study[297], 20 cross-sectional surveys[226,261,279-282,298-311], five surveillance reports[312-316], 23 case reports[254,317-338], eight case series[339-346]) on the relationship between e-cigarette use and respiratory measures or outcomes. Fourteen of the 78 studies were reported in the NASEM review[234,275-282,284-288] and 40 were excluded from the top-up review. Twenty-one studies were included in the top-up review, although only eight[233,235,291,292,295,312,316,335] are in the evidence synthesis as the other studies[317-321,325,326,328,330-332,338,340] did not fulfil the CDC criteria for a probable or confirmed case of EVALI. Three studies (one randomised controlled trial[289], one non-randomised intervention study[214], and

one case report[336]) were published prior to the date limit for the top-up review and were not in the NASEM review.

In the Canadian randomised crossover trial, 30 non-smokers (20 healthy volunteers and 10 asthmatic volunteers), aged between 20 and 40 years, trialled both a flavour-free ENNDS device and a placebo (empty ENNDS) for one hour. No significant effect of ENNDS on pulmonary function and respiratory mechanics was found.[289] The Greek non-randomised crossover study included 15 smokers and 15 never smokers (14 females and 16 males, age range of 18 to 57 years).[214] Each smoker underwent an active tobacco smoking session, a control session (pseudo-smoking an unlit cigarette) and an active e-cigarette session. Each never smoker underwent a passive tobacco smoking session, a control session (exposure to normal room air) and a passive e-cigarette smoking session. Neither passive nor active e-cigarette sessions significantly altered lung function (FVC, FEV_1, FEV_1/FVC, PEF, FEF_{25-75}) or exhaled breath (FeCO). Active but not passive tobacco smoking significantly affected lung function (FEV_1/FVC and FEF_{25-75}) ($p<0.001$). The case report described a 20-year-old active-duty male sailor with three days of facial flushing, persistent cough, and dyspnoea after e-cigarette use in the hour prior to symptom onset.[336] Following extensive investigation, a diagnosis of acute eosinophilic pneumonia was made, steroids were started, and he was discharged from hospital after five days with improvement in his symptoms. The CDC criteria for EVALI were all met, deeming him a confirmed case of EVALI.

Of note, the Irish Health Research Board literature map[15] included one case report from Australia, published in 2015.[323] To the best of our knowledge this is the earliest published report of an adverse respiratory outcome putatively attributable to e-cigarette use in Australia. The case report was not included in evidence synthesis because it did not meet the CDC criteria for EVALI.

The Public Health England 2018 review[11] included eight studies on the relationship between e-cigarette use and respiratory health outcomes; three randomised controlled trials[234,237,347], one cohort study[275], three cross-sectional surveys[281,308,348], and one case report[331]. Four of these studies were included in the NASEM review.[234,237,275,281] One case report was included in the top-up review count, but not evidence synthesis (did not meet EVALI criteria)[331], and the remaining three were excluded from the top-up review either due to study design (two cross-sectional surveys)[308,348], or for having an inappropriate comparator group (one randomised controlled trial)[347].

The CSIRO review[14] included 13 studies, four randomised controlled trials[233,234,289,349], two non-randomised intervention studies[292,350], two cohort studies[223,351], and five cross-sectional surveys[261,281,301,308,352], on the association between e-cigarette use and respiratory health. Two studies were in the NASEM review[234,281], three were in the top-up review[223,233,292] and seven were excluded from the top-up review due to their study design (four cross-sectional surveys[261,301,308,352], two abstracts[349,351], and one non-randomised intervention study which did not have an appropriate comparator group[350]). One study was published before the date limit of the top-up review and was not included in the NASEM review. It has been described under the Irish Health Research Board literature map.[289]

The SCHEER review[4] identified 11 studies (four reviews[353-356], three non-randomised intervention studies[214,288,357], one cohort study[358], one cross-sectional survey[261], one *in vitro* study[359], one viewpoint article[360]) with findings on respiratory health outcomes related to e-cigarette use. Two were included in the NASEM review[162,288] (although one has been discussed in the adverse events chapter rather than the respiratory chapter), seven[261,359, 360, 356, 355, 354, 353,] were excluded due to their study design, and three[214,357,358] were published before the date limit of the top-up review and not included in the NASEM review. Of the three studies, one[214] was previously discussed under the Irish Health Research Board literature map. The other two will be described further here.

In the Greek non-randomised before-and-after intervention study (n=76), the acute effects of 10 minutes of 11mg ENDS use on lung function and exhaled breath in 21 healthy never smokers, 28 healthy smokers and 27 smokers with obstructive airway diseases (16 with COPD and 11 with asthma) were assessed.[357] The acute effects of ENNDS use in never smokers was also assessed. 57.9% of the population were male and the mean age ranged from 34 ± 10 years in the never smoking group using ENNDS to 61 ± 9 years in smokers with COPD. There was no change in FeNO or exhaled breath airway temperature for any group after ENDS or ENNDS use. Airway resistance significantly ($p<0.05$) increased in asthmatic, healthy and never smokers after ENDS use and was also increased after ENNDS use in never smokers ($p<0.001$). Specific airway conductance significantly decreased for healthy and never smokers after ENDS use and for never smokers after ENNDS use. Results from the single breath nitrogen test, which is a measure of small airway function, showed a significant increase in the slope of the phase III curve for asthmatic

smokers only. The authors conclude that the results are suggestive of early dysfunction and deterioration of airway homogeneity of these small airways.

Although not the primary outcome, a 2011 Italian prospective cohort study measured FeCO in 40 regular smokers (65.0% males, mean age 42.9 ± 8.8 years) over 24-week follow-up.[358] Using smoking phenotype classifications (quitters, reducers, failures and heavy reducers), the results showed a reduction in mean FeCO for reducers, quitters, and heavy reducers and an increase for failures, at week 24 follow-up, compared to baseline. Statistical analysis was not undertaken on this measure so statistical significance cannot be determined.

The USPSTF review[16] identified six (five surveillance reports[312,361-364], one cross-sectional survey[261]) studies on the effects of e-cigarettes on respiratory health outcomes. The five surveillance reports were included in the top-up review and the cross-sectional survey was excluded from the top-up review due to its study design.

4.6.2 Summary of conclusions from previous reviews

The NASEM review[3] made four conclusions based upon the 17 clinical and epidemiological publications included in their review. This includes cross-sectional surveys which are not included in the current review.

- There is no available evidence whether or not e-cigarettes cause respiratory diseases in humans.
- 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).
- 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.

The conclusions from the Irish Health Research Board literature map[15] were:

- Both the poisoning cases and the respiratory disease cases highlighted a possible association between e-cigarettes and the use of other drugs such as alcohol, synthetic cannabinoids, and opiates.
- There was some early evidence of damage to cardiovascular and respiratory tissue, mainly due to metals and volatile organic compounds.
- There was variation in the direction of the impact of e-cigarettes on respiratory, cardiovascular, and oral disease outcomes, sometimes of a discordant nature. Some respiratory, cardiovascular, and oral diseases were noted to be less harmful in e-cigarette users than in conventional cigarette smokers but were as harmful in dual users.

The key findings from the Public Health England 2018 review[11] were:

- Comparative risks of … 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.

The CSIRO review[14], including cross-sectional and biomolecular studies, made two conclusions on the association between e-cigarette use and respiratory outcomes. First, in non-smokers:

- 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.
- The literature reviewed does not provide strong evidence that use of e-cigarettes improves lung function in smokers.

The conclusions from the SCHEER review[4] were:

- The overall weight of evidence is moderate for risks of local irritative damage to the respiratory tract of users of electronic cigarette due to the cumulative exposure to polyols, aldehydes and nicotine. However, the overall reported incidence is low.
- The overall weight of evidence for risks of carcinogenicity of the respiratory tract due to long-term, cumulative exposure to nitrosamines and due to exposure to acetaldehyde and formaldehyde is weak to moderate. The weight of evidence for risks of adverse effects, specifically carcinogenicity, due to metals in aerosols is weak.

- The overall weight of evidence for risks of other long-term adverse health effects, such as pulmonary disease CNS and reprotoxic effects based on the hazard identification and human evidence, is weak, and further consistent data are needed.

The USPSTF review[16] did not provide a summative conclusion on the respiratory health effects of e-cigarettes.

4.6.3 Top-up review

Search results

Overall, 83 respiratory articles (four randomised controlled trials[211,233,235,290], four non-randomised intervention studies[291,292,365,366], three cohort studies[28,223,295], 18 surveillance reports[312,316,361-364,367-378], 17 cross-sectional surveys[226,227,298,300,301,304,306-308,310,311,379-384], 26 case reports[317-321,325,326,328,330-332,335,338,385-397], 11 case series[340,398-407]) were identified. Four case series and 18 case reports were not eligible for inclusion in the evidence synthesis as they did not demonstrate a causal relationship and cross-sectional surveys were not considered to provide suitable evidence in this context. Therefore, 44 studies were included in the evidence synthesis (Table 4.6-1).

Four systematic reviews with findings on respiratory outcomes related to e-cigarette use were identified in the database search.[241,267,408,409] Glasser et al.[241] identified nine studies, comprised of two randomised controlled trials[286,347], four non-randomised intervention studies[214,283,284,288], two cohort studies[275,276], and one cross-sectional survey[282]. Of the nine papers, seven were included in the NASEM review[275,276,282-284,286,288] and one[347] was excluded from the top-up review for having a non-eligible comparator group. One non-randomised intervention study was published before the date limit of the top-up review and was not included in the NASEM review, however it was previously discussed under the Irish Health Research Board literature map.[214]

Tzortzi et al.[267] identified 46 studies (19 case reports[317,318,320,322,323,325,329-331,335,336,338,385,389,391,393,395,410,411], 15 surveillance reports[312,314,316,361,363,364,367-370,374,375,377,378,412], 11 case series[339-344,346,399,404,407,413], one case-control study[297]), of which 30 were included in the top-up review (19 were included in the evidence synthesis[312,316,335,361,363,364,367-370,374,375,377,378,385,389,393,399,407], and 11 (case reports/series) were included in the count, but not the evidence synthesis as they did not fulfil CDC criteria for a probable or confirmed case of EVALI[317,318,320,325,330,331,338,340,391,395,404]) and 14[297,314,322,329,339,341-344,346,410-413] were excluded from the top-up review due to reporting on e-cigarettes containing THC, for not meeting the peer-review requirement or for not fulfilling the CDC criteria for EVALI. Two papers[323,336] were published before the date limit of the top-up review and were not included in the NASEM review, however both, including the case report published in Australia, were discussed under the Irish Health Research Board literature map[15].

Gotts et al.[409] identified 89 studies (39 *in vitro* or molecular laboratory studies (including research on mouse/rat models, flavourings and e-cigarette constituents, chemicals and emissions), 15 cross-sectional surveys[227,261,279-282,300,305,306,308,311,414-417], 10 randomised controlled trials[212,233,234,237,278,286,289,290,418,419], eight case reports[317,321,323,325,335,336,338,395], six non-randomised intervention studies[214,283,288,292,350,420], two cohort studies[275,421], one case series[344], one surveillance report[378], two editorials[422,423], two reviews[424,425], one viewpoint article[426], one correspondence[427], one modelling study[428]). Eleven studies were included in the NASEM review[234,237,275,278-283,286,288], 10 were included in the top-up review (five were included in the evidence synthesis[233,290,292,335,378], and five (case reports) were included in the count, but not the evidence synthesis as they did not fulfil CDC criteria for a probable or confirmed case of EVALI[317,321,325,338,395]), and 63 did not meet the inclusion criteria. Four studies[214,289,323,336] were published prior to the date limit of the top-up review and were not included in the NASEM review, however all four, including the case report published in Australia, were discussed under the Irish Health Research Board literature map[15]. One study, a non-randomised intervention study from Italy, met the inclusion criteria and was not captured by any review.[420] Twenty-five healthy smokers (56.0% males, mean age 28 ± 9 years) each used a conventional cigarette, e-cigarette (ENDS and ENNDS) and an e-cigarette without liquid (control session) in different sessions. There was a statistically significant ($p<0.05$) before-and-after difference in FeNO levels for both smoking and e-cigarette (ENDS and ENNDS) sessions compared to the control session.

Jonas et al.[408] identified 83 studies. There were 33 case reports[254,317-323,325-327,329,332,333,335,336,338,385,386,389,393,395,411,429-438], nine case series[339-341,343-346,407,439], five surveillance reports[312-314,316,367], one cohort study[295], one non-randomised intervention study[288], three randomised controlled trials[233,290,440], four cross-sectional surveys[261,415,416,441], two reviews[424,442], one editorial[443], 24 *in vitro* or molecular laboratory studies (including research on mouse/rat models, flavourings and e-cigarette constituents, chemicals and emissions). Twenty-three studies were included in the top-up review (12 were

included in the evidence synthesis[233,290,295,312,316,335,367,385,386,389,393,407], and 11 (case reports/series) were included in the count, but not the evidence synthesis as they did not fulfil CDC criteria for a probable or confirmed case of EVALI[317-321,325,326,332,338,340,395]), one was included in the NASEM review[288] and 57 did not meet the inclusion criteria. Two studies[323,336] were published before the date limit of the top-up review and were not included in the NASEM review, however both, including the case report published in Australia, were discussed under the Irish Health Research Board literature map[15].

Clinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to clinical respiratory disease were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to clinical respiratory disease were located.

Cohort studies

There were two cohort studies identified for inclusion in the top-up review, both including smokers and non-smokers in their populations (Table 4.6.2).

One investigated the longitudinal association between e-cigarette use and several respiratory diseases using the Population Assessment of Tobacco and Health (PATH) survey from the United States. Bhatta and Glantz[28] included adults aged 18 years and over in PATH Wave 1 (data collection 2013-2014), Wave 2 (2014-2015), and Wave 3 (2015-2016). At Wave 1 baseline, 32,320 participants were analysed, 51.9% being female. The longitudinal association between e-cigarette use at Wave 1 and incident respiratory disease (chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or asthma) at Wave 2 and 3 combined was assessed among never, former and current e-cigarette users and smokers. It is important to note that at Wave 1, 0.6% of 'current e-cigarette users' were never combustible tobacco smokers, 13.9% were former combustible tobacco smokers, and 85.5% were current combustible tobacco smokers. For 'former e-cigarette users', 1.4% were never combustible tobacco smokers, 27.3% were former combustible tobacco smokers, and 71.3% were current combustible tobacco smokers. In 'never e-cigarette users', 35.6% were never combustible tobacco smokers, 50.2% were former combustible tobacco smokers, and 14.2% were current combustible tobacco smokers.

Compared to never e-cigarette users, former e-cigarette users were 31% more likely to be diagnosed with a respiratory disease at follow-up (AOR 1.31; 95% CI 1.07-1.60; p-value 0.009) and current e-cigarette users were 29% more likely (AOR 1.29; 95% CI 1.03-1.61; p-value 0.026). There was no significant difference in respiratory disease diagnosis at follow-up in ex-smokers compared to never smokers (AOR 1.16; 95% CI 0.87-1.57; p-value 0.315). The strongest effect size was for current smokers, who when compared with never smokers, had more than double the odds of having a respiratory disease diagnosis at follow-up (AOR 2.56; 95% CI 1.92-3.41; p-value <0.001). The lack of never-smoking e-cigarette users meant it was not possible to reliably separate the effects of e-cigarettes from those of variations in smoking behaviour.

One prospective cohort study reporting on the relationship of e-cigarette use to clinical respiratory disease exacerbation/progression in current or former smokers was located. Bowler et al.[295] recruited older adults at risk for or with COPD from two US longitudinal studies, with 4,595 participants (3,535 from COPDGene and 1,060 from SPIROMICS studies). Demographic factors were reported grouped by e-cigarette use status, not as a whole sample. The mean age ranged from 55 ± 7 (SD) years for current users in COPDGene to 64 ± 9 (SD) years for never users in SPIROMICS. The proportion of males ranged from 41% for current users in COPDGene to 55% for current users in SPIROMICS. 92% and 75% of current e-cigarette users were current conventional cigarette smokers, in COPDGene and SPIROMICS respectively.

At follow-up five years after baseline measurements, ever-using e-cigarettes was a statistically significant predictor (p=0.01) for COPD exacerbations in the COPDGene cohort. This relationship held after adjusting for potential confounding factors, including current tobacco smoking. There was insufficient prospective data to evaluate this relationship in the SPIROMICS cohort, however, data from the year prior to enrolment reported exacerbations associated with e-cigarette use (p=0.04). Ever e-cigarette users in the COPDGene cohort were more likely to have COPD progression (GOLD stage worsening) at five-year follow-up (p<0.001) than never users. Ever users also experienced a more rapid decline in FEV_1 (lung function) compared to never users (p=0.003). COPD progression and lung function results were statistically significant before adjustment, but not after adjusting for age, race, gender, and current smoking. Finally, after adjusting for age, race, gender, current tobacco smoking and pack-years, ever use of e-cigarettes was associated with an 8 ± 2% increased prevalence of chronic bronchitis

(p<0.001). At baseline, there was no statistically significant relationship of e-cigarette use to emphysema after adjusting for current tobacco smoking and other covariates. Once again, as mentioned earlier in this report, it is difficult to reliably separate the effects of e-cigarettes from those of smoking in these analyses, as 0% of current e-cigarette users in both of these cohort studies were never smokers.

Both studies were assessed as moderate quality and did not report any conflicts of interest.

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarette use to clinical respiratory disease were located.

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to clinical respiratory disease were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to respiratory health risk

There were 10 cross-sectional surveys[226,227,301,307,308,311,379,382-384] identified which reported on the relationship between e-cigarette use and clinical respiratory disease. In keeping with the protocol of this systematic review, the results of these studies are not considered further (Table 4.6-1).

Surveillance reports

There were 18 surveillance reports identified, all from the United States.[312,316,361-364,367-378] Fourteen[312,361-364,367,369-372,374-376,378] reported national data on e-cigarette, or vaping, product use-associated lung injury (EVALI), whilst four reported surveillance data from individual states (one report each from California[373], Indiana[377], Minnesota[368], and Utah[316]) (Table 4.6.3). Many time frames and data overlap, as each Morbidity and Mortality Weekly Report (MMWR) updates the cumulative data from the previous week's publication. To avoid discussing duplicated data, only the most recent data will be discussed here in detail. Data from the individual states will be considered separately.

Collection of surveillance data in the United States began in August 2019, after case definition, forms, and instructions for the reporting of EVALI cases were disseminated to state health departments by the US Centers for Disease Control and Prevention (CDC) (see *Appendix 8* for further information on case criteria).[367,374] The collection and submission of EVALI data by each US state and jurisdiction to the CDC is voluntary and therefore the reported statistics may not accurately capture prevalence.[370] According to the CDC, EVALI cases peaked in September 2019 and have since gradually decreased, resulting in the discontinuation of EVALI reporting by the CDC in February 2020.[373] As of February 18, 2020, 2,807 hospitalised EVALI cases were reported. Sixty-eight deaths have been confirmed in 29 states and the District of Columbia.[444]

Data from the most recently published US national data, correct as of January 14, 2020, included 2,668 hospitalised EVALI cases.[363] 1,401 (53%) were confirmed cases and 1,267 (47%) were probable cases. Sixty-six percent of cases were male and the highest proportion were in the 18-24-year age category (37%). The median age was 24 years (range 13-85), and the proportion of EVALI cases decreased with advancing age. THC-containing product use (in the three months preceding symptom onset) was implicated in 82% of cases, whilst nicotine products (57%) and use of both THC- and nicotine products (41%) were common. Fourteen percent reported exclusive use of nicotine products, whilst 33% reported exclusive THC-containing product use. Information on symptoms was not presented in this report, but the second most recently published report (data up until January 7, 2020 and including 2,618 cases) showed that 96% of cases had respiratory symptoms (any of chest pain, congestion, cough, haemoptysis, difficulty breathing, shortness of breath, sneezing, sore throat, runny nose, wheezing) and 79% had gastrointestinal symptoms (abdominal pain, diarrhoea, nausea, vomiting).[372] With respect to treatment, 98% received antibiotics, 88% glucocorticoids, 44% were admitted to an intensive care unit, 22% had endotracheal intubation and 19% received ventilatory support.

The California Department of Public Health reported 210 cases between June 2019 and February 2020;[373] and in April of 2020, the Department had reported eight hospitalised cases. Among the eight hospitalised cases, the median age was 17 years (range 14-50 years) and seven were aged <21 years. Cases were hospitalised a median of four days (range 4-13), 50% were admitted to intensive care, and 25% required mechanical ventilation. In Indiana, there were 97 hospitalised EVALI cases (41 confirmed and 56 probable) between August 8 and October 28, 2019. Medical record abstractions could only be completed for 54 cases due to staffing constraints. Seventy percent were male, 50% were aged between 18-29 years (median of 26 years), shortness of breath (89%) and cough (81%) were the most prevalent symptoms on

admission. The Minnesota Department of Health reported 96 cases (confirmed and probable) between August 9 and October 31, 2019, with 3 (3%) fatalities.[368] Sixty percent were male, the median age was 21 years (range 15-71), 91% were hospitalised and 27% were admitted to ICU. The Utah Department of Health reported 83 confirmed and probable cases of EVALI between August 6 and October 15, 2019.[316] Sixty-nine percent were male, the median age was 26 years (range 14-66), 89% were hospitalised, 75% received steroids, 44% were admitted to intensive care, 38% received ventilatory support (continuous positive airway pressure or bi-level positive airway pressure), and 11% were intubated and on mechanical ventilation.

Quality assessment was not conducted on the 16 MMWRs as they are considered grey literature (not peer-reviewed publications). The two non-MMWR publications[371,372] that were included were assessed as high quality. Conflicts of interest were reported in two studies.[361,375] GRADE was not applied.

Case series

Case series in which only some individual case reports meet our inclusion criteria have been retained in case series analysis however, only applicable results have been presented.

The search identified 11 case series reporting an association between e-cigarette use and respiratory disease.[340,398-407] However, four of these did not meet our specific inclusion criteria for respiratory case series and are not discussed further.[340,398,404,405] In four separate case series, there was only one case in each which met inclusion criteria (other cases used THC in their e-cigarettes).[399-401,406] All were from US hospital records. Therefore, of the seven case series, there were 14 cases (Table 4.6.4).

The first case series[402] reported on two males in the United States, aged 36 and 18 years. The 36-year-old was a frequent e-cigarette user who was previously healthy. A diagnosis of organising pneumonia was made after four weeks of fever, cough, weakness and weight loss. His treatment and outcome were not reported by the authors. The 18-year-old, who had a history of opiate use, presented with lower back pain, dyspnoea and fever. He was diagnosed with acute lung injury, and was discharged after six days, following antibiotic treatment. The authors stated that both cases met the CDC criteria for confirmed or probable EVALI, however insufficient information was provided to discern which one it was.

The second case series[403], also from the United States, presented hospital data from three adolescents. The first, a 16-year-old male, had used e-cigarettes intermittently for the preceding year and presented with dry cough, general malaise, decreased appetite, chills, fever, dyspnoea and vomiting. He met the CDC criteria for a confirmed or probable EVALI case (insufficient information provided to make a conclusive judgement). He was discharged after 23 days following intubation, antibiotic and steroid therapy. The second case was a 16-year-old male with a history of allergy-induced asthma. He presented to the hospital with fever, nausea, vomiting and diarrhoea having used e-cigarettes up to three times a week for two years. He was diagnosed with EVALI (confirmed or probable; insufficient information provided) and was discharged after eight days in hospital. A 15-year-old female, with possible asthma, chronic joint pain and sinopulmonary infections presented with symptoms of cough, dyspnoea and sputum production. Since her imaging was normal, she was neither a confirmed nor probable case. The outcomes of her treatment were not reported.

The third case series included five males with a mean age of 17.3 years. All used nicotine-e-cigarettes, four of them using the devices daily, and one using three-five days per week. All five were categorised as confirmed cases of EVALI, were admitted to hospital and received high-dose steroids as part of their treatment. Information on symptoms were grouped for the whole sample (includes patients using THC), and outcomes were not reported.[407]

In Temas and Meyer, only one of four cases was eligible for inclusion. The case was a 33-year-old male current daily tobacco smoker who presented with cough, dyspnoea, fever, hypoxia and tachycardia after using an e-cigarette the previous night.[406] The patient was treated with supplemental oxygen via high-flow nasal cannulae, antibiotics and steroids, and was diagnosed as a confirmed EVALI case. He was discharged six days after admission.

In the case series by Fryman et al. only one out of eight cases met inclusion criteria.[401] A 62-year-old female presented to the emergency department with a one-month history of dyspnoea and abdominal pain. The patient has been using ENDS for 6 months prior and was asthmatic. She was diagnosed with acute respiratory failure and considered a confirmed EVALI case. She remained in hospital for five days before being discharged.

Out of the three cases included in Ansari-Gilani et al. only one was eligible for inclusion.[399] A 20-year-old female presented with a one week history of shortness of breath, cough, intermittent nausea and diarrhoea. She reported use of an ENDS device three months prior. A confirmed EVALI diagnosis with hypersensitivity pneumonitis was given. The patient was discharged after 11 days.

In the cases series by Corcorcan et al., one of the seven cases met inclusion criteria.[400] A 17-year-old male presented with nausea, vomiting, cough, fever and dyspnoea for the past four days. The patient had a two-year history of daily nicotine pod use. The patient was defined as a probable EVALI case and discharged after six days.

Two case series were assessed as low[402,403], three as moderate[400,401,407] and two[399,406] as high quality. None reported any conflicts of interest. GRADE was not applied.

Case reports

The search identified 26 case reports reporting an association between e-cigarette use and respiratory disease. However, 18 did not meet the specific inclusion criteria for respiratory case reports and as such will not be discussed further.[317-321,325,326,328,330-332,338,391,392,394-397] Therefore, eight were included in the evidence synthesis. (Table 4.6.4)

There were six[385-388,390,393] confirmed 'explicit' cases of EVALI, and two[335,389] confirmed cases where all five criteria were incidentally met. The EVALI diagnosis is often associated with a specific respiratory disease. Three of the cases were diagnosed with acute respiratory distress syndrome[385,388,389], one with hypersensitivity pneumonitis[335], and one was diagnosed with diffuse alveolar haemorrhage[386]. Three cases did not specify the pathology.[387,390,393] Five reports were from the United States, and one each was from the United Kingdom, Spain and India. All of the reports were sourced from hospital records. There were five females and three males, the age range being 18 to 46 years. Five cases were using ENDS and three were using e-cigarettes of unreported composition.

Cough (six cases), dyspnoea (five cases), and chest pain (three cases) were the most common presenting signs/symptoms. There were no deaths. Two case reports included the duration of hospital stay; one confirmed EVALI case[385] with acute respiratory distress syndrome who stayed 12 days; and one confirmed EVALI case[393] who stayed for 12 days.

There was one case report involving a potential dual-user of e-cigarettes and combustible tobacco (smoking status ambiguous).[390] The individual, a 31-year-old male in India with a six-year history of tobacco smoking, began using ENDS three months prior to admission. He presented with acute onset breathlessness and dry cough of three days. After extensive investigation, he was diagnosed as a confirmed case of EVALI. His condition significantly improved after treatment.

One study was of low quality[388], five were of moderate quality[335,385,387,389,390] and two were of high quality[386,393]. There were no conflicts of interests reported in any studies. GRADE was not applied.

In addition to this evidence, there was a case report published in Australia, in October of 2021.[445] The report involved a 15-year-old girl with confirmed EVALI from a hospital in Sydney. As the publication of this case report is outside our search date, further information will be provided in Appendix 7.

Subclinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to intermediate respiratory outcomes were located.

Randomised controlled trials

There were four randomised controlled trials, three of which were crossover studies in smoker populations.

One randomised controlled trial in never smokers was located. The US study by Staudt et al.[233] randomised 10 participants (50.0% male, mean age 40.2 ± 9.7 (SD)) to either ENDS (seven participants) or ENNDS (three participants). The study found no consistent short-term (measurement within two hours of exposure) changes in lung function for participants using e-cigarettes with or without nicotine.

Kerr et al. randomly assigned 20 healthy Scottish male smokers, mean age of 31.6 ± 10.5 (SD) years, to a second-generation ENDS device (18mg/mL) and their own tobacco cigarettes.[235] There was no statistically significant change in FEV_1, FVC or FEV_1/FVC for both tobacco cigarettes and ENDS 25 minutes after exposure. PEF significantly decreased for ENDS (p=0.019), but not tobacco cigarettes

(p>0.05) 25 minutes after exposure. Three minutes following exposure, exhaled carbon monoxide significantly increased (p<0.001) for tobacco cigarette use, whereas it reduced for ENDS (p=0.007).

The Swedish study by Antoniewicz et al. randomly assigned 15 healthy occasional tobacco smokers, nine females and six males, mean age of 26 ± 3 (SD) years, to both 19mg/mL ENDS and ENNDS.[211]. Using impulse oscillometry, flow resistance at all frequencies increased 30 minutes after exposure to ENDS. No changes in flow reactance (a measure of the elastic properties of lungs and the obstruction of smaller airways) and resistance in peripheral airways were observed for either exposure. FeNO was significantly increased two hours after exposure to both ENDS and ENNDS. Vital capacity decreased after exposure to both e-cigarettes and there was no significant change in FEV_1.

Chaumont et al. was a Belgian randomised crossover study in 25 healthy occasional tobacco smokers although only nine completed the pulmonary assessments.[290] Demographic details were not provided for these nine participants. Participants completed two sessions in random order: one using a fourth-generation ENNDS device (25 puffs, one every 30 seconds) and another using a 3mg/mL ENDS device which was turned off (sham). Compared to baseline there was a statistically significant decrease in FEV_1, FEV_1/FVC, $FEF_{50\%}$, $FEF_{25\%}$, and forced mid-expiratory flow rate ($FEF_{25-75\%}$) for ENNDS, measured five-ten minutes after exposure.

All four studies were assessed as moderate quality, and there were no conflicts of interest reported.

Cohort studies

One prospective cohort study in non-smokers was located. Polosa et al.[223] recruited adult (≥18 years of age) daily e-cigarette users who were regular customers at specified e-cigarette retailers in Italy. Only users of e-cigarettes for three months or greater, who had never smoked, or smoked less than 100 cigarettes in their lifetime, were included. The control group was age- and sex-matched hospital staff who had never smoked and were not using e-cigarettes. There were 21 participants (nine e-cigarette users and 12 controls) in the sample. In the e-cigarette group, there were six males and three females, and the mean age was 26.6 ± 6.0 (SD) years. In the control group, there were eight males and four females and the mean age was 27.8 ± 5.2 (SD) years. A range of e-cigarette devices were used and the e-liquid nicotine concentration ranged from 0% to 1.8%.

Three broad outcomes were assessed at three follow-up points in the study: 12 ± 1 month after baseline, 24 ± 2 months after baseline and 42 ± 2 months after baseline. No significant differences between e-cigarette users and non-users were observed for lung function (FEV_1, FVC, $FEF_{25-75\%}$) and airway inflammation (exhaled nitric oxide and carbon monoxide). High-resolution computed tomography in eight e-cigarette users did not reveal any pathological findings at 42 months.

The study was assessed as moderate quality. One study author reported a potential conflict of interest.

Non-randomised intervention studies

Four non-randomised intervention studies were located, two in non-smoker populations and two in smokers (Table 4.6.2).

Brożek et al.[365], a Polish laboratory pre-post-post intervention study in non-smokers, used data from the YoUng People E-smoking Study (YUPESS). There were 120 participants, broken up into four equal groups: exclusive e-cigarette users, dual users, exclusive cigarette smokers and a non-smoker control group. Fifty-nine percent of the sample was male and the mean age was 22.6 ± 2.2 (SD) years. The e-cigarette and dual user groups were asked to use their own e-cigarettes in accordance with their everyday habits for five minutes, although every e-cigarette was filled with 12mg/mL nicotine. Participants in the smoking group were asked to smoke a popular brand cigarette (0.6mg nicotine per cigarette) according to their everyday habits, whilst the control group simulated the use of an e-cigarette device which did not contain e-liquid.

Acute respiratory responses (FeNO and FeCO, exhaled air temperature and spirometry (FVC, FEV_1/FVC, PEF, $MEF_{75,50,25}$)) were measured before exposure, one minute after exposure and 30 minutes after exposure to e-cigarettes and cigarettes. The study reported a statistically significant decrease (p<0.05) in MEF_{25} for all three intervention groups compared with the control group at the first minute. There was no statistically significant difference in any spirometric measure at minute 30 compared to baseline. FeNO concentration decreased significantly (p=0.0002) in the three intervention groups at minute one compared to baseline, however it returned to baseline at minute 30.

Coppeta et al.[291], an Italian-based pre-post laboratory study, recruited 30 healthy non-smokers (17 males and 13 females) with a mean age of 32.6 ± 2.75 (SD) years. For five minutes, participants used an e-

cigarette (15 puffs of an 18mg/mL nicotine e-cigarette) on day one and a tobacco cigarette (0.6mg nicotine) on day two with spirometric (FVC, FEV_1, FEV_1/FVC, $FEF_{25,75,25-75}$) measurements taken before exposure and at one and 15 minutes after exposure. There was a significant decrease in FEV_1 one minute after e-cigarette exposure (3.55 to 3.51; p=0.03), but not after 15 minutes (3.55 to 3.53; p=0.36). After one minute there was a significant decrease in the FEV_1/FVC ratio (82.1 to 81.6; p=0.01) and FEF_{25-75} (3.44 to 3.3; p<0.01). A persistent decline was seen at 15 minutes for FEF_{25-75} (3.44 to 3.35; p=0.03), but not for the FEV_1/FVC ratio (82.1 to 81.5; p=0.39).

Kotoulas et al.[366], a Greek pre-post intervention study, measured short-term respiratory effects after ENDS (11mg nicotine) use in 25 mildly asthmatic and 25 healthy smokers (42.0% male, mean age asthmatics: 40.6 ± 10.8 (SD) years; mean age healthy: 39.9 ± 10.2 (SD)). At 15-minute follow-up, PEF and FEV_1/FVC significantly decreased and respiratory impedance at 5Hz significantly increased in asthmatics, but not in controls. Respiratory resistance significantly increased at 15-miute follow-up in both groups at all resistances, except for 5Hz in asthmatics. FeNO significantly increased in asthmatics and significantly decreased in controls 30 minutes after exposure.

Lappas et al.[292], also a pre-post intervention study from Greece using healthy (n=27) and asthmatic (n=27) smokers, 61.1% male, mean age 23.0 ± 3.2 (SD) years, measured the short-term respiratory effects of using 12mg/mL ENDS for five minutes. Compared to baseline, respiratory impedance at 5Hz, respiratory resistance at 5Hz, 10Hz and 20Hz, resonant frequency and reactance area, significantly increased and reactance at 20Hz significantly decreased immediately after use for all participants. There were no significant changes from baseline in any parameters at 15 and 30-minute follow-up. FeNO significantly decreased in both groups immediately after use then returned to baseline levels after 30 minutes, and there was no significant difference between groups.

Two studies were moderate[291,365] and two were high quality[292,366]. There were no conflicts of interest declared in three[291,292,365] and one[366] did not provide a conflict of interest statement.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to intermediate respiratory outcomes were located.

Other study types not considered in the assessment of likely causality
No case reports or case series reporting on the relationship of e-cigarette use to intermediate respiratory outcomes were located.

There were two cross-sectional surveys[298,306] identified which reported an association between e-cigarette use and subclinical respiratory outcomes. In keeping with the protocol of this systematic review, the results of these studies will not be presented.

Other respiratory measures

Meta-analyses
No meta-analyses of the relationship of e-cigarette use to other respiratory measures were located.

Randomised controlled trials
No randomised controlled trials reporting on the relationship of e-cigarette use to other respiratory measures were located.

Cohort studies
No cohort studies of the relationship of e-cigarette use to other respiratory measures were located.

Non-randomised intervention studies
No non-randomised intervention studies reporting on the relationship of e-cigarette use to other respiratory measures were located.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to other respiratory measures were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to respiratory health risk
No case reports or case series reporting on the relationship of e-cigarette use to other respiratory measures were located.

There were five cross-sectional surveys[300,304,310,380,381] which reported an association between e-cigarette use and other respiratory measures. In keeping with the protocol of this systematic review, the results of these studies will not be presented.

4.6.4 Summary of findings from top-up review

There were two cohort studies, 18 surveillance reports, seven case series and eight case reports with evidence on clinical respiratory outcomes used in evidence synthesis, finding:

- Former and current e-cigarette users were significantly more likely to report respiratory disease (COPD, chronic bronchitis, emphysema, asthma) at three-year follow-up compared to never e-cigarette users in one large cohort study. Within e-cigarette users, between 0.6%-35.6% were never smokers, 13.9%-50.2% were former smokers and 14.2%-85.5% were current smokers. Hence, there is:
    - Insufficient evidence on the relationship of ENDS use to clinical respiratory outcomes including asthma, bronchitis and COPD in smokers, and no available evidence in non-smokers.
- E-cigarette use was a significant predictor for COPD exacerbations in current or former adult smokers. Compared to never e-cigarette users, there was no statistical difference in COPD progression, or decline in lung function, and a statistically significant increase in chronic bronchitis prevalence. Hence, there is:
    - Insufficient evidence on the relationship of e-cigarette use to COPD exacerbations and COPD progression in smokers, and no available evidence in non-smokers.
- Evidence from 18 national and state-based reports in the United States of acute and severe lung injury (EVALI) in both smokers and non-smokers. The most recent published data included in this review (January 2020), reported 2,668 hospitalised cases, although more recent US data from the CDC website (February 2020) included 2,807 hospitalised cases (68 deaths). Young males (18-24 years of age) have the highest representation. Reports largely related to the use of products containing THC (and the additive vitamin E acetate, identified in many, but not all THC-containing products), although 14% of cases reported exclusive use of nicotine-only products.
- Evidence from eight case reports that e-cigarette use is associated with a range of respiratory diseases (confirmed and probable cases of EVALI, diffuse alveolar haemorrhage, acute respiratory distress syndrome, acute respiratory failure, and hypersensitivity pneumonitis).
- Evidence from seven case series that the use of e-cigarettes is associated with a range of respiratory diseases (confirmed and probable cases of EVALI, organising pneumonia, acute lung injury).
- Case reports and case series are useful for describing rare and atypical events, particularly those where a direct relationship between cause and effect is clear. In the context where no other cause of the lung injury is apparent they are considered appropriate evidence for our conclusions.
- Hence, there is:
    - Conclusive evidence from surveillance reports, case reports and case series that the use of e-cigarettes is related to severe lung injury (EVALI) in smokers and non-smokers. Current evidence is that this lung injury is largely related to e-cigarettes delivering THC (and the additive vitamin E acetate, identified in many, but not all THC-containing products), and 14% of cases were in patients reporting the use of nicotine-delivering products only, indicating that these products can cause EVALI.

There were four randomised controlled trials, one cohort study, and five non-randomised intervention studies with evidence on subclinical respiratory outcomes finding:

- Among non-smokers, at one-minute follow-up, there was a significant decrease in three spirometry parameters after ENDS exposure in two separate non-randomised intervention studies. There was a significant decrease in one parameter at 15-minute follow-up in one small non-randomised intervention study, no difference in any parameters at 30-minute follow-up in another small non-randomised intervention study, and no change in spirometry two hours after exposure to ENDS and ENNDS in one very small randomised controlled trial.
- Among smokers, there was a significant decrease in five spirometry parameters, five-ten minutes after ENNDS use in one very small randomised controlled trial and a significant decrease in two parameters in asthmatic smokers, but not healthy smokers at 15-minutes after ENDS use in one very small non-randomised intervention study. At 25-minutes after ENDS use, there was a significant decrease in one and no change in three spirometry parameters in one very small randomised controlled trial. Two very small non-randomised intervention studies in healthy and

asthmatic smokers found a significant increase in respiratory impedance, resistance, resonant frequency, and reactance area in both groups immediately after use in one study and a significant increase in respiratory resistance for both groups and a significant increase in respiratory impedance for asthmatic smokers at 15-minute follow-up in the other study. There were no changes in any parameters at 30-minutes post-exposure. In one very small randomised controlled trial in smokers, there was a significant increase in flow resistance, and no change in flow reactance or resistance in peripheral airways 30 minutes after ENDS use.

- E-cigarette use was not associated with long-term (3.5-year follow-up) changes in lung function in one very small cohort study.
- Hence, there is:
    - Limited evidence in non-smokers and insufficient evidence in smokers that e-cigarettes have acute (up to two hours post-exposure) effects on spirometry parameters.
    - Limited evidence that e-cigarette use increases respiratory resistance and impedance in healthy and asthmatic smokers up to 30 minutes post-exposure.
- Among non-smokers, FeNO significantly decreased at one-minute follow-up then returned to baseline at 30-minute-follow-up in one small non-randomised intervention study.
- In two very small non-randomised intervention studies comparing healthy and asthmatic smokers, FeNO significantly decreased in both groups immediately after use and returned to baseline levels after 30 minutes in one trial, and significantly increased for asthmatic smokers and significantly decreased for healthy smokers at 30-minute follow-up in the other. At two-hour follow-up, FeNO significantly increased after ENNDS and ENDS use in one small randomised controlled trial.
- E-cigarette use was not associated with long-term (3.5-year follow-up) changes in exhaled breath in one very small cohort study.
- Hence, there is:
    - Insufficient evidence on the effect of e-cigarettes on exhaled breath outcomes among healthy and asthmatic smokers and non-smokers.

4.6.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence on clinical outcomes from the top-up systematic review with the evidence from the previous reviews:

- There were four cohort studies, 18 surveillance reports, seven case series and nine case reports with evidence on clinical respiratory outcomes:
- Compared to never-users, former and current e-cigarette users were more likely to report respiratory disease. Among adult smokers with COPD, e-cigarette use positively predicted COPD exacerbations and increased the frequency of chronic bronchitis, however it did not impact COPD progression. In smokers with COPD or asthma switching to e-cigarettes, there was no difference in asthma exacerbations, a decrease in COPD exacerbations, and a downgrading of COPD severity. Hence, there was:
    - Insufficient evidence on the relationship of e-cigarette use to other clinical respiratory outcomes, including asthma, bronchitis and COPD in smokers and no available evidence in non-smokers.
    - Insufficient evidence for a reduction in respiratory exacerbations and disease progression among adult healthy, asthmatic and COPD smokers who switch to exclusive or dual-use of e-cigarettes.
- Evidence from surveillance reports, case series and case reports indicated a clear association of e-cigarettes with respiratory disease (EVALI) among smokers and non-smokers. EVALI prevalence in the United States increased from 215 cases in August 2019 to 2,668 cases in January 2020, with young males aged 18-24 years having the highest representation. Reports largely related to the use of products containing THC (and the additive vitamin E acetate, identified in many, but not all THC-containing products), although cases with exclusive use of nicotine-only products were recorded. Hence, there was:
    - Conclusive evidence from surveillance reports, case reports and case series that the use of e-cigarettes is related to respiratory disease (EVALI) among smokers and non-smokers. There is substantial evidence that this lung injury is largely related to e-cigarettes delivering THC (and the additive vitamin E acetate, identified in many, but not all THC-containing products), although 14% of cases were in patients reporting the use of

nicotine-delivering products only, so a causal effect of these products cannot be excluded.

- The GRADE rating for evidence on clinical respiratory outcomes was very low for non-randomised intervention studies (surveillance reports, case series and case reports not included). There were no randomised controlled trials on clinical outcomes.

Combining evidence on subclinical outcomes from the top-up systematic review with the evidence from the previous reviews:

- There were nine randomised controlled trials, four cohort studies, and eight non-randomised intervention studies with evidence on subclinical respiratory outcomes.
- There were changes in one or more lung function parameters, respiratory resistance measures and exhaled breath less than 30 minutes after e-cigarette exposure with some reports of changes a few minutes or 30 minutes post-exposure. Hence, there was:
    - Limited evidence in non-smokers and insufficient evidence in smokers that e-cigarettes have acute (up to two hours post-exposure) effects on spirometry parameters.
    - Limited evidence that e-cigarette use increases respiratory resistance and impedance in healthy and asthmatic smokers up to 30 minutes post-exposure.
    - Insufficient evidence on the effect of e-cigarettes on exhaled breath outcomes among healthy and asthmatic smokers and non-smokers.
- The GRADE rating for evidence on subclinical respiratory outcomes was very low for both randomised and non-randomised evidence.

Combining evidence on other respiratory outcomes from the top-up systematic review with the evidence from the previous reviews:

- There was one randomised controlled trial and one cohort study with evidence on other respiratory measures.
- Among smokers, there were improvements in asthma outcomes and airway hyperresponsiveness in asthmatic smokers after using e-cigarettes (exclusive and dual use) and a reduction in sinonasal symptoms after ENDS use. Hence, there was:
    - Insufficient evidence on the relationship of e-cigarette use to other respiratory measures (sinonasal symptoms, airway hyperresponsiveness) in smokers and no available evidence in non-smokers.
- GRADE was not applied to other respiratory outcomes.

4.6.6 Main conclusions from the synthesised evidence on the respiratory health effects of e-cigarettes

- There is conclusive evidence that the use of e-cigarettes can cause respiratory disease (EVALI) among smokers and non-smokers. Current evidence from the largest study to date is that this lung injury is chiefly related to e-cigarettes delivering THC, with half of cases related to THC in conjunction with vitamin E acetate, and 14% being in patients reporting the use of nicotine-delivering products only, indicating that the latter products can cause EVALI.
- There is insufficient evidence on the relationship of e-cigarette use to other clinical respiratory outcomes, including asthma, bronchitis and COPD in smokers and no available evidence in non-smokers.
- There is insufficient evidence for a reduction in respiratory exacerbations and disease progression among adult healthy, asthmatic and COPD smokers who switch to exclusive or dual-use of e-cigarettes.

- There is limited evidence in non-smokers and insufficient evidence in smokers that e-cigarettes have acute (up to two hours post-exposure) effects on spirometry parameters.
- There is limited evidence that e-cigarette use increases respiratory resistance and impedance in healthy and asthmatic smokers up to 30 minutes post-exposure.
- There is insufficient evidence on the effect of e-cigarettes on exhaled breath outcomes among smokers and non-smokers (healthy and asthmatic).
- There is insufficient evidence on the relationship of e-cigarette use to other respiratory measures (sinonasal symptoms, airway hyperresponsiveness) in smokers and no available evidence in non-smokers.

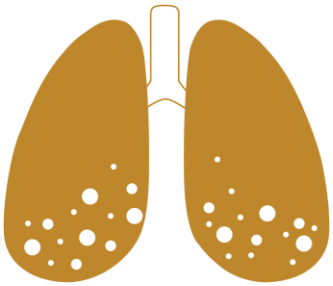


Table 4.6-2. Study details: respiratory health outcomes – randomised controlled trials, cohort studies and non-randomised intervention studies

Study details (author, year, location, study type, time frame, [data source])	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflict of interest, funding
Randomised controlled trials					
Antoniewicz et al., 2019[211] Sweden Randomised, double-blinded, crossover study Study date not reported Laboratory study	Study size 15 participants Sample Occasional users of tobacco products (max 10 cigarettes/ month), healthy Gender - n (%) Male: 6 (40) Female: 9 (60) Age - mean (SD) years 26 (3)	Intervention 1 ENDS: 19mg/mL nicotine Intervention 2 ENNDS: 0mg/mL nicotine Comparator Before session Materials Variable mod third generation e-cigarette with e-liquid base primarily 49.4% propylene glycol, 44.4% vegetable glycerin, 5% ethanol, without any added flavourings Pattern of exposure 30 puffs from ENDS for 30 min, each puff lasting approximately three seconds; measurements up to 6h	Impulse oscillometry Flow resistance at 5Hz/11Hz/13Hz/17Hz/19Hz (R5/11/13/17/19) Reactance at 5Hz (X5) Difference of R5Hz and R19Hz (R5-19Hz) Spirometry Reactance area (AX) Resonance frequency (fres) Vital capacity (VC) Forced expiratory volume in one second (FEV_1) Fractional exhaled nitric oxide (FeNO)	Impulse oscillometry Baseline / 0.5h / 2h / 4h / 6h R5 Hz – p_{time} = 0.001; $p_{time \times exposure}$ = 0.003 ENDS: 3.57 ± 0.73 / 3.85 ± 0.93 / 3.27 ± 0.88 / 3.24 ± 0.66 / 3.32 ± 0.80 ENNDS: 3.41 ± 0.75 / 3.26 ± 0.70 / 3.15 ± 0.64 / 3.30 ± 0.73 / 3.23 ± 0.72 R11 Hz – p_{time} = 0.002; $p_{time \times exposure}$ < 0.001 ENDS: 3.19 ± 0.55 / 3.52 ± 0.74* / 3.02 ± 0.72 / 2.96 ± 0.54 / 3.05 ± 0.67 ENNDS: 3.09 ± 0.67 / 2.95 ± 0.61 / 2.92 ± 0.51 / 3.02 ± 0.65 / 2.95 ± 0.63 R13 Hz – p_{time} = 0.002; $p_{time \times exposure}$ = 0.003 ENDS: 3.18 ± 0.55 / 3.51 ± 0.77* / 3.03 ± 0.70 / 2.96 ± 0.53 / 3.03 ± 0.64 ENNDS: 3.07 ± 0.67 / 2.94 ± 0.60 / 2.92 ± 0.53 / 3.01 ± 0.65 / 2.94 ± 0.64 R17 Hz – p_{time} = 0.002; $p_{time \times exposure}$ = 0.010 ENDS: 3.18 ± 0.55 / 3.48 ± 0.75* / 3.03 ± 0.66 / 2.96 ± 0.53 / 3.03 ± 0.61 ENNDS: 3.05 ± 0.68 / 2.97 ± 0.61 / 2.91 ± 0.57 / 3.00 ± 0.69 / 2.95 ± 0.65 R19 Hz – p_{time} = 0.004; $p_{time \times exposure}$ = 0.002 ENDS: 3.23 ± 0.55 / 3.55 ± 0.74* / 3.13 ± 0.67 / 3.04 ± 0.56 / 3.10 ± 0.61 ENNDS: 3.09 ± 0.69 / 3.04 ± 0.64 / 2.94 ± 0.58 / 3.06 ± 0.71 / 3.05 ± 0.68 X5 Hz – p_{time} = 0.057; $p_{time \times exposure}$ = 0890 ENDS: − 0.91 ± 0.29 / − 0.85 ± 0.28 / − 0.83 ± 0.31 / − 0.81 ± 0.30 / − 0.82 ± 0.35 ENNDS: − 0.92 ± 0.32 / − 0.85 ± 0.30 / − 0.81 ± 0.33 / − 0.82 ± 0.3 / − 0.81 ± 0.28 R5-R19 Hz – p_{time} = 0.058; $p_{time \times exposure}$ = 0.314	Moderate methodological quality Very small study size Conflicts of interest None declared Funding Supported by the Swedish Heart and Lung Association, the Swedish Society of Medicine, the Swedish Heart–Lung Foundation and Stockholm County Council

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame, [data source])	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflict of interest, funding
		following exposure		ENDS 0.34 ± 0.42; 0.30 ± 0.43; 0.14 ± 0.34; 0.20 ± 0.49; 0.22 ± 0.35 ENNDS 0.32 ± 0.41; 0.22 ± 0.29; 0.22 ± 0.37; 0.24 ± 0.47; 0.18 ± 0.26 Spirometry Baseline; 0.5h; 2h; 4h; 6h AX – p_{time} = 0.155; $p_{time \times exposure}$ = 0.281 ENDS 3.48 ± 2.41; 3.27 ± 2.15; 2.70 ± 2.19; 2.87 ± 2.56; 3.02 ± 2.40 ENNDS 3.64 ± 2.64; 3.03 ± 1.67; 2.90 ± 1.89; 4.27 ± 3.85; 2.57 ± 1.37 Fres – p_{time} = 0.018; $p_{time \times exposure}$ = 0.042 ENDS 12.28 ± 3.97; 12.06 ± 3.18; 10.86 ± 2.57; 11.20 ± 3.19; 11.73 ± 3.36 ENNDS 12.44 ± 3.66; 11.70 ± 2.70; 11.54 ± 2.99; 11.92 ± 3.35; 11.06 ± 2.19* VC – p_{time} = 0.020; $p_{time \times exposure}$ = 0.636 ENDS 5.01 ± 1.23; 4.92 ± 1.18†; 4.94 ± 1.22†; 4.96 ± 1.18; 4.96 ± 1.19 ENNDS 5.02 ± 1.21; 4.98 ± 1.21†; 4.96 ± 1.20†; 5.00 ± 1.20; 4.97 ± 1.20 FEV_1 – p_{time} = 0.0096; $p_{time \times exposure}$ = 0.788 ENDS 3.82 ± 0.76; 3.84 ± 0.79; 3.86 ± 0.82; 3.85 ± 0.81; 3.87 ± 0.80 ENNDS 3.86 ± 0.76; 3.86 ± 0.78; 3.90 ± 0.77; 3.90 ± 0.77; 3.89 ± 0.80 Fractional exhaled nitric oxide Baseline; 0.5h; 2h; 4h; 6h FeNO – p_{time} = 0.00; $p_{time \times exposure}$ = 0.002 ENDS 12.36 ± 2.87; 12.00 ± 3.55; 13.91 ± 3.21†; 13.09 ± 3.36; 11.36 ± 2.98 ENNDS 11.82 ± 3.87; 12.91 ± 4.04; 12.91 ± 4.01†; 12.18 ± 3.25; 11.27 ± 3.77	

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame, [data source])	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflict of interest, funding
				*Denotes significant change from baseline due to exposure (contrast for time × exposure) †Denotes significant change from baseline, not influenced by exposure (contrast for time)	
Kerr et al., 2019[235] UK Single-centre, prospective, randomised crossover study June-December 2016 Laboratory study	Study size 20 participants Sample Habitual tobacco smokers of one or more tobacco cigarettes per day Gender (%) Male: 100 Age - mean (SD) years 31.6 ± 10.5	Intervention 1 ENDS: 18mg/mL nicotine, tobacco flavoured Intervention 2 Conventional cigarette Comparator Before session Materials ENDS: SmokeMax, second generation; variable voltage rechargeable Conventional cigarette: own type Pattern of exposure 15 puffs	Spirometry Forced expiratory volume in one second (FEV_1) (l) Forced vital capacity (FVC) (l) FEV_1/FVC: Tiffeneau-Pinelli index (%) Peak expiratory flow (PEF) (l/min) Exhaled breath Carbon monoxide (CO) (ppm)	Spirometry and exhaled breath Pre / Post / Change / P-value FEV_1 ENDS 4.2 ± 0.6 / 4.1 ± 0.7 / -0.1 ± 0.2 / 0.132(a) Cigarette 4.3 ± 0.7 / 4.2 ± 0.6 / 0.0 ± 0.2 / 0.373(a) FVC ENDS 5.2 ± 0.7 / 5.1 ± 0.7 / -0.1 ± 0.3 / 0.433(b) Cigarette 5.3 ± 0.9 / 5.2 ± 0.8 / 0.0 ± 0.3 / 0.723(b) FEV_1/FVC ENDS 81.1 ± 6.8 / 80.9 ± 7.3 / -0.2 ± 2.0 / 0.629(b) Cigarette 81.3 ± 7.0 / 81.0 ± 7.2 / -0.3 ± 4.8 / 0.501(b) PEF ENDS 562 ± 62 / 531 ± 96 / -31 ± 54 / 0.019(a) Cigarette 567 ± 72 / 545 ± 81 / -22 ± 53 / 0.074(a) CO ENDS 9 ± 10 / 7 ± 7 / -2 ± 3 / 0.007(b) Cigarette 9 ± 10 / 20 ± 10 / 11 ± 2 / <0.001(b) P-values derived from: a) paired t-test b) related-samples Wilcoxon signed ranked test	Moderate methodological quality Very small study size Conflicts of interest None declared Funding Authors supported by British Heart Foundation Centre of Research Excellence

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Chaumont et al., 2018[290]

Belgium

Randomised, single-blinded, crossover study

2017

Laboratory study

Study size
25 participants in whole study. 9 in pulmonary testing

Sample
Healthy occasional tobacco smokers (not smoke >20 combustible cigarettes per week)

Gender
Not reported for subset of 9

Age – mean (SD) years
Not reported for subset of 9

Intervention 1
ENNDS session

Intervention 2
Sham 3mg/mL ENDS control session (device turned off)

Comparator
Before session

Materials
Fourth-generation ENNDS (50:50 PG/GLY, Alien 220 box mod, TFV8 baby beast tank)

Pattern of exposure
25 puffs – one every 30s (inhale for 4s, hold for 4s, exhale). Each session separated by minimum 1 week washout. Measurements within 5-10 minutes of exposure

Spirometry
Forced expiratory volume in one second (FEV_1) (l)

FEV_1/FVC: Tiffeneau-Pinelli index (%)

Peak expiratory flow (PEF) (l/s)

Forced expiratory flow at 75%, 50%, 25% of FVC (FEF) (l/s)
Forced expiratory flow between 25%-75% of FVC (FEF_{25-75}) (l/s)
Airway total resistance (ATR) (cm H_2O l^{-1} s^{-1})

Intrathoracic gas volume (IGV) (l)

Total lung capacity (TLC) (l)

Residual volume (RV) (l)

Residual volume/total lung capacity (RV/TLC) (%)

Spirometry

		Sham Vaping	p-value	ENNDS	p-value
FEV_1	Before	4.5 (4–4.6)	0.592	4.4 (4.2–4.6)	0.021
	After	4.2 (4–4.6)		4.3 (3.9–4.6)	
FEV_1/FVC	Before	82.2 (77.5–84.1)	0.79	83.5 (76.3–85.7)	0.002
	After	82 (77.7–84.8)		81 (74–82.6)	
PEF	Before	7.8 (7.4–9.8)	0.538	8.5 (7.2–9.3)	0.633
	After	9.2 (7.4–9.9)		7.85 (7–9.8)	
$FEF_{75\%}$	Before	6.9 (6.1–8.6)	0.522	7.2 (6.1–8.8)	0.112
	After	7.1 (5.5–8.8)		6.9 (5.9–8.2)	
$FEF_{50\%}$	Before	5 (3.6–5.4)	0.588	4.8 (4–6.1	0.009
	After	4.8 (3.6–5.1)		4.2 (3.7–5.5)	
$FEF_{25\%}$	Before	2.2 (1.5–2.5)	0.764	2.5 (1.7–2.6)	0.002
	After	2.1 (1.6–2.5)		2 (1.4–2.3)	
$FEF_{25-75\%}$	Before	4.5 (3.1–4.7)	0.545	4.2 (3.5–5.4)	0.003
	After	4.2 (3.1–4.6)		3.7 (3.1–4.9)	
ATR	Before	3.75 (3.2–5)	0.661	4 (3.35–4.5)	0.089
	After	3.9 (3.4–4.5)		4.5 (3.8–5.9)	
IGV	Before	3.2 (2.9–4)	0.943	3.5 (2.7–4)	0.486
	After	3.5 (3–3.8)		3.1 (2.7–3.7)	
TLC	Before	6.9 (6.2–8)	0.649	6.7 (6.2–7.9)	0.517
	After	6.9 (6.2–8)		6.6 (5.9–7.7)	
RV	Before	1.5 (1.1–2.4)	0.57	1.4 (1.2–2.5)	0.59
	After	1.8 (1.6–2.25)		1.5 (1.2–2.2)	
RV/TLC	Before	26 (19–30)	0.452	21 (19.5–31)	0.657
	After	27 (23.5–29.5)		23 (19.5–28)	
DL_{CO}	Before	32.65 (28.4–38.3)	0.401	34.1 (23.4–41)	0.398
	After	32.1(26.1–37.7)		30.7 (26.6–43.1)	

Values are medians (interquartile ranges)

Moderate methodological quality

Very small study size

Conflicts of interest
None declared

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Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type, time frame, [data source])</th><th>Sample characteristics</th><th>Intervention and control</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflict of interest, funding</th></tr>
<tr><td></td><td></td><td></td><td>Diffusion capacity of carbon monoxide (DL_{CO}) (mL min^{-1} $mmHg^{-1}$)</td><td></td><td></td></tr>
<tr><td>Staudt et al., 2018[233]

US

Randomised (unequal), before-and-after study

Study date not reported

Weill Cornell Medical College Clinical Translational and Science Center and the Department of Genetic Medicine Clinical Research Facility</td><td><u>Study size</u>
10 participants

<u>Sample</u>
Never smokers, self-reported history and confirmed by absence of tobacco metabolites in urine

<u>Gender (%)</u>
Male: 100

<u>Age – mean (SD) years</u>
31.6 ± 10.5</td><td><u>Intervention 1 (n=7)</u>
ENDS: nicotine concentration unknown

<u>Intervention 2 (n=3)</u>
ENNDS

<u>Comparator</u>
Before session

<u>Materials</u>
Blu branded ENDS and ENNDS

<u>Pattern of exposure</u>
10 puffs, 30 minutes rest, 10 puffs. Assessed 1 week after session</td><td><u>Spirometry</u>
Forced vital capacity (FVC)

Forced expiratory volume in one second (FEV_1)

FEV_1/FVC: Tiffeneau-Pinelli index

Total lung capacity (TLC)

Diffusion capacity for carbon monoxide (DL_{CO})

O_2 saturation</td><td><u>Spirometry</u>
<table><tr><th></th><th colspan="2">ENDS</th><th colspan="2">ENNDS</th></tr><tr><th></th><th>Baseline</th><th>Post</th><th>Baseline</th><th>Post</th></tr><tr><td>FVC (% predicted)</td><td>112 ± 16</td><td>112 ± 11</td><td>105 ± 6</td><td>98.3 ± 12</td></tr><tr><td>FEV_1 (% predicted)</td><td>112 ± 15</td><td>113 ± 11</td><td>103 ± 9</td><td>91 ± 8</td></tr><tr><td>FEV_1/FVC (% observed)</td><td>81 ± 3</td><td>83 ± 3</td><td>81 ± 4</td><td>76 ± 4</td></tr><tr><td>TLC (% predicted)</td><td>91 ± 11</td><td>92 ± 7</td><td>94 ± 13</td><td>91 ± 21</td></tr><tr><td>DL_{CO} (% predicted)</td><td>88 ± 10</td><td>85 ± 13</td><td>92 ± 9</td><td>87 ± 3</td></tr><tr><td>O_2 saturation</td><td>99 ± 1</td><td>99 ± 1</td><td>99 ± 2</td><td>98 ± 1</td></tr></table></td><td>Moderate methodological quality

Very small study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Supported by NIH and the Family Smoking Prevention and Tobacco Control Act</td></tr>
<tr><td colspan="6">Cohort studies</td></tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
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<tr>
<td>Bhatta & Glantz, 2020[28]

US

Nationally representative longitudinal study

2013-2016

PATH (Wave 1, 2 and 3)</td>
<td>Study size
32,320 participants at baseline

Sample
Current: ever used/smoked (fairly regularly) every day or some days
Former: ever used/smoked, but do not currently use/smoke
Never: never used/smoked

Gender (baseline) (%)
Male: 48.1
Female: 51.9

Age - mean (SD) at baseline (years)
18–24: 13.1%
25–34: 17.7%
35–44: 16.5%
45–54: 17.9%
55–64: 16.6%
65–74: 11.1%
≥75: 7.1%</td>
<td>Exposure 1 - EC
Current or former

Exposure 2 - smoker
Current or former

Note: EC and cigarette use were not exclusive, dual users are included in both populations

Comparator 1 - EC
Never EC or smoker

Materials - Device type
Not reported

Materials - Nicotine concentration
Not reported

Follow-up
1 and 2 years after baseline</td>
<td>Self-reported lung or respiratory disease
Chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma</td>
<td>Incident respiratory disease at wave 2 or 3 excluding people with respiratory disease at wave 1
<table>
<tr><th></th><th colspan="2">ENDS</th><th colspan="2">Smoker</th></tr>
<tr><th></th><th>AOR (95% CI)</th><th>P-value</th><th>AOR (95% CI)</th><th>P-value</th></tr>
<tr><td>Former</td><td>1.31 (1.07-1.60)</td><td>0.009</td><td>1.16 (0.87-1.57)</td><td>0.315</td></tr>
<tr><td>Current</td><td>1.29 (1.03-1.61)</td><td>0.026</td><td>2.56 (1.92-3.41)</td><td><0.001</td></tr>
</table>
Incident respiratory disease at wave 2 or 3 excluding people with respiratory disease at wave 1
<table>
<tr><th></th><th colspan="2">ENDS</th><th colspan="2">Smoker</th></tr>
<tr><th></th><th>AOR (95% CI)</th><th>P-value</th><th>AOR (95% CI)</th><th>P-value</th></tr>
<tr><td>COPD</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Former</td><td>1.82 (1.23-2.69)</td><td>0.004</td><td>1.47 (0.42-5.20)</td><td>0.550</td></tr>
<tr><td>Current</td><td>1.44 (0.79-2.62)</td><td>0.237</td><td>5.79 (1.64-20.44)</td><td>0.008</td></tr>
<tr><td>Chronic bronchitis</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Former</td><td>1.43 (1.02-2.00)</td><td>0.039</td><td>0.95 (0.56-1.59)</td><td>0.844</td></tr>
<tr><td>Current</td><td>1.60 (1.13-2.27)</td><td>0.010</td><td>1.96 (1.23-3.12)</td><td>0.005</td></tr>
<tr><td>Emphysema</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Former</td><td>1.40 (0.9-2.83)</td><td>0.348</td><td>0.85 (0.21-3.42)</td><td>0.831</td></tr>
<tr><td>Current</td><td>1.60 (0.75-3.44)</td><td>0.229</td><td>3.66 (0.98-13.60)</td><td>0.056</td></tr>
<tr><td>Asthma</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Former</td><td>1.23 (0.90-1.69)</td><td>0.200</td><td>0.87 (0.53-1.42)</td><td>0.575</td></tr>
<tr><td>Current</td><td>1.56 (1.10-2.22)</td><td>0.015</td><td>1.57 (1.02-2.42)</td><td>0.046</td></tr>
</table>
Referent: never users/smokers
Controlled for combustible tobacco smoking (former and current), age, BMI, sex, poverty level, race/ethnicity, and clinical variables at Wave 1</td>
<td>Moderate methodological quality

Large study size

Conflicts of interest
None declared

Funding
None</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame, [data source])	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflict of interest, funding
Bowler et al., 2017[295] US Prospective cohort study 2011-2016 Two longitudinal studies: COPDGene and SPIROMICS	Study size 4595 participants; COPDGene: 3,535 SPIROMICS: 1,060 Sample Adults (45-80 years) who are current or former smokers Gender – male (%) COPDGene Never: 51 Current: 41 Former: 43 SPIROMICS Never: 54 Current: 55 Former: 44 Age range (years) 45-80	Exposure Ever ENDS use Comparator Non-users Materials – Device type No details Materials - Nicotine concentration No details Follow-up 5 years	COPD exacerbations COPD progression (GOLD criteria) Lung function (spirometry) Adverse COPD outcomes	COPD exacerbations History of ever using e-cigarettes was significantly predictive of COPD exacerbations in COPDGene (p=0.01) after adjustment. SPIROMICS: ever using e-cigarettes was associated with reported exacerbations in the year prior to enrolment (p=0.04). COPD progression COPDGene: ever e-cigarette users were more likely to have progression of lung disease (defined by worsening of GOLD stage) after 5 years (p<0.001) than never users. Non-significant after adjustment. Lung function COPDGene: ever e-cigarette users were more likely to have a more rapid decline in lung function (FEV_1) than never users (43mL/year vs. 34mL/year; p=0.003). Non-significant after adjustment. Adverse COPD outcomes Ever using e-cigarettes was associated with 8 ± 2% increased prevalence of chronic bronchitis, after adjustment (p<0.001).	Moderate methodological quality Large study size Conflicts of interest None declared Funding SPIROMICS: supported by contracts from the NIH/NHLBI, supplemented by Foundation for the NIH COPDGene: supported by National Heart, Lung, and Blood Institute and COPD Foundation Both contributions from pharmaceutical companies

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame, [data source])	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflict of interest, funding
Polosa et al., 2017[223] Italy Prospective cohort study 2013-2017 Online survey, regular vape shop customers	Study size 31 never smokers enrolled, 21 included in analysis Sample Never smokers or <100 cigarettes smoked in lifetime, daily EC users for ≥3 months Gender – n (%) Male: 21 (67.7) Female: 10 (32.3) Age - mean (SD) years ENDS: 29.7 (6.1) Control: 32.5 (7.0)	Exposure (n=9) Daily e-liquid consumption (median SD): 4.0mL (2-5) Comparator (n=12) Non-smoker and non-EC user Materials - Device type Advanced refillable: 44% Standard refillable: 56% Materials - Nicotine concentration (%) 0%: 33 0.9%: 22 1.2%: 22 1.6%: 11 1.8%: 11 Follow-up Follow-up at 12, 24 and 42 months	Spirometry Forced expiratory volume in one second (FEV_1) (l) Forced vital capacity (FVC) (l) FEV_1/FVC: Tiffeneau-Pinelli index (%) Maximum mid-expiratory flow ($FEF_{25-75\%}$) (l/min) Exhaled air Carbon monoxide (eCO) (ppm) Fractional exhaled nitric oxide (FeNO) (ppb) High-resolution computed tomography (HRCT)	Spirometry and exhaled air at three follow-up visits FEV_1 (mean ± SD) - p=0.30 ENDS: Baseline 3.8 ± 0.8; FU1 3.8 ± 0.8; FU2 3.8 ± 0.7; FU3 3.9 ± 0.8 Control: Baseline 4.1 ± 0.3; FU1 4.1 ± 0.3; FU2 4.0 ± 0.3; FU3 4.1 ± 0.3 FVC (mean ± SD) - p=0.61 ENDS: Baseline 4.9 ± 1.0; FU1 4.8 ± 0.8; FU2 4.8 ± 0.9; FU3 4.9 ± 0.8 Control: Baseline 5.0 ± 0.5; FU1 5.0 ± 0.4; FU2 5.0 ± 0.5; FU3 5.0 ± 0.4 FEV_1/FVC (mean ± SD) - p=0.09 ENDS: Baseline 78.5 ± 3.5; FU1 79.0 ± 3.6; FU2 78.5 ± 2.3; FU3 79.1 ± 2.8 Control: Baseline 81.5 ± 5.0; FU1 82.0 ± 4.7; FU2 80.9 ± 6.2; FU3 82.1 ± 4.3 $FEF_{25-75\%}$ (mean ± SD) - p=0.36 ENDS: Baseline 3.3 ± 0.7; FU1 3.3 ± 0.6; FU2 3.3 ± 0.8; FU3 3.3 ± 0.6 Control: Baseline 3.4 ± 0.6; FU1 3.5 ± 0.6; FU2 3.5 ± 0.6; FU3 3.6 ± 0.6 eCO (median and IQR) - p=0.21 ENDS: Baseline 5.0 [3.5-7.3]; FU1 4.0 [2.8-6.0]; FU2 3.0 [3.0-5.8]; FU3 4.0 [2.8-6.3] Control: Baseline 4.0 [3.5-7.5]; FU1 5.5 [4.0-6.5]; FU2 7.0 [3.5-8.0]; FU3 5.0 [5.5-6.0] FeNO (median and IQR) - p=0.89 ENDS: Baseline 21.1 [16.2-24.5]; FU1 19.7 [17.2-22.3]; FU2 18.9 [18.2-24.7]; FU3 20.0 [18.2-22.7] Control: Baseline 18.6 [17.6-25.7]; FU1 19.4 [16.0-25.1]; FU2 18.7 [16.9-22.0]; FU3 20.0 [16.2-23.4] High-resolution computed tomography at 42 months HRCT scans obtained in 8/9 EC users. Visual assessment of the HRCT scans showed no pathological findings	Moderate methodological quality Very small study size Conflicts of interest Grants and consulting/speaking fees from pharmaceutical companies and electronic cigarette industry and trade associations Funding Supported by Catania University
Non-randomised intervention studies					

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame, [data source])	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflict of interest, funding
Kotoulas et al., 2020[366] Greece Pre-post-post intervention study Study date not reported Laboratory study	Study size 50 participants (25 mildly asthmatic smokers, 25 healthy smokers) Sample All participants were current daily smokers of combustible tobacco Gender – n (%) Male: 21 (42) Female: 29 (58) Age - mean (SD) years Asthmatic smokers 40.6 ± 10.8 Healthy smokers 39.9 ± 10.2	Exposure (n=25) E-cigarette Comparator (n=25) Before and after Materials - Device type NOBACCO (Halandri, Greece), powered by a lithium battery with 1.2 Ω coil resistance Materials - Nicotine concentration "Medium nicotine content" Pattern of exposure Used e-cigarette for 5 mins (10 puffs with 30 second inter-puff intervals, 1.0-1.5 mL of e-liquid)	Pulmonary function Forced vital capacity (FVC) (l) Forced expiratory volume in one second (FEV_1) (l) FEV_1/FVC: Tiffeneau-Pinelli index (%) Peak expiratory flow (PEF) (l/s) Residual volume (RV) (l) Expiratory reserve volume (ERV) (l) Total lung capacity (TLC) (l) Respiratory resistance Respiratory impedance at 5Hz (Z5Hz) (kPa/L/s)	Pulmonary function, respiratory resistance and exhaled air before and after e-cigarette use See table below	High methodological quality Small study size Conflicts of interest Not reported Funding Supported by Hellenic Society of Respiratory and Occupational Chest Diseases

		Pre	Post	Diff	p-value	p-value*
FVC	Healthy	4.02 ± 0.91	4.03 ± 0.90	+0.01	0.696	0.480
	Asthma	4.45 ± 1.15	4.43 ± 1.17	−0.02	0.534	
FVC (predict	Healthy	104.61 ± 15.17	104.74 ± 13.62	+0.13	0.873	0.977
	Asthma	104.61 ± 14.2	103.88 ± 13.62	−0.73	0.726	
FEV_1	Healthy	3.42 ± 0.79	3.39 ± 0.79	−0.03	0.267	0.628
	Asthma	3.43 ± 0.90	3.39 ± 0.91	−0.04	0.113	
FEV_1 (predict)	Healthy	105.20 ± 16.67	104.06 ± 14.29	−1.14	0.125	0.865
	Asthma	95.94 ± 13.18	94.64 ± 14.29	−1.30	0.067	
FEV_1/FVC	Healthy	82.63 ± 6.95	81.80 ± 6.38	−0.83	0.169	0.677
	Asthma	75.19 ± 8.23	74.58 ± 7.96	−0.61	0.040	
FEV_1/FVC (predict)	Healthy	101.83 ± 7.60	100.82 ± 6.98	−1.01	0.175	0.684
	Asthma	93.26 ± 9.25	92.52 ± 9.01	−0.74	0.042	
PEF	Healthy	7.42 ± 1.75	7.23 ± 2.17	−0.19	0.321	0.467
	Asthma	7.58 ± 2.02	7.12 ± 2.08	−0.46	0.003	
PEF (predict)	Healthy	98.80 ± 21.51	94.78 ± 22.40	−4.02	0.141	0.600
	Asthma	92.03 ± 19.55	84.84 ± 19.02	−7.19	0.001	
RV	Healthy	1.51 ± 0.43	1.53 ± 0.50	+0.01	0.59	0.946
	Asthma	1.87 ± 0.53	1.89 ± 0.44	+0.02	0.772	
RV (predict)	Healthy	87.30 ± 14.91	88.32 ± 18.03	+1.02	0.757	0.900
	Asthma	100.43 ± 26.64	101.69 ± 21.59	+1.26	0.738	
ERV	Healthy	1.08 ± 0.48	1.06 ± 0.49	−0.02	0.818	0.157
	Asthma	1.44 ± 0.65	1.29 ± 0.57	−0.15	0.051	
ERV (predict)	Healthy	87.52 ± 36.43	84.84 ± 32.09	−2.68	0.583	0.221
	Asthma	108.88 ± 39.00	96.69 ± 28.97	−12.19	0.053	

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame, [data source])	Sample characteristics	Intervention and control	Outcome measure	Results							Quality assessment, study size, conflict of interest, funding
			Respiratory resistance at 5 (R5Hz), 10 (R10Hz), and 20Hz (R20Hz) (kPa/L/s) Exhaled air Exhaled FeNO (ppb)	TLC	Healthy	5.56 ± 0.95	5.59 ± 0.97	+0.03	0.277	0.066	
					Asthma	6.20 ± 1.33	6.13 ± 1.28	−0.07	0.141		
				TLC (predict)	Healthy	97.41 ± 9.60	97.88 ± 8.08	+0.47	0.426	0.126	
					Asthma	97.52 ± 12.4	96.58 ± 11.33	−0.94	0.187		
				Z5Hz	Healthy	0.440 ± 0.098	0.461 ± 0.106	+0.021	0.063	0.515	
					Asthma	0.431 ± 0.121	0.464 ± 0.149	+0.033	0.040		
				R5Hz	Healthy	0.426 ± 0.099	0.450 ± 0.105	+0.024	0.034	0.712	
					Asthma	0.419 ± 0.115	0.449 ± 0.142	+0.030	0.054		
				R10Hz	Healthy	0.382 ± 0.096	0.402 ± 0.098	+0.020	0.038	0.668	
					Asthma	0.376 ± 0.104	0.403 ± 0.128	+0.027	0.043		
				R20Hz	Healthy	0.367 ± 0.097	0.388 ± 0.098	+0.021	0.034	0.816	
					Asthma	0.362 ± 0.101	0.386 ± 0.114	+0.024	0.026		
				FeNO	Healthy	15.12 ± 6.48	11.84 ± 5.19	−3.28	<0.001	<0.001	
					Asthma	14.88 ± 11.60	18.48 ± 13.38	+3.60	0.001		
				*mean difference between asthmatic and healthy smokers							
Brożek et al., 2019[365] Poland Laboratory pre-post study Study date not reported YoUng People E-smoking Study (YUPESS) –	Study size 120 participants: 30 participants in each exposure group Sample 1. Exclusive e-cigarette users 2. Dual users 3. Exclusive cigarette smokers 4. Non-smokers	Exposure 1 (n=30) Exclusive e-cigarette users Exposure 2 (n=30) Dual users Exposure 3 (n=30) Exclusive cigarette smokers	Spirometry Forced vital capacity (FVC) (l) Forced expiratory volume in one second (FEV_1) (l) Forced expiratory volume in one second to FVC (FEV_1/FVC) (%)	Relative difference since baseline – mean ± SD							Moderate methodological quality Moderate study size Conflicts of interest None declared Funding Medical University of Silesia
					ENDS	Cigarette	Dual	Non-smoker	P-value		
				FVC (1 min)	1.0 ± 4.1	1.5 ± 4.9	−0.5 ± 6.8	−0.8 ± 3.0	0.2		
				FVC (30 mins)	−0.2 ± 3.9	0.2 ± 5.4	1.4 ± 4.4	-	0.4		
				FEV_1 (1 min)	2.3 ± 5.7	2.8 ± 7.2	−0.2 ± 6.4	−0.3 ± 3.7	0.4		
				FEV_1 (30 mins)	1.0 ± 6.3	1.7 ± 7.3	0.4 ± 5.2	-	0.8		
				FEV_1/FVC (1 min)	1.3 ± 4.3	1.3 ± 5.9	0.2 ± 2.7	0.6 ± 2.4	0.8		
				FEV_1/FVC (30 mins)	1.3 ± 4.4	1.6 ± 5.2	−1.0 ± 3.8	-	0.09		
				PEF (1 min)	3.8 ± 12.0	4.6 ± 13.5	5.5 ± 9.9	2.4 ± 13.0	0.9		
				PEF (30 mins)	5.5 ± 15.3	0.2 ± 17.0	1.0 ± 17.0	-	0.5		
				MEF_{25} (1 min)	5.3 ± 16.0	4.3 ± 14.4	−7.3 ± 19.1	3.5 ± 15.6	0.02		

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame, [data source])	Sample characteristics	Intervention and control	Outcome measure	Results					Quality assessment, study size, conflict of interest, funding
multi-centre international project	Gender (%) Male: 59.2 Female: 40.8 Age - mean (SD) years 22.6 ± 2.2	Comparator (n=30) Non-smokers Materials - Device type ENDS: own device, multi-fruit flavoured e-liquid Cigarette: popular cigarette brand (0.6mg nicotine/cigarette) Pattern of exposure Everyday habits for 5 minutes	Peak expiratory flow (PEF) (l/s) Maximal expiratory flow at 25% and 75% of FVC ($MEF_{25,75}$) (l/s) Maximal expiratory flow between 25% and 75% of FVC (MEF_{25-75}) (l/s) Acute respiratory responses Exhaled nitric oxide (FeNO) (ppb) O_2 saturation (%) Exhaled air temperature (°C) Exhaled carbon monoxide (CO) (ppm)	MEF_{25} (30 mins)	0.8 ± 19.3	1.4 ± 13.3	−2.8 ± 16.1	-	0.6
				MEF_{75} (1 min)	3.1 ± 10.5	3.0 ± 15.7	4.9 ± 10.7	1.3 ± 13.6	0.6
				MEF_{75} (30 mins)	4.1 ± 14.6	1.8 ± 16.4	−0.2 ± 15.0	-	0.9
				MEF_{25-75} (1 min)	4.2 ± 11.8	4.8 ± 12.5	−0.5 ± 11.1	0.9 ± 9.6	0.7
				MEF_{25-75} (30 mins)	2.7 ± 11.2	3.8 ± 13.2	−2.0 ± 10.6	-	0.5
				FeNO (1 min)	7.3 ± 13.4	13.1 ± 11.2	12.8 ± 16.7	0.3 ± 13.4	0.0002
				FeNO (30 mins)	−8.4 ± 18.6	−3.9 ± 11.9	−5.6 ± 18.5	-	0.5
				O_2 saturation (1 min)	−0.1 ± 1.1	0.6 ± 1.1	0.2 ± 0.8	0.2 ± 0.7	0.09
				O_2 saturation (30 mins)	−0.1 ± 0.9	−0.0 ± 1.1	0.1 ± 1.0	-	0.6
				Exhaled air temp (1 min)	−0.5 ± 1.2	0.0 ± 1.1	−0.5 ± 0.9	−0.2 ± 1.1	0.4
				Exhaled air temp (30 mins)	−0.7 ± 1.3	−0.9 ± 1.0	−0.6 ± 1.0	-	0.4
				Exhaled CO (1 min)	−11.9 ± 27.7	−154.4 ± 115.1	−1.1 ± 13.8	−11.1 ± 31.4	0.0001
				Exhaled CO (30 mins)	−8.9 ± 26.9	−117.6 ± 90.5	11.0 ± 19.2	-	0.0001
				In the control group, under direction of the Ethics Committee, the 30-minute measurement was not allowed since the first and second measurement results did not differ					

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame, [data source])	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflict of interest, funding
Coppeta et al., 2018[291] Italy Crossover study Study date not reported Laboratory study	Study size 30 participants Sample Healthy non-smoker volunteers Gender - n (%) Male: 17 (56.7) Female: 13 (43.3) Age - mean (SD) years 32.6 ± 2.75	Exposure ENDS: 1.8% (18mg/mL) Comparator Tobacco cigarette (TC): 0.6mg nicotine, 8mg tar, 9mg CO Materials - Device type eGo P (L) with manual start, Latakia tobacco flavour Pattern of exposure 15 puffs of ENDS	Spirometry Forced expiratory volume in one second (FEV_1) (l) Forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) (%) Forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) (l/s)	Lung function parameters (baseline, 1 minute and 15 minutes) for the traditional cigarette and the e-cigarette Mean / 95% CI Baseline / Post / Diff / SD / SE / Lower / Upper / P-value FEV_1 (Post = 1 min) ENDS 3.55 3.51 0.04 0.11 0.02 0.00 0.09 0.03 TC 3.53 3.48 0.04 0.10 0.028 0.01 0.08 0.00 FEV_1 (Post = 15 mins) ENDS 3.55 3.53 0.02 0.14 0.03 -0.03 0.07 0.36 TC 3.53 3.51 0.02 0.054 0.016 0.01 0.04 0.05 FEV_1/FVC (Post = 1 min) ENDS 82.1 81.6 1.03 2.00 0.37 0.29 1.78 0.01 TC 82.2 81.7 0.5 1.28 0.38 0.98 1.02 0.04 FEV_1/FVC (Post = 15 mins) ENDS 82.1 81.5 0.40 2.49 0.46 -0.53 1.33 0.39 TC 82.2 81.0 1.2 1.16 0.35 0.75 1.68 0.01 FEF_{25-75} (Post = 1 min) ENDS 3.44 3.30 0.23 0.31 0.06 0.12 0.35 0.00 TC 3.45 3.38 0.06 0.13 0.04 0.01 0.11 0.01 FEF_{25-75} (Post = 15 mins) ENDS 3.44 .35 0.09 0.32 0.06 0.02 0.25 0.03 TC 3.45 3.31 0.14 0.14 0.04 0.08 0.12 0.00	Moderate methodological quality Small study size Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Lappas et al., 2018[292]

Greece

Pre-post intervention study

Study date not reported

Laboratory study

Study size
54 participants (27 asthmatic smokers, 27 healthy smokers)

Sample
Dual e-cigarettes and combustible cigarettes. Smokers were healthy or with mild intermittent well controlled asthma

Gender – n (%)
Male: 21 (38.9)
Female: 33 (61.1)

Age – mean (SD) years
23.0 (3.2)

Exposure
ENDS: 12mg/mL nicotine

Comparator
Before

Materials - Device type
New-generation e-cigarette (adjustable voltage), propylene glycol 46.13% w/v, glycerol 34.3% w/v, nicotine 1.18% w/v and tobacco essence (<5% w/v)

Pattern of exposure
Use for five minutes (10 puffs). Follow-up immediately after, 15 and 30 minutes after session

Impulse oscillometry
Respiratory system total impedance at 5Hz (Z5) (kPa/(L/s))

Respiratory system resistance at 5Hz/10Hz/20Hz (R5/R10/R20) (kPa/(L/s))

Resonant frequency (f_{res}) (Hz)

Respiratory system reactance at 5Hz/20Hz (X5/X20) (kPa/(L/s))

Reactance area (AX) (kPa/L)

Impulse oscillometry parameters - mean difference at baseline

	Z5	R5	R10	R20	FRes	X5	X20	AX
Healthy	0.33 (0.07)	0.31 (0.06)	0.29 (0.06)	0.29 (0.06)	10.43 (2.01)	-0.10 (0.03)	0.10 (0.03)	0.24 (0.12)
Asthmatic	0.38 (0.08)	0.37 (0.08)	0.33 (0.07)	0.33 (0.06)	12.4 (4.2)	-0.11 (0.03)	0.08 (0.05)	0.36 (0.32)
p-value	0.011	0.009	0.008	0.043	0.032	0.435	0.094	0.065

Impulse oscillometry - mean (SD) difference baseline to follow-up

	Directly after	p-value	15 mins post	p-value	30 mins post	p-value
Z5						
Healthy	0.36 (0.09)	<0.001	0.34 (0.08)	0.154	0.33 (0.08)	>0.999
Asthma	0.44 (0.09)	<0.001	0.40 (0.08)	0.128	0.38 (0.06)	>0.999
R5						
Healthy	0.34 (0.08)	<0.001	0.33 (0.08)	0.183	0.31 (0.08)	>0.999
Asthma	0.42 (0.08)	<0.001	0.38 (0.07)	0.238	0.36 (0.06)	>0.999
R10						
Healthy	0.31 (0.07)	0.001	0.30 (0.07)	0.293	0.29 (0.08)	>0.999
Asthma	0.38 (0.07)	<0.001	0.35 (0.06)	0.184	0.33 (0.05)	>0.999
R20						
Healthy	0.31 (0.06)	0.033	0.30 (0.06)	0.465	0.30 (0.07)	>0.999
Asthma	0.36 (0.07)	<0.001	0.34 (0.06)	0.250	0.33 (0.05)	>0.999
F_{res}						
Healthy	11.61 (3.05)	0.001	11.04 (2.78)	0.389	10.38 (2.43)	>0.999
Asthma	14.07 (4.48)	<0.001	12.45 (3.82)	>0.999	11.77 (3.46)	0.339
X5						
Healthy	-0.10 (0.03)	>0.999	-0.10 (0.03)	>0.999	-0.09 (0.03)	>0.999
Asthma	-0.12 (0.04)	<0.001	-0.10 (0.03)	>0.999	-0.10 (0.03)	>0.999
X20						
Healthy	0.08 (0.04)	<0.001	0.09 (0.04)	0.076	0.12 (0.11)	0.616
Asthma	0.05 (0.05)	<0.001	0.08 (0.05)	>0.999	0.08 (0.05)	>0.999
AX						
Healthy	0.33 (0.23)	0.041	0.28 (0.2)	0.490	0.23 (0.15)	>0.999
Asthma	0.55 (0.53)	<0.001	0.37 (0.28)	>0.999	0.30 (0.22)	0.108

High methodological quality

Small study size

Conflicts of interest
None declared

Funding
Behrakis Foundation

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Table 4.6-3. Study details: respiratory health outcomes – surveillance reports

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
National surveillance systems						
Adkins et al., 2020[371] US August 2019 - December 17, 2019 CDC	EVALI cases: 2,155 Gender (N=2,141) – n (%) Female: 671 (31.3) Male: 1,470 (68.7) Age (N=2,155) – n (%) 13-17 years: 360 (16.7) 18-24 years: 859 (39.9) 25-49 years: 936 (43.4)	ENDS patterns of use in past 90 days – n Any ENDS or vaping: 1,793 Exclusive ENDS or vaping: 1,793 Daily ENDS or vaping: 603 ENDS and THC: 1,793	EVALI symptoms – n Respiratory: 1,532 Gastrointestinal: 1,452 Constitutional*: 1,523 Gastrointestinal or constitutional symptoms, but no respiratory symptoms: 1,477 * Fever, chills, malaise	EVALI clinical course and treatment – n Hospitalisation: 2,026 ICU admission: 1,300 Corticosteroids: 1,203 Intubated: 632	Not reported	High methodological quality Conflicts of interest None declared Funding Not reported
Ellington et al., 2020[376] US August 2019 - January 7, 2020 CDC	EVALI cases: 2,602 Gender (N=2,486) – n (%) Female: 828 (33) Male: 1,658 (67) Age (N=2,497) – n (%) 13-17 years: 383 (15) 18-24 years: 931 (37) 25-34 years: 605 (24) 35-44 years: 322 (13) 45-64 years: 213 (9) 65-85 years: 43 (2)	EC composition 3 months preceding symptom onset (N=1,979) – n (%) Any nicotine: 1,128 (57)	Not reported	Clinical course – n (%) Severe*: All (N=2,533) 810 (32); Any Nicotine (N=1,122) 409 (36); Exclusive nicotine (N=262) 156 (60) Not severe: All (N=2,533) 1,723 (68); Any Nicotine (N=1,122) 713 (64); Exclusive nicotine (N=262) 106 (40) *Hospital stay ≥10 days, ICU admission, endotracheal intubation, continuous airway pressure, bilevel airway pressure or death	Outcome – n (%) Died / Survived: All (N=2,533) 57 (2) / 2,298 (98) Any nicotine (N=1,060) 26 (2) / 1,034 (98) Only nicotine (N=244) 16 (7) / 228 (93)	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Evans et al., 2020[361] US August 2019 - December 10, 2019 CDC	Hospitalised EVALI: 2,409 Median age – years Died: 54 Rehospitalised: 27 Neither died nor rehospitalised: 23	Not reported	Not reported	Not reported	Deaths: 52 (2%) Outcomes after discharge (N=1,139) – n (%) Rehospitalised: 31 (2.7) Died: 7 (0.6)	Grey literature-no quality assessment Conflicts of interest One member of the Lung Injury Response Clinical Working Group reported receiving grants and personal fees from the FDA/NIH and the pharmaceutical industry Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Krishnasamy et al., 2020[363] US August 2019 - January 14, 2020 CDC and the National Syndromic Surveillance Program (NSSP)	Hospitalised EVALI cases (N=2,668) – n (%) Confirmed: 1,401 (53) Probable: 1,267 (47) Gender (N=2,606) – n (%) Female: 875 (34) Male: 1,731 (66) Age (N=2,619) – n (%) 13-17 years: 404 (15) 18-24 years: 979 (37) 25-34 years: 631 (24) 35-44 years: 335 (13) 45-64 years: 223 (9) ≥65 years: 47 (2) Median age (range) years: 24 (13-85)	EC composition 3 months preceding symptom onset (N=2,022) – n (%) Any nicotine: 1,162 (57) Both THC and nicotine: 834 (41) Exclusive nicotine: 274 (14) No THC or nicotine: 44 (2)	Not reported	Not reported	Not reported	Grey literature- no quality assessment Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Mikosz et al., 2020[370] US August 2019 - December 10, 2019 CDC	Hospitalised EVALI: 2,409 Gender (N=804) – n (%) Female: 275 (34) Male: 528 (66) Other: 1 (0) Age (N=804) – n (%) 13-17 years: 136 (17) 18-24 years: 309 (38) 25-50 years: 309 (38) ≥51 years: 50 (6)	Not reported	Symptoms at first reported clinical encounter – n (%) Any respiratory: 758 (96) Any constitutional*: 710 (92) Any gastrointestinal: 621 (81) *Fever, chills, malaise, fatigue, headache, body aches	Clinical course – n (%) Corticosteroids: 577 (88) ICU admission: 299 (43) Respiratory failure necessitating intubation and mechanical ventilation: 60 (17) Extracorporeal membrane oxygenation: 5 (1)	Outcome – n Deaths: 52 (2%) Rehospitalisation: 31 Death after discharge: 7 No rehospitalisation nor death: 768	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported
Werner et al., 2020[372] US August 2019 – January 7, 2020 CDC	Hospitalised EVALI cases (N=2,618) - n (%) Confirmed: 1,378 (53) Probable: 1,240 (47) Gender (N=2,558) - n (%) Female: 860 (34) Male: 1,698 (66) Age (N=2,574) - n (%) <35 years: 1,979 (77) ≥35 years: 595 (23) Median age (range) years Fatal cases: 51 (15-75)	EC composition and pattern of use 3 months preceding symptom onset (N=2,066) – n (%) Nicotine (non-exclusive): 1,134 (55) Nicotine (exclusive): 292 (14) THC and nicotine: 815 (39) Neither THC nor nicotine: 124 (6)	Symptoms Respiratory: 1,762 (96) Gastrointestinal: 1,369 (79)	Clinical course Antibiotics: 1,211 (98) Glucocorticoids: 1,297 (88) ICU admission: 690 (44) Endotracheal intubation: 178 (22) Ventilatory support (CPAP or BiPAP): 211 (19)	Deaths: 60 (2%)	High methodological quality Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
	Non-fatal cases: 24 (13-85)					
Blount et al., 2019[312] US August 2019 - October 15, 2019 CDC	EVALI cases: 867	Substances used in the 3 months preceding symptom onset - % THC-containing products: 86	Not reported	Not reported	Not reported	Grey literature- no quality assessment Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Chatham-Stephens et al., 2019[369] US August 2019 - November 5, 2019 CDC	EVALI case status (N=2,006) – n (%) Confirmed: 1,052 (52) Probable: 954 (48) Gender – n (%) (N=1,905) Female: 607 (32) Male: 1,298 (68) Age (N=1,906) – n (%) 13-17 years: 293 (15) 18-24 years: 721 (38) 25-34 years: 459 (24) 35-44 years: 256 (13) 45-64 years: 141 (7) ≥65 years: 36 (2) Median age (range) years: 24 (13-78)	EC composition used 3 months preceding symptom onset (N=1,184) – n (%) Any nicotine: 723 (61) Both THC and nicotine: 573 (48) Nicotine only: 150 (13) No THC or nicotine: 50 (4)	Symptoms among non-hospitalised EVALI cases – n (%) Any respiratory: 47 (85) Any constitutional: 41 (76) Any gastrointestinal: 27 (57) Symptoms (cases with complete information) – n (%) Respiratory only: 4 (9) Gastrointestinal only: 0 (0) Constitutional only*: 1 (2) *Fever, chills, weight loss	Not reported	EVALI cases and hospitalisation status (2,016) – n (%) Hospitalised: 1,906 (95) Non-hospitalised: 110 (5)	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported
Jatlaoui et al., 2019[362] US August 2019 - November 13, 2019 CDC	EVALI cases: 2,172	Not reported	Not reported	Not reported	Deaths: 42 (1.9%)	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Lozier et al., 2019[374] US August 2019 - December 3, 2019 CDC	Hospitalised EVALI cases: 2,291 EVALI status (N=2,288) – n (%) Confirmed: 1,221 (53) Probable: 1,067 (47) Gender (N=2,155) – n (%) Female: 706 (33) Male: 1,499 (67) Age (N=2,159) – n (%) 13-17 years: 341 (16) 18-24 years: 817 (38) 25-34 years: 524 (24) 35-44 years: 278 (13) 45-64 years: 165 (8) ≥65 years: 34 (2) Median age (range) years: 24 (13-77)	EC composition and pattern of use 3 months preceding symptom onset (N=1,782) – n (%) Any nicotine: 956 (54) Nicotine only: 227 (13) Daily nicotine: 482 (85) Both THC and nicotine: 713 (40)	Not reported	Not reported	Deaths: 48 (2%)	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, time frame, data source)</th><th>Demographics</th><th>Exposure (e-liquid description)</th><th>Presentation and symptoms</th><th>Treatment</th><th>Outcome</th><th>Quality assessment, conflict of interest, funding</th></tr>
<tr>
<td>Moritz et al., 2019[364]

US

August 2019 - October 15, 2019

CDC</td>
<td>EVALI cases: 1,378

<u>Gender (N=1,378) – n (%)</u>
Female: 414 (30)
Male: 964 (70)

<u>Age (N=1,364) – n (%)</u>
13-17 years: 196 (14)
18-24 years: 541 (40)
25-34 years: 344 (25)
35-44 years: 172 (13)
45-64 years: 87 (6)
65-75 years: 24 (2)

Median age (range) years: 24 (13-75)</td>
<td><u>EC composition used 3 months preceding symptom onset (N=867) – n (%)</u>
Any THC: 749 (86)
Any nicotine: 522 (64)
Both THC and nicotine: 455 (52)
THC only: 294 (34)
Nicotine only: 97 (11)
No THC or nicotine: 21 (2)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Grey literature-no quality assessment

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Not reported</td>
</tr>
<tr>
<td>Perrine et al., 2019[367]

US

August 2019 - September 24, 2019

CDC</td>
<td>EVALI cases: 805

<u>Gender (N=771) – n (%)</u>
Female: 234 (30)
Male: 531 (69)
Missing: 6 (1)

<u>Age (N=771) – n (%)</u>
<18 years: 125 (16)
18-24 years: 293 (38)
25-34 years: 184 (24)
35-44 years: 93 (12)
≥45 years: 42 (6)
Missing: 34 (4)</td>
<td><u>Product use (N=514) – %</u>
Any THC: 77
Any nicotine: 57
Nicotine only: 16

<u>EC composition used in the 3 months preceding symptom onset (N=514) – n (%)</u>
<table><tr><th></th><th>Yes</th><th>No</th><th>Missing</th></tr><tr><td>Nicotine</td><td>292 (57)</td><td>173 (34)</td><td>49 (10)</td></tr><tr><td>Flavoured e-liquid</td><td>102 (20)</td><td>132 (26)</td><td>280 (55)</td></tr></table></td>
<td>Not reported</td>
<td>Not reported</td>
<td>Deaths: 12 (1.5%)</td>
<td>Grey literature-no quality assessment

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Not reported</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Schier et al., 2019[378] US August 2019 - August 27, 2019 CDC	215 possible cases of severe pulmonary disease	Not reported	Not reported	Not reported	Not reported	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported
Siegel et al., 2019[375] US August 2019 - October 3, 2019 CDC	EVALI cases: 1,299* Gender (N=1,043) – n (%) Female: 313 (30) Male: 730 (70) Age (only where full medical chart available (N=338) Median age (range) years: 22 (13-71) *October 8, 2019	EC composition used 3 months preceding symptom onset (N=573) – n (%) Any THC: 435 (76) Any nicotine: 332 (58) THC only: 183 (32) Nicotine only: 74 (13)	Symptoms (only where full medical chart available) (N=339) – n (%) Any respiratory: 323 (95) Any constitutional*: 289 (85) Any gastrointestinal: 262 (77) *Self-reported fever, chills, and unexpected weight loss	Clinical course (only where full medical chart available) – n (%) Corticosteroids: 252 (88) ICU admission: 159 (47) Intubation and mechanical ventilation: 74 (22) Average hospital stay [mean (median) days]: 6.7 (5)	Deaths: 26 (2%)* *October 8, 2019	Grey literature-no quality assessment Conflicts of interest One member of the Lung Injury Response Clinical Working Group received grants and fees from the pharmaceutical industry Funding Not reported
State-based surveillance systems						

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Armatas et al., 2020[373] California, US 2019-2020 California Department of Public Health (CDPH)	Hospitalised EVALI cases June 18, 2019–February 23, 2020: 210 patients April 2020: 8 patients Age range (April 2020) (N=8) 14-50 years (median: 17 years); 7 aged <21 years	April 2020 (N=8) – n (%) THC: 6 (75) ENDS only: 1 (13) Unspecified: 1 (13)	Not reported	Clinical course, April 2020, (N=8) – n ICU admission: 4 Mechanical ventilation: 2 SARS-CoV-2 testing: all negative Hospitalisation Median (range) days: 4 (4-13)	Not reported	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported
Gaub et al., 2019[377] Indiana, US August 8-October 28, 2019 Indiana State Department of Health (ISDH)	Hospitalised EVALI cases (N=97) – n (%) Confirmed: 41 (42) Probable: 56 (58) Gender (N=54) – n (%) Male: 38 (70%) Female: 16 (30%) Age (N=54) – n (%) 13–17 years: 7 (13) 18–29 years: 27 (50) 30–39 years: 12 (22) 40–49 years: 3 (6) 50–59 years: 3 (6) ≥60 years: 2 (4) Median age (range) years: 26 (16-68)	Not reported	Symptoms on admission (N=54) – n (%) Shortness of breath: 48 (89) Cough: 44 (81) Nausea: 27 (50) Vomiting: 27 (50) Chest pain: 17 (31) Diarrhea: 15 (28) Abdominal pain: 12 (22) Sweating: 11 (20) Weight loss: 8 (15)	Medical care – % Antibiotics: 86 Steroids: 65 Bronchoscopy: 30 ICU admission: 25 Lung biopsy: 16 Intubation/mechanical ventilation: 14	Deaths: 3 (3%)	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographics	Exposure (e-liquid description)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Lewis et al., 2019[316] Utah, US August 6-October 15, 2019 Utah Department of Health (UDOH)	Confirmed or probable cases of EVALI: 83 Gender (N=83) – n (%) Female: 14 (17) Male: 69 (83) Age (N=83) – n (%) 14-19 years: 11 (13) 20-29 years: 43 (52) 30-39 years: 23 (28) 40-66 years: 6 (7) Median age (range) years: 26 (14-66)	Not reported	Not reported	Medical care (N=79) – n (%) Hospitalisation: 70 (89) Steroids: 59 (75) ICU admission: 35 (44) CPAP/BiPAP support* (no intubation): 30 (38) Acute respiratory distress syndrome: 20 (25) Intubation and mechanical ventilation: 9 (11) *Continuous positive airway pressure/bilevel positive airway pressure	Not reported	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported
Taylor et al., 2019[368] Minnesota, US August 9-October 31, 2019 Minnesota Department of Health (MDH)	Confirmed or probable EVALI cases: 96 Gender (N=96) – n (%) Female: 38 (40) Male: 58 (60) Median age (range) years: 21 (15-71)	Not reported	Not reported	Clinical course – n (%) (N=96) Hospitalised: 87 (91) ICU admission: 26 (27)	Deaths: 3 (3%)	Grey literature-no quality assessment Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Table 4.6-4. Study details: respiratory health outcomes - case reports and case series

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure	Presentation	Treatment	Outcome	Quality assessment, conflict of interest and funding
Case series						
Ansari-Gilani et al., 2020[399] US Hospital record Time frame: not reported	Female 20 years Medical history Never smoker, no past medical history	Nicotine-e-cigarette use for 3 months, last used night before presentation	Dyspnoea, cough, intermittent diarrhea, nausea EVALI diagnosis Confirmed case (hypersensitivity pneumonitis)	Antibiotics, steroids, supplemental oxygen	Discharged after 11 days, significant improvement in follow-up clinic	High methodological quality Conflicts of interest None declared Funding Not reported
Corcoran et al., 2020[400] US Hospital record August-November 2019	Male 17 years Medical history Hypertension	2 years: daily nicotine-e-cigarette pods	Nausea, vomiting, cough, fever, dyspnoea for four days EVALI diagnosis Probable case	Nasal cannula, paediatric intensive care unit (PICU), antibiotics	Discharged after 6 days	Moderate methodological quality Conflicts of interest None declared Funding National Heart, Lung, and Blood Institute

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure	Presentation	Treatment	Outcome	Quality assessment, conflict of interest and funding
Fryman et al., 2020[401] US Hospital record November 2018-August 2019	Female 62 years Medical history Mild intermittent asthma	6 months: nicotine-based products	Dyspnoea and abdominal pain for one month EVALI diagnosis Confirmed case (acute respiratory failure)	Antibiotics	Improved over 5 days without steroids, discharged home	Moderate methodological quality Conflicts of interest None declared Funding None declared
Isakov et al., 2020[402] US Hospital record Time frame: not reported * Authors do not specify if the case is confirmed or probable EVALI	Male 36 years Medical history Previously healthy, nil tobacco/illicit drug use	Frequent e-cigarette use, variety of flavours	Fever, cough, weakness, weight loss for four weeks EVALI diagnosis Confirmed/probable case* (organising pneumonia)	Not reported	Not reported	Low methodological quality Conflicts of interest None declared Funding None received
	Male 18 years Medical history History of opiate use	Not reported	Lower back pain, headache, dyspnoea, fever EVALI diagnosis Confirmed/probable case* (acute lung injury)	Paediatric intensive care unit (PICU), antibiotics	Discharged after 6 days	
Kass et al., 2020[403] US Hospital record	Male 16 years Medical history Appendicitis after surgical intervention	Intermittent use for 1 year	Dry cough, general malaise, decreased appetite, chills, fever, dyspnoea, vomiting EVALI diagnosis Confirmed case	Intubation, nasal cannula, antibiotics, steroids	Discharged after 23 days	Low methodological quality Conflicts of interest None declared

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure	Presentation	Treatment	Outcome	Quality assessment, conflict of interest and funding
April 2019-January 2020	Male 16 years Medical history Allergy-induced asthma, delayed puberty, small stature, renal diverticulum, penile adhesions	2 years: up to 3 times/week	Fever, nausea, vomiting, diarrhoea EVALI diagnosis Confirmed case	Antibiotics, nasal cannula	Discharged after 8 days	Funding Not reported
	Female 15 years Medical history Possible asthma, chronic joint pain, sinopulmonary infections	Rare personal use of Juul and mod device (unknown brand), but frequent 'hotboxing' (filling closed space (car) with e-cigarette exhalant)	Cough, dyspnoea, sputum production EVALI diagnosis Neither confirmed nor probable case (imaging is normal)	Antibiotics, steroids	Not reported	
Temas & Meyer, 2020[406] US Hospital record July-August 2019	Male 33 years Medical history Remote history of asthma as child, community-acquired pneumonia two years prior, current smoker (one pack/day)	Regular use and used "all night" prior to presentation	Cough, dyspnoea, fever for two days, hypoxia, tachycardia EVALI diagnosis Confirmed case	Nasal cannula, antibiotics, steroids	Discharged on day 6 with steroid taper	High methodological quality Conflicts of interest None declared Funding Not reported
Thakrar et al., 2020[407] US	Male 16.5 years Medical history Not reported	EC 6-8 months prior, daily use for several weeks prior to admission	Not reported per patient, no information EVALI diagnosis Confirmed case	Admitted to hospital and received high-dose steroids	Not reported	Moderate methodological quality

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure	Presentation	Treatment	Outcome	Quality assessment, conflict of interest and funding
Hospital record June 2019-August 2019	Male 17.0 years Medical history Not reported	Use of nicotine-e-cigarette 3-5 days/week for unknown duration	Not reported per patient, no information EVALI diagnosis Confirmed case	Admitted to hospital and received high-dose steroids	Not reported	Conflicts of interest None declared Funding Not reported
	Male 17.7 years Medical history Not reported	Daily use of nicotine-e-cigarette for 2-3 months, most recent use five months prior to admission	Not reported per patient, no information EVALI diagnosis Confirmed case	Admitted to hospital and received high-dose steroids	Not reported	
	Male 17.5 years Medical history Not reported	Daily use of nicotine-e-cigarette for unknown duration	Not reported per patient, no information EVALI diagnosis Confirmed case	Admitted to hospital and received high-dose steroids	Not reported	
	Male 17.7 years Medical history Not reported	Daily use of nicotine-e-cigarettes for 4 months	Not reported per patient, no information EVALI diagnosis Confirmed case	Admitted to hospital and received high-dose steroids	Not reported	
Case reports						

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure	Presentation	Treatment	Outcome	Quality assessment, conflict of interest and funding
Edmonds et al., 2020[386] US Hospital record Time frame not reported	Female 31 years Medical history Former smoker (pack/day), vaginal delivery five weeks prior, untreated hepatitis c virus, chronic pain, PTSD, family history (systemic lupus erythematosus and scleroderma), medications (buprenorphine/naloxone, prazosin, venlafaxine)	Switched to e-cigarettes four years prior to presentation: 17mL of 3mg/mL nicotine fiery cinnamon e-liquid daily	Productive cough, haemoptysis EVALI diagnosis Confirmed case (diffuse alveolar haemorrhage)	Antibiotics	Haemoptysis gradually resolved during hospitalisation/cessation of e-cigarette use	High methodological quality Conflicts of interest None declared Funding U.S. Department of Veterans Affairs
Farooq et al., 2020[387] US Hospital record Time frame not reported	Male 19 years Medical history Multiple emergency department visits over four months prior (diffuse abdominal pain, nausea, vomiting, diarrhoea)	1 year: intermittent use of nicotine-e-cigarettes	Acute gastroenteritis, hypoxia EVALI diagnosis Confirmed case	Antibiotics, antifungal therapy, steroids	Hypoxia improved with treatment, asymptomatic at follow-up with e-cigarette abstinence	Moderate methodological quality Conflicts of interest None declared Funding None received
Patterson et al., 2020[388] UK Hospital record	Male "In his 40s" Medical history Former smoker (twenty-pack/year), appendectomy, marijuana use in distant past	Switched to e-cigarettes 6 weeks prior: 18mg/mL nicotine, peppermint flavour	Coryzal symptoms, pleuritic chest pain, dyspnoea, hypoxia, tachycardia EVALI diagnosis Confirmed case (severe acute respiratory distress syndrome)	Intubation, mechanical ventilation, veno-venous extracorporeal membrane oxygenation (ECMO)	Survived, repatriated to referring hospital	Low methodological quality Conflicts of interest None declared Funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure	Presentation	Treatment	Outcome	Quality assessment, conflict of interest and funding
Time frame not reported						Not reported
Sakla et al., 2020[389] US Hospital record Time frame not reported	Female 25 years Medical history Unremarkable medical history	One year: use two-three hours/day, three times/week	Pleuritic chest pain, dyspnoea, dry cough, hyperventilation EVALI diagnosis Confirmed case (acute respiratory distress syndrome)	Saline, antibiotics, intubation, veno-venous extracorporeal membrane oxygenation (ECMO)	ECMO for three weeks, currently under care of speech management to establish dietary goals	Moderate methodological quality Conflicts of interest None declared Funding Not reported
Venkatnarayan et al., 2020[390] India Hospital record Time frame not reported	Male 31 years Medical history Smoker of 6 years (unclear if still using), nil known comorbidities, nil history of fever, haemoptysis, chest pain, palpitations or orthopnoea	3 months nicotine e-cigarettes, multiple flavours: last exposure four days before symptom onset	Acute onset breathlessness, dry cough for 3 days EVALI diagnosis Confirmed case	Nebulised bronchodilators and beta-agonists (after initial acute bronchitis diagnosis), antibiotics, antivirals, steroids	Condition significantly improved with treatment, advised not to use e-cigarettes, given smoking cessation advice	Moderate methodological quality Conflicts of interest None declared Funding None received
Aftab et al., 2019[385] US Hospital record Time frame not reported	Female 46 years Medical history Asthma, remote history of using marijuana and cocaine, nil history of lung disease, recent travel or sick contact	E-cigarette use for 1 month prior to admission	Dyspnoea and dry cough for 2 days EVALI diagnosis Confirmed case (acute respiratory distress syndrome)	High flow nasal cannula, antibiotics, intubation, high-dose steroids	Recovered/discharged to rehabilitation centre after 12 days, participated in physical therapy	Moderate methodological quality Conflicts of interest None declared Funding None received

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure	Presentation	Treatment	Outcome	Quality assessment, conflict of interest and funding
Casanova et al., 2019[393] Spain Hospital record Time frame not reported	Female 31 years Medical history Unremarkable medical history	Daily use of nicotine-e-cigarettes (with e-liquid) for 3 months, used nicotine salts (same device) in week preceding admission	Fever, myalgia, dry cough, fatigue and dyspnoea for 3 days EVALI diagnosis Confirmed case	Antibiotics, steroids	Discharged after 12 days	High methodological quality Conflicts of interest None declared Funding Not reported
Sommerfeld et al., 2018[335] US Hospital record Time frame not reported	Female 18 years Medical history Mild intermittent exertional asthma, recent reaction to Brazil nut, nil recent travel or animal exposure	2-3 weeks e-cigarette use, used 1-2 days before symptom onset	Dyspnoea, cough, pleuritic chest pain, afebrile EVALI diagnosis Confirmed case (hypersensitivity pneumonitis)	Paediatric intensive care unit (PICU), antibiotics, intubation, norepinephrine therapy, bilateral chest tubes, steroids	Discharged on steroid taper	Moderate methodological quality Conflicts of interest None declared Funding No external funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.7 Oral health

Main conclusions from the synthesised evidence on e-cigarette use and oral health

- There is no available evidence on the relationship of e-cigarette use to clinical or intermediate/subclinical oral health outcomes in exclusive e-cigarette users, independent of the effect of smoking.
- There is insufficient evidence of reduced plaque, gingival and papillary bleeding in smokers switching to e-cigarette use.
- In populations including exclusive e-cigarette users, dual users, and non-smokers (never and former smokers), there is insufficient evidence as to the relationship of e-cigarette use to increased gum disease, bone loss around the teeth and any periodontal disease.

Table 4.7-1. Overview of studies of oral health outcomes identified in the systematic review by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Oral health			2 1 / 1	2 2 / 0			19 1 / 18		1 0 / 1

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g. molecular measures.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Periodontal disease (reported gum disease, gum recession, bone resorption, bleeding after probing), tooth loss.
- **Intermediate/subclinical outcomes**: Plaque index, quantification of gingival crevicular fluid, measurements of gingival cytokines and subgingival microbiota.
- **Other oral health measures:** Blood flow in mucosa.

4.7.1 Findings from previous reviews

The NASEM review[3] identified four studies on oral health outcomes. Two studies, one cohort study[446] and one non-randomised intervention study[447] reported on clinical and subclinical oral health outcomes. One non-randomised intervention study reported other oral health outcomes.[448] One cross-sectional survey[449] was also included in the NASEM review[3] however, in this context, cross-sectional surveys are not considered suitable evidence and no further description has been included.

Reuther et al.[448] conducted a very small non-randomised clinical interventional pilot study in 10 non-smokers (aged 27-38 years, 70% male) from the UK. The study compared nicotine and non-nicotine e-cigarette aerosols on blood flow in the buccal mucosa after a five-minute exposure. There was a wide variation in results and a significant, albeit small, increase in capillary blood flow to the buccal mucosa after nicotine e-cigarette exposure (p=0.008). Blood flow for both type of e-cigarettes returned to baseline values after 30 minutes.[448]

A second non-randomised pilot intervention study from the UK included 20 established smokers with mild periodontal disease aged between 18 and 65 years.[447] The study reported that the number of sites that bled on probing (indicative of gingival inflammation) increased significantly (p<0.0008) when smokers quit and switched to e-cigarette use for two weeks. Gingival crevicular fluid increased after smokers switched to e-cigarettes, but no statistical test was conducted.[447]

In the Italian longitudinal cohort study by Tatullo et al.,[446] 110 smokers (60 smokers with <10 years smoking history and 50 smokers with >10 years smoking history) with an average age of 31 years and 81% males, switched to e-cigarettes and were followed for 120 days. A total of three intraoral examinations were performed, at baseline, 60-day and 120-day follow-up, and participants were also asked to report their general health status. Mean plaque index scores decreased from 0.9 ± 0.3 to 0.0 for smokers with <10-year smoking history and from 2.13 ± 0.5 to 0.25 ± 0.45 for smokers with >10-year smoking history at 120-day

follow-up. Gingival bleeding after probing declined for both smoker groups, from 61% at baseline to 8% at follow-up for smokers with <10-year smoking history and from 65% at baseline to 2% at follow-up in smokers with >10-year smoking history at 120-day follow-up. At 120-day follow-up, the mean values of the papillary bleeding index reduced from 0.4 ± 0.49 to 0.0 for smokers with <10 year smoking history and 1.25 ± 1.34 to 0.0 for smokers with >10 year smoking history however, no statistical test was conducted.[446]

The Irish Health Research Board literature map[15] identified 24 studies on how e-cigarette use affects oral health; one randomised controlled trial,[450] two non-randomised intervention studies,[447,448] two cohort studies,[446,451] four case reports,[452-455] and 15 cross-sectional surveys.[449,456-469] Two non-randomised intervention studies[447,448] and one cohort study[446] were included in NASEM review, one cohort study[451] was included in the top-up review. One randomised controlled trial[450] was excluded because it reported on a molecular outcome not included in our inclusion criteria and four case reports[452-455] and 15 cross-sectional surveys[449,456-469] did not meet inclusion for the top-up review due to ineligible study designs.

The Public Health England review[11] did not include oral health as a main outcome, nor did they include any discussion of articles on how the use of e-cigarettes effects oral health in any other sections.

The CSIRO review[14] identified three studies, all of which were cross-sectional surveys[266,449,468] on how e-cigarettes affect oral health. Cross-sectional surveys are not considered further.

No studies on oral health outcomes related to e-cigarette use were identified in the SCHEER[4] and USPSTF[16] reviews.

4.7.2 Summary of conclusions from previous reviews

The NASEM review,[3] including two intervention studies, a cohort study, and a cross-sectional survey, concluded that:

- Because the lack of rigorously designed studies examining the effects of e-cigarettes on oral health, there is no available evidence from epidemiological studies on an association between e-cigarette use and incidence or progression of periodontal disease.
- There is limited evidence suggesting that switching to e-cigarettes will improve periodontal disease in smokers.

The Irish Health Research Board literature map,[15] including interventional studies, cohort studies, cross-sectional surveys, and case reports, concluded that:

- There were inconsistent findings on the relationship of e-cigarette use to oral diseases across all the studies.
- The majority of the studies reported that there was a harmful association between e-cigarettes and oral health whereas a few of them suggested that e-cigarettes were less harmful than conventional tobacco cigarettes for oral diseases or have similar levels of oral health to never-smokers.

The CSIRO review,[14] including cross-sectional surveys, concluded that:

- There is some evidence of a relationship between e-cigarette use and some types of oral mucosal lesions.

4.7.3 Top-up review

Search results

Overall, 20 articles were located in the top-up systematic literature search. One was a cohort study,[451] 18 were cross-sectional surveys[266,456-462,464-467,469-474] and one was a case report[475]. The cross-sectional surveys and case report did not meet eligibility criteria, thus one article was available for the top-up synthesis of evidence (Table 4.7-1).

Two systematic reviews reporting on oral health outcomes related to e-cigarette use were identified in the top-up review search. Rahlo et al.[476] identified eight studies, seven cross-sectional surveys and one cohort study. Of the eight studies, two were included in the NASEM review[446,449] and six were included in the top-up review.[266,457,460,461,466,467]

Yang et al.[477] identified 99 studies on the oral health impacts of e-cigarette use, eight randomised control (or crossover) trials, 11 quasi-experimental studies, 46 correlational or descriptive studies, 15 case reports, and 19 *in vitro*. Excluding the 19 *in vitro* studies, of the 80 potentially relevant studies included in Yang et al., 21 were included in the NASEM review,[118,131,157,161,162,237,245,246,252,447-449,478-486] 14 were included in the top-up review,[266,302,457-462,464-467,469,471] 22 were published before the date limit of the top-up review and not included in NASEM[147,175,176,178,255,415,452,487-501] and 23 did not meet eligibility criteria for the top-up review. Of the 22

studies not captured by NASEM, seven were discussed under the Irish Health Research Board literature map under burns and injuries,[487-492,502] one under cancer,[255] and 14 did not meet inclusion eligibility criteria.

Oral health: clinical outcomes

Meta-analyses
No meta-analyses of the relationship of e-cigarette use to clinical oral health outcomes were located.

Randomised controlled trials
No randomised controlled trials reporting on the relationship of e-cigarette use to clinical oral health outcomes were located.

Cohort studies
One cohort study[451] comparing periodontal disease in a mixed population of exclusive e-cigarette users, dual users, smokers and non-smokers (never smokers and former smokers) was identified (Table 4.7.2). Atuegwu et al.[451] analysed data from 18,289 adults (18 years and above), between 2013-2016, with no history of gum disease, from the US Population Assessment of Tobacco study. At baseline, 46% were male. There were 9,632 never-, 329 regular and 8,298 infrequent electronic nicotine product users (electronic product use included e-cigarettes, vape pens, personal vaporisers and mods, e-cigars, e-pipes, e-hookahs and hookah pens). Of never electronic nicotine product users, 4.3% were conventional cigarette smokers and 20.5% were former smokers. In regular electronic nicotine product users, 38.6% were also current cigarette smokers (dual users) and 38.6% were former smokers. In infrequent electronic nicotine product users, 40.1% were dual users and 14.5% were former smokers. All analyses adjusted for conventional cigarette smoking and other risk factors such as age, sex, race, education, income level, current tobacco use or current second-hand exposure to tobacco smoke, use of nicotine replacement therapy products, marijuana use, alcohol use, illicit and non-prescribed drug use, visits to the dentist and medical history.

Compared to participants who had never used electronic nicotine products, regular electronic nicotine product users were more likely to report new cases of gum disease at either one- or two-year follow-up (OR 1.76; 95% CI 1.12–2.76). There was no statistically significant difference in new cases of gum disease for infrequent electronic nicotine product users compared to never electronic nicotine product users (OR 1.09; 95% CI 0.87-1.35).

Regular electronic nicotine product users were also more likely than never electronic nicotine product users to self-report bone loss around teeth, an indicator of advanced periodontal disease, at two-year follow-up (OR 1.67; 95% CI 1.06–2.63). There was no statistically significant difference in bone loss around teeth for infrequent electronic nicotine product users compared to never electronic nicotine product users (OR 1.10; 0.91-1.33).

Any periodontal diseases (measured as positive response to both bone loss and new gum disease) were more likely to occur in regular electronic nicotine product users (OR 1.58; 95% CI 1.06–2.34) than never electronic nicotine product users. There was no statistically significant difference in any periodontal disease for infrequent electronic nicotine product users compared to never electronic nicotine product users (OR 1.09; 0.93-1.29).[451]

This study was rated high quality using the Joanna Briggs Institute's critical appraisal checklist and no conflicts of interest were declared.

Non-randomised intervention studies
No non-randomised intervention studies reporting on the relationship of e-cigarette use to clinical oral health outcomes were located.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to clinical oral health outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to clinical oral health
Three cross-sectional surveys[266,456,470] and one case report[475] on the relationship between e-cigarette use and clinical oral health outcomes were identified. In this context, cross-sectional surveys and case reports are not considered suitable evidence and no further description has been included (Table 4.7-2).

Oral health: subclinical outcomes

Meta-analyses
No meta-analyses of the relationship of e-cigarette use to subclinical oral health outcomes were located.

Randomised controlled trials
No randomised controlled trials reporting on the relationship of e-cigarette use to subclinical oral health outcomes were located.

Cohort studies
No cohort studies reporting on the relationship of e-cigarette use to subclinical oral health outcomes were located.

Non-randomised intervention studies
No non-randomised intervention studies reporting on the relationship of e-cigarette use to subclinical oral health outcomes were located.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to subclinical oral health outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to subclinical oral health outcomes
Fifteen cross-sectional surveys[457-462,464-467,469,471-474] on the relation of e-cigarette to clinical oral health outcomes were identified. Cross-sectional surveys were not considered suitable evidence for this outcome and no further description has been included (Table 4.7.2).

Oral health: other oral health outcomes
No studies on other oral health outcomes were located.

4.7.4 Summary of findings from top-up review
There was one study reporting on the relationship of e-cigarettes to clinical oral health outcomes, finding:

- There is no available evidence on how e-cigarette use affects clinical oral health outcomes in exclusive e-cigarette users who are non-smokers.
- Among a mixed population of exclusive e-cigarette users, dual users, and non-smokers, one cohort study found regular but not infrequent use of electronic nicotine products increased the likelihood of gum disease, bone loss around teeth and any periodontal diseases compared to never electronic product users. Hence:
    - There is insufficient evidence on how regular nicotine e-cigarette use is related to gum disease, bone loss around the teeth and any periodontal disease in a mixed population of exclusive e-cigarette users, dual users, and non-smokers.

No studies on subclinical or other oral health outcomes were identified.

4.7.5 Summary of findings integrating evidence from previous review and top-up review
Combining clinical evidence from the top-up systematic review with the evidence from previous reviews:

- There were two cohort studies and one non-randomised intervention study reporting on clinical oral health outcomes.
- No available evidence on the relationship of e-cigarettes to clinical oral health outcomes among exclusive e-cigarette users who are non-smokers. Hence:
    - There is no available evidence on the relationship of e-cigarettes to clinical oral health outcomes in non-smokers.
- Among smokers, bleeding on probing significantly increased in smokers that switched to e-cigarettes for two weeks in one very small non-randomised intervention study and significantly decreased in one small cohort study. Hence:
    - There is insufficient evidence as to the relationship of e-cigarette use to gingival inflammation and periodontal disease in smokers.
- In a mixed population of exclusive e-cigarette users, dual users, and non-smokers there was one cohort study (sample size of 18,289) identified on the relationship of e-cigarette use to gum disease, bone loss around teeth and any periodontal disease. Hence, there is:

    - Insufficient evidence as to the relationship of e-cigarette use to gum disease, bone loss around the teeth and any periodontal disease in mixed populations including exclusive e-cigarette users, dual users, and non-smokers.
- The GRADE rating was very low certainty.

Combining intermediate/subclinical evidence from the top-up systematic review with the evidence from previous reviews:

- Two studies, one cohort and one non-randomised intervention study were identified.
- No evidence on the relationship of e-cigarette use to subclinical oral health outcomes among exclusive e-cigarette users (non-smokers) was located. Hence:
    - There is no available evidence on the relationship of e-cigarettes to subclinical/intermediate oral health.
- Among smokers that switched to e-cigarettes, gingival crevicular fluid increased in one very small non-randomised intervention study. In one small cohort study, mean plaque index scores and mean papillary bleeding scores decreased. No statistical tests were conducted in either study. Hence:
    - There is insufficient evidence of reduced plaque, gingival and papillary bleeding with switching from combustible smoking to e-cigarette use.
- The overall certainty of the evidence was very low using the GRADE approach.

Combining evidence on other oral health measures from the top-up systematic review with the evidence from previous reviews:

- One non-randomised intervention study on other oral health outcomes was identified.
- Among exclusive e-cigarette users, there was a small but significant increase in blood flow to the buccal mucosa in e-cigarette users at five-minutes post-exposure that returned to baseline at 30 minutes in one very small non-randomised intervention study. Hence:
    - There is insufficient evidence on the relationship of e-cigarettes to buccal mucosal blood flow in non-smokers.

4.7.6 Main conclusions from the synthesised evidence on the oral health effects of e-cigarette use

- There is no available evidence on the relationship of e-cigarette use to clinical or intermediate/subclinical oral health outcomes in exclusive e-cigarette users, independent of the effect of smoking.
- There is insufficient evidence of reduced plaque, gingival and papillary bleeding in smokers switching to e-cigarette use.
- In populations including exclusive e-cigarette users, dual users, and non-smokers (never and former smokers), there is insufficient evidence as to the relationship of e-cigarette use to increased gum disease, bone loss around the teeth and any periodontal disease.

Table 4.7-2. Study details: oral health – cohort studies

<table>
<tr><th>Study details (author, year, location, study type time frame, data source)</th><th>Sample characteristics</th><th>Intervention/ exposure and comparator</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflicts of interest, funding</th></tr>
<tr>
<td>Atuegwu et al., 2019[451]

US

Longitudinal cohort study

2013-2016

Population Assessment of Tobacco and Health (PATH) waves 1-3</td>
<td>Study size
32,320 adults without gum disease at baseline; 18,289 participants in analysis

Sample
Never electronic nicotine product user: no use
Regular electronic nicotine product user: regular (regularly every day or some days) across waves
Infrequent electronic product user: ever users that did not use electronic nicotine product regularly every day or some days across waves

Gender – male (%)
Never users: 44.4%
Regular users: 53.2%
Infrequent users: 52.3%

Age – % (95% CI) years
<table>
<tr><th>18-24:</th><th>25-34:</th><th>35-44:</th><th>45-54:</th><th>55+</th></tr>
<tr><td colspan="5">Never users</td></tr>
<tr><td>9.6 (9.2-10)</td><td>15.7 (14.8-16.6)</td><td>17.4 (16.5-18.3)</td><td>19.3 (18. 5-20.1)</td><td>38 (37-39)</td></tr>
<tr><td colspan="5">Regular users</td></tr>
<tr><td>23.8 (19.5–28.2)</td><td>30.8 (24.4-37.1)</td><td>15.9 (10.5-21.3)</td><td>14.4 (9.5-19.3)</td><td>15.1 (11.6-18.5)</td></tr>
<tr><td colspan="5">Infrequent users</td></tr>
<tr><td>30.8 (29.8-31.8)</td><td>29 (27.8-30.3)</td><td>16.6 (15.6-17.6)</td><td>12.4 (11.6-13.3)</td><td>11.1 (10.2-12)</td></tr>
</table>
</td>
<td>Exposure 1 (n=329)
Regular electronic nicotine product user

Exposure 2 (n=8,298)
Infrequent electronic nicotine product user

Comparator (n=9,632)
Never electronic nicotine product user

Materials
Device details unknown

Follow-up
3 years</td>
<td>New cases of gum disease
Baseline to wave 2 or 3

Bone loss
Around teeth, baseline to wave 3

Any periodontal disease
Baseline to wave 2 or 3. Diagnosis past 12 months</td>
<td>Oral health outcomes – n (%) [95% CI]
<table>
<tr><th></th><th>Never users</th><th>Regular users</th><th>Infrequent users</th></tr>
<tr><td>New cases of gum disease</td><td>49 (15.1%) [4.5–5.6]</td><td>32 (9.8%) (6.4–13.3)</td><td>515 (6.2%) [5.6–6.7]</td></tr>
<tr><td>Bone loss around teeth</td><td>809 (8.4%) [7.6–9.2]</td><td>37 (11.2%) [7.6–14.8]</td><td>606 (7.3%) [6.6–8.1]</td></tr>
<tr><td>Any periodontal disease</td><td>1127 (11.7%) [10.8–12.6]</td><td>55 (16.7%) [12.2–21.2]</td><td>946 (11.4%) [10.6–12.2]</td></tr>
</table>
Results of the Multivariable Logistic Regression Models - OR (95% CI)
<table>
<tr><th></th><th>New cases of gum disease</th><th>Bone loss around teeth</th><th>Any periodontal disease</th></tr>
<tr><td>Never users</td><td>Reference</td><td>Reference</td><td>Reference</td></tr>
<tr><td>Regular users</td><td>1.76 (1.12–2.76)</td><td>1.67 (1.06–2.63)</td><td>1.58 (1.06–2.34)</td></tr>
<tr><td>Infrequent users</td><td>1.09 (0.87–1.35)</td><td>1.10 (0.91–1.33)</td><td>1.09 (0.93–1.29)</td></tr>
</table>
Adjusted for age, gender, race, education, income, history of illicit/prescription drug use, tobacco, alcohol and marijuana use history, history of ulcers, respiratory disease, diabetes, high blood pressure, high cholesterol, dental visits</td>
<td>High methodological quality

Large study size

Conflicts of interest
None declared

Funding
Support from the NIH</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.8 Developmental and reproductive effects

Main conclusions from synthesised evidence on developmental and reproductive effects in relation to e-cigarette use

- There is no available evidence as to how use of e-cigarettes affects the development of children or adolescents.
- There is insufficient evidence as to how e-cigarette use relates to pregnancy and foetal outcomes, such as low birth weight, preterm birth, Apgar score and small-for-gestational-age birth, among exclusive e-cigarette users and dual users.
- There is no available evidence as to how use of e-cigarettes affects other reproductive outcomes.

Table 4.8-1: Overview of studies of developmental and reproductive effects identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Developmental and reproductive effects			2 0 / 2				1 0 / 1		

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Primary outcomes:** Measures of child and adolescent development (e.g. physical, social, emotional, cognitive, speech and language development) and reproductive outcomes including: infertility; pregnancy complications (e.g. placental abruption, ectopic pregnancy, hypertensive disorders, anaemia during pregnancy, preterm birth); and foetal development (e.g. low birthweight, small-for-gestational-age, congenital abnormalities) and maternal or infant mortality.

4.8.1 Findings from previous reviews

The NASEM review sought to include epidemiological studies on the relationship of e-cigarette use to developmental and reproductive effects, however, none were identified (Table 4.8-1).[3]

The Irish Health Research Board literature map[15] identified one cohort study which is also included in the top-up systematic review below.[503]

The Public Health England 2018 review[11] identified no studies on the relationship of e-cigarette use to developmental and reproductive outcomes. A 2020 evidence update[12] focusing on pregnancy outcomes identified one cohort study[503] which has also been included in the top-up review.

The CSIRO review included no epidemiological studies reporting on the relationship of e-cigarette use to human developmental and reproductive outcomes.[14]

No studies were identified in the SCHEER[4] and USPSTF[16] reviews on developmental and reproductive effects in relation to e-cigarette use.

4.8.2 Summary of conclusions from previous reviews

The NASEM review[3] concluded that:

- There was no available evidence whether or not e-cigarettes affect pregnancy outcomes.

- There was insufficient evidence whether or not maternal e-cigarette use affects foetal development.

The Public Health England review[11] concluded that:

- Due to limitations related to sample size and unverified exclusive e-cigarette use status in pregnant women, there was insufficient evidence whether or not maternal e-cigarette use affects foetal and postnatal development.

The Irish Health Research Board literature map[15] did not provide summative conclusions on the relationship of e-cigarette use and developmental and reproductive effects.

4.8.3 Top-up review

Search results

Overall, three articles were located in the top-up systematic literature search. One of these studies was cross-sectional[504] and was considered to be informative in this context, thus three articles[503-505] were available for the top-up synthesis of evidence (Table 4.8-1; Appendix 5).

Three systematic reviews with findings on developmental and reproductive health outcomes in relation to e-cigarette use were identified from the database search.[267,506,507] No human studies were identified by Cardenas et al.[506] The one study,[508] a cohort study, identified by Glover and Phillips did not meet inclusion criteria for the top-up review.[507] Tzortzi et al.[267] identified one case report[509] published in 2014 and in this context, case reports are not considered informative and no further discussion is provided.

Developmental and reproductive: primary outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to primary developmental and reproductive outcomes were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to primary developmental and reproductive outcomes were located.

Cohort studies

Two prospective cohort studies, one in the US[503] and one in Ireland,[505] reported on the relationship of e-cigarette use to foetal development and post-natal outcomes (Table 4.8.2).

Cardenas et al.[503] included six current exclusive e-cigarette users (use within the previous month), 56 current smokers (smoked within the previous month), 17 current dual users (smoking and e-cigarette use in the previous month), and 97 unexposed (non-current smokers and non-current e-cigarette users) who gave birth to a live birth singleton infant. The majority of participants were aged 27-years or less (approximately 69%) and 45.2% were non-Hispanic Blacks, 38.3% were non- Hispanic Whites, 12.1% were Hispanic, and 4.4% belonged to other ethnicities. Thirty-four percent of participants enrolled at less than 20 weeks' gestation and 65% enrolled at greater than 20 months' gestation, missing data for two participants.

Compared to non-smoking, non-e-cigarette using participants, current exclusive e-cigarette users had no significant difference in the risk of having a small-for-gestational-age infant after adjustment (RR 3.1; 95% CI 0.8-11.7; 11/97 events in non-exposed and 2/6 in exclusive e-cigarette users). There was no statistical difference in gestational age-specific and sex-specific birth weight z-scores in exclusive e-cigarette users compared to unexposed after adjustment (mean difference: -0.498; SD 0.411). After excluding participants from the unexposed group that reported no exposure but returned a positive cotinine or carbon monoxide test from the reference group, current exclusive e-cigarette users were at a significantly higher risk of having a low birthweight baby after adjustment (RR 5.1; 95% CI 1.2–22.2; 5/64 events in non-exposed and 2/6 in exclusive e-cigarette users).[503] Using the same reduced reference group, gestational age-specific and sex-specific birth weight z-scores did not differ significantly according to e-cigarette use (exclusive e-cigarette users mean difference: -0.540; SD 0.417).

There was no statistically significant difference in smallness for gestational age between unexposed mothers and current dual users after adjustment (RR 1.9; 95% CI 0.6-5.5). There was no significant difference in gender- and gestational age-specific birth weight z-scores between current dual users and unexposed mothers after adjustment (mean difference: -0.297; SD 0.266). After excluding participants from the unexposed group who reported no exposure but returned a positive cotinine or carbon monoxide test from the reference group, there was still no statistical different in smallness for gestational age

between dual users and unexposed mothers after adjustment (RR 2.5; 95% CI 0.7–8.8). There was no difference in gender- and gestational age-specific birth weight z-scores between dual users and the restricted unexposed group after adjustment (mean difference: -0.303; SD 0.274).[503]

McDonnell et al.[505] included 218 exclusive e-cigarette users (e-cigarette use at any point during pregnancy excluding those that quit after conception and before the first study visit), 108 never smokers, 99 current smokers (at least one cigarette per day), and 195 dual users (concurrent e-cigarette use and combustible cigarette smoking) who gave birth to a live birth singleton infant. The average age of exclusive e-cigarette mothers was 31 years (SD 5.3), 29 years (SD 5.7) for dual users and 33 years (SD 5.9) for never smokers.

Exclusive e-cigarette users less frequently reported breastfeeding at discharge compared to never smokers (e-cigarette: 106/218 participants (48.6%); never smokers: 66/108 participants (61.1%); p=0.03). There was no significant difference between exclusive e-cigarette users and never smokers in the proportion admitted to the neonatal intensive care unit (6.9% (15/218 participants) vs. 4.6% (5/108 participants) respectively, p=0.42). There was also no significant difference in overall birthweight (e-cigarette: 3470g; never smokers: 3471g; p=0.97), mean birth centile (e-cigarette: 47th; never smokers: 47th; p=0.97) and incidence of low birthweight (e-cigarette: 11% (24/218 participants); never smokers: 12.9% (14/108 participants); p=0.60). Gestation at delivery (both 39 months) and Apgar scores, a measure of a baby's condition immediately after birth, (both score of 9, 10) were the same but no statistical test was reported.[505]

Both studies were of high methodological quality as assessed by the Joanna Briggs Institute's critical appraisal checklist and no conflicts of interest were declared.

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarette use to primary developmental and reproductive outcomes were located.

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to primary developmental and reproductive outcomes were located.

Other study types

One study on developmental and reproductive outcomes from other study types was identified (Table 4.8.2).[504] Although this study could technically be considered cross-sectional and would not generally be considered further, it is less plausible that birth outcomes could influence the exposure than for other cross-sectional surveys and hence findings are outlined here.

The study by Wang et al. collected retrospective data from the 2016 US Pregnancy Risk Assessment Monitoring System (PRAMS), on a wide range of exposures from women who had given birth to a liveborn singleton infant.[504] In the last three months of pregnancy, there were 28,770 non-users (no definition), 2,632 exclusive smokers, 126 exclusive e-cigarette users and 265 dual users (concurrent smoking and e-cigarette use). E-cigarettes also included the use of vape pens, e-hookahs, hookah pens, e-cigars and e-pipes.

There was no statistically significant difference in preterm birth between non-users and exclusive e-cigarette users after adjustment (AOR 1.6; 95% CI 0.7-3.4). After controlling for smoking and e-cigarette use in the three months prior to pregnancy, there was still no statistical difference between non-users and exclusive e-cigarette users (AOR 1.2; 95% CI 0.5-2.7). There was also no difference in preterm birth outcomes between non-users and dual users with (AOR 1.3; 95% CI 0.8-2.3) and without (AOR 1.2; 95% CI 0.8-2.0) controlling for pre-pregnancy smoking and e-cigarette status.

Compared to non-users, there was no statistically significant difference in smallness for gestational age in exclusive e-cigarette users after adjustment (AOR 2.0; 95% CI 0.8-4.7). After controlling for smoking and e-cigarette use in the three months prior to pregnancy, exclusive cigarette users were significantly more likely to report smallness for gestational age than non-users (AOR 2.4; 95% CI 1.0-5.7). Compared to non-users, dual users were significantly more likely to report smallness for gestational with (AOR 2.3; 95% CI 1.3-4.1) and without (AOR 2.2; 95% CI 1.3-3.8) controlling for pre-pregnancy smoking and e-cigarette status.[504]

The study was of high methodological quality using the Joanna Briggs Institute's critical appraisal checklist and no conflicts of interest were declared.

Additional studies post-search

Two cross-sectional surveys on developmental and reproductive health were non-systematically identified after the search dates, with further details in Appendix 7.

4.8.4 Summary of findings from top-up review

Three studies, two cohort studies and one cross-sectional survey, on primary reproductive and developmental outcomes were identified, finding:

- Among non-smokers, the risk of having a small-for-gestational-age baby was significantly higher in women who used versus did not use e-cigarettes in two studies, and not significantly different in another. Exclusive e-cigarette use was related to lower rates of breastfeeding at discharge compared to non-smoking non-users of e-cigarettes in one small cohort study. Hence:
    - There was insufficient evidence on the relationship of exclusive e-cigarette use to foetal developmental outcomes.
- Compared to non-smoking non-users of e-cigarettes, the risk of having a small-for-gestational-age baby in dual e-cigarette users and tobacco smokers was significantly higher in one study and not significantly different in another. Hence:
    - There was insufficient evidence on the relationship of dual e-cigarette and smoking use to foetal developmental outcomes.
- No studies on the relationship of e-cigarette use to other reproductive outcomes were identified. Hence:
    - There was no available evidence as to how use of e-cigarettes affects other reproductive outcomes.
- No studies on the relationship of e-cigarette use to child or adolescent development outcomes were identified. Hence:
    - There was no available evidence as to how use of e-cigarettes affects the development of children or adolescents.
- The GRADE rating was very low certainty.

4.8.5 Summary of findings integrating evidence from this top-up review with previous reviews

As no additional evidence was sourced from other reviews, please see findings from the top-up review for the summary.

4.8.6 Main conclusions from synthesised evidence on developmental and reproductive effects in relation to e-cigarette use

- There is no available evidence as to how use of e-cigarettes affects the development of children or adolescents.
- There is insufficient evidence as to how e-cigarette use relates to pregnancy and foetal outcomes, such as low birth weight, preterm birth, Apgar score and small-for-gestational-age birth, among exclusive e-cigarette users and dual users.
- There is no available evidence as to how use of e-cigarettes affects other reproductive outcomes.

Table 4.8-2. Study details: developmental and reproductive effects - cohort studies and cross-sectional surveys

Study details (author, year, location study type [time frame, data source])	Sample characteristics	Exposure/Comparison groups	Outcome measure	Results	Quality assessment, study size, conflicts of interest, funding
Cohort studies					
McDonnell et al., 2020[505] Ireland Prospective cohort study No data period provided Large urban maternity hospital	<u>Study size</u> 620 participants who gave birth to live singleton infants <u>Sample</u> ENDS: e-cigarette use at any point during pregnancy excluding those that quit after conception and before first study visit Never smokers: never smoked <u>Age – mean (SD) years</u> ENDS: 31 (5.3) Never smokers: 33 (5.9)	<u>Exposure (n=218)</u> Exclusive ENDS users <u>Comparator (n=108)</u> Never smokers <u>Materials</u> Device and nicotine concentrations not specified <u>Follow-up</u> 13 months	Birthweight (g) Mean birth centile Incidence of birthweight < 10th centile Mean gestation at delivery Mean Apgar score Neonatal Intensive Care Unit (NICU) admission Breastfeeding at discharge	Outcome / ENDS n (%) / Never smokers n (%) / ENDS compared to never smokers Birthweight (g): 3470 ± 555 / 3471 ± 504 / p=0.97 Mean birth centile: 47th / 47th Incidence of birthweight <10th percentile: 24 (11%) / 14 (12.9%) / p=0.60 Mean gestation at delivery: 39+3 / 39+4 Mean Apgar score: 9, 10 / 9, 10 NICU admission: 15 (6.9%) / 5 (4.6%) / p=0.42 Breastfeeding at discharge: 106 (48.6%) / 66 (61.1%) / p=0.03	High methodological quality Small study size <u>Conflicts of interest</u> None declared <u>Funding</u> Friends of the Coombe' research charity and by Coombe Women and Infants University Hospital

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location study type [time frame, data source])</th><th>Sample characteristics</th><th>Exposure/Comparison groups</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflicts of interest, funding</th></tr>
<tr>
<td>Cardenas et al., 2019[503]

US

Prospective cohort study

2015-2017

University affiliated pregnancy centre in Little Rock, Arkansas</td>
<td><u>Study size</u>
248 participants who gave birth to live singleton infants

<u>Sample</u>
Exclusive ENDS: ENDS use within the previous month
Dual users: current ENDS and smoking
Smokers: smoking in the previous month
Unexposed: non-current smokers/non-current ENDS users not exposed to secondhand smoke or ENDS aerosols or other tobacco products

<u>Age (%) years</u>
18-22: 37.9%
23-27: 30.6%
≥28: 31.5%

<u>Ethnicity (%)</u>
Non-Hispanic Blacks: 45.2%
Non-Hispanic Whites: 38.3%
Hispanic: 12.1%
Other: 4.4%</td>
<td><u>Exposure 1 (n=6)</u>
Exclusive current ENDS

<u>Exposure 2 (n=17)</u>
Dual users

<u>Exposure 3 (n=56)</u>
Current smokers

<u>Comparator (n=97)</u>
Unexposed

<u>Materials</u>
Device and nicotine concentrations not specified

<u>Follow-up</u>
6 months</td>
<td>Birthweight

Smallness for gestational age (SGA)</td>
<td><u>Pregnancy outcomes (n=232)</u>
<table>
<tr><th></th><th>Multivariate* mean z-score birthweight difference (SE)</th><th>SGA n (%)</th><th>SGA multivariate* risk ratio (95% CI)</th></tr>
<tr><td>Exclusive ENDS</td><td>-0.498 (0.411)</td><td>2 (33.3)</td><td>3.1 (0.8-11.7)</td></tr>
<tr><td>Current smoker</td><td>-0.482 (0.177)**</td><td>13 (23.1)</td><td>1.9 (0.9-4.3)</td></tr>
<tr><td>Dual</td><td>-0.297 (0.266)</td><td>4 (23.5)</td><td>1.9 (0.6-5.5)</td></tr>
<tr><td>Unexposed (n=97)</td><td>0 (Referent)</td><td>11 (11.3)</td><td>1 (Referent)</td></tr>
</table>
* Model included maternal age and race/ethnicity as covariates
** p<0.05

<u>Pregnancy outcomes, excluding unexposed participants who returned positive cotinine or carbon monoxide tests (n=199)</u>
<table>
<tr><th></th><th>Multivariate* mean z-score birthweight difference (SE)</th><th>SGA (%)</th><th>SGA multivariate* risk ratio (95% CI)</th></tr>
<tr><td>Exclusive ENDS</td><td>-0.540 (0.417)</td><td>2 (33.3)</td><td>5.1 (1.2–22.2)</td></tr>
<tr><td>Current smoker</td><td>0.490 (0.190)**</td><td>13 (23.1)</td><td>2.6 (0.9-7.2)</td></tr>
<tr><td>Dual</td><td>-0.303 (0.274)</td><td>4 (23.5)</td><td>2.5 (0.7–8.8)</td></tr>
<tr><td>Unexposed (n=64)</td><td>0 (Referent)</td><td>5 (7.8)</td><td>1 (Referent)</td></tr>
</table>
* Model included maternal age and race/ethnicity as covariates
** p<0.05</td>
<td>High methodological quality

Very small study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
None received</td>
</tr>
<tr><td colspan="6">Cross-sectional surveys</td></tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location study type [time frame, data source])	Sample characteristics	Exposure/Comparison groups	Outcome measure	Results	Quality assessment, study size, conflicts of interest, funding
Wang et al., 2020[504] US Cross-sectional 2016 Pregnancy Risk Assessment Monitoring System (PRAMS)	Study size 31,793 participants who gave birth to live singleton infants Sample Exclusive ENDS, sole smokers, dual users and non-users as reported 3 months before and last 3 months of pregnancy. No demographic data reported	Exposure 1 (n=126) ENDS: ENDS and other electronic nicotine products (vape pens, e-hookahs, hookah pens, e-cigars, e-pipes) in the last 3 months of pregnancy Exposure 2 (n=2,632) Smokers: smoked cigarettes in the last 3 months of pregnancy Exposure 3 (n=265) Dual: concurrent ENDS and cigarette use in the last 3 months of pregnancy Comparator (n=28,770) Non-users Materials Not specified	Preterm Small-for-gestational-age	Smoking and e-cigarette use 3 months before pregnancy and in the last 3 months of pregnancy Status in the last 3 months of pregnancy Status 3 months pre-pregnancy: Neither / Smoker / ENDS / Dual user Neither: 25,501 / 17 / 3 / 0 Exclusive smoker: 2,622 / 2342 / 18 / 47 Exclusive ENDS: 215 / 3 / 49 / 0 Dual user: 432 / 270 / 56 / 218 Total: 28,770 / 2,632 / 126 / 265 Adjusted odds ratios (95% CI) for pregnancy outcomes associated with tobacco use in the last 3 months of pregnancy ENDS / Smoker / Dual user Preterm: 1.6 (0.7-3.4) / 1.5 (1.2-1.8) / 1.2 (0.8-2.0) Small-for-gestational-age: 2.0 (0.8-4.7) / 2.6 (2.2-3.1) / 2.2 (1.3-3.8) Adjusted for pre-pregnancy smoking/e-cigarette status Preterm: 1.2 (0.5-2.7) / 1.6 (1.2-2.0) / 1.3 (0.8-2.3) Small-for-gestational-age: 2.4 (1.0-5.7) / 2.4 (1.8-2.9) / 2.3 (1.3-4.1) Adjusted for: mother's age, education level, race/ethnicity, marital status, previous preterm history, plurality, Kotelchuck index of prenatal care, pre-pregnancy BMI, drinking alcohol before pregnancy, and gestational weight gain	High methodological quality Large study size Conflicts of interest None declared Funding No specific funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.9 Burns and injuries

Main conclusions from the synthesised evidence on burns and injuries due to e-cigarette use

- There is conclusive evidence that e-cigarettes can cause burns and injuries, which can be severe and can result in death.

Table 4.9-1: Overview of studies of burns and injuries identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Burns and injuries						7 1 / 6		24 14 / 10	16 5 / 11

Notes:
- The top large number is the total combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation for this health outcome.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes:** Thermal burns, chemical burns, bone fractures, displacement or cracking of teeth, lodgment of foreign body or projectiles and lacerations.

4.9.1 Findings from other reviews

Trauma resulting from the explosion of e-cigarettes has the potential to affect multiple body structures and systems. As such, some studies included in this chapter have also been discussed in other chapters such as neurological outcomes.

The NASEM review[3] included 46 case reports or case series reporting burns and injuries as a result of malfunctioning devices, however only 20 papers were referenced; five case reports,[502,510-513] 14 case series or burn centre reports,[479,488,514-525] and one surveillance report[482]. The majority of burns occurred on the thigh and were the result of device malfunction whilst in the wearer's trouser pocket[479,510,511,513-518,520,521] – in some cases, malfunction occurred after the device came into contact with other items stored in the pocket such as keys or coins. There were also case reports of facial trauma due to projectiles as a consequence of the device exploding.[502,512,519] No epidemiological studies were identified.

The Irish Health Research Board literature map[15] identified a total of 51 papers describing burns and injuries due to e-cigarette explosions, including 28 case reports, 19 case series, and four surveillance reports. Of the 28 case reports, six were included in the NASEM review[502,510-513,522], five were captured in the top-up review[526-530], and 17 were published prior to our time limit but not mentioned in NASEM[487,489-492,501,531-541]. Of those cases not included in NASEM or the top-up review, the most common type of injury was a thermal burn,[534-536,541] blast injury[491,533,537,540] or fracture.[487,492,532] A burn or injury occurred most frequently to the face,[487,489-491,532,536,537,540,541] followed by the hand.[489,491,533,541]

The Irish Health Research Board literature map[15] identified 19 case series, 10 of which included two or three cases and nine which included eight to fourteen. Of the 19 case series included in the literature map, 10 were included in the NASEM review[479,488,516-521,523,524], six were included in the top-up review[542-547], two were published prior to our time frame but not included in NASEM[548,549] and one was excluded as poor quality[550]. Of the studies not included in NASEM or the top-up review, blast injuries were the most commonly reported type of injury,[488,548-550] with burn and injury most frequently reported to the thigh,[488,524,549] face[488,548,549] and hand.[488,548] Two papers did not report outcomes beyond the sustained injury.[549,550]

Four surveillance reports, all from the US, were identified by the Irish Health Research Board literature map.[15] One[482] was included in the NASEM review and three[551-553] were included in the top-up review.

The Public Health England review[11] identified 27 papers on injuries or burns from e-cigarette explosions; 12 case reports, 12 case series and three surveillance reports. Of the 27 studies, 14[479,482,502,510,513-515,517-521,523,525] were included in the NASEM review, one[543] was included in the top-up review and 12[487-490,492,532,533,535,537,538,548,549] were published prior to the date limit of the top-up review and not included in the

NASEM review. All 12 studies have been described under the Irish Health Research Board literature map summary.

The CSIRO review[14] identified 11 case reports, 10 case series or single centre reports and three passive surveillance reports detailing burns or injuries after a device exploded or caught fire. Of the 24 studies, eight[482,511,514,517,521,523,524,540] were included in the NASEM review, nine were included in the top-up review[526-528,530,543,544,546,547,551] and seven[487,488,492,501,531,533,549] were published prior to the time limit in the top-up review and not published in the NASEM review. All studies not captured by the NASEM review have been previously discussed under the Irish Health Research Board summary. The CSIRO review also included a cross-sectional survey suggesting that daily e-cigarette use may be a risk factor for cracked or broken teeth.[462] This study has not been included in this chapter, rather was captured in the oral health chapter.

The SCHEER[4] review identified 11 studies, three case reports, six case series and two surveillance reports on burns and injuries related to e-cigarette use. Of the 11 studies, four were included in the NASEM review,[518,522,524,525] one was included in the top-up review,[546] and six were published before the top-up review date limit but not included in NASEM.[488,532,533,537,548,549] All six studies were also included in the Irish Health Research Board literature map and are discussed above.

No studies were identified in the USPSTF review.[16]

4.9.2 Summary of conclusions from other reviews

The NASEM review,[3] including only case reports, case series and surveillance reports, concluded that:

- 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 modified by users.

The Irish Health Research Board literature map,[15] using only case reports, case series and surveillance reports, found evidence of acute harm arising from burns and injuries caused from e-cigarette device or battery malfunction and explosion.

Evaluating case reports, case series and surveillance reports, the Public Health England review[11] concluded that:

- 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.

The CSIRO review[14] including case reports, case series and one cross-sectional survey concluded that:

- 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.

The SCHEER review [4]did not provide any summative conclusions on burns and injuries due to e-cigarettes.

4.9.3 Top-up review

Search results

Overall, 27 articles articles were located in the top-up systematic literature search and included in evidence synthesis (Table 4.9.1).

Four systematic reviews with findings on burns and injuries from e-cigarettes were identified in the database search.[241,267,554,555] Glasser et al.[241] identified one study,[482] a surveillance report, that was also included in the NASEM review. Jones et al. identified 21 studies, one surveillance report, 15 case series, and five case reports.[554] Of the 21 studies, 14 were included in the NASEM review,[479,502,511,514-523,525] three were included in the top-up review,[527,543,545] four published before the date limit for the top-up review and not included in NASEM.[488,490,524,535] The studies not captured by the NASEM review were included in the Irish Health Research Board literature map and are discussed above. Seitz and Kabir 2018[555] identified 31 articles, 11 case reports, 19 case series or burn centre reports and one surveillance report. Seven were identified in the top-up review[527,530,542,543,545-547], 15 were included in the NASEM review[479,502,510,513-523,525], and nine were published before the top-up date of the top-up review and not in the NASEM review[489,490,524,534,535,538,548,549,556]. Of the nine articles not included in either the top-up or NASEM reviews, all but one article[556] has been previously discussed under the Irish Health Research Board literature map summary. The case report by Schoeder et al. described a case where a 27-year-old male experienced superficial partial thickness burn to the lower extremity, total body surface area of burn 15-25%, after his device exploded in his trouser pocket.[556] Tzortzi et al. identified 51 studies, 26 case reports, 20 case series and five surveillance reports.[267] Of the 51 studies, 20 were included in the NASEM review,[479,482,502,510-525,540]

15 were included in the top-up review[526-530,542-547,551,553,557,558], 16 were published prior to the date limit for the top-up review and not included in the NASEM review.[487,489-492,531-533,535-539,548,549,556] Of the studies not captured by NASEM, all were discussed in the Irish Health Research Board literature map summary except one[556] which was discussed in the summary of Seitz and Kabir.[555]

Burns and injuries: Clinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to injuries or burns were located.

Randomised controlled trials

No randomised controlled trials were located reporting on the relationship of e-cigarettes to injuries or burns.

Cohort studies

No cohort studies were located reporting on the relationship of e-cigarettes to injuries or burns.

Non-randomised intervention studies

No non-randomised intervention studies were located reporting on the relationship of e-cigarettes to injuries or burns.

Case-control studies

No case-control studies were located reporting on the relationship of e-cigarettes to injuries or burns.

Other study types

There were 27 articles, 11 case reports,[526-530,557,559-563] 10 case series or burn centre reports[402,542-547,558,564,565] and six passive surveillance reports[551-553,566-568] identified and included in evidence synthesis (Table 4.9.1).

Surveillance reports

There were six passive surveillance reports, five from the US[551-553,567,568] and one from Canada[566] (Table 4.9.2). Three of the US reports collected data from the National Electronic Injury Surveillance System, Dohnalek and Harley[552] included reports from 2008-2017 and covered data included in Corey et al.[551] and Rossheim et al.[553] The other two US studies collected data from the National Fire Data Centre[567] and the National Poison Data System.[568] The Canadian Hospitals Injury Reporting and Prevention Program network was used in the Canadian report.[566] The largest number of cases identified was 69[568] and the smallest was four.[566] Males constituted greater than 94% in three reports[551-553] and 57% in one report.[568] All ages were included in four reports.[551-553,568] Two reports reported no demographic information.[566,567]

Burns were the most common type of injury, with the most frequently reported location of the burn or injury being the thigh area, including lower abdomen and genitals, followed by the hand. One study reported the head as the most frequent body location of injury or burn, with multiple injury sites second most frequent.[568] In two studies, the most common type of burn was thermal.[551,568] Three studies reported information about the circumstance of the e-cigarette leading to explosion, with one study reporting most incidences originated from a battery stored in the pocket,[551] one reported similar frequencies of incidences occurring when the device was in use, from a spare battery and during charging,[567] and one study reported overheating as the primary cause.[566] Time trend information was reported in one case and indicated an increasing frequency of incidents.[552]

Three papers calculated national estimates; all used the National Electronic Injury Surveillance System in the US. Dohnalek and Harley[552] covered the longest time period from 2007 to 2017 and captured data from Rossheim et al.,[553] which used data from 2015 to 2017, and Corey et al.,[551] which used only 2016 data. Dohnalek and Harley[552] estimated that there were 1,866 cases of ENDS-related trauma in the US between 2007 and 2017, with an average of 835 cases per year. No cases were reported between 2007 and 2012 nor in 2014. In 2013 there were an estimated 25 cases. This increased substantially and peaked in 2016 with 944 cases.[552]

Four of the reports were of high quality[551-553,568] and two were low quality[566,567] using the Joanna Briggs Institute's critical appraisal checklist and GRADE was not applied. No conflicts of interest were declared in four reports.[551,553,566,568] Two reports did not have any information on conflicts of interests.[552,567]

Case series and burn centre reports

Case series in which only some individual case reports met our inclusion criteria have been retained in case series analysis however, only applicable results have been presented.

In the case series by Isakov et al.,[402] one out of the 10 case reports met our inclusion criteria for analysis in burns and injuries due to e-cigarette use. In this case, a 22-year-old male sustained lower lip lacerations,

multiple displaced teeth, and a fractured maxilla due to his device exploding during use. The lacerations were repaired and a dentoalveolar splint implanted. No follow-up was reported.

Claes et al.[564] and Harshman et al.[543] described two cases in their case series. Both cases included in Claes et al., were male and aged 45 and 47 years. Case one was injured when his device spontaneously ignited in his pants pocket and case two was injured when the spare battery in his pants pocket went into 'thermal runaway'. Case one received superficial partial and deep partial thickness burns on his right upper leg covering 9% of this total body surface area. Case two received superficial partial thickness, deep partial thickness and full thickness burns to upper leg and superficial burns to his fingers covering 9% of this total body surface area. Both cases had their wounds cleaned and covered with an allograft. Complete wound healing was reported 35 and 61 days after the initial injury for case one and two respectively.

The two cases described in Harshman et al.[543] were both males and aged 31 and 36 years, and both incurred their injury when their e-cigarette spontaneously ignited in their trouser pocket. Case one received mixed partial thickness and full thickness flame burns to the thigh, buttock and leg and case two received deep partial and full thickness burns to the thigh, superficial partial thickness burns to his hand and had part of the battery case embedded in the thigh. The total body surface area of the burn was 10% and 3% for case one and two respectively. Burns were irrigated and dressed in both cases. Case two was also treated with antibiotics due to a skin infection in the burn area. Full recovery was reported at two months for both cases.

There were seven studies collecting data from a single burns centre or hospital, five[542,544,545,547,558] from the US and two from France,[546,565] ranging in size from six[558] to 16[565] cases (Table 4.9.2). Five studies reported only males[545-547,558,565] and two reported 93% males and 7% females.[542,544] Mean age ranged from 29-41 years and the greatest reported age range was 19-50 years.[544] Devices or batteries exploded in pants pockets in 70%[547]-100% of the cases,[558] breast pockets in 13%[545] and hands in 7%[544]-20%.[546] Burns constituted between 2%[558] and 16%[545] total surface body area. The most common body areas injured were the thighs and the hands/fingers. Average healing time varied from 18[544]-46[565] days.

Of the cases series, Harshman et al.[543] and Isakov et al. were rated moderate and Claes et al.[564] high using the Joanna Briggs Institute's critical appraisal checklist and GRADE was not applied. There were no conflicts of interest declared in all three studies. Of the burn centre reports, the quality was rated moderate for five[542,545,547,558,565] studies and high in two[544,546] using the Joanna Briggs Institute's critical appraisal checklist and GRADE was not applied. There was no conflict of interest reported in four studies[542,546,558,565] and no information provided in three [544,545,547] (Table 4.9.3).

Case reports

All of the 11 case reports occurred in the US. Nine cases were male[526,528-530,557,559,560,562,563] and two were female,[527,561] ranging in age from 16[563] to 40[557,562] years. Injuries due to explosions during use occurred in eight cases, two of these with a modified device.[560 561]There was one case of spontaneous combustion of the device in pockets,[557] of spontaneous combustion of the spare batteries in pockets[562] and inadvertent aspiration of the cartridge cap.[563] Burns ranged from 2%-80% total body surface area. The more frequently reported locations of injury were the mouth (including lips, tongue, jaw and teeth) reported in five cases[528,529,559-561] and the thighs[527,557,562] or hand[526,530,561] reported in three cases. Other injuries included harm to the head and/or face,[527,529] spine[561] and airways.[563] Many reported multiple burns or injury sites per case. Beining et al.[560] was the only case report in which the individual died as a result of the injuries caused by the e-cigarette explosion (death due to projectile wound to the head). Treatment consisted of sutures, debridement and/or allografts, splints and dental replacements.

The quality was rated low for four[527,559,562,563] reports, moderate for six[526,528,529,557,560,561] reports, and high for one[530] report using the Joanna Briggs Institute's critical appraisal checklist. GRADE was not able to be applied. No conflict of interest statement was provided in six studies[526,527,529,559,560,562] and five studies[528,530,557,561,563] reported no conflicts of interest (Table 4.9.3).

4.9.4 Summary of findings from top-up review

There were six surveillance reports on burns and injuries from an e-cigarette device or battery malfunction, finding:

- Thermal burns to the lower body were the most common type of injury related to e-cigarette use.
- The face was also a common burn and injury location from e-cigarette use.
- Burns and injuries from e-cigarette use are most common in young males.
- The incidence of burns and injuries from e-cigarettes has increased over time as usage has increased. National estimates indicate an increase from no cases between 2007-2012 to 726 in 2017.

- National estimates from the US suggest there are 835 cases of burns and injuries per year from 2007-2017.

There were 11 case reports and 10 case series or burn centre reports on burns and injuries from an e-cigarette device or battery malfunction, finding:

- Use of e-cigarettes can result in burns and injuries.
- Thermal burns were the most common injury from e-cigarette use, varying in severity and the amount of total surface body area burnt.
- Thighs were the most common burn and injury location and these generally occurred while the e-cigarette device or battery was stored in the pants pocket.
- The hands and mouth were also common burn and injury locations resulting from explosion of the e-cigarette device while in use.
- One fatality resulted from head trauma as a consequence of a projectile from an exploding e-cigarette.
- Information on e-cigarette device type was largely unknown with specific details reported only in one case report. Two reported modifications to the device but no specifics were given. Five studies distinguished between e-cigarette batteries and the device.

4.9.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence from the top-up systematic review with the evidence from previous reviews on clinical outcomes:

- There was a total of 68 studies of burns and injuries in relation to e-cigarette use: 34 case reports, 27 case series or burn centre reports, and 7 passive surveillance or single burn centre reports.
- Thermal burns are the most common type of injury and varied in severity with burns to the lower body most frequent. One death from an e-cigarette explosion was reported.
- Trauma from e-cigarette explosions can impact many difference body structures and systems.
- Hence:
    - There is conclusive evidence that the use of e-cigarettes is related to burns and injuries.
    - There is conclusive evidence that burns and injuries resulting from e-cigarette use can be severe and can result in death.
- Case reports and case series are particularly useful for describing events where a direct relationship between cause and effect is clear. In the context where no other cause of the burn or injury is apparent they are considered appropriate evidence for our conclusions.
- No epidemiological studies on the relationship of e-cigarette use to burns and injuries were identified. Hence:
    - There is no available quantitative evidence as to the relative risk and incidence of burns and injuries related to the use of e-cigarettes.
- Due to the study types available, the GRADE approach was not applied.

4.9.6 Main conclusions from the synthesised evidence on burns and injuries related to e-cigarette use

- There is conclusive evidence that e-cigarettes can cause burns and injuries, which can be severe and can result in death.

Table 4.9-2. Study details: burns and injuries – surveillance reports

Study details (author, year, location, time frame, data source)	Demographic characteristics	Circumstance of injury	Presentation or details of injuries	Treatment	Outcome and recovery	Quality assessment, study size, conflict of interest, funding
McFaull et al., 2020[566] Canada 2013-2019 Canadian Hospitals Injury Reporting and Prevention Program network	N=4 Demographic information not reported	Explosion or overheating of the device: 2 Swallowed part of device: 1 Crushing injury by piece of disassembled device: 1	Thigh burn: n=2 Foreign body in alimentary tract: n=1 Crushing injury to finger: n=1	Not reported	Not reported	Low methodological quality Very small study size Conflicts of interest None declared Funding Not reported
Wang et al., 2020[568] US 2010-2019 National Poison Data System (NPDS)	N=69 Gender - n (%) Male: 39 (56.5) Female: 28 (40.6) Unknown: 2 (2.9) Age - n (%) years <5: 2 (2.9) 5–11: 0 (0.0) 12–17: 8 (11.5) 18–24: 20 (29.0) 25+: 30 (43.5) Unknown: 9 (13.0)	Not reported	Type of Burn Thermal: 42 (60.9%) Chemical: 21 (30.4%) Both Thermal and Chemical: 5 (7.2%) Not Specified: 1 (1.4%) Body Part Burned More than One Body Part: 18 (26.1%) Face Only: 23 (33.3%) Leg/Thigh Only: 13 (18.8%) Hand Only: 10 (14.5%) Shoulder/Chest Only: 1 (1.4%) Genitals Only: 1 (1.4%) Not Specified: 3 (4.3%) Severity of Burn Superficial burn: 40 (58.0%) Second- or third-degree burn: 25 (36.2%)	Admitted: 4 (5.8%) Treated, evaluated, and released: 45 (65.2%) Not referred: 11 (15.9%) Refused referral: 3 (4.4%) Lost to follow-up: 6 (8.7%)	Minor, resolved rapidly: 21 (30.4%) Moderate: 33 (47.8%) Major, life-threatening: 2 (2.9%) Not followed-up: 13 (18.9%)	High methodological quality Conflicts of interest None declared Funding Supported by the Center for Tobacco Products, U.S. Food and Drug Administration

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographic characteristics	Circumstance of injury	Presentation or details of injuries	Treatment	Outcome and recovery	Quality assessment, study size, conflict of interest, funding
Dohnalek & Harley, 2019[552] US 2007-2017 National Electronic Injury Surveillance System (NEISS)	N=49 Sex unweighted – n (%) Male: 47 (95.9) Female: 2 (4.1) Age unweighted – n (%) years <18: 3 (6.1) 18–29: 26 (53.1) 30–44: 14 (28.6) 45- 60: 5 (10.2) 60+: 1 (2.0) Ethnicity unweighted – n (%) Non-Hispanic white: 20 (40.8) Black: 3 (6.1) Hispanic: 1 (2.0) Not stated: 25 (51.1)	No information available on the e-cigarette used nor the exposure circumstances	Affected Body Part (2008-2017) Head: 4.1% Shoulder: 2.0% Lower arm: 6.1% Lower abdomen: 8.2% Hand: 16.3% Upper leg: 59.2% Lower leg: 4.1% Events 2007-2012: 0 2013: 1 2014: 0 2015: 5 2016: 25 2017: 18	Required hospitalisation: 13 (26.5%)	Not reported	High methodological quality Small study size Conflicts of interest Not reported Funding Not reported
Corey et al., 2018[551] US 2016 National Electronic Injury Surveillance System (NEISS)	Unweighted N=26 Sex unweighted – n (%) Male: 25 (96.2) Female: 1 (3.8) Age unweighted counts - n (%) years <18: 3 (11.3) 18–24: 4 (15.4) 25–54: 18 (69.2) ≥55: 1 (3.8)	Device batteries in pocket: 20 (76.9%) Details of e-cigarette devices used were not reported	Burn type – unweighted n (%) Thermal burn: 22 (84.6) Chemical burn: 3 (11.5) Electric burn: 1 (3.4) Affected body part – unweighted n (%) Upper leg/lower trunk: 19 (73.1) Hand/lower arm: 5 (19.2) Other body parts: 2 (7.7)	Unweighted – n (%) Treated/discharged: 13 (50.0) Hospitalised: 12 (46.2) Other: 1 (3.8)	Not reported	High methodological quality Very small study size Conflicts of interest None declared Funding Supported by Center for Tobacco Products, U.S. Food and Drug Administration
	National estimate N=1007 Sex national estimate – n (%; 95% CI) Male: 992 (98.5; 95.1-100.0) Female: 15 (1.5; 0.0-4.9)	Not reported	Burn type – national estimate n (%; 95% CI) Thermal burn: 809 (80.4; 53.2-100.0) Chemical burn: 134 (13.3; 0.0-38.3) Electric burn: 64 (6.3; 0.0-19.9)	National estimate – n (%; 95% CI) Treated/discharged: 626 (62.2; 28.9-95.5) Hospitalised: 278 (27.6; 2.6-52.5)	Not reported	

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographic characteristics	Circumstance of injury	Presentation or details of injuries	Treatment	Outcome and recovery	Quality assessment, study size, conflict of interest, funding
	Age national estimate – n (%; 95% CI) <18: 190 (18.9; 12.2-25.6) 18–24: 109 (10.8; 0.0-24.8) 25–54: 693 (68.8; 58.7-78.9) ≥55: 15 (1.5; 0.0-5.1)		Affected body part- national estimate n (%; 95% CI) Upper leg/lower trunk: 778 (77.3; 60.4-94.2) Hand/lower arm: 198 (19.7; 2.0-373) Other body parts: 31 (3.1; 0.0-7.3)	Other: 103 (10.3; 0.0-34.7)		
	National estimate N=1,866 Average per year – national estimate N=835	Not reported	National estimate – n 2007 – 2012: 0 2013: 25 2014: 0 2015: 171 2016: 944 2017: 726	Not reported	Not reported	
Rossheim et al., 2018[553] US 2015-2017 US Consumer Product Safety Commission's (CPSC) National Electronic Injury Surveillance System (NEISS)	Unweighted N=52 National estimate – n (95% CI) N=2,035 (1107-2964) Sex national estimate % (95% CI) Male: 94 (85-100) Age national estimate % (95% CI) Median: 26 (22-30) Ethnicity national estimate % (95% CI) White: 87 (72-100)	Not reported	Burn location – national estimate % (95% CI) Burns: 97 (93-100) Upper leg: 61 (45-77) Hand/fingers: 25 (9-42)	National estimate - % (95% CI) Treated/released same visit: 69 (47-91) Admitted: ~ 26 (5-47) Left without being seen: 5 (0 -15)	Not reported	High methodological quality Conflicts of interest None declared Funding Supported by the National Institute on Drug Abuse of the National Institutes of Health

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, time frame, data source)	Demographic characteristics	Circumstance of injury	Presentation or details of injuries	Treatment	Outcome and recovery	Quality assessment, study size, conflict of interest, funding
Saxena et al., 2018[567] US (1) 2009-2016 (2) 2009-2017 (1) National Fire Data Center (2) Blog reports (Ecigone Blog)	Total cases N=636 (1) 195 (2) 243 No demographic information reported	Not reported	Not reported	Not reported	Not reported	Low methodological quality <u>Conflicts of interest</u> Not reported <u>Funding</u> Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Table 4.9-3. Study details: burns and injuries – case reports and case series

Study details (author, year, location, [time frame], data source)	Demographics and medical history	Exposure (location of device, circumstance	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Case series and burn centre reports						
Boissiere et al., 2020[565] France 2014-2019 Montpellier University Hospital Burn Centre	N=16 Males Age-mean: 41 years	Device or battery in pocket: 100% One battery in their pocket possibly in contact with other objects: 56% Presence of flame: 100% Overheating before the fire: 50%	Second or third-degree burns: 100% Average TBSA: 5% burned Affected body area: buttocks, pelvis and genitals and/or the thigh areas	Hospitalisation: 37.5% Surgery: 37.5%	Average healing length 46.25 days	Moderate methodological quality Conflicts of interest None declared Funding Not reported
Claes et al., 2020[564] Belgium No time frame reported Ghent Burn Center	Case 1 Male 45 years Case 2 Male 47 years	Case 1 Spontaneous ignition of device in jeans pocket Case 2 Spare battery went into thermal runaway in pocket	Case 1 Superficial partial and deep partial thickness burn on his right upper leg – 9% TBSA Case 2 Superficial partial thickness, deep partial thickness and full thickness burn to upper leg and superficial burn to his fingers – 9% TBSA	Case 1 Cleaned and covered with allograft Case 2 Cleaned and covered with allograft	Case 1 Complete wound healing 35 days after the initial injury. Scarring Case 2 Complete wound healing 61 days after the initial injury. Scarring	High methodological quality Conflicts of interest None declared Funding No specific funding
Isakov et al., 2020[402] US No time frame reported Hospital record	Male 22 years	Device exploded during use	Lower lip laceration, multiple displaced teeth, and fractured maxilla	Lacerations repaired and dentoalveolar splint placed	Not reported	Moderate methodological quality Conflicts of interest None declared Funding None received

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, [time frame], data source)	Demographics and medical history	Exposure (location of device, circumstance	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Gibson et al., 2019[542] US 2012-2016 Hospital electronic medical record (EMR) system-Oregon Clinic and Legacy Emmanuel Hospital	N=14 Male: 92.9% Female: 7.1% Age range 16-49 years	Device or battery exploded in pocket: 85.7% Device exploded in hand: 14.3% Details of device Loose battery: 50.0% E-cigarette device: 42.9% Vape pen: 7.1%	Location of burn injury Burns to thighs only: 42.9% Burns to thigh and hand: 42.9% Burn to hand: 7.1% Burn to hand and lip: 7.1% Degree of burn injury Full thickness burns: 21.4% Partial thickness burns: 71.4% Mixed partial/full thickness burns: 7.1% Burn size ranged from 1% to 6% TBSA	21.4% of patients required excision and autografting	Average recovery time was 24.5 days 14.9% lost to follow-up	Moderate methodological quality Conflicts of interest None declared Funding None received
Quiroga et al., 2019[558] US 2018 Johns Hopkins Bayview Burn Center	N=6 Male Age-range: 27-46 years	Device or battery exploded in pants pocket: 100%	Side and degree of burn injury Burns to thigh: 50.0% Burns to thigh and hand: 33.3% Burns to thigh, knee and hand: 16.7% Superficial partial thickness burn: 83.3% Intermediate burn: 16.7% TBSA range: 2%-6%	Tangential excision and skin grafting: 16.7% Complex wound care: 83.3%	Discharged within a week: 83.3% Stayed for 8 days: 16.7%	Moderate methodological quality Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, [time frame], data source)	Demographics and medical history	Exposure (location of device, circumstance	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Hickey et al., 2018[544] US 2015-2017 Massachusetts General Hospital Burn Center	N=14 Male: 93% Female: 7% Age - mean (SD): 28.6 (8.6) years Age-range: 19-50 years	Location of device Pant pocket: 86% Hand: 7% Purse: 7% Details of e-cigarette used were not reported	Side and degrees of burn injury Isolated upper extremity burns: 7% Multiple burns at thigh, buttock, genitalia and/ or hand: 29% Second- and third-degree burns: 57% Deep second-degree burns: 29% Superficial second-degree burn: 14% Average TBSA: 4.7% (SD=2.4%)	Admitted: 86% Discharged, local wound care only: 7% Refused admission: 7% Split-thickness skin graft (STSG): 57% Local wound care only: 29% Xenograft and local wound care: 7% Enzymatic debridement and wound care: 7% Lost to follow-up: 7%	Average hospital stay length 6.6 days (SD=4.7) Range: 0-15 days Time to 95% wound closure 18.4 days (SD=10.8) Range: 8-40 days	High methodological quality Conflicts of interest Not reported Funding Not reported
Maraqa et al., 2018[545] US No time frame reported Trauma Services Hurley Medical Center/Michigan State University, College of Human Medicine, Flint	N=8 Male Age-range: 17-47 years	Device or battery exploded in pants pocket: 87.5% Device exploded in their breast pocket: 12.5%	Side and degrees of burn injury Burns to lower extremity: 87.5% Burns to hand: 37.5% Burns to scrotum/penis: 25% Burns to chest: 12.5% Partial thickness burns: 62.5% Mixed partial and full: 37.5% TBSA range: 4%-16%	Skin grafting: 25.0%	Time to discharge Few hours to 6 days	Moderate methodological quality Conflicts of interest Not reported Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, [time frame], data source)	Demographics and medical history	Exposure (location of device, circumstance	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Harshman et al., 2017[543] US No time frame reported Burn centre	Case 1 Male 31 years Case 2 Male 36 years	Case 1 Spontaneous ignition of device in jeans pocket while driving Case 2 Spare battery in pocket that spontaneous ignited	Case 1 Mixed partial thickness and full thickness flame burns to right anterolateral thigh, buttock, leg, and inner thigh. 10% TBSA Case 2 Deep partial and full thickness burns to thigh and superficial partial thickness burns to hand. 3% TBSA. Part of the battery case embedded in thigh	Case 1 Irrigated and dressed Case 2 Irrigated and dressed. Skin infection two days after injury treated with antibiotics. Skin allograft	Case 1 Full recovery within 2 months Case 2 In hospital for 12 days, returned to full function within 2 months	Moderate methodological quality Conflicts of interest None declared Funding Not reported
Serror et al., 2017[511] France 2016-2017 Saint Louis Hospital Burn Center, Paris	N=10 Male: 100% Age – mean (SD): 39 (26-55) years	Exploded in pocket: 80% Exploded in hands: 20%	Affected body parts Thigh: 80% Hands: 50% Partial thickness: 50% Full thickness: 30% Mixed partial and full thickness: 20% Average TBSA: 3% (0.5%-5%)	Non-operative management: 70% Surgery: 30%	Spontaneously healed within 21 days: 70%	High methodological quality Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, [time frame], data source)	Demographics and medical history	Exposure (location of device, circumstance	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Smith et al., 2017[547] US 2015-2016 Single burn centre	N=10 Male: 100% Age range: 20-47 years	Device/battery exploded in pants pocket: 70% Device exploded in hand: 10% Device exploded while driving tractor trailer and fell into lap: 10% Pouring liquid nicotine then engulfed in flames: 10%	Affected body part Thigh, hand, buttock: 10% Hand, foot, thigh: 10% Face, trunk, arms, hands, ankles, feet: 10% Fingers, thigh, knee: 10% Thigh, fingers: 10% Hand, fingers: 10% Thigh, hand: 30% Thigh: 10% Average TBSA: 4.2%	Skin graft: 80% Not reported: 20%	Average length of hospital stay 4.9 days Range: 0-11 days Return to work 3 weeks: 10% 4 weeks: 30% 5 weeks: 10% No time taken off: 30% Unknown: 20%	Moderate methodological quality Conflicts of interest None declared Funding Not reported
Case reports						
Beining et al., 2020[560] US District Six Medical Examiner's Office	Male 38 years	Modified device exploded during use	Burns covering 80% of body and wound to face/mouth Projectile wound to the head present to face	N/A	Death	Moderate methodological quality Conflicts of interest Not reported Funding Not reported
Hagarty & Luo, 2020[561] US University of Illinois College of Medicine at Rockford, OSF St Anthony Medical Centre	Female 30 years Recent tonsillar and ear infection	Device unable to be identified by emergency responders Modified device exploded upon activation	Superficial partial thickness burn and a full thickness complex laceration of the lower lip Tongue, hand and finger lacerations, teeth extensively broken, comminuted spinal fracture and evidence of left vertebral artery dissection	Fracture stabilised Artery dissection treated with aspirin and low-molecular-weight heparin Soft tissue injuries reconstructed after extensive irrigation	Discharged, healing well	Moderate methodological quality Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, [time frame], data source)	Demographics and medical history	Exposure (location of device, circumstance	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Sedaghat & Morgan, 2020[563] US Hospital record	Male 16 years	Inadvertent aspiration of the cartridge cap	Foreign body in the right main stem bronchus	Foreign body removed	Not reported	Low methodological quality Conflicts of interest Not reported Funding Not reported
Ashburn et al., 2019[559] US Level 1 trauma/burn centre	Male 28 years	Device exploded during use	Two fractured teeth, tongue laceration, stellate upper lip laceration and foreign bodies in lower lip	Lacerations repaired	Discharged	Low methodological quality Conflicts of interest Not reported Funding Not reported
Katz & Russell, 2019[529] US Unknown data source	Male 17 years	Device exploded during use	Puncture to the chin, extensive lacerations to mouth, multiple disrupted teeth and mandibular fracture	Internal fixation of the fracture, dental extraction, and debridement of devitalised tissue	6-week follow-up Recovered well	Moderate methodological quality Conflicts of interest Not reported Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, [time frame], data source)	Demographics and medical history	Exposure (location of device, circumstance	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Michael et al., 2019[557] US Hospital burn unit	Male 40 years	Spontaneous combustion of device in pant pocket	Severe burns on the left posterior thigh	Split thickness autograft and additional use of an allograft matrix 4 days after injury	Graft incorporated One-month post-injury Intermittent pain, irritation, and a mildly antalgic gait. Loss of terminal extension of the knee joint. Clinical evidence of iliotibial band tightness The cosmetic appearance of his graft and donor site is of great emotional concern to the patient	Moderate methodological quality Conflicts of interest None declared Funding Not reported
Sangani et al., 2019[562] US Hospital record	Male 40 years Patient denied any medical history	Combustion of device spare batteries in pant pocket	Superficial and deep partial thickness burns to thigh, 9% TBSA	Wound irrigated	Not reported	Low methodological quality Conflicts of interest Not reported Funding Not reported
Ackley et al., 2018[526] US Hospital record	Male 17 years	Device exploded when about to take a puff	Burnt left thumb with sensory loss, decreased motor control, heavy bleeding	Immediate irrigation, debridement, and a left-hand carpal tunnel release	Post-operative day 2 Discharged Post-operative day 8 Blackened thumb without capillary refill or sensation and limited motor function. Required 6 additional operative procedures	Moderate methodological quality Conflicts of interest Not reported Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, [time frame], data source)	Demographics and medical history	Exposure (location of device, circumstance	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Chi et al., 2018[528] US Emergency Dental Clinic, Medical University of South Carolina	Male 20 years	Device exploded during use	Burns and lacerations of the upper and lower lips, dislodgement of teeth	Lacerations sutured, teeth extracted. Antibiotic and pain medication prescribed	Lost to follow-up	Moderate methodological quality Conflicts of interest None declared Funding None received
Satteson et al., 2018[530] US Emergency Department, Trauma Centre, Wake Forest University of Medicine	Male 35 years	Device (Dark Horse atomiser with a SMPL Mec Mod battery) rapidly heated and suddenly exploded after battery was changed	Significant for deep partial and full thickness burns to thumb and embedded foreign body	Surgery and debridement of devitalised tissue and carpal tunnel release	15 months after initial injury Thumb interphalangeal joint is fixed in 30° of flexion with no ability to actively or passively flex or extend	High methodological quality Conflicts of interest None declared Funding None received
Anderson et al., 2017[527] US University of Kentucky Emergency Department	Female 30 years	Device exploded during use	2% TBSA burns to face, forearm, and thigh and bilateral corneal burns	Treated with erythromycin to corneal burns, Silvadene to the extremities, and bacitracin to the face	Discharged, healing well	Low methodological quality Conflicts of interest Not reported Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.10 Poisoning

Main conclusions from the synthesised evidence on poisoning related to e-cigarettes

- There is conclusive evidence that intentional or accidental exposure to nicotine e-liquids can lead to poisoning, which can be severe and can result in death. A significant number of accidental poisonings occur in children under the age of six.
- There is conclusive evidence that use of e-cigarettes can result in nicotine toxicity.

Table 4.10-1: Overview of studies of poisoning identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Poisoning						25 13 / 12		4 2 / 2	23 14 / 9

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes:** Intentional and unintentional exposure to e-liquid resulting in poisoning, nicotine toxicity.

4.10.1 Findings from other reviews

The NASEM review[3] assessed 29 articles on poisonings. There were 16 articles (two case series[569,570] and 14 case reports[436,539,571-582]), reporting on 19 cases of either oral or dermal poisonings, from exposure to e-cigarettes. Of these cases, 12 were reported as intentional poisonings. Patients often experienced vomiting and lactic acidosis and there were three cases resulting in fatalities.[573,581,582] Some of the cases of unintentional exposure occurred in young children. Thirteen surveillance reports[481,583-594] (from poison control centres or passive surveillance systems) were identified and described an increasing frequency of e-cigarette related incidents over time and a greater number of incidents in children than in older individuals. One of these studies found that children experiencing poisonings related to e-cigarettes and e-liquid were five times as likely to require health care admission and twice as likely to have severe outcomes than if they experienced poisoning from exposure to conventional tobacco products.[481] No cohort or case-control studies were identified.

The Irish Health Research Board literature map[15] identified a total of 49 papers describing poisonings due to e-cigarette use and exposure, including 21 case reports, five case series and 23 surveillance reports.[15] Of the 49 studies, 24 were included in the NASEM review[436,481,570-582,584-589,591,593,594], 13 were included in the top-up review[595-607] and two were published before the date limit of the top-up review and not included in the NASEM review[592,608]. Eight studies did not meet eligibility criteria and were excluded,[609-616] one was classified as a review in the top-up review[617], and one was discussed in the adverse events chapter[618]. The two studies published before the top-up review time limit and not included in the NASEM review, were both surveillance reports.

The report by Cantrell examined cases reported to the California Poison Control System from 2010-2012. A total of 35 cases were identified, nicotine concentrations ranged from 4mg/mL to 30mg/mL and 14 were in children eight years or less.[608] Of the 14 cases in children, 9 ingested the e-liquid and 5 inhaled from the device. Of the 21 cases in adults, there were four cases of accidental ingestion of e-liquid (either via leaky cartridges or the cartridge mistaken for another substance). Symptoms of adults and children included vomiting, nausea, cough, dizziness, confusion, chest pains and oral irritation.[608]

Weiss et al. examined calls to Wisconsin Poison Control Centers between 2010–2015.[592] During this period, 98 e-cigarette related calls were identified, with the majority of cases aged five years or less or 20 years

and above and in males. Main routes of exposure were ingestion, followed by inhalation, ocular and dermal. Eight percent were intentional, 87% were accidental and 5% had other reasons. There were no medical effects reported in 38%, minor in 38%, moderate in 4% and 20% were not followed.

The Public Health England report[11] identified peer-reviewed articles on e-liquid poisoning. Of the 16 studies, 13 were included in the NASEM review[436,481,570,571,573,575,577,578,580,582,585,588,589], one included in the top-up review[606] and two were published after the time limit of the top-up review and not included in the NASEM review [592,619]. Of the two studies included in the NASEM or top-up reviews, one surveillance report has previously been discussed under the Irish Health Research Board literature map summary.

The case report by Räsänen et al. described the death of a 29-year-old woman who injected 10mL of e-liquid, administering an estimated 100-400mg dose of nicotine.[619] The patient had a history of severe depression and was taking diazepam, of which 75mg was also consumed at the same time as the e-liquid injection. The patient was taken to hospital where she suffered a cardiac arrest 2.5 hours after presentation. She was resuscitated and admitted to the ICU where she was pronounced brain dead.[619]

Two non-peer-reviewed articles were mentioned in the Public Health England review[11]: a letter to an academic journal[539] and a conference abstract.[620] The letter was included in the NASEM review and the conference abstract did not meet inclusion criteria.

The CSIRO review[14] identified three case reports and one case series on poisonings from e-liquid exposure. One study[577] was included in the NASEM review and three[602,604,605] were included in the top-up review.[602,605]

Ten studies were identified in the SCHEER review[4]: six surveillance reports, two case reports and two case series. Of the 10 studies, three were in the NASEM review,[573,586,590] six were in top-up review,[597,598,604,606,617,621] and one was published before the date limit of the top-up review and not included in the NASEM review.[622] The study not captured by the NASEM review or top-up review describes the case of a two-month-old boy ingesting a small amount of 1.8% nicotine e-liquid. The infant experienced vomiting, tachycardia, grunting respirations, and truncal ataxia and returned to baseline health six hours post-exposure without antidote therapy.[622]

The USPSTF review[16] identified one study[481] which was also captured in the NASEM review.

4.10.2 Summary of conclusions from other reviews

The NASEM review,[3] including only case reports, case series and surveillance reports, concluded that:

- 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.

The Irish Health Research Board literature map,[15] using only case reports, case series and surveillance reports, found evidence of acute e-cigarette related harm arising from poisonings caused by e-liquid exposure.[15]

After evaluation of case reports, case series and surveillance reports, the Public Health England review,[11] concluded that:

- Poisonings have predominantly involved accidental ingestion with fewer incidences of other routes (e.g 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.

The CSIRO review[14] including case reports and a case series conclude that nicotine intoxication due to e-liquid ingestion can cause serious injury or death.[14] The review states that, although consistent with the NASEM review,[3] their findings do not contribute further to the body of evidence.

The SCHEER review[4] did not provide any summative conclusions on poisoning due to e-cigarettes.

4.10.3 Top-up review

Search results

Overall, 23 articles were located in the top-up systematic literature search and included in evidence synthesis (Table 4.10-1). Three systematic reviews with findings on poisonings related to e-cigarette exposure were identified in the database search.

Glasser et al.[241] identified five surveillance reports, three of which were included in the NASEM review[481,588,589] and two which were published prior to the date limit for the top-up review and not included in the NASEM review.[623,624] Both studies not captured in the NASEM review were annual reports from the American Association of Poison Control Centres' National Poison Data System for the year 2014 and 2015. In 2014, 29.5% (3,910 calls) of all calls were tobacco- and nicotine-related, up from 14.7% (1,495 calls) in 2013.[623,624]

Maessen et al. identified 26 studies, 21 case reports and five case series.[617] Of the 26 studies, 13 were included in the NASEM review,[436,569-575,578-582] four were included in the top-up review,[602-605] eight were published prior to the date limit for the top-up review and were not included in the NASEM review[610-613,619,622,625,626] and one did not meet inclusion criteria[627]. Of the eight not captured by the NASEM or top-up reviews, five were discussed in the Irish Health Research Board literature map[578,610,612,613,619] and one was discussed in the SCHEER summary[622]. Of the remaining two studies, one described the case of a 22-year-old woman ingesting and injecting 18mg nicotine e-liquid in addition to other drugs. She presented with tachycardia, flushing, salivation and nausea and after her symptoms progressively improved she was discharged three hours after admission.[625] The other described the case of an 18-month-old infant consuming some 18mg nicotine e-liquid who presented with vomiting, drowsiness and drooling.[626] No other details were provided.

Tzortzi et al. identified 35 studies, 21 case reports, four case series and 10 surveillance reports.[267] Of the 33 studies, 17 were included in the NASEM review,[436,539,569-576,578,579,581,582,586,589,591] 13 were included in the top-up review,[595-599,602-604,606,607,621,628,629] three were published prior to the date limit of the top-up review and not published in the NASEM review[625,626,630] and two did not meet inclusion criteria[631,632]. Of the three studies not captured by the NASEM or top-up reviews, two[625,626] have been described under the Maessen review[617] summary above. The remaining study described the case of a 10-month-old boy that consumed 18mg/mL nicotine e-liquid [630] The patient presented with vomiting, tachycardia, grunting respirations, and truncal ataxia. No antidote therapy was administered and the child returned to normal health six hours after exposure.

Poisoning: primary outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarettes to poisonings were located.

Randomised controlled trials

No randomised controlled trials were located reporting on the relationship of e-cigarettes to poisonings were located.

Cohort studies

No cohort studies were located reporting on the relationship of e-cigarettes to poisonings were located.

Non-randomised intervention studies

No non-randomised intervention studies were located reporting on the relationship of e-cigarettes to poisonings were located.

Case-control studies

No case-control studies were located reporting on the relationship of e-cigarettes to poisonings were located.

Other study types

Surveillance reports

There were 12 surveillance reports identified: six from the US,[597,598,600,601,607,633] two from Canada,[566,634] and one each from the Czech Republic,[621] the UK,[595] Australia[635] and EU member states[606] reporting on data from 2008[595] to 2019 (Table 4.10.2).[566] Of the six reports from the US, two used the National Poison Data System,[600,607] three used the National Emergency Injury Surveillance System[597,598,633] and one used the Oregon Poison Centre.[601] The Canadian Hospitals Injury Reporting and Prevention Program network[566] was used in one of the Canadian reports and the British Columbia Drug and Poison Information Centre was used

in the other.[634] Other sources included the UK National Poisons Information Service Database,[595] Toxicological Information Centre in the Czech Republic,[621] the Australian Poisons Information Centres[635] and EU members national poisons centres.[606] Four of the studies included cases in children aged 16 years or less,[595,597,598,600] and eight included children and adults.[566,601,606,607,621,633-635]

Of the reports including children only, two included children four years and under,[597,598] one included children under the age of six[600] and another included children 16 years or less.[595] The smallest number of reported cases was 26, capturing data from one year,[597] and the largest number of cases was 8,269 capturing data over five years from 2012-2017.[600] Males accounted for 55.3%[600]-59.4%[595] of cases. Ingestion was the most common route of exposure accounting for 92.5%-99.4% of cases. The most common symptom was vomiting with other commonly reported symptoms including seizures, coma, cardiopulmonary complications and sleepiness. One fatality was reported.[600] Two reports calculated national estimates for the US population using the National Emergency Injury Surveillance System.[597,598] One study estimated that there were 885 poisoning cases in children in the US four years or less in 2018[597] and the other estimated that there were 4,745 cases for the same age group between 2013-2017.[598]

The report from Australia documents 202 e-cigarette-related telephone calls to Poisons Information Centres from 2009-2016, demonstrating a rapid increase from 1 in 2009 to over 70 in 2016.[635] Most patients had mild symptoms at the time of the call; 12 had moderate symptoms including gastrointestinal disturbance and sedation.[635] The article also mentions the death of an Australian toddler from ingestion of concentrated nicotine solution, which was not part of the surveillance report, but which we assume to be "Baby J" (Appendix 5).[636]

In the reports including cases of all ages, the smallest sample included 39 cases between 2013-2017[633] and the largest sample included 17,358 cases between 2010-2018.[607] Males accounted for 50.6%[606]-64% of cases.[621] Ingestion was the most common route of exposure, occurring in 56.1%[601]-77.5%[607] of cases. Cardiovascular symptoms were most common (29.7%) in one report.[633]

Of the 12 reports, six[597,598,607,621,633,634] were rated high quality, four were rated moderate[566,600,601,606] and two low[595,635] quality using the Joanna Briggs Institute's critical appraisal checklist. GRADE was not applied. No conflicts of interest were declared in 10 reports, conflict of interest were not reported in one study[633], and one, Wylie et al. from Australia[635], declared having received consultancy fees from pharmaceutical companies (Table 4.10.2).

Case series

Case series in which only some individual case reports meet our inclusion criteria have been retained in the case series analysis however, only applicable results have been presented. As such, only one of the 10 cases described in Isakov et al.[402] was included in this analysis (Table 4.10.3).

Two case series were identified on e-liquid poisonings, one from the US[402] and another from South Korea.[604] The study in the US by Isakov et al. described a single poisoning incident in which a 13-year-old female accidentally ingested a vape pen containing nicotine e-liquid. There were concerns that if the pen were to leak, a lethal dose of nicotine would be administered. The pen was removed intact and the patient was discharged with no complications.[402] The case series by Park and Min described two cases of poisoning from the ingestion of e-liquid as part of a suicide attempt.[604] Both cases were males, aged 17 and 27 years. One case ingested an unknown quantity of 16mg/mL and 18mg/mL nicotine containing e-liquid and the other ingested 10mL of nicotine containing e-liquid with a concentration of 210mg/mL.[604] Both cases experienced cardiac arrest, with one discharged after 13 days and the other transferred to a rehabilitation facility after 32 days.

Of the two case series, one was rated low[402] and one moderate[604] using the Joanna Briggs Institute's critical appraisal checklist. GRADE was not applied. Neither case series declared any conflicts of interest.

Case reports

Nine case reports were identified, two from South Korea[603,637] and Italy[629,638] and one each from Japan[628], Switzerland,[596] UK,[602] Turkey,[599] and the Netherlands.[605] Three cases occurred in females[599,628,629] and six in males,[596,602,603,605,637,638] and ranged in age from four years[629] to 53 years.[603] The e-liquid was injected in two cases,[596,628] one intentionally[596] and the other with unknown intent, but suggestive of a suicide attempt.[628] E-liquid was ingested in seven cases, three of which were accidental,[599,602,629] two were intentional as part of a suicide attempt,[603,637] and two with unknown intent.[605,638] Of cases that reported details of the e-liquid, nicotine concentration ranged from 6mg/mL[629] to 990mg/mL[637] with volumes of e-liquid ranging from 3mL[603] to two e-liquid refills.[638] The majority of patients experienced vomiting and nausea. Five cases[602,603,605,628,638] also presented with cardiovascular complications such as cardiac arrest, tachycardia

and bradycardia and one case[599] experienced sudden sensorineural hearing loss. There were three cases of brain death,[605,637,638] two fatalities[602,628] and three cases in which the patient fully recovered.[596,603,629] One case continued to experience hearing loss at six month follow-up.[599]

There was one high,[599] six moderate[596,602,603,605,637,638] and two low[628,629] quality cases reports using the Joanna Briggs Institute's critical appraisal checklist. GRADE was not applied. Six reported no conflicts of interest[596,599,603,628,629,638] and three provided no information (Table 4.10.3).[602,605,637]

4.10.4 Summary of findings from top-up review

There were 12 surveillance reports on poisonings from an e-liquid, finding:

- Ingestion was the most common route of exposure.
- Vomiting and nausea were the most frequently reported symptoms.
- Nicotine concentration was not frequently reported. In reports with information on nicotine content, concentrations ranged from 0mg/mL to at least 200mg/mL, but most ranged from 6-23mg/mL.
- A significant number of poisonings occurred in children under the age of six (8,296 between 2012-2017 in the US). National estimates from the United States suggested there were 4,745 cases in children four years or less between 2013-2017.
- Between 2010-2018 there were 17,358 cases of poisoning relating to e-cigarettes across all ages in the United States. The occurrence of poisonings from e-liquids increased over time, from 57 cases in 2010 to 2,901 cases in 2018.

There were nine case reports and two case series on poisonings from exposure to e-liquid, finding:

- Ingestion was the most common route of administration and was either consumed accidentally or as part of a suicide attempt. Intentional injection of e-liquids also occurred as a means to attempt suicide.
- Volume and nicotine content of e-liquid involved varied significantly. Volumes consumed ranged from 3mL to two entire e-liquid refill bottles of unspecified volume. Nicotine concentrations ranged from 6mg/mL to 990mg/mL.
- Cases generally experienced vomiting and nausea and some also experienced cardiovascular complications including cardiac arrest, tachycardia, bradycardia and hypotension. Other symptoms experienced included cramps, bradypnea, lactic acidosis, sensory hearing loss, weakness, diarrhea, loss of consciousness, muscle paralysis and coma.
- Full recovery was reported in half of the cases. Severe outcomes, including fatalities and brain deaths were also reported.

4.10.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence from the top-up systematic review with the evidence from previous reviews on clinical poisoning outcomes:

- There was a total of 61 studies on poisonings due to e-liquid exposure: 28 case reports, four case series, and 29 passive surveillance reports. Ingestion was the most frequent route of exposure and the most common symptoms included nausea, vomiting and cardiovascular complications, and multiple fatalities have been reported. A significant number of accidental poisonings occurred in children under the age of six. Hence:
    - There is conclusive evidence that ingestion, injection, inhalation and ocular or dermal exposure to nicotine e-liquid can cause poisonings.
- Case reports and case series are particularly useful for describing events where a direct relationship between cause and effect is clear. In the context where no other cause of poisoning is apparent they are considered informative for this review.
- No epidemiological studies on the relationship of e-liquids to the incidence or relative risk of poisonings were identified. Hence:
    - There is no available evidence as to the relative risk or incidence of poisonings related to exposure to e-liquids.
- Due to the study types available, the GRADE approach was not applied.

4.10.6 Main conclusions from the synthesised evidence on poisoning related to e-cigarette use

- There is conclusive evidence that intentional or accidental exposure to nicotine e-liquids can lead to poisoning, which can be severe and can result in death. A significant number of accidental poisonings occur in children under the age of six.
- There is conclusive evidence that use of e-cigarettes can result in nicotine toxicity.

Table 4.10-2. Study details: poisoning – surveillance reports

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
Chang et al., 2020[633] US 2013-2017 National Center for Injury Prevention under the NEISS All Injury Program (NEISS-AIP)	Unweighted sample n=39 Gender – n (%) Male: 14 (35.9) Female: 25 (64.1) Age – n (%) 5-11 years: 4 (10.3) 12-17 years: 10 (25.6) 18-24 years: 10 (25.6) ≥25 years: 15 (38.5)	All cases aged 5-11 years experienced unintentional liquid ingestions or chemical exposure	Symptoms – n (%) Cardiovascular: 11 (28.2) Allergic reaction: 7 (17.9) Other: 7 (17.9) Unspecified: 6 (15.4) Gastroenteric: 5 (12.8) Chemical exposure: 3 (7.7)	Treatment – n (%) Treated and released: 33 (84.6) Left without being seen: 3 (7.7) Treated and admitted to a hospital: 3 (7.7)	Not stated	High methodological quality Conflicts of interest Not reported. No financial disclosures Funding Center for Tobacco Products, U.S. Food and Drug Administration
	National estimates n=1410 Gender (%) Male: 48.1 Female: 51.9 Age (%) 5-11 years: 4.7 12-17 years: 16.5 18-24 years: 27.1 ≥25 years: 51.7	Not stated	National estimates - n (%) Cardiovascular: 808 (29.7) Allergic reaction: 700 (25.7) Other: 587 (21.6) Unspecified: 308 (11.3) Gastroenteric: 249 (9.2) Chemical exposure: 68 (2.5)	National estimates - n (%) Treated and released: 2,082 (76.6) Left without being seen: 423 (15.9) Treated and admitted to a hospital: 203 (7.5)	Not stated	

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
McFaull et al., 2020[566] Canada 2011-2019 The electronic Canadian Hospitals Injury Reporting and Prevention Program network	Total cases n=55 Age - n (%) 0-4 years: 36 (65.5) 5-14 years: 12 (21.8) 15-19 years: 7 (12.7) 20-29 years: 0 (0) 30-49 years: 0 (0)	Route of administration - n (%) Unintentional ingestion of vaping solution: 36 (65.5)	Not reported	Not reported	Not reported	Moderate methodological quality Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
Obertova et al., 2020[621] Czech Republic 2012-2018 Toxicological Information Centre (TIC)	Total cases n=145 Gender – n (%) Male: 95 (65.5) Female: 48 (33.1) Unknown: 2 (1.4) Age (%) ≤2 years: 37 2-18 years: 25 18+ years: 35 Unknown age: 1	Volume Range (mL): 10 – 30 Nicotine concentration Range (mg/mL): 1 – 24 Dosage (%) Severe/lethal: 4 Toxic: 36 Low-to-moderate: 24 Cause of exposure (%) Accidental: 74 Incorrect application: 7 Abuse: 4 Suicide attempt: 4 Other/unknown reasons: 11 Unknown: 36 Route of administration (%) Ingestion: 67 Licking: 14 Suspected ingestion: 7 Inhalation: 6 Ocular: 4 Intravenous: 2	Symptoms – n (%) Asymptomatic: 82 (55.4) Symptomatic post-exposure: <1 hour: 42 (70) 1-4 hours: 14 (24) >4 hours: 4 (6) Symptoms not stated: 6 (4) Symptoms included: nausea, feeling of burning in the mouth and throat, salivation, repeated vomiting, diarrhea, abdominal pain, tachycardia, tremor and respiratory irritation	Treatment (%) Medical examination: 78 Observation: 72 Activated charcoal: 53.7 Home observation: 22 Symptomatic treatment: 70.1 Atropine: 1.9 Gastric lavage: 0.9 Not stated: 8.5 In one 33-year-old patient with coma and general convulsions, intubation was performed, and benzodiazepines were applied	Prognosis (%) Good: 10 Probably good: 42 Uncertain: 44 Unknown: 4	High methodological quality Conflicts of interest None declared Funding First Faculty of Medicine, Charles University; Ministry of Health Czech Republic

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
Wang et al., 2020[607] US 2010-2018 National Poison Data System (NPDS)	Total cases n=17,358 Gender (%) Male: 55.5 Female: 44.1 Unknown: 0.5 Age (%) <5 years: 64.8 5–11 years: 3.0 12–17 years: 3.4 18–24 years: 8.3 25+ years: 15.4 Missing: 5.1	Quantity (mL) of e-liquid by medical outcome – Mean (min-max) No effect (n=37): 7.5mL (0.2-60.0) Minor (n=22): 13.1mL (0.6-60.0) Moderate (n=5): 56.2mL (1.0-200.0) Quantity (mg) of nicotine by medical outcome – Mean (min-max) No effect (n=11): 19.3 (3.0-96.0) Minor (n=11): 49.7 (6.0-240.0) Route of administration (%) Ingestion: 77.5 Dermal: 13.0 Inhalation/nasal: 10.4 Ocular: 7.1 Other: 0.4 Unknown: 0.2 Number of events by year 2010: 57 2011: 237 2012: 415 2013: 1,435 2014: 3,742 2015: 3,500 2016: 2,751 2017: 2,320 2018: 2,901	Symptoms (%) Vomiting: 25.4 Nausea: 11.8 Ocular irritation/pain: 11.3 Red eye conjunctivitis: 5.5 Dizziness/vertigo: 5.1	Level of care at health care facility (%) Admitted (critical): 0.6 Admitted (noncritical): 0.8 Admitted (psychiatric): 0.3 Lost to follow-up/left: 6.2 Treated and released: 27.4 Refused referral/no show: 3.9 Not referred: 60.9	Medical Outcome (%) Minor: 22.6 Moderate: 3.3 Major: 0.1 Death: 0.01 No effect: 35.0 Missing: 39.0	High methodological quality Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
Chang and Rostron, 2019[597] US 2018 National Emergency Injury Surveillance System (NEISS)	Unweighted sample n=26 Gender – n (%) Male: 15 (57.7) Female: 11 (42.3) Age – n (%) <2 years: 17 (65.4) 2-4 years: 9 (44.6)	Nicotine concentration, unweighted sample – n 0.6mg: 2 E-liquid volume, unweighted sample – n 60mL: 2 10mL: 1 Route of exposure – unweighted sample – n (%) Ingestion: 25 (96.2) Other/not stated: 1 (3.8) Ingested cotton filters: 3 (11.5)	Symptoms, unweighted - n Vomiting: 3 Emesis: 2	Treatment, unweighted – n Admitted to hospital: 2 Treated and released: 23 Left without being seen: 1	Not reported	High methodological quality Conflicts of interest None declared Funding Center for Tobacco Products, U.S. Food and Drug Administration
	National estimates n=885 Gender - national estimates (%) Male: 30.1 Female: 69 Age - national estimates (%) <2 years: 59.4 2-4 years: 40.6	Route of exposure – national estimates (%) Ingestion: 99.4 Other/not stated: 0.56	Not reported	Treatment, national estimates – n (%) Treated and admitted to a hospital: 10 (1.1) Treated and released: 797 (90.0) Left without being seen: 78 (8.9)	Not reported	

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
Chang et al., 2019[598] US 2013-2017 National Emergency Injury Surveillance System (NEISS)	Unweighted sample n=116 Gender – n (%) Male: 67 (57.8) Female: 49 (42.2) Age – n (%) <2 years: 62 (53.4) 2-4 years: 54 (46.6)	Nicotine concentration, unweighted – mean (min-max) mg (n=6): 3 (1.8-100) E-liquid volume, unweighted – mean (min-max) mL (n = 19): 16.8 (0.2-118.3) bottle (n = 26): 0.875 (0.5-1.0) Route of administration, unweighted – n (%) Ingestion: 111 (95.7) Dermal: 3 (2.6) Ingestion + ocular: 1 (0.9) Unknown: 1 (0.9)	Symptoms, unweighted (%) Vomiting, nausea, emesis: 63.6 Crying, eye redness: 18.2 Cough: 9.1 Sleepy: 9.1 Oral cyanosis/unresponsive: 9.1	Treatment, unweighted – n (%) Treated and admitted to a hospital: 11 (9.5) Treated and released: 103 (88.8) Left without being seen: 2 (1.7)	Not reported	High methodological quality Conflicts of interest None declared Funding Center for Tobacco Products, U.S. Food and Drug Administration
	National estimates n=4,745 Gender (%) Male: 54.3% Female: 45.7% Age (%) <2 years: 56.2% 2-4 years: 43.8%	Route of administration – national estimates (%) Ingestion: 96.9 Dermal: 2.6 Ingestion + ocular: 0.12 Unknown: 2.1	Not reported	National estimates (%) Treated and admitted to a hospital: 4.1 Treated and released: 95.5 Left without being seen: 0.43	Not reported	

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
Choi et al., 2019[634] Canada 2012-2017 The British Columbia Drug and Poison Information Centre (DPIC)	Total cases n=186 Gender (%) Male: 58.1 Female: 40.9 Unknown: 1.1 Age (%) ≤4 years: 43.5 5–14 years: 3.8 15–19 years: 9.7 20–24 years: 3.8 ≥25 years: 16.7 Not recorded: 22.6	Nicotine concentration (%) 0mg/mL: 4 0.1-5mg/mL: 18 6-17mg/mL: 53 18-23mg/mL: 15 ≥24mg/mL: 7 Route of administration (%) Ingestion: 65.6 Inhalation: 15.0 Dermal: 11.8 Ocular: 6.4 Nasal: 0.5 Vaginal: 0.5 Cause of exposure (%) Accidental access: 45.7 Usual e-cigarette use: 13.4 E-cigarette malfunction: 9.1 Other/not recorded: 8.6 Spill: 7.0 Mistaken identity: 6.4 Handling device: 5.4 Intentional inappropriate use: 3.8 Making e-juice: 0.5	Symptoms present (%) Yes: 46.8 No: 37.6 Not recorded: 15.6 Symptoms – local (%) Ocular: 5.9 Oral/pharyngeal: 4.8 Dermal: 2.7 Respiratory: 1.6 Vaginal: 0.5 Symptoms – systemic (%) Not typical for nicotine exposure: 24.2 Typical for low nicotine exposure: 22.6 Typical for high nicotine exposure: 1.1	Care trajectory (%) Managed outside of health facility: 70.4 Treated at health facility and released: 17.2 Admitted (noncritical): 4.3 Admitted (critical): 0.5 Lost to follow-up: 7.5	Not reported	High methodological quality Conflicts of interest None declared Funding Internal funding at the BC Centre for Disease Control

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
Hughes & Hendrickson, 2019[601] US 2014-2017 Oregon Poison Centre	Total cases n=265 Age - n (%) Children: 193 (72.8) Adults: 72 (27.2) Median (range): 2 years (0.5–65)	Route of administration: children (%) Ingestion: 56 Exposures by handling device: 15 Oral mucosal exposures: 12 Dermal exposures: 12 Inhalational exposures: 5 Route of administration: adults (%) Ingestion exposures: 32 Mucosal exposures: 21 Ocular exposures: 19 Dermal exposures: 18 Inhalational exposure: 10	Asymptomatic (%) Children: 72 Adults: 19 Symptomatic (%) Children: 28 Adults: 81	Not reported	Asymptomatic – (n) Children: 96 Adults: 33 Missing: 16 Symptomatic on initial call – (n) Children: 4 Adults: 18 Missing: 49	Moderate methodological quality Conflicts of interest None declared Funding Not reported
Ang et al., 2018[595] UK 2008-2016 UK National Poisons Information service (NPIS) Database	Total cases n=278 Gender – n (%) Male: 165 (59.4) Female: 112 (40.3) Unknown: 1 (0.3) Age (%) <4 years: 79.8 5-16 years: 20.2	Not reported	Symptoms (%) Minor: 22.7 Most incidents were accidental and asymptomatic Common clinical features (%) Vomiting: 9.5 Tachycardia: 2 Dysesthesia: 1 Irritation: 1 Increased creatine kinase: 1	Not reported	Not reported	Low methodological quality Conflicts of interest None declared Funding No specific funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
Govindarajan et al., 2018[600] 2012-2017 US National Poison Data System (NPDS)	Total cases n=8,269 Gender (%) Male: 55.3 Female: 44.7 Age (%) <3 years: 83.9 3-6 years: 16.1 Median (IQR): 2.0 years (1.3 – 2.0)	Route of administration (%) Ingestion: 92.5	Clinical effects (%) >1 clinical effects: 24.6 Severe clinical effects: 12 Coma: 4 Seizure: 4 Respiratory arrest: 3 Cardiac arrest: 1 Medical outcome (%) Minor: 20.3 Moderate: 1.6 Major: 0.1 Death: 1	Treatment – (%) Treated and released: 35.1 Admitted: 1.4	Not reported	Moderate methodological quality Conflicts of interest None declared Funding Centers for Disease Control and Prevention and the Child Injury Prevention Alliance stipend
Wylie et al., 2018[635] Australia 2009-2016 Australian Poisons Information Centers (PICs)	Total cases n=202 Age (%) Children: 38 Adults and adolescents: 62	Nicotine concentration of e-liquid – median (range) 20.2mg/mL (0.06–200mg/mL) Route of administration – Children Uncapped vials, sucking the mouthpiece, drinking from separated liquid containers, inhaling the liquid, eating the cartridge, or having splashed liquid in their eyes Route of administration, adults and adolescents – deliberate self-harm - n Ingestion: 10 Injection: 2	12 had moderate symptoms, usually a gastrointestinal disturbance combined with sedation	Not reported	Not reported	Low methodological quality Conflicts of interest Consultancy fees from pharmaceutical company Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, study size, conflict of interest, funding
Vardavas et al., 2017[606] Europe (Sweden, Ireland, The Netherlands, Portugal, Austria, Slovakia, Lithuania and Hungary) 2012-2015 National Poisons Centers	Total incidents n=277 By country – n (%) Sweden: 121 (43.7) Netherlands: 78 (28.2) Ireland: 37 (13.4) Portugal: 25 (9.0) Austria: 8 (2.9) Slovakia: 5 (1.8) Lithuania: 2 (0.7) Hungary: 1 (0.4) Gender (%) Male: 140 (50.6) Female: 137 (49.4) Age – n (%) 5 years: 91 (33.2) 6-18 years: 27 (9.8) ≥19 years: 158 (57.0)	Cause of exposure (%) Unintentional: 71.3 Intentional: 17.8 Abuse: 5.5 Misuse: 2.2 Suspected suicide: 1.1 Unknown: 2.2 Route of administration (%) Ingestion: 67.5 Respiratory/inhalation: 16.6 Dermal: 9.0 Ocular: 7.6 Other: 2.2	Symptoms (%) Vomiting: 20.3 Dizziness: 14.5 Nausea: 13.8 Throat Conditions: 9.1 Throat irritation: 3.3 Burning throat: 1.8 Oral mucosal: 2.9 Salivation: 0.7 Pharyngitis: 0.4 Abdominal Conditions: 6.2 Eye Conditions: 5.0 Headache: 4.0 Diarrhea: 2.9 Breathing Conditions: 2.9 Tremor: 1.4 Other: 27.3	Management of incident (%) Residence/on site: 70.1 Hospital: 23.7 Ambulance: 1.7 Other/unknown: 4.6	Medical outcome (%) Minor: 53.8 Moderate: 6.3 Major: 0.5 Death: 0 No effect: 39.4	Moderate methodological quality Conflicts of interest None declared Funding EU Health Programme

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Table 4.10-3. Study details: poisoning – case reports and case series

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation	Treatment	Outcome	Quality assessment, conflict of interest, funding
Case series						
Isakov et al., 2020[402] US Hospital record No time frame reported	Female 13 years Not reported	Ingestion of a vape pen containing nicotine. Concern for a potentially lethal dose of nicotine if the vape pen were to leak Ingestion Accidental	The patient was taken for an exploratory laparotomy for removal of the pen At the time of the laparotomy, the vape tip was in the colon	The colon was repaired primarily with colostomy closure and the patient tolerated the procedure well	She was subsequently discharged without complications	Low methodological quality Conflicts of interest None declared Funding None received
Park & Min, 2018[604] South Korea Emergency department Dec 2015-April 2016	Case 1 Male 27 years Not reported Case 2 Female 17 years Not reported	Case 1 DIY Flavor Shack® 16mg/mL nicotine concentration and Halo® 18mg/mL nicotine concentration Ingestion Suicide attempt Case 2 10mL EC liquid named 'Pure Nicotine®' with a nicotine concentration of 210mg/mL Ingestion Suicide attempt	Case 1 Showing seizure-like movements, cardiac arrest, comatose with fixed pupil size of 3mm Case 2 Cardiac arrest, generalised tonic clonic movement for 5 minutes. Comatose with a fixed pupil size of 3mm	Case 1 Cardiac arrest care, targeted temperature management (TTM) Case 2 Cardiac arrest care, targeted temperature management (TTM)	Case 1 24-hour after TTM: alert and aware Day 13: discharged Case 2 24-hour after TTM: alert and aware Day 32: transferred to a rehabilitation facility	Moderate methodological quality Conflicts of interest None declared Funding Not reported
Case reports						

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation	Treatment	Outcome	Quality assessment, conflict of interest, funding
De Pieri et al., 2020 [629] Italy Emergency department	Female 4 years Not reported	Approx. 10mL of 6mg/mL nicotine containing e-liquid Ingestion Accidental substituted for ibuprofen syrup	Vomiting but was alert and general conditions remained stable	N/A	Full recovery	Low methodological quality Conflicts of interest None declared Funding Not reported
Lee et al., 2020[637] South Korea Emergency department	Male 26 years Severe depression, medicated	Approximately 10mL of 99% liquid nicotine (990mg/mL) Ingestion Suicide attempt	No pulse identified and performed cardiopulmonary resuscitation	Cardiopulmonary resuscitation and transferred to ICU	Hypoxic ischemic encephalopathy (brain death) caused by lethal nicotine intoxication	Moderate methodological quality Conflicts of interest None declared Funding None received
Scarpino et al., 2020[638] Italy, Florence Emergency department	Male 23 years Not reported	2 e-cigarettes refills Ingestion Unknown	Sudden loss of consciousness with vomiting, followed by bradycardia and respiratory muscle paralysis. Patient was in coma	Not reported	Day nine of coma Loss of respiratory drive and evolved toward brain death	Moderate methodological quality Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation	Treatment	Outcome	Quality assessment, conflict of interest, funding
Aoki et al., 2019[628] Japan Emergency department	Female 19 years Non-smoker, history of depression	Nicotine containing e-liquid Intravenous injection Unknown: suggestive of suicide, but no conclusive evidence	Cardiorespiratory arrest and was confirmed dead upon arrival at emergency department The nicotine concentration was extremely high in the tissues around the injection mark on the right upper arm and reached a lethal level in the blood	N/A	Death due to high concentration of injected nicotine	Low methodological quality Conflicts of interest None declared Funding Not reported
Belkoniene et al., 2019[596] Switzerland Emergency department	Male 51 years Active e-cigarette user, history of cigarette smoking, type 2 diabetes mellitus and a personality disorder	10mL of 100mg/mL nicotine e-liquid Injection Suicide attempt	Abdominal cramps; psychomotor agitation and mydriatic pupils followed by bradypnea and coma Developed a transitory neurological impairment with the appearance of tetraparesis, gaze palsy and myoclonus due to nicotinic syndrome Lactic acidosis	Intubated in ICU using rapid sequence induction (etomidate, succinylcholine and fentanyl)	7-10 hours post-injection: woke up and answered simple questions. Pupils were still mydriatic and poorly responsive to light 11 hours post-injection: complete recovery of motor response and normalisation of deep tendon reflexes allowing extubation 24 hours later: discharged	Moderate methodological quality Conflicts of interest None declared Funding No funding provided

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation	Treatment	Outcome	Quality assessment, conflict of interest, funding
Demir & Topal, 2018[599] Turkey Pediatric emergency department	Female 6 years Not reported	7mL liquid and 8.4mg nicotine with the nicotine ratio of 1.2mg/mL that was storage in an e-liquid bottle. The estimated nicotine intake of the whole bottle was 8.4mg Ingestion Accidental	Nausea and vomiting Bilateral sudden sensorineural hearing loss (SSNHL) after 24-hour fluid intake	Gastric lavage	6th month of follow-up: audiometric test results same as the results at the 10th day. Patient started using bilateral conventional hearing devices	High methodological quality Conflicts of interest None declared Funding Not reported
Paik et al., 2018[603] South Korea Emergency department	Male 53 years No known medical illness	3mL of e-liquid, brand name 'Pure Nicotine', concentration unknown Ingestion Suicide attempt	Immediately after ingestion The patient exhibited tachycardia, vomiting, diarrhea, and sweating without hypotension One hour after ingestion Bradycardia, hypotension, and severe weakness	Administered dopamine	Blood pressure normalised within 18 hours of admission, discharged after 3 days	Moderate methodological quality Conflicts of interest None declared Funding Inha University Research Grant
Morely et al., 2017[602] United Kingdom Hospital record	Male 32 years Not reported	Approximately 20mL from a e-liquid bottle containing 72mg/mL nicotine liquid Ingestion Accidental, inebriated at the time	Agitated, collapsed then went into cardiac arrest prior to reaching hospital	Cardiopulmonary resuscitation and transferred to ICU	Death due to brain hypoxia, attributed to prolonged cardiopulmonary resuscitation	Moderate methodological quality Conflicts of interest Not reported Funding None received

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source [time frame])	Demographics and medical history	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation	Treatment	Outcome	Quality assessment, conflict of interest, funding
van der Meer et al., 2017[605] The Netherlands ICU	Male 42 years Bipolar disorder	Nicotine containing e-liquid 450mg/mL Ingestion Unknown	No heart rhythm. Poor neurological status. High nicotine level in body: 3.0mg/L (Reference values for a smoker are 0.01-0.05mg/L)	Cardiac massage and symptomatic treatment	Died of post anoxic encephalopathy	Moderate methodological quality Conflicts of interest Not reported Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.11 Mental health effects

Main conclusions from the synthesised evidence on the mental health effects of e-cigarette use

- There is no available evidence as to how e-cigarette use affects clinical mental health outcomes.
- There is insufficient evidence as to the relationship of e-cigarette use to depressive symptoms and no available evidence regarding their effects on alternative subclinical mental health measures.

Table 4.11-1. Overview of studies of mental health outcomes identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Mental health effects			1 0 / 1				8 0 / 8*		

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g. qualitative study.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors
* One paper includes both cross-sectional and longitudinal analyses;[145] however the longitudinal analysis was not relevant for the top-up review and the paper has been included as a cross-sectional survey.

Outcomes

- **Clinical outcomes**: Clinical mental health disorders, including major depressive disorder, anxiety disorders, emotional disorders, attention deficit disorder, bipolar disorder, and schizophrenia.
- **Subclinical outcomes**: Depressive symptoms, anxiety symptoms and suicidality.

4.11.1 Findings from previous reviews

No studies examining clinical mental health disorders or subclinical outcomes in relation to e-cigarette use were identified in the NASEM review.[3] Some aspects of mental health were included in the review but were discussed in relation to problematic e-cigarette use and dependence. These findings are summarised in the dependence chapter of the top-up review.

The Irish Health Research Board literature map[15] also reported on mental health outcomes in relation to dependence and abuse liability. A total of 12 articles were identified; one randomised crossover trial,[639] four cohort studies[143-146], and seven cross-sectional surveys.[145,169-174] One cohort study was included in the top-up review,[146] two were not included in the review as they were published prior to our time frame but not reported in the NASEM review,[143,144] one was classified as cross-sectional for the purpose of this review[145] and neither the crossover trial nor the cross-sectional surveys met the inclusion criteria for the top-up review.

Both cohort studies were conducted in the US[143,144] and had a six-month and 12-month follow-up. Depressive symptoms were measured in youth and adolescent non-smokers[144] and former and current smokers using e-cigarettes (dual users).[143]

Lechner et al.[144] included 2,460 people who had never used tobacco products at baseline. After follow-up, there were 347 exclusive e-cigarette users, 104 of whom were considered sustained users (use at both waves) and 312 were non-sustained users (use at only one wave), with a mean age of 14.1 years (SD=0.41) and 55.6% were female.[144] Compared to non-users (no use of tobacco products across all waves), sustained exclusive e-cigarette users reported depressive symptoms more frequently at 12-month follow-up (p=0.01) but not non-sustained users. Within sustained exclusive e-cigarette users, higher frequency of use was also associated with more severe depressive symptoms (p=0.04).[144]

The cohort study by Bandiera et al.,[143] included 5,445 college students at wave 1. The mean age was 20.5 years (SD=2.4; range 18-29 years), with approximately 63% females at wave 1. The smoking status of e-cigarette users was not reported. The study found current e-cigarette use (including e-cigarette, vape

pen, or e-hookah and multiple product use status unknown) did not predict elevated depressive symptoms at six-month or one-year follow-up.

The Public Health England 2018 review[11] identified no studies on the relationship of e-cigarette use to mental health outcomes. A 2020 evidence update[12] focused on the patterns of e-cigarette use among people with mental health conditions and no studies relevant to the top-up review were identified.

The CSIRO review[14] identified four studies on the relationship of e-cigarette use to mental health outcomes; one cohort study,[144] one randomised crossover trial,[639] one cross-sectional survey[183] and one qualitative study.[640] The cohort study by Lecher et al.[144] was published prior to the top-up review's time frame but not included in the NASEM review[3] and is discussed above. All other studies were not eligible for the top-up review.

One study,[641] also included in the top-up review, was identified in the SCHEER review.[4] No studies on mental health were included in the USPSTF review.[16]

4.11.2 Summary of conclusions from other reviews

The NASEM review,[3] the Irish Health Research Board literature map[15] and the Public Health England review[11] did not provide summative conclusions on mental health outcomes.

The CSIRO review,[14] incorporating evidence from a randomised crossover trial and cohort, cross-sectional survey and qualitative studies, concluded that:

- There appears to be a consistent link between mental health, stress, depression and e-cigarette use.

4.11.3 Top-up reviews

Search results

Overall, nine articles were located in the top-up systematic literature search: one cohort study and eight cross-sectional surveys. The eight cross-sectional surveys[145,173,641-646] did not meet eligibility criteria – hence one article[146] was available for the top-up synthesis of evidence (Table 4.11-1).

Mental health: Clinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to clinical mental health outcomes were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to clinical mental health outcomes were located.

Cohort studies

No cohort studies reporting on the relationship of e-cigarette use to clinical mental health outcomes were located.

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarette use to clinical mental health outcomes were located.

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to clinical mental health outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to mental health risk

Three cross-sectional surveys reporting on the relationship of e-cigarette use to clinical mental health symptoms were identified.[641-643] Of those three studies, two[641,642] also reported subclinical mental health outcomes in relation to e-cigarette use. In this context, cross-sectional surveys are not able to provide reliable evidence on causality and no further description has been included.

Mental health: subclinical

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to subclinical mental health outcomes were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to subclinical mental health outcomes were located.

Cohort studies
One US cohort study of 5,236 tobacco product users[146], reported a dose-response relationship of increasing depressive symptoms with increasing e-cigarette use, among e-cigarette users (Table 4.11.2). Participants were aged between 18 and 29 years and there were fewer males (36.7%) than females (63.3%). Among 1,071 e-cigarette users, 768 used refillable and 303 used disposable e-cigarettes, although the proportion using each device exclusively (single product use rather than dual use with tobacco smoking) is unknown. Data were collected at approximately six-month intervals over three years. The numbers of participants experiencing outcome events was not reported.

The authors found that for every five days of use in the past 30 days, there was a 1% increase in depressive symptoms compared to baseline, over the course of the study, in refillable e-cigarettes users (RR 1.01; 95% CI 1.00-1.03; p=0.02) and 3% in cigarette smokers (RR 1.03; 95% CI 1.02-1.04; p<0.001) compared to baseline levels. There was no significant difference in depressive symptoms with higher frequency use among disposable e-cigarette users (RR 1.00; 95% CI 0.98-1.03; p=0.92). However, there was no significant difference in effect between refillable and disposable e-cigarette use. Both e-cigarette groups included both exclusive and other tobacco product users.

Significant increases in depressive symptoms since baseline were observed with five days and 15 days of exclusive refillable e-cigarette use in the past 30 days (RR 1.04; 95% CI 1.02-1.07 and RR 1.07; 95% CI 1.04-1.11 respectively). Similarly, significant increases in depressive symptoms were observed in cigarette smokers with five days of use (RR 1.07; 95% CI 1.04-1.09) and 15 days of use (RR 1.13; 95% CI 1.10-1.16) in the past 30 days. There was no statistically significant difference in depressive symptoms in exclusive disposable e-cigarette users (5 days of use: RR 1.05; 95% CI 0.99-1.11 and 15 days of use: RR 1.05; 95% CI 0.98-1.13). Once again, no significant difference in effect between refillable and disposable e-cigarette use was observed.[146]

The study was rated as low methodological quality using the Joanna Briggs Institute's critical appraisal checklist. No conflicts of interest were declared (Table 4.11.2).

Non-randomised intervention studies
No non-randomised intervention studies reporting on the relationship of e-cigarette use to other mental health outcomes were located.

Case-control studies
No case-control studies reporting on the relationship of e- use to other mental health outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to mental health risk
Seven cross-sectional surveys[145,173,641,642,644-646] reporting on the relationship of e-cigarette use to other mental health outcomes were located. Two[641,642] also reported clinical mental health outcomes in relation to e-cigarette use. In this context, cross-sectional surveys are not considered suitable evidence and no further description has been included.

4.11.4 Summary of findings from top-up review
There was one study among exclusive e-cigarette users and dual users reporting on subclinical outcomes related to mental health, finding:

- Evidence from one moderate-sized cohort study that among a mixed population of exclusive and dual users, exclusive use of e-cigarettes and increased frequency of use is related to increased depressive symptoms.

Hence, there is:

- No available evidence as to how the use of e-cigarettes affects the risk of clinical mental health conditions; and
- Insufficient evidence on the relationship of e-cigarette use to depressive symptoms in smokers and non-smokers.

4.11.5 Summary of findings integrating evidence from previous reviews and top-up review
Combining clinical evidence from the top-up systematic review with the evidence from previous reviews:

- No studies on the relationship of e-cigarette use to clinical mental health disorders were identified. Hence:
    - There is no available evidence as to how the use of e-cigarettes affects the risk of clinical mental health conditions.

Combining evidence from subclinical outcomes related to mental health from the top-up systematic review with the evidence from previous reviews:

- There were three cohort studies with findings on subclinical outcomes related to mental health.
- Compared to non-users, sustained exclusive e-cigarette use was associated with more frequent reporting of depressive symptoms in one study.
- Among non-smokers (exclusive e-cigarette use), there was a greater rate of increase in depressive symptoms associated with increased frequency of e-cigarette use in two studies.
- One study found e-cigarette use did not predict elevated depressive symptoms (smoking status unknown).
- Hence:
    - There was insufficient evidence on the relationship of e-cigarette use to depressive symptoms.
- The GRADE rating was very low certainty.

4.11.6 Main conclusions from the synthesised evidence on the mental health effects of e-cigarette use

- There is no available evidence as to how e-cigarette use affects clinical mental health outcomes.
- There is insufficient evidence as to the relationship of e-cigarette use to depressive symptoms and no available evidence regarding their effects on alternative subclinical mental health measures.

Table 4.11-2. Study details: mental health effects – cohort studies

Study details (author, year, location, time frame, [data source])	Sample characteristics	Exposure/ Comparator	Outcome measure	Results	Quality assessment, study size, conflicts of interest, funding
Marsden et al., 2019[146] US 2014-2017 Marketing and Promotions across Colleges in Texas project (M-PACT)	Study size 5,236 participants Sample Past 30-day user Gender (%) Male: 36.7 Female: 63.3 Age – mean (SD) years 21.0 (2.3) Range: 18–29	Exposure 1 (n=768) Refillable e-cigarettes Exposure 2 (n=303) Disposable e-cigarettes Comparator Within person Materials No information Follow-up Six waves of data from October 2014 through June 2017; approximate 6-monthly follow-up	Depressive symptoms (measured with the Center for Epidemiologic Studies Depression 10 scale – CES-D-10)	Hierarchical Poisson model - includes multiple product user Frequency of use[1] / Rate ratio / 95% CI / p-value Refillable EC 1.01 1.00-1.03 0.02 Disposable EC 1.00 0.98-1.03 0.92 Cigarettes 1.03 1.02-1.04 <0.001 Past 30-day use[2] Refillable EC 1.03 1.00-1.05 0.04 Disposable EC 1.05 0.99-1.11 0.13 Cigarettes 1.04 1.01-1.06 <0.01 -Adjusted for race/ethnicity, sex, baseline age, two- vs. four-year college, father's education and survey wave [1]The number of days of tobacco product use in the past 30 days was scaled so that each one-unit increase represents an additional 5 days of use. [2]Past 30-day use was adjusted for frequency of use Model-based estimates of the associations - include single product users 5 days of use in the past 30 days / Rate ratio / 95% CI Refillable EC 1.04 1.02-1.07 Disposable EC 1.05 0.99-1.11 Cigarettes 1.07 1.04 -1.09 15 days of use in the past 30 days Refillable EC 1.07 1.04-1.11 Disposable EC 1.05 0.98-1.13 Cigarettes 1.13 1.10-1.16 Estimates account for frequency of use, past 30-day use and relevant interactions. All associations are adjusted for race/ethnicity, sex, baseline age, two- vs. four-year college, father's education and survey wave	Low methodological quality Large study size, number of events not reported Conflicts of interest None declared Funding National Cancer Institute at the National Institutes of Health and the US Food and Drug Administration

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.12 Environmental hazards with health implications

Main conclusions from the synthesised evidence on the relationship of e-cigarettes to environmental hazards with health implications

- There is conclusive evidence that e-cigarette use results in increased airborne particulate matter in indoor environments.
- There is limited evidence that e-cigarette use results in increased concentrations of airborne nicotine and of nicotine and cotinine on indoor surfaces.
- There is insufficient evidence that e-cigarette use results in increased air levels of carbon dioxide, carbon monoxide, propylene glycol, volatile organic compounds and carbonyls.
- There is substantial evidence that e-cigarettes can cause fires and environmental waste and insufficient evidence as to the extent that these present a hazard to human health.

Table 4.12-1: Overview of studies of environmental hazards with health implications identified in the systematic review, by study design

Health outcome	Meta-analysis	Randomised controlled Trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Environmental hazards with health implications*				17 9 / 8		2 0 / 2		5 0 / 5	

Notes:
* Characterisation of studies in environmental differs from other outcomes. Those included in non-randomised intervention studies are controlled experimental studies and those included in case series are natural experiments.
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Environmental hazards with health implications**: Air quality (airborne particulate matter (PM), carbonyls, gases and volatile organic compounds), surface contamination (nicotine and cotinine), fire (occurrence of fire, reported fires, fire spread and structural damage or loss due to fire/explosion) and waste (discarded e-cigarette devices, e-liquid cartridges, pods, e-liquids or nicotine salts).

4.12.1 Findings from previous reviews

The NASEM review[3] identified nine studies[647-655], eight non-randomised intervention studies examining the characteristics and chemical composition of second-hand e-cigarette aerosol (air quality) and one study assessing nicotine on home surfaces of users of e-cigarettes. Only studies in which the aerosol was generated by a person using the e-cigarette, reflecting the most realistic exposure to bystanders, was included in the NASEM and top-up reviews.

Air quality studies were conducted in a variety of settings (exposure chambers and rooms, homes, conventions) investigating mainly particulate matter and nicotine, with some other constituents assessed by some studies. Across studies, significantly elevated levels were consistently found for particulate matter[647,649-651,653-655] and nicotine,[647-649,651,652] with a dose-response relationship observed demonstrating higher nicotine levels with increasing rates of active ENDS use.[653,655] Total volatile organic compounds were elevated with e-cigarette use,[653] and one study identified specific compounds that increased (benzene, isoprene, toluene)[648] while others showed no significant effect.[647,648] Elevated compound levels from e-cigarette use were also reported for propylene glycol and glycerol,[648] aluminium,[651] some carbonyls (acetaldehyde, hexaldehyde),[648] and polycyclic aromatic hydrocarbons.[651] The NASEM review stated[3] that, "Overall, these exposure studies indicate that e-cigarette vaping contributes to some level of indoor air pollution, which, although lower than what has been observed from second-hand combustible tobacco cigarettes, is above the smoke-free level recommended by the Surgeon General and the WHO FCTC."

The Irish Health Research Board literature map[15] reported on a study by Coppeta et al.,[291] which included air quality data, however, it was discussed under respiratory outcomes. This study has been included in both the respiratory chapter and the environmental chapter in the top-up review.

The Public Health England review[11] reported on fire service data from the UK Fire and Rescue Incident Recording System.[656] The data covered a two-year period from April 2015 to March 2017, including data from 49 out of 52 services. They identified 151 fires relating to e-cigarettes and the outcomes of fires were not reported. A single service, the London Fire Brigade, reported 13 e-cigarette-related fires out of a total 3,527 smoking-related fires between April 2015 and March 2017 (0.4%). The review also included studies on air quality effects from use of heated tobacco products, but not e-cigarettes.

The SCHEER review[4] identified two studies on environmental hazards related to e-cigarette use. One, a systematic review[657], did not meet inclusion criteria for the top-up review and the other, a natural experiment, was included in the NASEM review.[652]

The CSIRO review[14] reported no studies on the environmental impacts of e-cigarettes relevant to humans and no studies were identified in the USPSTF review.[16]

4.12.2 Summary of conclusions from previous reviews

The NASEM review[3] concluded that:

- There is conclusive evidence that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with background levels.
- 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.

The Public Health England review[11] concluded that:

- 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.

There were no relevant environment-related conclusions made regarding e-cigarettes in the Irish Health Research Board[15] or CSIRO reviews.[14,15]

4.12.3 Top-up review

Search results

Overall, 15 articles were identified for inclusion in the results from the initial search, 14 from the initial search and one from a grey literature search (Table 4.12-2).

Meta-analyses

No meta-analyses on the relationship of e-cigarettes to environmental hazards were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarettes to environmental hazards were located.

Cohort studies

No cohort studies reporting on the relationship of e-cigarettes to environmental hazards were located.

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarettes to environmental hazards were located.

In the context of environmental hazards, experiments with controlled parameters have been placed under non-randomised intervention studies.

Controlled experiments

Eight controlled experimental studies on air quality related to e-cigarette use were identified (Table 4.12.2). Three were from Italy,[291,658,659] and one each were from Greece,[660] Portugal,[661] Spain,[662] Canada[663] and Germany.[664]

In the study by Coppeta et al., indoor particulate matter concentration during and immediately after e-cigarette use was higher than that of cigarette smoking although no statistical test was reported (49,690pp/cm^3 vs. 42,645pp/cm^3).[291] Concentrations return to baseline five minutes after e-cigarette use

and 30 minutes after smoking. Loupa et al. found the higher concentrations of indoor particulate matter during e-cigarette use than that of combustible cigarette smoking for PM10 (ENDS: 74.78mg/m^3 vs. cigarette: 55.32mg/m^3) and PM2.5 (ENDS: 82.06mg/m^3 vs. cigarette: 62.19mg/m^3), however no statistical tests were reported.[660] In the study by Protano,[659] indoor PM1 concentrations were significantly higher after e-cigarette use for each for the four different e-liquids ($p<0.001$). In an earlier study by Protano,[658] indoor PM1 concentrations were significantly higher after e-cigarette use for each generation, voltage and resistance manipulation ($p<0.001$). Compared to no indoor smoking conditions, e-cigarette use significantly increased indoor concentrations of PM1, PM2.5, PM10 and ultrafine particles ($p<0.05$), but not black carbon, carbon monoxide or carbon dioxide in the study by Savdie et al.[661] The authors conducted the same experiment inside a medium volume car and found only PM10 to be significantly higher during e-cigarette use compared to no use. Van Drooge et al. found higher indoor concentrations of PM10, PM2.5, PM1, particle number concentrations and nicotine during e-cigarette use compared to no use, however, no statistical tests were reported.[662] In the study by Volesky, average indoor PM2.5 and ultrafine concentrations were significantly higher during e-cigarette use than before or after ($p<0.001$) but only when measured one metre from the user rather than half a metre from the user.[663] In the German study by Schober, particulate number concentration, PM2.5, propylene glycol and nicotine were all higher during e-cigarette use than no use in each of the seven different model of car tested, but no statistical test was reported.[664]

Seven of the studies were rated of high methodological quality[658-664] and one of moderate methodological quality[291] using the Joanna Briggs Institute's critical appraisal checklist. No conflicts of interest were noted for any study.

Case-control studies

No case-control studies reporting on the relationship of e-cigarettes to environmental hazards were located.

Other study types

Seven articles with other study types were identified (Table 4.12.2).

Natural experiments

Five natural experiments on environmental hazards were identified: two on nicotine and cotinine surface deposits, two on particulate matter concentration in the air and one on e-cigarette waste. In the context of environmental hazards, natural experiments have been placed under case series.

Two natural experiments on air quality were identified. Cammalleri et al.[665], conducted in the US, found a statistically significant increase in outdoor PM1 concentrations after e-cigarette use over a 10 hour period ($p<0.023$). Outdoor PM1 levels during e-cigarette use peaked at 427 times higher than no e-cigarette use.[665] In the US study by Nguyen et al.,[666] six vape shops were measured for real time concentrations of fine and ultrafine particles on both busy and slow days, indoors and outdoors. Across the six vape shops, particle number concentration ranged from 5.5×10^3 to 3.3×10^4 particles/cm^3 and PM2.5 ranged from 3.2 to 39µg/m^3 in the absence of active e-cigarette use. During active e-cigarette use, particle number concentration ranged from 1.3×10^4 to 4.8×10^5 particles/cm^3 and PM2.5 concentrations ranged from 15.5 to 37,500µg/m^3. Average outdoor particle number concentration ranged from 8.5×10^3 to 5.6×10^4 particles/cm^3 and PM2.5 ranged from 7.5–72µg/m^3. On average, particle number concentration was 1.5 times higher indoors than outdoors and 22 times higher for indoor PM2.5 than outdoor PM2.5, but no statistical tests were reported.

In one study, Khachatoorian et al.[667] assessed nicotine and cotinine deposits on fabric samples and air filters in a shop adjacent to a vape shop. Samples were collected after one, four, and eight days and after one, two and three months. Levels of nicotine and cotinine generally increased as exposure time increased, with nicotine the most abundant marker (highest concentration=23,260ng/g of fabric). The amount of nicotine and cotinine differed by the type of fabric and substance, with cotton found to have nicotine on it 100%, compared to 92% for paper towel, and paper towel 83% of the time by cotinine, compared to 22% for cotton towel. Only two control samples reported low nicotine levels; no nicotine or cotinine were otherwise detected in control fabrics.

In the second study, Khachatoorian et al.[668] assessed accumulated levels of nicotine and cotinine in two indoor settings; a home and a vape shop. Fabric samples, one polyester and one cotton, placed inside the home and vape shop were compared to control locations (a non-smokers home and on an external window of the vape shop). Fabric samples were collected after one, two, three, four, five, and six months of exposure in the home and after six, seven, 18, 24, and 48 hours, one week and one month in the vape shop. In the home, nicotine was detected at each month over six months on cotton, but detected in only the final two months on polyester. On cotton, nicotine levels ranged from 2,000-3,000ng/gram with the exception

of month three which was 5,100ng/gram. Cotinine was detected in each of the six months on cotton samples, but only in three months (months one, three and four) on polyester. Levels ranged from approximately 25 – 120ng/gram on cotton and 25 – 35ng/gram on polyester. Control results were not reported. In the vape shop, nicotine levels were highest on the display case (283,775ng/g) and lowest at the back of the store (17,655ng/g) after one month. The control site recorded very low levels of nicotine over the one-month exposure period with a maximum of 719ng/g. Cotinine followed the same pattern, with the highest amount recorded for the display case (approximately 900ng/g), lowest at the back of the store (175ng/g), and undetected in the control samples.

Mock and Hendlin[669] reported the results of a garbology study (an ethno-archaeological study of a community or cultural group by analysing its waste) measuring waste from e-cigarettes (Table 4.12.2). They reported e-cigarette waste around 12 public high schools, most of which was from JUUL brand e-cigarettes. There were 172 reported waste items identified, the large majority of which were pod caps, followed by pods. The authors concluded that "measures are needed to eliminate environmental contamination from e-cigarette…waste in and around schools".

The four studies were of moderate[666-669] and one of high[665] methodological quality and no conflicts of interest for any study were noted.

Surveillance reports

Two surveillance reports reporting on the relationship of e-cigarettes to fires were identified (Table 4.12.3).

The identified grey literature report was from the US Fire Administration,[670] reporting on the scope and nature of explosions and fires attributable to e-cigarettes occurring between January 2009 and December 2016. A total of 195 incidents were reported. The most common incident context reported was when being carried in the individual's pocket (n=61) and almost as frequent, when the device was in active use (n=60), followed by during charging (n=48). Less common were incidents whilst the device was in storage (n=18), and one incident occurred on a cargo aircraft. Of the 128 reports of fire spread, 10 were recorded as major (involved significant portions of a building, and required suppression by the fire department), 27 as moderate (the burned area was larger than six inches in diameter, but the fire was extinguished by occupants before the fire department arrived), and 91 as minor (the scorching or flames either self-extinguished or were extinguished very quickly by persons nearby). Authors made several concluding points, which included that consumers should look for and demand e-cigarette products that have been evaluated for safety and that lithium-ion batteries should not be used in e-cigarettes.

Saxena et al.[567] reported surveillance and case data on fires and explosions attributable to e-cigarette use drawing on surveillance data from the US National Fire Data Centre over an eight-year period (2009 to 2016), and cases reported on a blog site (Ecigone) which captured reports from any country over a nine-year period (2009 to 2017). As data from the US National Fire Data Centre has already been described, only information from the blog will be described. The blog reported 243 fires/explosions of which 31% occurred in pockets, 31% while in use, 25% while charging, 0.01% while in transport and 4% were unknown.

The methodological quality of the study was rated as low and no conflicts of interest were declared by the authors. As the US National Fire Data Centre report was not a peer-reviewed article, no quality assessment was conducted and conflicts of interest were not reported.

4.12.4 Summary of findings from top-up review

There were 15 studies: eight controlled experiements, five natural experiements and two surveillance reports, finding:

- In indoor environments, including cars, rooms and shops selling e-cigarettes:
  - E-cigarette use significantly increases concentrations of particulate matter, including PM1, PM2.5, PM10 and ultrafine particles;
  - No statistically significant effect could be determined for air levels of nicotine, carbon dioxide, propylene glycol, volatile organic compounds, carbonyls and carbon monoxide.
- E-cigarette use is related to indoor surface contamination with nicotine and cotinine;
- E-cigarettes can cause fires and explosions that may result in the destruction of property;
- E-cigarettes can contribute to environmental waste.

Hence:

- There is substantial evidence that e-cigarette use leads to air pollution with particulate matter of varying sizes in indoor environments;

- There is insufficient evidence on the relation of e-cigarettes to air levels of nicotine, carbon dioxide, propylene glycol, volatile organic compounds, carbonyls and carbon monoxide in indoor environments;
- There is insufficient evidence on the relation of e-cigarettes to nicotine and cotinine fabric indoor surface contamination;
- There is substantial evidence that e-cigarettes can cause fires and explosions and environmental waste, but insufficient evidence on the extent to which these present a hazard to human health.

4.12.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence from the top-up systematic review with the evidence from previous reviews:

- There was a total of 25 studies on environmental hazards with health implications in relation to e-cigarette use: 17 controlled experiements, five natural experiments and three survillence reports.
- In indoor environments, including cars, rooms and vape shops:
    - E-cigarette use significantly increases concentrations of particulate matter, including PM1, PM2.5, PM10 and ultrafine particles;
    - No statistical effect could be determined for air levels of nicotine, carbon dioxide, propylene glycol, volatile organic compounds, carbonyls and carbon monoxide;
    - A dose-reponse relationship was observed (higher nicotine levels with increased rates of ENDS use)
- E-cigarette use is related to indoor surface contamination with nicotine and cotinine;
- E-cigarettes can cause fires and explosions that may result in the destruction of property;
- E-cigarettes can contribute to environmental waste;
- Hence:
    - There is conclusive evidence that e-cigarette use leads to increased airborne concentration of particulate matter of varying sizes in indoor environments compared to background levels;
    - There is limited evidence on the relation of e-cigarettes to air levels of nicotine in indoor environments compared to background levels;
    - There is insufficient evidence on the relation of e-cigarettes to air levels of carbon dioxide, propylene glycol, volatile organic compounds, carbonyls and carbon monoxide in indoor environments compared to background levels;
    - There is limited evidence on the relation of e-cigarettes to nicotine and cotinine indoor surface contamination compared to background levels;
    - There is substantial evidence that e-cigarettes can cause fires and environmental waste, but insufficient evidence as to the extent to which these present a hazard to human health.
- The GRADE rating was very low certainty. (Appendix 6).

4.12.6 Main conclusions from the synthesised evidence on the environmental hazards with health implications of e-cigarettes

- There is conclusive evidence that e-cigarette use results in increased airborne particulate matter in indoor environments.
- There is limited evidence that e-cigarette use results in increased concentrations of airborne nicotine and of nicotine and cotinine on indoor surfaces.
- There is insufficient evidence that e-cigarette use results in increased air levels of carbon dioxide, carbon monoxide, propylene glycol, volatile organic compounds and carbonyls.
- There is substantial evidence that e-cigarettes can cause fires and environmental waste and insufficient evidence as to the extent that these present a hazard to human health.

Table 4.12-2 Study details: environmental hazards with health implications – controlled and natural experiments

Study details (author, year, study design)	Setting	Experimental conditions	Outcome measure	Results	Quality assessment, conflict of interest, funding
Controlled experiments					
Protano et al., 2020[659] Italy Open-label, single-centre, controlled study	Room with closed window and door, single occupant, 3 participants Area size 52.7m^3 Temperature 20-23°C Relative humidity 36%-40%	Experimental During vaping session; 12 puffs were made for each session (approximately 5–6 minutes); 2 blocks, 15 sessions in each Control Before vaping session Device JUUL, 4 flavours (Golden Tobacco, Mango, Mint, Royal Crème)	Particulate matter PM1 (µg/m^3) Average session time 5.5 minutes	PM1 – mean (SD) Flavour / Experimental / Control Golden Tobacco: 1637.9 (6387.6) / 8.3 (2.3) Mango: 37.7 (208.3) / 10.9 (1.5) Mint: 16.7 (5.4) / 13.8 (1.9) Royal Crème: 16.0 (5.0) / 13.3 (1.5) Statistically significant difference (<0.001) before and after vaping session for all tests Median also published. Mean and median approximately equal in control condition. Mean notably higher than median in experimental condition for Golden Tobacco and Mango flavours only	High methodological quality Conflicts of interest None declared Funding No external funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, study design)</th><th>Setting</th><th>Experimental conditions</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, conflict of interest, funding</th></tr>
<tr><td rowspan="2">Savdie et al., 2020[661]

Portugal

Open-label, single-centre, controlled studies</td><td>Sitting room occupied by 2 people

<u>Area size</u>
73m^3</td><td><u>Experimental</u>
During vaping session; one participant took 10 puffs for 5 minutes, 10-minute rest, repeated 8 times

<u>Control</u>
Non-smoking/vaping (“background” not further specified)

<u>Device</u>
1. JUUL (Slate JUUL, 4.5V, 8W, 5% nicotine pods)
2. Vape (IStick TC40W, nicotine free liquid) (ENNDS)</td><td><u>Particulate matter</u>
1. PM1 (µg/m^3)
2. PM2.5 (µg/m^3)
3. PM10 (µg/m^3)
4. Ultrafine particles (UFP) (#/cm^3)

<u>5. Black carbon (BC) (µg/m^3)</u>

<u>Gases</u>
6. Carbon monoxide (CO) (mg/m^3)
7. Carbon dioxide (CO_2) (mg/m^3)

Average session time
5 minutes</td><td><u>Particulate matter, black carbon and gases</u> – mean
<table><tr><th></th><th>Control</th><th>Experimental</th></tr><tr><td>PM1</td><td>21.0</td><td>1,350*</td></tr><tr><td>PM2.5</td><td>22.6</td><td>1,370*</td></tr><tr><td>PM10</td><td>25.4</td><td>1,380*</td></tr><tr><td>UFP</td><td>4,690</td><td>37,800*</td></tr><tr><td>BC</td><td>0.21</td><td>4.3</td></tr><tr><td>CO</td><td>1.66</td><td>1.00</td></tr><tr><td>CO_2</td><td>1,810</td><td>2,890</td></tr></table>* Statistically different to control (p<0.05)
^ Approximate from graphed data
Statistical significance test results not reported for BC, CO, CO_2

Note: JUUL and ENNDS not reported separately</td><td rowspan="2">High methodological quality

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Supported by LIFE Index-Air project and Portuguese Foundation for Science and Technology</td></tr>
<tr><td>Medium volume car (Diesel Opel Corsa, from 2007) occupied by 2 people</td><td><u>Experimental</u>
During vaping session; one participant took 10 puffs for 3 minutes, 7-minute rest, repeated 3 times

<u>Control</u>
Non-smoking/vaping (test drive)

<u>Device</u>
1. JUUL (Slate JUUL, 4.5V, 8W, 5% nicotine pods)</td><td><u>Particulate matter</u>
1. PM1 (µg/m^3)
2. PM2.5 (µg/m^3)
3. PM10 (µg/m^3)
4. Ultrafine particles (UFP) (#/cm^3)

<u>5. Black carbon (BC) (µg/m^3)</u>

<u>Gases</u></td><td><u>Particulate matter, black carbon and gases</u> – mean
<table><tr><th></th><th colspan="2">JUUL</th><th colspan="2">ENNDS</th></tr><tr><th></th><th>Exp</th><th>Control</th><th>Exp</th><th>Control</th></tr><tr><td>PM1</td><td>129</td><td>19.2</td><td>1,150</td><td>21.0</td></tr><tr><td>PM2.5</td><td>131</td><td>21.1</td><td>1,170</td><td>21.8</td></tr><tr><td>PM10</td><td>134*</td><td>24.5</td><td>1,170*</td><td>23.3</td></tr><tr><td>UFP</td><td>47,800</td><td>28,500</td><td>56,300</td><td>17,600</td></tr><tr><td>BC</td><td>1.15</td><td>0.57</td><td>0.70</td><td>0.59</td></tr><tr><td>CO</td><td>0.82</td><td>0.43</td><td>1.09</td><td>0.43</td></tr><tr><td>CO_2</td><td>982</td><td>883</td><td>1,090</td><td>956</td></tr></table>* Statistically different to control (p<0.05)</td></tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, study design)</th><th>Setting</th><th>Experimental conditions</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, conflict of interest, funding</th></tr>
<tr><td></td><td></td><td>2. Vape (IStick TC40W, nicotine free liquid) (ENNDS)</td><td>6. Carbon monoxide (CO) (mg/m^3)
7. Carbon dioxide (CO_2) (mg/m^3)

Average session time
3 minutes</td><td>Statistical significance test results not reported for PM1, PM2.5, UFP, BC, CO, CO_2</td><td></td></tr>
<tr><td>Loupa et al., 2019[660]

Greece

Open-label, single-centre study</td><td>Residential living room, with wall-mounted air conditioner, occupied by two people

<u>Area size</u>
$126m^3$</td><td><u>Experimental</u>
During vaping session, one participant vaped for 10 minutes, approximately 2 puffs per minute with 1-minute interval between puffs

<u>Control</u>
Tobacco cigarettes

<u>Device</u>
E-cigarette, no nicotine (ENNDS)</td><td><u>Particulate matter</u>
1. PM2.5 ($\mu g/cm^3$)
2. PM10 ($\mu g/cm^3$)

Average session time
10 minutes</td><td><u>Particulate matter</u>
<table><tr><th></th><th colspan="2">PM2.5</th><th colspan="2">PM10</th></tr><tr><th></th><th>Mean (SD)</th><th>Min-Max</th><th>Mean (SD)</th><th>Min-Max</th></tr><tr><td>ENDS</td><td>74.78 (96.12)</td><td>1.44-288.72</td><td>82.06 (98.95)</td><td>2.02-294.76</td></tr><tr><td>Cigarettes</td><td>55.32 (31.32)</td><td>2.37-97.25</td><td>62.19 (31.11)</td><td>3.67-106.83</td></tr></table></td><td>High methodological quality

<u>Conflicts of interest</u>
Not reported

<u>Funding</u>
University funds</td></tr>
<tr><td>Schober et al., 2019[664]

Germany

Open-label, multi-centre, controlled study</td><td>1. Large (4–5m^3): Skoda Octavia (Skoda), Volvo S (Volvo)
2. Medium (3–4m^3): VW Golf (2001,-05,-06) (Golf 01, Golf 05, Golf 06)
3. Small (2–3m^3): Smart</td><td><u>Experimental</u>
During vaping session; passenger used e-cigarette, four second inhalation twice per minute

<u>Control</u>
No vaping/smoking (test drive)

<u>Device</u></td><td><u>Particulate matter</u>
1. Nano particle concentration (PNC diameter 25–300nm) ($\#/cm^3$)
2. Fine particle concentration (PNC diameter >300nm) ($\#/cm^3$)
3. PM2.5 ($\mu g/m^3$)

4. Propylene glycol</td><td><u>Particulate matter</u> – mean
<table><tr><th></th><th colspan="2">PNC (25–300nm)</th><th colspan="2">PNC (>300nm)</th><th colspan="2">PM2.5</th></tr><tr><th></th><th>Exp</th><th>Control</th><th>Exp</th><th>Control</th><th>Exp</th><th>Control</th></tr><tr><td>Skoda</td><td>53,579</td><td>10,491</td><td>2,145</td><td>20</td><td>490</td><td>6</td></tr><tr><td>Volvo</td><td>14,209</td><td>20,231</td><td>659</td><td>41</td><td>170</td><td>10</td></tr><tr><td>Golf 06</td><td>33,014</td><td>20,675</td><td>1,362</td><td>22</td><td>262</td><td>7</td></tr><tr><td>Golf 05</td><td>73,954</td><td>73,941</td><td>1,188</td><td>40</td><td>269</td><td>11</td></tr><tr><td>Golf 01</td><td>10,248</td><td>8,434</td><td>289</td><td>18</td><td>75</td><td>7</td></tr><tr><td>Smart</td><td>13,543</td><td>17,716</td><td>90</td><td>14</td><td>18</td><td>4</td></tr><tr><td>Fiat</td><td>19,901</td><td>18,626</td><td>28</td><td>19</td><td>8</td><td>9</td></tr></table></td><td>High methodological quality

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Not reported</td></tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, study design)</th><th>Setting</th><th>Experimental conditions</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, conflict of interest, funding</th></tr>
<tr><td></td><td>ForFour (Smart), Fiat Punto (Fiat)

Each occupied by 2 people

Passenger window 2cm or 5cm open</td><td>SubTwin Neo; tobacco-flavoured liquid, nicotine content 18mg/mL</td><td><u>5. Nicotine</u>

<u>Volatile organic and organic compounds</u> ($\mu g/m^3$)
6. Benzene
7. Toluene
8. Furfural
9. 3-Ethenylpyridine

<u>Carbonyls</u>
10. Formaldehyde
11. Acetaldehyde
12. Propionaldehyde
13. Acetone
14. 2-Butanone

Average session time
20–23 minutes</td><td><u>Propylene glycol</u> passenger window: 2cm open/5cm open – mean
<table><tr><th></th><th>Skoda</th><th>Volvo</th><th>Golf 06</th><th>Golf 05</th><th>Golf 01</th><th>Smart</th><th>Fiat</th></tr><tr><td>ENDS</td><td>262/502</td><td>196/226</td><td>341/370</td><td>762/611</td><td>50/59</td><td><LD</td><td><LD</td></tr><tr><td>Control</td><td><LD</td><td><LD</td><td><LD</td><td><LD</td><td><LD</td><td><LD</td><td><LD</td></tr></table>
<u>Nicotine</u> passenger window: 2cm open/5cm open – mean
<table><tr><th></th><th>Skoda</th><th>Volvo</th><th>Golf 06</th><th>Golf 05</th><th>Golf 01</th><th>Smart</th><th>Fiat</th></tr><tr><td>ENDS</td><td>4/5</td><td><LD</td><td>4/<LD</td><td>10/7</td><td>5/<LD</td><td><LD</td><td><LD</td></tr><tr><td>Control</td><td><LD</td><td><LD</td><td><LD</td><td><LD</td><td><LD</td><td><LD</td><td><LD</td></tr></table>
<LD: measurement was below the limit of detection (LD)
No significance testing was reported
No correlation found between the different ventilation conditions (PW 2cm vs. 5cm open)

<u>Other compounds</u>
No effect reported

<u>Carbonyls</u>
No effect reported</td><td></td></tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, study design)	Setting	Experimental conditions	Outcome measure	Results	Quality assessment, conflict of interest, funding
Coppeta et al., 2018[291] Italy Open-label, single-centre, controlled study	Unknown setting with single occupant, 30 participants	Experimental Active vaping; one participant performing 15 puffs over 5 minutes, and temporal variation during the subsequent 60 minutes Control Before vaping session Device EGO P (L) with manual start; Latakia tobacco flavour containing nicotine 1.8% (18 ml/L)	Particulate matter Concentration of airborne particles (#/cm^3) Average session time: approximately 5 minutes (time to return to baseline particle concentration)	Particulate matter – mean (range) ENDS: 49,690pp/cm^3 (5,040-50,000) Control: 42,645pp/cm^3 (2,310-50,000) No statistical tests conducted	Moderate methodological quality Conflicts of interest None declared Funding Not reported
van Drooge et al., 2019[662] Spain Open-label, single-centre, controlled study	Closed room without direct contact with external air, occupied by 10 people Area size 146m^3	Experimental During vaping; 5 active vapers ab libium use during 12-hour period Control Non-vaping (day prior) Device E-liquid composition: Power (W), Nicotine (mg/mL), Proportion glycerine/propylene glycol 1. 50, 3, 70/30 2. 70, 3, 80/20 3. 45, 6, 50/50 4. 20, 3, 40/60 5. 15, 12, 30/70	Particulate matter 1. PM10 (µg/m^3) 2. PM2.5 (µg/m^3) 3. PM1 (µg/m^3) 4. Particle number concentration (PNC) (#/cm^3) Organic compounds 5. Nicotine (µg/m^3) Average session time 12 hours	Particulate matter – mean PM10 / PM2.5 / PM1 / PNC ENDS: 60 / 20 / 14 / 9.6 × 10^3 Control: 25 / 10 / 6 / 5.2 × 10^3 Nicotine – mean ENDS 16 Control 0.1	High methodological quality Conflicts of interest Not reported Funding Partial funding from EU projects HEALS, NEUROSOME, and EPPA S.A

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, study design)	Setting	Experimental conditions	Outcome measure	Results	Quality assessment, conflict of interest, funding
Protano et al., 2018[658] Italy Open-label, single-centre, controlled study	Room with closed window and door, unspecified number of occupant participants Area size 52.7m^3	Experimental During vaping session; 12 puffs were made for each session lasting approximately 5.5 minutes (1 puff about each thirty seconds); unknown number of active vapers Control Before vaping session Device 1: First generation e-cigarettes (Young Category®) 2: Second generation e-cigarettes (Smooke®) 3: Third generation e-cigarettes (JustFog Q16 Kit®, voltage 3.4V - 4.8V, resistance 1.6 Ohm) 4: Fourth generation e-cigarettes (G 150 Smok Kit® with V8 Baby-Q2 Smok atomizer®, wattage variation from 25 to 150W, and the resistance of either 0.15 and 0.4 Ohm) ENDS and ENNDS 0.15Ω and 0.4Ω 25W, 50W, 55W, 80W, 100W and 150W	Particulate matter 1. PM1 (µg/m^3) Average session time 5.5 minutes	PM1 – mean (SD) Experimental / Control **First generation** ENNDS: 79.69 (80.13) / 41.27 (19.09) ENDS: 105.52 (117.10) / 43.86 (18.75) **Second generation** ENNDS: 534.00 (1266.88) / 21.34 (7.67) ENDS: 3428.85 (5857.54) / 18.33 (6.74) **Third generation** ENNDS (3.4V): 789.48 (2300.46) / 21.56 (6.31) ENDS (3.4V): 54.39 (179.23) / 26.22 (6.58) ENNDS (4.8V): 522.29 (1729.70) / 21.45 (6.75) ENDS (4.8V): 1005.81 (4405.06) / 26.22 (13.58) **Fourth generation** ENNDS (0.15Ω, 25W): 384.53 (1327.67) / 20.96 (2.74) ENDS (0.15Ω, 25W): 963.24 (4605.46) / 35.44 (6.32) ENNDS (0.4Ω, 55W): 74.50 (40.70) / 31.67 (8.79) ENDS (0.4Ω, 55W): 472.93 (1181.44) / 43.87 (6.23) ENNDS (0.4Ω, 80W): 2238.34 (3931.00) / 35.44 (6.32) ENDS (0.4Ω, 80W): 14887.00 (25725.24) / 41.66 (7.36) ENNDS (0.15Ω, 50W): 177.69 (80.61) / 41.27 (19.09) ENDS (0.15Ω, 50W): 5949.16 (15452.17) / 43.55 (7.73) ENNDS (0.15Ω, 100W): 5637.34 (19136.38) / 39.28 (17.21) ENDS (0.15Ω, 100W): 2572.72 (4301.85) / 43.55 (7.73) ENNDS (0.15Ω, 150W): 12925.34 (31590.92) / 41.27 (19.09) ENDS (0.15Ω, 150W): 14640.47 (32776.91) / 44.67 (8.59) Statistically significant difference (<0.001) before and after vaping session for all tests. Median also published. Mean and median approximately equal in control condition. Mean notably higher than median in experimental condition	High methodological quality Conflicts of interest None declared Funding No external funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, study design)	Setting	Experimental conditions	Outcome measure	Results	Quality assessment, conflict of interest, funding
Volesky et al., 2018[663] Canada Open-label, single-centre, controlled study	Closed room with two occupants, volunteer e-cigarette user situated near the centre facing the measurement devices either 0.5m or 1m away Area size ~38m^3	Experimental During vaping; one active vaper took 4-second puffs 7 times, repeated 3 times Control No vaping (before and after vaping session) Device 1. Cigalike e-cigarette (cigalike) 2. Tank e-cigarette (tank) 3. Adjustable voltage e-cigarette (adjustable) E-liquid: Gold Seal™ brand "sweetish berry", 12mg/mL nicotine, 70% propylene glycol, 30% vegetable glycerin	Particulate matter 1. Particulate matter size <2.5µm (PM2.5) (µg/m^3) 2. Ultrafine particles (UFP) (#/cm^3) Average session time 6.5 minutes	PM2.5 0.5 metres from user: Mean C(B) 2, ENDS 709, C(A) 2; Adjust C(B) 2, ENDS 364, C(A) 2; p=0.665 1 metre from user: Mean C(B) 3, ENDS 168, C(A) 31; Adjust C(B) 2, ENDS 235, C(A) 3; p<0.001 Maximum Cigalike: 0.5m C(B) 48, ENDS 174,160, C(A) 514; 1m C(B) 369, ENDS 20,333, C(A) 24 Tank: 0.5m C(B) 46, ENDS 164,164, C(A) 20; 1m C(B) 7, ENDS 28,288, C(A) 1,683 Adjust: 0.5m C(B) 87, ENDS 77,181, C(A) 88; 1m C(B) 92, ENDS 28,991, C(A) 186 C(B) = Control (before); C(A) = Control (after) Ultrafine particles 0.5 metres from user: Mean C(B) 1,173, ENDS 11,106, C(A) 4,353; Adjust C(B) 2,073, ENDS 8,060, C(A) 4,499; p=0.710 1 metre from user: Mean C(B) 2,828, ENDS 10,366, C(A) 6,326; Adjust C(B) 3,124, ENDS 9,699, C(A) 5,910; p<0.001 Maximum Cigalike: 0.5m C(B) 4,801, ENDS 284,260, C(A) 14,044; 1m C(B) 5,879, ENDS 255,713, C(A) 11,015 Tank: 0.5m C(B) 1,182, ENDS 270,368, C(A) 10,551; 1m C(B) 6,533, ENDS 232,524, C(A) 37,628 Adjust: 0.5m C(B) 3,064, ENDS 235,840, C(A) 8,992; 1m C(B) 4,832, ENDS 249,281, C(A) 12,190 C(B) = Control (before); C(A) = Control (after)	High methodological quality Conflicts of interest Not reported Funding No specific funding. Health Canada provided measurement devices and technical expertise and Carleton University's covered material costs
Natural experiments					

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, study design)	Setting	Experimental conditions	Outcome measure	Results	Quality assessment, conflict of interest, funding
Cammalleri et al., 2020[665] Italy Open-label, single-centre, controlled study	Outdoors of the "Del Vecchio" library of the Department of Public Health and Infectious Diseases of Sapienza University of Rome, unknown number of participants No known other sources of PM1	Experimental During vaping session; one participant vaping one e-cigarette or JUUL Control Before vaping session Device 1. Electronic cigarette (not further defined) (E-cig)	Particulate matter PM1 (μg/m^3)	PM1 With e-cigarette use: Mean (SD) 394.82 (1317.66); Median (IQR) 23.00 (29.00) No e-cigarette use: Mean (SD) 28.81 (1.94); Median (IQR) 23.00 (2.00) E-cig P-value <0.023	High methodological quality Conflicts of interest None declared Funding No external funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, study design)	Setting	Experimental conditions	Outcome measure	Results	Quality assessment, conflict of interest, funding
Khachatoorian et al., 2019[668] US Two site, natural experiment	Living room with adequate ventilation Area size 187.5ft^2 (47.78m^3)	Experimental Vaping use approximately 3 hours/day; average 15 days per month; fabric hung on a desk located near a window Control Non-smokers home (no further information provided) Device Innokin iTaste MVP and Wotofo ZNA 30 clone by A-mod Technology Co., LTD with Aspire Nautilus tank; e-liquid nicotine concentration of 6mg/mL Duration 1-6 months	1. Nicotine (ng/g) 2. Cotinine (ng/g) Collected on polyester or cotton fabric sample Fabrics were collected after 1, 2, 3, 4, 5, and 6 months of exposure	Nicotine – total Most abundant marker of EC exhaled aerosol residue contamination Maximum: 5100ng/gram on cotton fabric at month 3 Range: 2000-3000ng/gram on cotton fabric (excluding month 3) Only detected month 5 and 6 on polyester samples Cotinine – total Detected at all months for cotton sample, only detected at month 1, 3 and 4 for polyester sample	Moderate methodological quality Conflicts of interest None declared Funding Supported by Tobacco-Related Disease Research Program of California; the National Institute on Drug Abuse, USA and the National Center for Research Resources

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, study design)	Setting	Experimental conditions	Outcome measure	Results	Quality assessment, conflict of interest, funding
Mock & Hendlin, 2019[669] US July 2018–April 2019 Garbology study (ethno-archaeological study of a community or cultural group by analysing its waste)	Purposively selected, non-random sample of 12 public high schools in Alameda, Contra Costa, Marin, and San Francisco counties in California; student parking lots and exterior school perimeter	Not applicable	1. JUUL or JUUL-compatible pods 2. JUUL or JUUL-compatible caps 3. JUUL 4-packs 4. Total number of JUUL and JUUL-compatible items	Count of product waste items (#) Total Pods 47 Caps 123 4-Packs 3 Total* 173 *Reported total=172	Moderate methodological quality Conflicts of interest None declared Funding Not stated

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, study design)	Setting	Experimental conditions	Outcome measure	Results	Quality assessment, conflict of interest, funding
Nguyen et al., 2019[666] US Multi-centre, natural experiment	Vape shop (location, ventilation type) 1. Storefront, A/C 2. Storefront, Central 3. Plaza, Natural 4. Storefront, Natural 5. Plaza, None 6. Storefront, A/C Area size (m^3) 1. 318 2. 262 3. 244 4. 323 5. 168 6. 175	Experimental dimensions Indoor Control dimensions Outdoor Pattern of use Total vaping frequency (TVF) #/30 minutes (average across all conditions) 1. 88 ± 96 2. 19 ± 16 3. 16 ± 15 4. 9 ± 5 5. 91 ± 25 6. 13 ± 3	Particulate matter 1. Particle number (#/cm^3) 2. PM2.5 (µg/m^3) Average session time 8–10 hours	Particle number – range Indoor - no active e-cigarette use: 5.5×10^3 to 3.3×10^4 particles/cm^3 Indoor - active e-cigarette use: 1.3×10^4 to 4.8×10^5 particles/cm^3 Outdoor - 8.5×10^3 to 5.6×10^4 particles/cm^3 PM2.5 – range Indoor - no active e-cigarette use: 3.2 to 39 µg/m^3 Indoor - active e-cigarette use: 15.5 to 37,500 µg/m^3 Outdoor - 7.5–72µg/m^3 Due to a small number of sampled vape shops, significant linear correlations between real-time PM concentrations could not be observed	Moderate methodological quality Conflicts of interest Not reported Funding Supported by the Tobacco-Related Disease Research Program and the Center for Occupational and Environmental Health at the University of California, Los Angeles

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, study design)</th><th>Setting</th><th>Experimental conditions</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, conflict of interest, funding</th></tr>
<tr>
<td>Khachatoorian et al., 2018[667]

US

One site, natural experiment</td>
<td>Actively operated shop located on basement floor of two-story mall next to active vape shop

<u>Area size</u>
Vape shop: 405ft^2 (37m^2)

<u>Study site-adjacent shop</u>
311ft^2 (28m^2)</td>
<td><u>Experimental</u>
Fabric placement inside shop located next to vape shop;
Filter placement
- in the return vent towards the back of suite
- in the middle of the suite

<u>Control</u>
Unexposed samples plus Control fabrics (terrycloth) placed
- in a hallway outside the field site
- in a non-smoker home in the same community

<u>Duration</u>
Short-term exposure: 1 day (24 hours), 4 days (96 hours) and 8 days (192 hours)
Long-term exposure: 1, 2 and 3 months</td>
<td>1. Nicotine (ng/g)
2. Cotinine (ng/g)

Collected on cotton towels, paper towels, terrycloth towels samples and air filters

Samples were collected after 1, 4, and 8 days and after 1, 2 and 3 months</td>
<td><u>Nicotine</u> – total
Nicotine was the most abundant marker of EC aerosol contamination (highest concentration=23,260ng/g of fabric)
Its concentration generally increased with exposure time

<u>Cotinine</u> – total
Cotinine concentrations generally increased as exposure time increased. The air filters appeared to trap cotinine

Frequency of nicotine and cotinine
<table><tr><th></th><th>Cotton towel</th><th>Paper towel</th></tr><tr><td>Nicotine</td><td>100%</td><td>92%</td></tr><tr><td>Cotinine</td><td>22%</td><td>83%</td></tr></table>
Control samples of paper towels and terrycloth towels exposed both in the home of a non-smoker and in the mall had no detectable nicotine or cotinine except for a low nicotine level (107ng/g and 93ng/g) in two samples</td>
<td>Moderate methodological quality

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Supported by Tobacco-Related Disease Research Program of California; the National Institute on Drug Abuse, USA and the National Center for Research Resources</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Table 4.12-3 Study details: environmental hazards with health implications – surveillance reports

Study details (author, publication year)	Context (country, time frame, data source)	Number of fires/explosions	Circumstance of e-cigarette fire/explosion	Loss of property/fire spread	Quality assessment, conflict of interest, funding
Saxena et al., 2018 [567]	US January 2009 to December 31 2016 National Fire Data Center* *Same data sources as below	Total fires/explosions* n=195 *Same data sources as below	Battery operating conditions during occurrence of e-cigarette fire incidents*: Usage: 31% Spare battery: 31% Charging: 25% Transport/storage/unknown: 13% *Same data sources as below	Not reported	Low methodological quality Conflicts of interest Not reported Funding Not reported
	Various August 2009 to April 2017 Blog reports (Ecigone Blog)	Total fires/explosions n=243	Battery operating conditions during occurrence of e-cigarette fire incidents: Usage: 26% Spare battery: 18% Charging: 35% Transport/storage/unknown: 21%	Not reported	
US Fire Administration, 2017 [670]	US January 2009 to December 31 2016 National Fire Incident Reporting System (NFIRS)	Total fires/explosions n=195	Battery operating conditions during occurrence of e-cigarette fire incidents: In pocket: 61 (31%) In use: 60 (31%) Charging: 48 (25%) Not reported: 7 (4%) Transport: 1 (0.01%)	Resulted in ignition of nearby contents: 128 Fire spread Minor: 91 (47%) None reported: 97 (50%) Moderate: 27 (14%) Major: 10 (5%)	Grey literature -no quality assessment Conflicts of interest Not reported Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.13 Neurological outcomes

Main conclusions from the synthesised evidence on the relationship between use of e-cigarettes and neurological outcomes

- There is conclusive evidence that the use of e-cigarettes can lead to seizures.
- There is limited evidence that injuries due to e-cigarette explosions can lead to nerve damage.
- There is no available evidence as to how the use of e-cigarettes affects the risk of other clinical neurological outcomes.

Table 4.13-1: Overview of studies of neurological outcomes identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Neurological outcomes						3 0 / 3		2 0 / 2	7 1 / 6

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Cerebral palsy, epilepsy, seizures, motor neuron disease, dementia, multiple sclerosis, Parkinson's disease, tremor, syncope, nerve injuries.

4.13.1 Findings from previous reviews

The NASEM review[3] and the Irish Health Research Board literature map[15] did not include neurological conditions as a primary outcome. Instead, seizures related to e-cigarette exposure were considered in the poisonings chapter. For this review, poisoning cases and injuries demonstrating neurological symptoms have also been considered in this chapter.

The NASEM review[3] included one case report in which a six-year-old girl was accidentally administered e-liquid instead of ibuprofen, and experienced seizures in addition to other poison-related symptoms. The girl was admitted to intensive care and stayed overnight. She was discharged the following day in a stable condition with intact neurologic and physical function.[578]

The Irish Health Research Board literature map[15] included nine studies, seven case reports, one case series and one surveillance report with evidence on neurological symptoms related to e-cigarette use. One case report was included in the NASEM review,[578] five case reports,[526,530,596,599,601] the case series[604] and the surveillance report[600] were included in the top-up review, and one case report[671] was published prior to the date limit for the top-up review and not included in the NASEM review[3]. This study described the case of a 39-year-old male who experienced severe headaches and seizures after e-cigarette initiation and was subsequently diagnosed with reversible cerebral vasoconstriction syndrome triggered by e-cigarette use. One month after treatment and e-cigarette cessation, the patient was deemed physically and neurologically normal.[671]

The Public Health England[11] review identified one case report,[578] also included in the NASEM review[3], on the relationship of e-cigarette use and neurological outcomes.

The CSIRO[14] review identified one case report[526] and one case series[604] with evidence on neurological outcomes related to e-cigarette use, both of which were included in the top-up review.

The SCHEER[4] review identified two studies, one case series[604] and one surveillance report[621] with evidence on neurological outcomes, both of which were included in the top-up review.

The USPSTF[16] review did not include neurological outcomes as a main outcome nor identify or discuss any studies elsewhere.

4.13.2 Summary of conclusions from previous reviews

The NASEM review[3] concluded that:

- 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.

The Irish Health Research Board literature map,[15] Public Health England,[11] CSIRO[14] and SCHEER[4] reviews did not provide any summative conclusions on how e-cigarette use affects neurological outcomes.

4.13.3 Top-up review

Search results

Overall, 11 articles[526,530,596,599-601,604,621,672-674] were located in the top-up systematic literature search and included in the evidence synthesis of the top-up review (Table 4.13-2).

Neurological: clinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to clinical neurological outcomes were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to clinical neurological outcomes were located.

Cohort studies

No cohort studies reporting on the relationship of e-cigarette use to clinical neurological outcomes were located.

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarette use to clinical neurological outcomes were located.

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to clinical neurological outcomes were located.

Other study types

Eleven studies, three surveillance reports,[600,621,672] two case series[604,673] and six case reports,[526,530,596,599,601,674] were identified on how e-cigarette use affects neurological outcomes, specifically seizures (Table 4.13-1)

Surveillance reports

Three surveillance reports with records relating to neurological outcomes were identified. One included only neurological outcomes and two reported neurological outcomes in relation to poisonings cases.

Using data from the US Food and Drug Administration (FDA) Center for Tobacco Products surveillance system, Faulcon et al. reported on 123 e-cigarette users who experienced some type of neurological symptom (Table 4.13.2).[672] The median age was 20 years and the sex distribution unknown. Information was provided in only a few reports of which JUUL, Suorin, SMOK, and Vuse brands were the most commonly named.

Of the 123 reports, 114 reported seizures, eight reported syncope (fainting) and one reported tremors. Six cases reported prior history of seizures. There was one reported unexplained death from a seizure in a 25-year-old woman who had an underlying autoimmune disease. Seizures occurred after first use in eight cases. Of the 79 cases with information regarding symptom onset, 49 seizures occurred within 30 minutes of last use, five within two hours of last use and 67 within 24 hours of last use. Fifty-three cases reported repeat seizures or neurological symptoms with continued e-cigarette use.

Of the 123 cases, 82 (67%) occurred in youths and young adults aged between 14 and 24 years of which 66% were male, and 88% were white. In this age group, there were 77 seizure cases (93.9%), 4 syncope cases (4.9%) and 1 case (1.2%) of tremors. Approximately 55% of youth and young adults continued to use e-cigarettes after experiencing neurological symptoms, of whom 73% went on to report repeat seizures.[672]

Between 2012 and 2018, there were 145 e-cigarette related cases reported to the Toxicological Information Centre in the Czech Republic, of which six included neurological symptoms.[621] In the third surveillance report, there were two cases of tremors, three of convulsions, and one of auditory hallucination. No other information specific to these cases was reported. Out of the 8,269 cases reported

to the National Poisons Data System in the US between 2012-2017 there were eight cases with neurological symptoms, four cases of coma and four of seizures.[600]

One study each was of low,[672] moderate[600] and high[621] methodological quality using the Joanna Briggs Institute's critical appraisal checklist and no conflicts of interest were declared. No GRADE rating was applied.

Case series

Two case series, one in the US and another in South Korea, both describing two cases each from hospital emergency departments, were identified (Table 4.13.3).

The first case in Liu and McIntosh (2020)[673] occurred in a 17-year-old female. The patient had a history of eating disorders and was taking 50mg Trazodone as needed for insomnia and 20mg Flozetine daily. Seconds prior to the seizure, the patient inhaled one full hit, described as inhaling the maximum amount of vapour in one breath, from a 5% nicotine SMOK NOVO e-cigarette device. The patient experienced a generalised-onset, generalised tonic-clonic seizure lasting 60-90 seconds and had typical postictal state of somnolence and confusion lasting 45-60 minutes. There were no residual neurological deficits, and the patient was discharged without prescription of prophylactic antiepileptic drugs. Three months later, the patient experienced a second stereotypic seizure lasting 30 seconds after taking another full hit from the same e-cigarette device. The second case occurred in a 17-year-old male with a history of mild anxiety and nightly Trazodone use (50mg). Five minutes prior to the seizure, the patient inhaled from a 5% Puff Bar e-cigarette. No other possible seizure precipitants were reported. The patient experienced a generalised tonic-clonic seizure lasting 60-90 seconds and had a typical postictal state. There were no residual neurological deficits, and the patient was discharged without prescription of prophylactic antiepileptic drugs. The patient was seizure free after five months.[673]

In Park and Min (2018),[604] the first case report occurred in a 27-year-old male after the ingestion of two different e-liquids, 16 and 18mg/mL nicotine concentration, as part of a suicide attempt. The patient initially presented with seizure like movements and then went into cardiac arrest and coma. The patient was alert and aware 24-hours post-ingestion, however, did not remember the events of the past two months. Six days post-exposure, the patient experienced involuntary myoclonic movement of all the extremities without any changes in brain MRI, and nine days post-exposure amnesia resolved. The patient was discharged 13-days post-exposure with a cerebral performance category of 2 (conscious and alert with moderate cerebral performance). The second case involved a 17-year-old female who ingested 10mL of 210mg/mL nicotine containing e-liquid as part of a suicide attempt. The patient displayed generalised tonic clonic movement (seizures) for five minutes and then went into cardiac arrest and coma. Four-days post-exposure, the somatosensory evoked potential demonstrated bilateral absence of N20 on median nerve, a poor neurological outcome associated with cardiac arrest, and an electroencephalogram showed generalised suppression without seizure. Generalised myoclonic movement were noted. The patient was transferred to a rehabilitation facility 32-days post-exposure with a cerebral performance category of 4 (comatose or in persistent vegetative state).[604]

One study was of low[673] and the other of moderate[604] methodological quality using the Joanna Briggs Institute's critical appraisal checklist and no conflicts of interest were declared. No GRADE rating was applied.

Case reports

Six case reports were identified on e-cigarette use and neurological outcomes (Table 4.13.3).

Hughes and Hendrickson (2020)[601] detailed the case of a 13-year-old female that presented to a hospital emergency department. The patient experienced recurring seizures and was tachycardic, hypertensive, tremulous, confused, and hallucinating at admission. She was treated with several doses of lorazepam and isotonic fluids with her condition improving over 24-hours and leading to full recovery. Prior to symptom onset, the patient reported inhaling the entire contents of an e-cigarette cartridge, and there were no other exposures reported.

Wharton et al.[674] described the case of a 16-year-old female from the US with a history of idiopathic generalised epilepsy and four-months nicotine e-cigarette use. After seven months seizure-free, the patient reported five occurrences of early morning seizures over approximately two weeks. Known triggers were absent and the patient reported e-cigarette use on the night prior to the seizures in four out of the five incidences.

In the case by Faulcon et al.,[596] a 51-year-old male injected 10mL of 100mg/mL nicotine e-liquid as part of a suicide attempt. In addition to cramps, psychomotor agitation and bradypnea, the patient also

developed a transitory neurological impairment with the appearance of tetraparesis, gaze palsy and myoclonus due to nicotinic syndrome and subsequently went into a coma. He then presented with periodic myoclonic movements of both lower limbs and a brain CT excluded any cerebral lesion. At 24-hours post-injection, the patient was discharged with a normalised neurologic status.

The Turkish case report by Demir and Topal (2018)[599] described the case of a six-year-old girl who accidentally consumed approximately the entire 1.2mg/mL nicotine e-liquid bottle while playing. The patient presented to the emergency department with nausea, vomiting and hearing loss. Bilateral sensorineural hearing loss was detected in both ears. Hearing improved from day one to day 10 post-exposure but at six-month follow-up, hearing was the same as day 10.

Ackely et al. reported the case of a 17-year-old male in the US who presented to the emergency department after his e-cigarette device exploded as he was about to take an inhalation.[526] The explosion caused damage to his thumb and resulted in sensory loss and decreased motor control still present eight days after the operation.

In the US case described by Satteson et al., a 35-year-old male presented to the emergency department after his e-cigarette device rapidly heated and suddenly exploded after the battery was changed.[530] In addition to significant burns, the patient also had defects in digital nerves with decreased sensation to light touch and pinprick on the thumb and index finger. Loss of sensation remained after sural nerve grafting.[530]

Two studies were of low methodological quality,[601,674] two were moderate[596,526] and two were high[599,530] methodological quality using the Joanna Briggs Institute's critical appraisal checklist. No conflicts of interest were declared in five studies and not reported in one.[526] No GRADE rating was applied.

4.13.4 Summary of findings from top-up review

There were 11 studies, six case reports, two case series and three surveillance reports, with evidence on clinical outcomes finding:

- Neurological symptoms and seizures can occur after e-cigarette exposure in new and experienced users. Seizures typically occur within 24 hours of last use and are more commonly reported in youth and young adults. Many users that continue to use e-cigarettes after their first seizure report repeat events.
- Nerve damage resulting in sensory loss and loss of motor control can occur when e-cigarettes explode.
- Case reports and case series are particularly useful for describing events where a direct relationship between cause and effect is clear. In the context where no other cause of seizure is apparent, they are considered appropriate evidence for our conclusions. Hence:
    - There is conclusive evidence that the use of e-cigarettes is related to seizures.
- The lack of epidemiological evidence means that the incidence and quantitative risk of seizures in e-cigarette users are not known. However, based on the apparent frequency of events from the US, they would appear to be rare. Hence:
    - There is no available quantitative evidence as to the relative risk and incidence of seizures related to the use of e-cigarettes.

4.13.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining clinical evidence from the top-up systematic review with the evidence from previous reviews:

- There was a total of 13 studies, three surveillance reports, two case series and eight case reports on the relationship between e-cigarette use and clinical neurological outcomes, such as seizures and nerve damage.
- Seizures are the most common outcome and other outcomes include reversible cerebral vasoconstriction syndrome, tremors, syncope, transitory neurological impairment and sensorineural hearing loss. Sensory loss and motor control impairment can occur from injuries due to e-cigarette explosions. Hence, there is:
    - Conclusive evidence that the use of e-cigarettes is related to seizures.
    - Limited evidence that injuries due to e-cigarette explosions can damage nerves leading to sensory loss and motor control impairment.
- The lack of epidemiological evidence means that the incidence and quantitative risk of seizures in e-cigarette users are not known. However, based on the apparent frequency of events from the US, they would appear to be rare. Hence:

    - There is no available quantitative evidence on the incidence of seizures in relation to the use of e-cigarettes.
- Due to the study types available, the GRADE approach was not applied and the certainty of evidence is automatically rated as very low.

4.13.6 Main conclusions from the synthesised evidence on the relationship between e-cigarette use and neurological outcomes

- There is conclusive evidence that the use of e-cigarettes can lead to seizures.
- There is limited evidence that injuries due to e-cigarette explosions can lead to nerve damage.
- There is no available evidence as to how the use of e-cigarettes affects the risk of other clinical neurological outcomes.

Table 4.13-2. Study details: neurological outcomes – surveillance reports

Study details (author, publication year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Obertova et al., 2020[621] Czech Republic 2012-2018 Toxicological Information Centre (TIC)	Total cases in surveillance report n=145 Cases with neurological outcomes n=6	Not reported	Symptoms – n (%) Tremor: 2 (1.4) Convulsion: 3 (2.0) Auditory hallucination: 1 (0.7)	Not reported	Not reported	High methodological quality Conflicts of interest None declared Funding First Faculty of Medicine, Charles University; Ministry of Health Czech Republic
Faulcon et al., 2019[672] US 2010-2019 The Food and Drug Administration (FDA) Center for Tobacco Products	Sample size 123 new and experienced e-cigarette users, 82 in 14-24 years Sex - 14-24 years (%) Male: 66 Age - median (IQR) years 20 (17-27) Prior history of seizures – n (%) Total sample: 6 (4.9) 14-24 years: 5 (6.1) Ethnicity - 14-24 years (%) White: 88	JUUL, Suorin, SMOK, and Vuse brands were the most commonly named	Symptoms - Total sample - n (%) Seizure: 114 (92.7) Syncope: 8 (6.5) Tremor: 1 (0.8) Symptoms - 14-24 years - n (%) Seizure: 77 (93.9) Syncope: 4 (4.9) Tremor: 1 (1.2) Timing – Total sample - n (%) After first use: 8 Seizure within 30 minutes of last use*: 49 (62) Seizure within 2 hours of last use*: 5 (6) Seizure within 24 hours of last use*: 67 (85) *Information available for 79 reports Seizures occurred immediately after one puff, all-day use, and with use weeks before the event	Not stated	Continued use after seizure – n (%) 14-24 years: 45 (54.9) Repeat seizures with continued ENDS use – n (%) Total sample: 53 14-24 years: 33 (73)	Low methodological quality Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, publication year, country, time frame, data source)	Demographics	Exposure (e-liquid description, route of administration, cause of exposure)	Presentation and symptoms	Treatment	Outcome	Quality assessment, conflict of interest, funding
Govindarajan et al., 2018[600] 2012-2017 US National Poison Data System (NPDS)	Total cases in surveillance report n=8,269 Cases with neurological outcomes n=8	Not reported	Neurological effects (n) Coma: 4 Seizure: 4	Not reported	Not reported	Moderate methodological quality Conflicts of interest None declared Funding Centers for Disease Control and Prevention and the Child Injury Prevention Alliance stipend

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Table 4.13-3. Study details: neurological outcomes - case reports and case series

Study details (author, year, location, data source)	Demographic characteristics and medical history (if applicable)	Exposure (device, e-liquid, rout of admission)	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Case series						
Lui and McIntosh, 2020[673] US Emergency department	Case 1 Female 17 years Eating disorder, taking 50mg Trazodone as needed for insomnia and 20mg Flozetine daily Case 2 Male 17 years Mild anxiety, 50mg Trazodone nightly	Case 1 Daily e-cigarette use. Seconds before the seizure, took one full hit from a 5% nicotine SMOK Novo e-cigarette after two weeks without nicotine exposure. Typically uses 5% nicotine e-cigarettes but usually avoids taking "full" hits as she did that day Case 2 Five minutes before the seizure, he took one hit from a 5% nicotine Puff Bar e-cigarette. There were no other possible seizure precipitants. History of vaping 2.5% nicotine e-cigarettes daily	Case 1 Generalised-onset, generalised tonic-clonic seizure lasting 60-90 seconds. Typical postictal state of somnolence and confusion lasting 45-60 minutes without residual neurological deficits Case 2 Generalised tonic-clonic seizure lasting 60-90 seconds. Typical postictal state without residual neurological deficits	Case 1 Not prescribed prophylactic antiepileptic drugs Case 2 Not prescribed prophylactic antiepileptic drugs	Case 1 Discharged 3 months post-discharge: second stereotypic seizure 30 seconds after taking one full hit from a 5% nicotine SMOK Nord e-cigarette Case 2 Discharged Seizure free for 5 months	Low methodological quality Conflicts of interest None declared Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source)	Demographic characteristics and medical history (if applicable)	Exposure (device, e-liquid, rout of admission)	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Park & Min, 2018[604] South Korea Emergency department	Case 1 Male 27 years Not reported Case 2 Female 17 years Not reported	Case 1 DIY Flavor Shack® 16mg/mL nicotine concentration and Halo® 18mg/mL nicotine concentration were at the scene, actual consumption not detected Ingestion Suicide attempt Case 2 10mL EC liquid named 'Pure Nicotine®' with a nicotine concentration of 210mg/mL Ingestion Suicide attempt	Case 1 Showing seizure-like movements, cardiac arrest, comatose with fixed pupil size of 3mm Case 2 Cardiac arrest, generalised tonic clonic movement for 5 minutes. Comatose with a fixed pupil size of 3mm	Case 1 Cardiac arrest care, targeted temperature management (TTM) Case 2 Cardiac arrest care, targeted temperature management (TTM)	Case 1 24-hours after TTM: alert and aware. Did not remember events during the previous two months. Brain MRI showed bilateral hippocampal disruption Day 6: involuntary myoclonic movement of all the extremities without any changes in brain MRI Day 9: amnesia recovered Day 13: discharged cerebral performance category (CPC) of 2 Case 2 24-hours after TTM: alert and aware Day 4: somatosensory evoked potential on the 4th day of admission showed bilateral absence of N20 on median nerve. Generalised myoclonic movement was noted Day 32: transferred to a rehabilitation facility with a CPC of 4	Moderate methodological quality Conflicts of interest None declared Funding Not reported
Case reports						

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source)	Demographic characteristics and medical history (if applicable)	Exposure (device, e-liquid, rout of admission)	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Hughes and Hendrickson, 2020[601] US Emergency department	Female 13 years Depression (taking fluoxetine)	Vaped the entire contents of an e-cigarette cartridge just prior to symptom onset No product information	Tachycardic, hypertensive, tremulous, confused, and hallucinating. She experienced recurrent seizures Patient tested positive for THC, but unclear if exposure was from e-cigarette or other source	Treated with several doses of lorazepam and isotonic fluids	Condition improved over the following 24 hours and she made a full recovery	Low methodological quality Conflicts of interest None declared Funding Not reported
Wharton et al., 2020[674] US Unknown	Female 16 years Idiopathic epilepsy	Four-month history of e-cigarette use “a few times per week,” and vaped on the nights before four of her last five seizures Pre-made commercial device with a nicotine juice flavoured in spearmint, fruit punch, or watermelon	Early morning seizures, known triggers (sleep deprivation and misuse of medication) were absent Five seizures in 12 days	Not stated	Not stated	Low methodological quality Conflicts of interest None declared Funding No external funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source)	Demographic characteristics and medical history (if applicable)	Exposure (device, e-liquid, rout of admission)	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Belkoniene et al., 2019[596] Switzerland Emergency department	Male 51 years Active e-cigarette user, history of cigarette smoking, type 2 diabetes mellitus and a personality disorder	10mL of 100mg/mL nicotine e-liquid Injection Suicide attempt	Abdominal cramps; psychomotor agitation and mydriatic pupils, followed by bradypnea and coma Developed a transitory neurological impairment with the appearance of tetraparesis, gaze palsy and myoclonus due to nicotinic syndrome Lactic acidosis	Intubated in ICU using rapid sequence induction (etomidate, succinylcholine and fentanyl)	7-10 hours post-injection: woke up and answered simple questions. Pupils were still mydriatic and poorly responsive to light 11 hours post-injection: complete recovery of motor response of deep tendon reflexes allowing extubation. 24 hours later: discharged	Moderate methodological quality Conflicts of interest None declared Funding No funding provided
Ackley et al., 2018[526] US Hospital record	Male 17 years Not reported	Device exploded when about to take a puff	A burned left thumb with sensory loss, decreased motor control, and heavy bleeding	Immediate irrigation, debridement, and a left-hand carpal tunnel release.	Post-operative day 2: discharged Post-operative day 8: blackened thumb without capillary refill or sensation and limited motor function. Required 6 additional operative procedures	Moderate methodological quality Conflicts of interest Not reported Funding Not reported

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, data source)	Demographic characteristics and medical history (if applicable)	Exposure (device, e-liquid, rout of admission)	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest, funding
Demir & Topal, 2018[599] Turkey Pediatric emergency department	Female 6 years Not reported	7mL liquid and 8.4mg nicotine with the nicotine ratio of 1.2mg/mL that was storage in an e-liquid bottle. The estimated nicotine intake of the whole bottle was 8.4mg Ingestion Accidental	Nausea and vomiting Bilateral sudden sensorineural hearing loss (SSNHL) after 24-hour fluid intake	Gastric lavage	6th month of follow-up: audiometric test results same as the results at the 10th day. Patient started using bilateral conventional hearing devices	High methodological quality Conflicts of interest None declared Funding Not reported
Satteson et al., 2018[530] US Emergency Department, Trauma Centre, Wake Forest University of Medicine	Male 35 years Not reported	Device (Dark Horse atomiser with a SMPL Mec Mod battery) rapidly heated and suddenly exploded after battery was changed	Significant for deep partial and full thickness burns to thumb and embedded foreign body. Decreased sensation to light touch and pinprick on the thumb and index finger. Defects to the radial and ulnar proper and common digital nerves	Surgery and debridement of devitalised tissue and carpal tunnel release. Sural nerve grafting	15 months after the initial injury: thumb interphalangeal joint fixed in 30° of flexion with no ability to actively or passively flex or extend. Decreased sensation in thumb and index finger	High methodological quality Conflicts of interest None declared Funding None received

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.14 Sleep outcomes

Main conclusions from the synthesised evidence on sleep outcomes in relation to e-cigarette use

- There is no available evidence as to the effect of e-cigarettes on clinical sleep outcomes.

Table 4.14-1: Overview of studies of sleep outcomes identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Sleep outcomes							4 0 / 4		

Notes:
- The top large number is the total count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Sleep quality, sleep patterns (duration, sleep latency, habitual sleep efficiency), sleep disturbances, and daytime sleepiness.

4.14.1 Findings from previous major international reviews

The Irish Health Research Board literature map[15] identified three cross-sectional surveys on the effects of e-cigarettes on sleep.[166-168] These were analysed in relation to dependence and abuse liability rather than as an independent outcome. In this context, cross-sectional surveys are not considered suitable evidence for assessing causality and are not discussed further.

The NASEM,[3] Public Health England,[11] CSIRO,[14] SCHEER,[4] and USPSTF[16] reviews did not include sleep as a primary health outcome and no papers on sleep were identified.

4.14.2 Summary of conclusions from previous reviews

The Irish Health Research Board literature map[15] did not provide any summative conclusions regarding sleep and e-cigarettes.

4.14.3 Top-up review

Search results

Overall, four articles were located in the top-up systematic literature search.[166-168,675] As they were cross-sectional surveys, and therefore did not meet eligibility criteria, no articles were available for the top-up synthesis of evidence (Table 4.14.1).

Sleep: Clinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to sleep were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to sleep were located.

Cohort studies

No cohort studies reporting on the relationship of e-cigarette use to sleep were located.

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarette use to sleep were located.

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to sleep were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to sleep outcomes

Four cross-sectional surveys reporting on the relationship of e-cigarette use to sleep were located, but not included in evidence synthesis.[166-168,675]

4.14.4 Summary of findings from top-up review

No studies on the relationship of e-cigarette use to sleep outcomes were identified.

4.14.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence from the top-up systematic review with the evidence from previous reviews:

- No studies on the relationship of e-cigarette use to clinical sleep outcomes were identified.

4.14.6 Main conclusions from the synthesised evidence on sleep outcomes in relation to e-cigarette use

- There is no available evidence as to the effect of e-cigarettes on clinical sleep outcomes.

4.15 Less serious adverse events

Main conclusions from the synthesised evidence on less serious adverse events related to e-cigarette use

- There is moderate evidence that less serious adverse events – such as throat irritation, cough, dizziness, headache and nausea – occur with use of nicotine e-cigarettes.

Table 4.15-1: Overview of studies of less serious adverse events identified in the systematic review, by study design

Health outcome	Meta-analysis	Randomised controlled Trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Less serious adverse events		11 3 / 8	3 1 / 2	2 2 / 0		1 0 / 1	3 0 / 3		

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Less serious adverse events (serious adverse events are considered elsewhere)**: Cough, dizziness, throat/mouth irritation, headache, nausea, chest tightness, shortness of breath, wheezing, phlegm production.

4.15.1 Findings from previous reviews

The NASEM review did not include adverse events as a main health outcome, however, six papers with adverse event findings were included in their discussion on harm reduction and respiratory outcomes.[3] In the randomised controlled trial by Cravo et al., a total of 1,740 adverse events were reported over 12 weeks: 1,515 events from 271 participants (88.6%) randomised to e-cigarettes and 225 events in 80 participants (78.4%) randomised to combustible cigarettes.[237] Using the least square mean method, the adverse event incidence rate was greater for those randomised to e-cigarettes versus combustible cigarettes (1.60 (95% CI 1.55-1.65) and 0.79 (95% CI 0.66-0.92) respectively). There were five serious adverse events in the e-cigarette group and none in the combustible cigarette group. The authors stated that none of the serious adverse events were suspected to be related to e-cigarette use, although they did not provide criteria for this determination nor their classification system of 'possibly related', 'probably related', 'almost definitely related' and 'unlikely to be related'. Of adverse events in those randomised to e-cigarettes, 29.6% were mild, 54.6% were moderate and 15.8% were severe. This was similar to those randomised to combustible cigarettes. Headache, sore throat, desire to smoke, cough, increased appetite, nasopharyngitis and irritability were very common adverse events. A greater percentage of participants in the e-cigarette group reported oropharyngeal pain (27.8%) compared to the conventional cigarette group (8.8%) and cough (17.0% vs. 7.8%), however all other adverse events remained relatively stable.[237] In the randomised controlled trial by Adriaens et al., the only complaint that was unique to the e-cigarette group was related to technical problems with the e-cigarette unit.[157] Otherwise, there was no significant difference in the proportion of adverse events between the e-cigarette and the combustible cigarette groups. The adverse events common to both groups included bad taste; dry/irritated mouth/throat; dizziness; headache; nausea; increased heart rate; increased weight and shortness of breath.[157]

Four studies in the respiratory chapter of the NASEM review contained findings on adverse events. Two very small non-randomised intervention studies (laboratory-based, pre-post) in US non-smoker populations were identified. The first had a sample size of 30, 50.0% males and mean age of 29.8 ± 4.5 (SD) years.[283] The second study had a sample size of 17, 64.7% males and a mean age of 29.6 ± 3.2 (SD) years.[284] In both studies, ENDS significantly inhibited cough reflex sensitivity and urge to cough 15 minutes after exposure, but returned to baseline after 24 hours.[283,284] No effect for cough reflex was found for ENNDS and urge to cough was not measured.[283]

In an Italian cohort study, 40 adult smokers (65.0% males, mean age 43.0 ± 8.8 (SD) years) non-exclusively using ENDS were prospectively followed for two years.[162] At six-month follow-up, throat irritation (14.8%), dry cough (11.1%) and mouth irritation (7.4%) were the most frequently reported symptoms, whilst headache (3.7%), nausea (3.7%), dry mouth (3.7%) and dizziness (3.7%) were infrequent. These symptoms remained stable during the study, other than nausea and dizziness which disappeared at the two-year visit, whilst dry cough was the most frequently reported (13.1%). No serious adverse events were reported.[162]

The NASEM review included a further two publications (randomised controlled trials) on symptoms/adverse events.[277,278] Since both were published by the same group and involve the same population and procedures, they will be referred to as one study, but their results described separately. In the double-blinded Italian randomised controlled trial, smokers were randomised to either 2.4% ENDS for 12 weeks, 2.4% ENDS for six weeks/1.8% ENDS for six weeks, or 0% ENDS for 12 weeks. Despite this randomisation process, results were grouped and analysed by smoking phenotype classification (quitters: complete self-reported and biochemically-verified abstinence from tobacco smoking; reducers: sustained self-reported ≥50% reduction in the number of cigarettes per day, also biochemically verified; and failures: not categorised in either of the above categories) at one-year follow-up. Although there were 300 smokers randomised, data grouped by smoking phenotype classification were only available for 130 participants in one publication and 134 in the other. In one publication, a high prevalence of respiratory symptoms (a cumulative symptom score of eight different symptoms) at baseline 'virtually disappeared' in reducers and quitters at follow-up. In the other publication, participants did not report any chest tightness or wheezing, whilst cough/phlegm and shortness of breath decreased at each follow-up visit, regardless of smoking phenotype, when compared to baseline. Cough/phlegm and shortness of breath disappeared completely for quitters, and changes in respiratory symptoms from baseline were significantly greater for reducers and quitters compared to failures ($p<0.0001$).[277,278]

The Irish Health Research Board literature map did not include adverse events as a main outcome however, adverse events were discussed under exposure to toxins, dependence and other health outcomes.[15] Of the 11 papers identified, three were included in the top-up review, [350,618,676] two were included in the NASEM review,[157,237], five did not meet inclusion criteria,[350,677,678] and one, found in the respiratory section, was published prior to the date limit for the top-up review and was not in the NASEM review. The study was a randomised before-and-after crossover trial conducted in Canada in 30 non-smokers (20 healthy volunteers and 10 asthmatic volunteers), aged between 20 and 40 years, trialling both flavour-free ENNDS and placebo (empty ENNDS) for one hour.[289] The authors stated that there was no significant impact of ENNDS on cough, chest tightness, breathlessness, secretions or wheezing in healthy and asthmatic volunteers, although 'a few subjects' noticed cough, chest tightness and secretions when using the ENNDS device. Other than differences in parameter levels, no statistical information was provided.[289]

The Public Health England review[11] found no population-based studies on adverse events but instead reported data from the MHRA Yellow card scheme, a reporting system to record suspected adverse reactions to medicines from health professionals, manufacturers or members of the public. Between January 2015 and October 2017, 37 reports describing 99 adverse events related to e-cigarette use were received. Of these, the most common adverse events were gastrointestinal disturbance and respiratory problems. One report of a non-fatal cardiac arrest in a patient with relevant cardiac history was recorded. The Public Health England review also mentions the systematic review on the effect of e-cigarettes on cessation by Hartmann-Boyce et al.[679] The 2021 update of this review has been described below.

The CSIRO review included one study[350] with findings on adverse events, however, this study did not meet the inclusion for the top-up review and is not discussed further.[14]

The SCHEER review[4] discussed three studies, and one study, Cravo et al.,[237] was also included in the NASEM review[3] and two studies Palamidas et al.[357] and Polosa et al.[358] were published before the top-up review and not included in the NASEM review[4]. Palamidas et al., a non-randomised intervention study in healthy never smokers, healthy smokers and smokers with obstructive airway diseases, found that acute mouth and/or throat irritation and cough were reported by some e-cigarette users and that the effects were not related to nicotine content.[357] Polosa et al.[358] was an early publication of the same cohort study,[162] already described under the NASEM review[3] and presents identical findings for six-month follow-up. Therefore, no further description of the study has been provided and the two publications[162,358] will be considered one for the purpose of this review.

The USPSTF review[16] identified nine randomised controlled trials with findings on adverse events related to e-cigarette use. Of the nine trials, three were included in the NASEM review,[237,480,680] three were included in the top-up review,[419,681,682] [480]one was published before the date limit of the top-up review and

not included in the NASEM review[683], one did not meet inclusion for the top-up review[684] and one was not captured by the top-up review.[685]

The randomised controlled trial on smoking cessation by Tseng et al., the study not captured in the NASEM review, reported no difference in side effects between ENDS users and ENNDS at weeks one (p=0.09) and three (p=0.14).[683] Common side effects included mouth or throat irritation, cough, insomnia or difficulty sleeping, abnormal dreams, headache and fatigue.[683] Masiero et al.[685] was published within the top-up review time limit but was not identified through screening and there was no mention of adverse events in the title or abstract. In their randomised controlled trial on the efficacy of e-cigarettes for smoking cessation among chronic smokers, Masiero et al. reported 23% of participants using ENDS and 4% of participants using ENNDS reported burning throats at one month and 10% of both groups reported cough. Symptoms declined over time.[685]

The 2021 Cochrane review by Hartmann-Boyce et al.[686] also provides data on serious and less serious adverse events. It was identified from the literature included in a previous review on the efficacy of e-cigarettes for cessation of smoking commissioned by the Australian Department of Health.[10] This review identified 39 studies, 23 randomised controlled trials[138,285,350,419,480,680-684,687-699] and 16 cohort studies[147,161,162,245,246,447,496,497,499,700-705] with data on adverse events.

Of the 23 randomised controlled trials, one was included in the NASEM review,[285] eight were in the top-up review[350,419,681,682,692,695,698,699] and three were excluded (one for not being peer-reviewed,[687] one for not including any outcomes of interest[684] and one poster[697]). Eleven studies were either published prior to the date limit for the top-up review or were not captured by the top-up review. One[683] has previously been described under the USPSTF review[16] and the other 10 studies will be described here.[138,480,680,688-691,693,694,696] Several meta-analyses were conducted and risk of bias was assessed using the Cochrane tools.[706,707]

The randomised controlled trial of 657 smokers by Bullen et al.[680] found no significant differences in the proportion of participants experiencing either a serious or less serious adverse event between treatment groups (ENDS vs. NRT: RR 0.99; 95% CI 0.81-1.22, ENDS vs. ENNDS: RR 0.97; 95% CI 0.71-1.34). No serious adverse events were related to product use.

Caponnetto et al.[480] found 26% of all study participants (300 smokers) experienced cough; 22% shortness of breath; 20% throat irritation and 17% experienced a headache. There was no difference in frequency distribution of adverse events between nicotine e-cigarette users and non-nicotine e-cigarette users, and there were no serious adverse events reported.

In Ozga-Hess et al., 60 smokers were randomised to either four weeks of 18mg/mL ENDS plus own brand cigarettes or to own brand cigarettes. Follow-up was after one month, and there was the option to quit all tobacco products and enter a cessation program at any point during the study.[694] Independent of quit choice status, the percentage of study days with which negative effects were reported were comparable between treatment groups (66.1%-97.4% for cigarettes only, 61.3%-97.3% for ENDS plus cigarettes, ps>0.05).[694] Among non-quitters, throat irritation, cough and dry mouth were more frequently experienced in the ENDS plus cigarette group compared to cigarette only.[694]

In the randomised controlled trial conducted by Bonevski et al. (Hartmann-Boyce refer to this study as Guillaumier et al.[708], however the reference provided for this is for a protocol document and both authors are from the same Australian group), 100 smokers recently discharged from a smoke-free residential substance use disorder (SUD) treatment service, were randomised to either 12 weeks of nicotine replacement therapy or nicotine e-cigarettes. There was no significant difference in adverse events (RR 1.50; 95% CI 0.84-2.67) or serious adverse events (RR 3.00; 95% CI 0.13-70.30) between the groups.[691]

In their smoking cessation randomised controlled trial of nicotine patches versus ENDS, Lee et al. reported no serious adverse events among 50 randomised veterans.[689] There was no difference in adverse events between the two groups (RR 0.74; 95% CI 0.31-1.73).[689] Headache (40%), throat irritation (30%) and skin irritation (30%) were the most prevalent events in the patches group, while intermittent dry cough (30%), nausea (25%) and throat irritation (25%) were the most common adverse events in the e-cigarette group.[689]

The randomised controlled trial of 186 smokers by Pulvers et al. compared tobacco cigarettes and ENDS, finding the ENDS group had significantly reduced (RR 0.63; 95% CI 0.47-0.85) respiratory-related adverse events compared to the cigarette group at six week follow-up.[693] In the study by Felicione et al., 25 daily smokers with opioid use disorders (OUDS) were randomised to either 18mg/mL nicotine ENDS or ENNDS for two weeks. Headache (32%), throat irritation (24%), nausea (16%), and dry mouth (12%) the most common adverse events.[696] No serious adverse events were reported in the trial by George et al., in which 114 adult smokers were randomised to either nicotine or non-nicotine e-cigarettes for four weeks.[690] In a cluster randomised controlled trial of four homeless centres in Great Britain, 80 smokers were randomly

allocated to usual-care or to e-cigarettes for smoking cessation with the highest (worse) ratings for 'nervous', 'headache', 'sweaty' and 'weak' reported in the e-cigarette arm.[688] There was no statistical difference in adverse events (RR 1.50; 95% CI 0.27-8.19) between ENDS and ENNDS. No serious adverse events were reported in the trial by Meier et al., in which 24 smokers not motivated to quit trialled either active 16mg e-cigarettes or non-nicotine e-cigarettes.[138]

In a pooled analysis from randomised controlled trials, there was no statistical difference in the number of participants reporting adverse events between ENDS and NRT (RR 0.98; 95% CI 0.80-1.19), ENNDS and ENDS (RR 1.01; 95% CI 0.91-1.11). Compared to no intervention or behavioural support, ENDS users reported significantly more adverse events (RR 1.22; 95% CI 1.12-1.32).[686] Six studies reported data on serious adverse events for ENDS compared with behavioural support only or no support. There were no events in four studies, and pooled results from the two studies in which events occurred showed no statistical difference between the groups (RR 1.17; 95% CI 0.33-4.09). Three studies provided data on serious adverse events for ENDS and NRT versus NRT alone. The pooled estimate showed no statistical difference between the two groups (RR 1.26; 95% CI 0.46-3.42).

There were 16 cohort studies with findings on adverse events related to e-cigarettes. One study[162] was included in the NASEM review and none of the remaining studies were identified in the NASEM, top-up or other reviews. One study did not meet inclusion criteria as it was unpublished and not peer-reviewed. One study was a randomised crossover trial,[245] however, as both treatment groups received e-cigarettes Hartmann-Boyce classified it a cohort study for the purposes of their review. All studies were rated high risk of bias.

In the Australian prospective cohort study by Bell et al.,[700] 30 smokers (29 male, one unspecified) living with HIV, with a mean age of 42 years, who were motivated to quit tobacco smoking, were provided with a refillable 12mg/mL nicotine e-cigarette for smoking cessation. Four participants were lost to follow-up for unspecified reasons. Over the six-month observation period, 41 adverse events were recorded, of which 27 were possibly, probably or definitely related to the use of ENDS. The frequency of adverse events decreased over time. The most common adverse events reported were throat irritation (29.6%), headache (25.9%), cough or chest irritation (18.5%), nausea (14.8%), breathing difficulty (3.7%), gastroesophageal reflux and oesophagitis (3.7%) and heart palpitations (3.7%).

In Hickling et al.[701] 50 daily smokers from the UK unwilling to quit (24% women; mean age 39 years) were provided with disposable 4.5% nicotine e-cigarettes and were followed for six weeks. Two participants were lost to follow-up due to loss of contact and disengagement. A further seven withdrew consent. Throat irritation (28.3%), dry cough (19.6%), and dry mouth (15.2%) were most the most common adverse events and there was no significant change in adverse event frequency over time.

In the Italian prospective cohort study by Caponnetto et al.,[639] 14 daily smokers, 57% women and a mean age of 44.6 years, were provided with a 7.4mg nicotine e-cigarette and instructed to use them up to four times per day. No participants were lost to follow-up. The number of adverse events decreased over the one-year follow-up, and nausea (14.4%), throat irritation (14.4%), headache (14.4%), dry cough (28.6%) were most common.

Goniewicz et al.[705] followed 22 Polish current daily smokers motivated to quit (60% women; mean age 31) supplied with an e-cigarette and tobacco-flavoured cartridges (11.0 +/- 1.5mg of nicotine). Participants were encouraged to substitute cigarettes for e-cigarettes. Two subjects dropped out in the first week of study due to adverse events (nausea). Compared to baseline, there were significantly less participants reporting chest tightness, visual disturbances, daytime cough, difficulty concentrating, irritability, and presence of phlegm at two-week follow-up.

In the prospective cohort study in the UK by Hajek et al.,[496] 100 smokers, 38% women and an average age of 41 years, from a stop-smoking service, were offered a choice of 1.6% or 2.2% nicotine e-cigarettes for smoking cessation, to be used in isolation or in conjunction with other cessation therapies. During four-week follow-up, throat irritation and minor coughing were reported and there was one incident of mouth irritation due to a leaky e-cigarette.

Oncken et al.[245] for two weeks followed 27 US daily smokers, 45% women with a mean age of 42 years, who were willing to abstain from conventional cigarette smoking and instead use 18mg/mL nicotine e-cigarettes. Seven participants were lost to follow-up for various reasons, with one participant lost due to an adverse event. Commonly reported adverse events included cough (19%), mouth or throat irritation (15%), nausea (4%), headache (4%) and irritability or stomach cramps (4%). One participant reported a severe adverse event (itchy throat and cough) but also reported a history of childhood asthma and was thus discontinued from ENDS use as previously reported.

A study by Polosa et al.[704] followed 50 Italian daily smokers not motivated to quit (40% women; mean age 41 years) using 9mg/mL nicotine e-cigarettes ad libitum over six months. Twelve participants were lost to follow-up for unspecified reasons. Frequency of adverse events declined over time and throat or mouth irritation (35.6%), dry throat or mouth (28.9%), headache (26.7%), dry cough (22.2%) were the most common reported.

Pratt et al.[497] followed 21 US daily smokers with a history of failed quit attempts but not currently motivated to quit for four weeks. Sixty-eight percent were women with a mean age of 42. Two participants were lost to follow-up for unspecified reasons. Participants were supplied with an ENDS device and cartridges each containing a concentration of nicotine equivalent to two packs of conventional cigarettes, dependant on the participant's usual use of cigarettes. Fifty-eight percent of participants reported at least one adverse event during follow-up, which included dry or sore throat, mild nausea, and cough. Of those that did report adverse events, 55% experienced only one symptom for just one week. Thirty-seven percent of this group reported more than one symptom for 1–2 weeks, and only one participant reported experiencing a symptom for more than two weeks (mild cough).

Among 12 US moderate or heavy conventional cigarette smokers (50% women; mean age 45.9 years) that switched completely to e-cigarettes, the most commonly reported adverse effects were headaches (33%), coughing (33%), increased appetite (33%), difficulty concentrating (33%), and anxiety or nervousness (33%) during nine-week follow-up in the study by Stein et al.[499] Two participants also reported changes in how this tasted, sore throat, and sleep problems and one participant each reported dry mouth, dizziness and a desire or craving to smoke.

In the South African study by Van Staden et al.,[246] 15 current daily smokers (38.5% women; mean age 38 years) were supplied with an e-cigarette and a 0.8mL cartridge of 0.0144mg nicotine e-liquid to use exclusively over two weeks. Two participants were lost to follow-up for unspecified reasons. It should be noted that the supposed nicotine concentration was unusually low and was suspected to be due to an error in units, with the actual amount likely being 0.0144g of nicotine. Little data was reported however one participant dropped out due to illness, having reported headache and fever.

No adverse events were reported in the Swiss prospective cohort study by Humair et al.,[702] in which 17 smokers motivated to reduce tobacco use, that had failed to quit using other medicinal aids, used e-cigarettes for smoking cessation. No serious adverse events were reported during eight-week follow-up in 43 daily smokers unmotivated to quit (7% women; mean age 56.9) using either 12 or 24mg/mL nicotine e-cigarettes in the US study by Valentine et al.[703] Among 29 daily smokers not motivated to quit (44% women; mean age 43 years) using a 26mg nicotine e-cigarette, 14 mild and one moderate (throat irritation) adverse events were reported in 29 smokers in the 12-week cohort study by Nides et al.[161] In the study by Wadia et al.[447] no adverse event were reported among 20 smokers, of which the proportion that were women and average age was not specified. Participants were provided with an ENDS device and tobacco-flavoured e-liquid (18mg of nicotine) and followed over two weeks.

4.15.2 Summary of conclusions from previous reviews

No summative conclusions regarding adverse events were provided in the NASEM, CSIRO, Public Health England, SCHEER and Irish Health Research Board reviews.[3,4,11,14,15]

4.15.3 Top-up review

Search results

Overall, six articles were located in the top-up systematic literature search.[302,618,676,709] As three of these studies were cross-sectional,[302,676,709] they did not meet the eligibility criteria of our systematic review and have not been discussed further.

Many studies with data on adverse events may not have been captured in the literature search as often studies did not list these as key words or in their abstract. Randomised trial data on adverse events published from 2017 onwards were located from a previous review on the efficacy of e-cigarettes for cessation of smoking commissioned by the Australian Department of Health (Table 4.15.2). It should be noted that all of these trials were in smokers and comparisons of the occurrence of adverse events were between those randomised to receive nicotine e-cigarettes and comparators, which included approved NRT, no intervention/usual care and non-nicotine e-cigarettes (ENNDS). Furthermore, as the trials were not designed or powered to specifically measure adverse events, the results should be interpreted with caution.

Thus, 11 studies, one surveillance report[618] , two cohort studies and eight randomised controlled trials in smokers and non-smokers were included in the evidence synthesis (Table 4.15-2).

One systematic review with findings on adverse events related to e-cigarette use was located in the database search. Glasser et al. identified three studies, one surveillance report and two randomised controlled trials.[241] One study was included in the NASEM review[480], one study did not meet inclusion criteria[710] and the other[147] was published prior to the date limit of the top-up review and not captured by the NASEM review. This study was a non-randomised intervention study in which the effect of e-cigarettes on smoking cessation and reduction in 14 smokers with schizophrenia was assessed.[147] The most frequently reported adverse events were nausea (14.4%), throat irritation (14.4%), headache (14.4%), and dry cough (28.6%). Events were more common at the beginning of the trial and no serious adverse events were reported.

Adverse events: less serious outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to adverse events were located.

Randomised controlled trials

Eight studies with findings on adverse events were located from a previous review on the efficacy of e-cigarettes for cessation of smoking commissioned by the Australian Department of Health (Table 4.15-2).

Of the smokers randomised to receive nicotine e-cigarettes of different concentrations in the study by Carpenter et al.,[681] 52% (24mg/mL) and 36% (16mg/mL) experienced at least one adverse event over the trial period. Combining e-cigarette nicotine concentration groups, 32% of all e-cigarette-assigned participants experienced cough, 24% experienced nausea and 16% experienced mouth/throat irritation. In the control group of smokers receiving no intervention, the most common adverse events were headache (24%), cough (21%), and mouth/throat irritation (17%). No AE resulted in study termination.

In their smoking cessation randomised controlled trial of very low nicotine concentration e-cigarettes (0.01mg/mL) versus nicotine gum, Lee et al.[682] reported no serious adverse events. Adverse events were significantly less common in the ENDS group compared to the nicotine gum group (6.7% vs. 17.3%, p=0.044). The most common adverse events in both groups were oral pain, cough, dry mouth, headache, and nausea/vomiting. The AEs were considered mild to moderate intensity and none led to withdrawal from the study.

Hajek et al.[419] reported adverse event data for nausea, sleep disturbances and throat/mouth irritation (pre-specified in the study protocol). Nausea was more common in the smokers randomised to receive NRT (37.9%) compared to those receiving the e-cigarette (31.3%). Throat/mouth irritation was more common in the e-cigarette group compared to NRT (65.3% vs. 51.2%). Sleep disturbances were common in both groups (65% for e-cigarette vs. 68% for NRT). The authors state that there were 27 serious adverse events in the e-cigarette group, and 22 in the NRT group. Of these, there were five respiratory events in the e-cigarette group and one respiratory event in the NRT group. No serious adverse event was classified by the trial clinician as being related to product use.

Myers-Smith et al.[711] reported cough/throat/chest irritation to be the most common in smokers randomised to ENDS (seven incidences) and itchiness/skin irritation in NRT users (11 incidences).

Holliday et al.[698] reported no serious adverse events among 80 smokers with periodontitis participating in their trial. There were 56 largely oral or dental adverse events reported: 35 in the ENDS group and 20 in the control group.

At three month follow-up, Lucchiari et al.[695] reported throat irritation in 5.7% of smokers in the ENDS group and 2.9% of the ENNDS group, and cough in 10% of the ENDS group and 2.9% of the ENNDS group. At six months, 15.9% of the ENDS group and 5.6% of the ENNDS group reported throat irritation and 5.8% and 2.8%, respectively, reported cough.

In the study by Baldassari et al.,[692] the most commonly reported adverse event across all smoking groups randomised to ENDS were cough (30%), sore throat (22.5%), increased appetite (17.5%) and vivid dreams (17.5%). There was no statistical difference between the groups.

Eisenberg et al.[712] reported seven serious adverse events in seven smoking participants. There was one serious respiratory event in ENDS users, and one serious cardiovascular and three other serious events in ENNDS users. There was one serious cardiovascular and other serious events in counselling only participants. There were several mild adverse events, the most common being cough (73%-94% across all participants). Occurrence of adverse events were comparable between ENDS and ENNDS groups, but more frequent compared with counselling only participants.

Of the eight randomised controlled trials, one was of low,[681] six were of moderate[419,682,692,695,698,711] and one was of high[712] methodological quality using the Joanna Briggs Institute's critical appraisal tool. No

conflicts of interest were declared in three studies.[682,695,698] At least one study author has received fees from pharmaceutical companies in five studies[419,592,681,692,711,712] and in one study, at least one author[692] was an advisory board member for pharmaceutical companies.[681] Two studies had at least one study author that had been an expert witness in litigation against the tobacco industry.[681,692]

Cohort studies

Two studies with findings on adverse events were located from the literature search (Table 4.15-2).

Using the same sample as Cravo et al.,[237] Walele et al.[350] assigned participants to 1.6% nicotine e-cigarettes for two years. Although this study was a clinical trial, all participants received the same interventions, and as such, this has been reclassified as a cohort study for the purpose of this review. Results were grouped for the sample as a whole (n=209) as well as by product compliance and study completion, with 'EVP-compliant subjects' (abstinent from conventional cigarettes for at least 80% of the completed study days) and 'completers' (completed the study) being the two subgroups.

Overall, 159 (76.1%) subjects reported a total of 971 adverse events and seven serious adverse events, with 51.8% of adverse events being moderate severity, 33.3% mild and 14.9% severe. 41.3% were possibly related to the study product, 33.0% unrelated, 21.3% unlikely related, 3.3% probably related and 1.1% almost definitely related. Headache (28.7%), nasopharyngitis (28.7%), sore throat (19.6%), and cough (16.7%) were experienced by the highest proportion of subjects. Eleven subjects were required to withdraw from the study due to adverse events, all judged to be unrelated or unlikely to be related to the e-cigarette. The seven serious adverse events were also judged to be unrelated or unlikely to be related to the study product. There were no deaths or life-threatening adverse events. For each of the aforementioned judgments, no criteria or descriptions were provided detailing how the judgements were made.

For EVP-compliant subjects, 90 (81.8%) subjects reported a total of 575 adverse events, three serious adverse events with 50.8% of adverse events being moderate severity, 38.6% being mild and 10.6% being severe. 40.9% were deemed unrelated to the study product, 33.4% possibly related, 19.8% unlikely related, 4.7% probably related and 1.2% almost definitely related.[350]

In the Italian prospective cohort study (n=21) by Polosa et al., nine non-smoking daily e-cigarette-using adults (≥18 years), and a control group of 12 age- and sex-matched hospital staff who were never smokers and not using e-cigarettes, were assessed for four adverse events (cough, wheeze, shortness of breath and tight chest) at three follow-up visits (12 ± 1 month, 24 ± 2 months, 42 ± 2 months).[223] The study found that no participants reported chest tightness, wheezing or shortness of breath, and there were no severe adverse events. In the e-cigarette group, cough was reported by one user at baseline and another at the second follow-up, whilst cough was reported by three participants on three occasions in the control group. The authors concluded that there was no difference between the groups in regard to adverse events, despite not conducting statistical analysis.[223]

One study was of low methodological quality[350] and the other was of moderate quality[223] using the Joanna Briggs Institute's critical appraisal checklist. Conflicts of interest were reported in both, one noting that several authors had personal fees or 'other' from Fontem Ventures and/or the tobacco and pharmaceutical industries.[350]

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarette use to adverse events were located.

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to adverse events were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to adverse events

Three cross-sectional surveys on adverse events related to e-cigarette use were identified.[302,676,709] In this context, cross-sectional surveys are not considered suitable evidence and no further description of the studies have been included.

One passive surveillance report on adverse events related to e-cigarette use was identified (Table 4.15.3). Motooka et al. found 27 cases in the US Food and Drug Administration Adverse Event Reporting System database between 2004 and 2016.[618] Age and sex of the cases was unknown. A variety of adverse events were reported and the most common were dizziness and dyspnoea, reported in four cases each. Nausea, chest pain, increased heart rate, tremor, disorientation, cough, wheezing and pain were the next most commonly reported adverse events with two reports of each symptom.[618]

The methodological quality of the evidence was rated low using Joanna Briggs Institute's critical appraisal checklist and no conflicts of interest were reported. GRADE was not applied.

4.15.4 Summary of findings from top-up review

There were eight randomised controlled trials in smokers, two cohort studies and one passive surveillance report, with relevant adverse event outcomes, finding:

- A range of adverse events are documented to occur in e-cigarette users.
- The evidence is primarily in smokers, so direct comparisons with outcomes in never smokers is not possible.
- The most common adverse events were throat irritation, nausea, cough, and headache, with additional reported events including dizziness, dyspnoea, chest pain, insomnia, increased heart rate, tremor, disorientation, wheezing and pain.

4.15.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence of less serious adverse events from the top-up systematic review with the evidence from previous reviews:

- There was a total of 57 studies on adverse events related to e-cigarette use: 33 randomised controlled trials, four non-randomised intervention studies, 17 cohort studies, two passive surveillance reports and one meta-analysis.
- The most common adverse events were throat irritation, nausea, cough, and headache, with additional reported events including dizziness, dyspnoea, chest pain, insomnia, increased heart rate, tremor, disorientation, wheezing and pain.
- Few very serious adverse events were reported.
- The majority of evidence was among smokers (many using nicotine e-cigarettes as a cessation aid) and no direct comparisions with never smokers were reported. Hence:
    - There is substantial evidence that less serious adverse events such as throat irritation, cough, dizziness, headache and nausea are related to nicotine e-cigarette use.
- The GRADE rating for the randomised controlled trial evidence was very low certainty.
- The GRADE rating for the non-randomised evidence was very low certainty.

4.15.6 Main conclusions from the synthesised evidence on less serious adverse events related to e-cigarette use

- There is moderate evidence that less serious adverse events – such as throat irritation, cough, dizziness, headache and nausea – occur with use of nicotine e-cigarettes.

Table 4.15-2. Study details: less serious adverse events – randomised controlled trials and cohort studies

Study details (author, year, location, study type, time frame)	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflicts of interest, funding
Randomised controlled trials					
Myers Smith et al., 2021[711] UK Randomised controlled trial 2017-2018	Study size 135 smokers Sample Smokers Gender – male (%) ENDS: 52.9 NRT: 49.3 Age – median (IQR) years ENDS: 41 (16) NRT: 40 (19)	Intervention (n=68) ENDS: concentration of choice Comparator (n=57) Nicotine replacement therapy Materials ENDS of choice Follow-up 6 months	Adverse events	Frequency of adverse events at week 1-24 - n ENDS / NRT Throat irritation 2 / 0 Nausea 1 / 2 Cough 3 / 1 Itchiness/skin irritation 0 / 11 Vivid dreams 0 / 1 Hiccups 0 / 1 Cough/throat/chest irritation 7 / 0 Dry mouth/throat 2 / 1 Indigestion 0 / 2 Sleep problems 0 / 1 Sore glands 0 / 1	Moderate methodological quality Moderate study size Conflicts of interest Research funding from and provided consultancy to pharmaceutical companies Funding Tobacco Advisory Group project grant, Cancer Research UK

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type, time frame)</th><th>Sample characteristics</th><th>Intervention and control</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflicts of interest, funding</th></tr>
<tr>
<td>Eisenberg et al., 2020[699]

Canada

Multi-centre randomised controlled trial

2016-2019</td>
<td><u>Study size</u>
376 smokers

<u>Sample</u>
Current smoker who smoked a mean of 10 cigarettes or more per day

<u>Gender – male (%)</u>
ENDS: 49
ENNDS: 56
Control: 53

<u>Age - mean (SD) years</u>
ENDS: 53 (13)
ENNDS: 53 (13)
Control: 53 (12)</td>
<td><u>Intervention 1 (n=128)</u>
ENDS: 15mg/mL nicotine, and behavioural counselling

<u>Intervention 2 (n=127)</u>
ENNDS: 0mg/mL nicotine, and behavioural counselling

<u>Comparator (n=121)</u>
Counselling only

<u>Materials</u>
Rechargeable EC with prefilled, disposable, tobacco-flavoured liquid cartridges

<u>Follow-up</u>
Telephone call at weeks 1, 2, 8 and 18. Laboratory visit at weeks 4, 12, and 24</td>
<td>Serious and mild adverse events</td>
<td><u>Serious Adverse Events - n (%)</u>
<table>
<tr><th></th><th>ENDS</th><th>ENNDS</th><th>Control</th></tr>
<tr><td>Participants</td><td>1 (0.8)</td><td>4 (3.1)</td><td>2 (1.7)</td></tr>
<tr><td>Death</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Respiratory</td><td>1 (0.8)</td><td>0</td><td>0</td></tr>
<tr><td>Cardiovascular</td><td>0</td><td>1 (0.8)</td><td>1 (0.8)</td></tr>
<tr><td>Neuropsychiatric</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Other</td><td>0</td><td>3 (2.4)</td><td>1 (0.8)</td></tr>
</table>
<u>Mild Adverse Events – n (%)</u>
<table>
<tr><th></th><th>ENDS</th><th>ENNDS</th><th>Control</th></tr>
<tr><td>Participants</td><td>120 (94)</td><td>118 (93)</td><td>88 (73)</td></tr>
<tr><td>Cough</td><td>95 (74)</td><td>81 (64)</td><td>66 (55)</td></tr>
<tr><td>Dry mouth</td><td>72 (56)</td><td>74 (58)</td><td>55 (46)</td></tr>
<tr><td>Headache</td><td>70 (55)</td><td>69 (54)</td><td>46 (38)</td></tr>
<tr><td>Rhinitis</td><td>70 (55)</td><td>67 (53)</td><td>51 (42)</td></tr>
<tr><td>Throat irritation</td><td>70 (55)</td><td>53 (42)</td><td>30 (25)</td></tr>
<tr><td>Dyspnoea</td><td>53 (41)</td><td>61 (48)</td><td>43 (36)</td></tr>
<tr><td>Sore throat</td><td>44 (34)</td><td>39 (31)</td><td>21 (17)</td></tr>
<tr><td>Light headedness</td><td>42 (33)</td><td>34 (27)</td><td>28 (23)</td></tr>
<tr><td>Dizziness</td><td>39 (31)</td><td>31 (24)</td><td>37 (31)</td></tr>
<tr><td>Mouth irritation</td><td>38 (30)</td><td>24 (19)</td><td>15(12)</td></tr>
<tr><td>Nausea</td><td>37 (29)</td><td>30 (24)</td><td>20 (17)</td></tr>
<tr><td>Indigestion</td><td>31 (24)</td><td>33 (26)</td><td>28 (23)</td></tr>
<tr><td>Mouth ulcers</td><td>19 (15)</td><td>16 (13)</td><td>7 (6)</td></tr>
<tr><td>Vertigo</td><td>16 (13)</td><td>11 (9)</td><td>9 (7)</td></tr>
</table>
</td>
<td>High methodological quality

Moderate study size

<u>Conflict of interest</u>
Grants and compensation from pharmaceutical companies

<u>Funding</u>
Canadian Institutes of Health Research</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type, time frame)</th><th>Sample characteristics</th><th>Intervention and control</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflicts of interest, funding</th></tr>
<tr>
<td>Hajek et al., 2019[419]

UK

Two-group, pragmatic, multi-centre, individually randomised, controlled trial

2015-2018</td>
<td><u>Study size</u>
150 smokers

<u>Sample</u>
Adult smokers

<u>Gender – male (%)</u>
100

<u>Age - mean (SD) years</u>
42.3 (8.3)</td>
<td><u>Intervention (n=75)</u>
ENDS

<u>Comparator (n=75)</u>
Nicotine replacement therapies (NRTs)

<u>Materials</u>
ENDS: One Kit, any flavour of strength e-liquid
NRTs: range of Nicotine replacement products

<u>Follow-up</u>
4, 26 and 52 weeks</td>
<td>Adverse events</td>
<td><u>Respiratory symptoms at baseline and 52 weeks</u>
<table>
<tr><th></th><th colspan="2">ENDS</th><th colspan="2">NRTs</th><th>Relative risk (95% CI)</th></tr>
<tr><th></th><th>Baseline</th><th>52 wks</th><th>Baseline</th><th>52 wks</th><th></th></tr>
<tr><td>Shortness of breath</td><td>120 (38.1)</td><td>66 (21.0)</td><td>92 (33.0)</td><td>64 (22.9)</td><td>0.9 (0.7–1.1)</td></tr>
<tr><td>Wheezing</td><td>102 (32.4)</td><td>74 (23.5)</td><td>86 (30.8)</td><td>59 (21.1)</td><td>1.1 (0.8–1.4)</td></tr>
<tr><td>Cough</td><td>173 (54.9)</td><td>97 (30.8)</td><td>144 (51.6)</td><td>111 (39.8)</td><td>0.8 (0.6–0.9)</td></tr>
<tr><td>Phlegm</td><td>137 (43.5)</td><td>79 (25.1)</td><td>121 (43.4)</td><td>103 (36.9)</td><td>0.7 (0.6–0.9)</td></tr>
</table>
<u>Serious Adverse Events - n</u>
ENDS: 27
NRT: 22

No serious adverse event in either group was classified by the trial clinician as being related to product use</td>
<td>Moderate methodological quality

Moderate study size

<u>Conflicts of interest</u>
Grants and personal fees from pharmaceutical companies outside current study

<u>Funding</u>
National Institute for Health Research and Cancer Research UK Prevention Trials Unit</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame)	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflicts of interest, funding
Holliday et al., 2019[698] UK Single-centre, two-arm, parallel group, individually randomised controlled pilot trial 2016-2017	Study size 80 smokers Sample Smoker of burnt tobacco (≥10 factory-made cigarettes per day or 7g [0.25 oz]) loose tobacco/day or 14 hand-rolled cigarettes per day), diagnosed with periodontitis Gender (%) Male: 47.5 Female: 52.5 Age - mean (SD) years 44.3 (10.7)	Intervention (n=40) ENDS Comparator (n=40) Usual care (behavioural therapy) Materials ENDS: Vype eTank clearomiser (tank), Flavour options: Blended Tobacco, Crisp Mint, Dark Cherry and Vpure (flavourless)*. Nicotine strength concentrations: 0mg/mL, 6mg/mL, 12mg/mL, 18mg/ml. Follow-up 6 months	Dental adverse events	Dental adverse events – n Control: AEs (n) / No. participants ENDS: AEs (n) / No. participant Toothache: 4 / 4 / 11 / 9 Dentine hypersensitivity: 3 / 3 / 3 / 3 Tooth/teeth loss: 5 (6 teeth) / 4 / 5 (9 teeth) / 3 Dental/ periodontal abscess: 2 / 2 / 3 / 3 Mouth ulceration: 0 / 0 / 2 / 2 Soreness of intra-oral soft tissue: 0 / 0 / 3 / 3 Fractured/carious filling or tooth: 3 / 3 / 2 / 2 Other: 3 / 2 / 6 / 5	Moderate methodological quality Small study size Conflicts of interest None declared Funding National Institute for Health Research

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type, time frame)</th><th>Sample characteristics</th><th>Intervention and control</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflicts of interest, funding</th></tr>
<tr>
<td>Lee et al., 2019[682]

Korea

Single-centre, prospective, open-label, randomised controlled, clinical pilot trial

2012</td>
<td><u>Study size</u>
150 smokers

<u>Sample</u>
Current smoker who smoked at least 10 cigarettes per day during the preceding year, had smoked for at least 3 years

<u>Gender – male (%)</u>
100

<u>Age - mean (SD) years</u>
42.3 (8.3)</td>
<td><u>Intervention (n=75)</u>
ENDS: 16mg/mL nicotine

<u>Comparator (n=75)</u>
Nicotine gum

<u>Materials</u>
ENDS: eGO-C Ovale, nicotine 0.01mg/mL; Janty-Korea Co.
Gum: Nicoman, nicotine 2mg/tablet

<u>Follow-up</u>
Laboratory visits at 12 and 24 weeks</td>
<td>Tolerability</td>
<td><u>Adverse event (%)</u>
ENDS: 6.7%
Gum: 17.3%
p=0.044

<u>Frequency of adverse events</u>
<table>
<tr><th></th><th>ENDS</th><th>Gum</th><th>p-value</th></tr>
<tr><td>Subjects with any AE</td><td>5 (6.7)</td><td>13 (7.3)</td><td>0.044</td></tr>
<tr><td>Total AEs</td><td>9 (100)</td><td>27 (100)</td><td></td></tr>
<tr><td>Sore throat</td><td>-</td><td>2 (7.4)</td><td>0.497</td></tr>
<tr><td>Oral pain</td><td>2 (22.2)</td><td>5 (18.5)</td><td>0.442</td></tr>
<tr><td>Cough</td><td>3 (3.33)</td><td>3 (11.1)</td><td>1.000</td></tr>
<tr><td>Dry mouth</td><td>2 (22.2)</td><td>2 (7.4)</td><td>1.000</td></tr>
<tr><td>Oral ulcer</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Dizziness</td><td>-</td><td>5 (18.5)</td><td>0.058</td></tr>
<tr><td>Headache</td><td>1 (11.1)</td><td>2 (7.4)</td><td>1.000</td></tr>
<tr><td>Nausea/vomiting</td><td>1 (11.1)</td><td>8 (29.6)</td><td>0.034</td></tr>
<tr><td>Other</td><td>-</td><td>-</td><td>-</td></tr>
</table>
No serious adverse events were reported</td>
<td>Moderate methodological quality

Moderate study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
None</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

<table>
<tr><th>Study details (author, year, location, study type, time frame)</th><th>Sample characteristics</th><th>Intervention and control</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflicts of interest, funding</th></tr>
<tr>
<td>Lucchiari et al., 2019[695]

Italy

Double-blind randomised controlled trial

2015-2016</td>
<td><u>Study size</u>
210 smokers

<u>Sample</u>
Smoker who smoked an average of 10 cigarettes or more a day for at least the past 10 years

<u>Gender (%)</u>
Male: 62.9
Female: 37.1

<u>Age - mean (SD) years</u>
62.8 (4.58)</td>
<td><u>Intervention 1 (n=70)</u>
ENDS

<u>Intervention 2 (n=70)</u>
ENNDS

<u>Comparator (n=70)</u>
Counselling

<u>Materials</u>
ENDS: e-cigarette kit and 12 x 10mL liquid cartridges (8mg/mL nicotine concentration)
ENNDS: e-cigarette kit and 12 x 0mL liquid cartridges (8mg/mL nicotine concentration)

<u>Follow-up</u>
3 and 6 months</td>
<td>Adverse events</td>
<td><u>Adverse events at 3 and 6 months</u>
<table><tr><th></th><th colspan="2">3 months</th><th colspan="2">6 months</th></tr><tr><th></th><th>ENDS</th><th>ENNDS</th><th>ENDS</th><th>ENNDS</th></tr><tr><td>Burning throat</td><td>5.7%</td><td>2.9%</td><td>15.9%</td><td>5.6%</td></tr><tr><td>Cough</td><td>10%</td><td>2.9%</td><td>5.8%</td><td>2.8%</td></tr><tr><td>Nausea</td><td>1.4%</td><td>2.9%</td><td>5.8%</td><td>7.0%</td></tr><tr><td>Headache</td><td>-</td><td>-</td><td>-</td><td>1.4%</td></tr><tr><td>Insomnia</td><td>1.4%</td><td>-</td><td>1.4%</td><td>-</td></tr><tr><td>Stomach ache</td><td>-</td><td>-</td><td>4.3%</td><td>4.2%</td></tr><tr><td>Confusion</td><td>1.4%</td><td>-</td><td>1.4%</td><td>-</td></tr></table></td>
<td>Moderate methodological quality

Moderate study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Fondazione Umberto Veronesi</td>
</tr>
</table>

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame)	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflicts of interest, funding
Baldassari et al., 2018[692] US Double-blinded, randomised controlled trial Study date not reported	Study size 40 smokers Sample Current smokers: smoking 1 or more tobacco cigarettes per day Gender - male (%) ENDS + patch: 60 ENNDS + patch: 35 Total: 47.5 Age - mean (SD) years ENDS + patch: 52.2 (12.2) ENNDS + patch: 53.8 (7.8) Total: 53.0 (10.1)	Intervention (n=20) ENDS: 24mg/mL nicotine, nicotine patch and counselling Comparator (n=21) ENNDS, nicotine patch and counselling Materials 2nd generation eGO style device (650 mAh battery, EVOD clearomiser, 3.7V, 1.8Ω single bottom coil), e-liquid: 70/30 propylene glycol/vegetable glycerin, tobacco flavour) Nicotine patch: 21mg or 14mg nicotine Follow-up Laboratory visits 24 weeks	Adverse events	Commonly reported side effects-all participants Cough: 30% Sore throat: 22.5% Increased appetite: 17.5% Vivid dreams: 17.5% No significant differences by treatment group	Moderate methodological quality Small study size Conflict of interest Grants and consulting/speaking fees from pharmaceutical companies and funding as an expert witness in litigation filed against the tobacco industry Funding Yale University and the National Heart, Lung, and Blood Institute

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame)	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflicts of interest, funding
Carpenter et al., 2017[681] US Randomised controlled trial Study date not reported	Study size 68 smokers Sample Current smoker of ≥5 cigarettes per day for ≥1 year Gender - male (%) ENDS 16mg: 28 ENDS 24mg: 57 Control: 36 Age - mean (SD) years ENDS 16mg: 43.3 (14.4) ENDS 24mg: 40.9 (12.3) Control: 42.3 (14.2)	Intervention 1 (n=25) ENDS: 16mg/mL nicotine Intervention 2 (n=21) ENNDS: 24mg/mL nicotine Comparator (n=22) No intervention Materials Blu Starter Pack or BluPlus+, traditional tobacco or menthol flavour Follow-up Laboratory visits at 8, 12, 16 weeks	Adverse events	Total number of Adverse Events - % participants, number of AEs ENDS 16mg: 36%, 17 AEs ENDS 24mg: 52%, 21 Aes Control: none Adverse Events (%) - ENDS Cough: 32% Nausea: 24% Mouth/throat irritation: 16% Control Headache: 24% Cough: 21% Mouth/throat irritation: 17%	Low methodological quality Small study size Conflict of interest Consultant/advisory board members for and grants from pharmaceutical companies and expert witness testimony against cigarette manufacturers Funding Not stated
Cohort studies					

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame)	Sample characteristics	Intervention and control	Outcome measure	Results				Quality assessment, study size, conflicts of interest, funding
Walele et al., 2018[350] UK Prospective cohort study Study date not reported	Study size 209 smokers Sample Healthy smokers (5-30 cigarettes per day for at least one year), aged between 21 and 65 years, BMI 18-35kg/m^2, all from a previous randomised controlled trial[237] (must have been compliant in previous study to be included in this study) Gender (%) Male: 55 Female: 45 Age – mean (SD) years 36.6 (10.2)	Intervention (n=209) ENDS: 1.6% (16mg/g) nicotine Puritane™ device, in tobacco or menthol flavour Comparator None Materials Puritane™ (closed system ENDS) Follow-up Two years	Adverse events (AEs) Serious adverse events (SAEs) Analysed as whole sample, and subgroups: 'EVP-compliant' – abstinent from conventional cigarettes for at least 80% of the completed study days 'Completers' – completed the study		All subjects (n=209)	EVP-compliant subjects (n=110)	Completers (n=102)	Low methodological quality Moderate study size Conflicts of interest Personal fees or 'other' from Fontem Ventures and/or the tobacco and pharmaceutical industries Funding Funded and supported by Fontem Ventures (parent company is Imperial Brands Group)
				Total	971 (100%)	575 (100%)	640 (100%)	
				SAEs	7 (0.7%)	3 (0.5%)	1 (0.2%)	
				AEs leading to study withdrawal	11 (1.1%)	6 (1.0%)	0	
				AEs by severity (% of AEs)				
				Mild	323 (33.3%)	222 (38.6%)	236 (36.9%)	
				Moderate	503 (51.8%)	292 (50.8%)	318 (49.7%)	
				Severe	145 (14.9%)	61 (10.6%)	86 (13.4%)	
				AEs by relationship to study product (% of AEs)				
				Almost definitely related	11 (1.1%)	7 (1.2%)	3 (0.5%)	
				Probably related	32 (3.3%)	27 (4.7%)	17 (2.7%)	
				Possibly related	401 (41.3%)	192 (33.4%)	259 (40.5%)	
				Unlikely related	207 (21.3%)	114 (19.8%)	122 (19.1%)	
				Unrelated	320 (33.0%)	235 (40.9%)	239 (37.3%)	

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Study details (author, year, location, study type, time frame)	Sample characteristics	Intervention and control	Outcome measure	Results	Quality assessment, study size, conflicts of interest, funding
Polosa et al., 2017[223] Italy Prospective cohort study 2013-2017 Online survey, regular vape shop customers	Study size 31 never smokers enrolled, 21 included in analysis Sample Never smokers or <100 cigarettes smoked in lifetime, daily EC users for ≥3 months Gender - n (%) Male: 21 (67.7) Female: 10 (32.3) Age – mean (SD) years ENDS: 29.7 (6.1) Control: 32.5 (7.0)	Exposure (n=9) Daily e-liquid consumption, median (SD): 4.0mL (2-5) Comparator (n=12) Non-smoker and non-EC user Materials - device type Advanced refillable: 44% Standard refillable: 56% Materials - nicotine concentration (%) 0%: 33 0.9%: 22 1.2%: 22 1.6%: 11 1.8%: 11 Follow-up Follow-up at 12, 24 and 42 months	Self-reported adverse events at baseline and each study visit Cough, wheeze, shortness of breath, tight chest	None of the participants in this study reported any wheezing, shortness of breath, or chest tightness. Cough was reported by one EC user at baseline and by another at F/up2. In the control group, three participants reported cough on three separate occasions. Of note, study participants reported no severe adverse reactions.	Moderate methodological quality Very small study size Conflicts of interest Grants and consulting/speaking fees from pharmaceutical companies and electronic cigarette industry and trade associations Funding Supported by Catania University

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

Table 4.15-3. Study details: less serious adverse events - surveillance reports

Study details (author, year, country, time frame, data source)	Demographics (sample size, sex, age)	Exposure (details of device)	Presentation	Treatment	Outcome	Quality assessment, conflict of interest, funding
Motooka et al., 2018[618] US 2004-2016 Food and Drug Administration Adverse Event Reporting System database	N=27 Sex: unknown Age: unknown	Not stated	Adverse events (n) Dizziness: 4 Dyspnoea: 4 Nausea: 2 Chest pain: 2 Increased heart rate: 2 Tremor: 2 Disorientation: 2 Cough: 2 Wheezing: 2 Thermal burn: 1 Pulmonary edema: 1 Throat irritation: 1 Altered visual depth perception: 1 Chills: 1 Device component issue: 1 Device deposit issue: 1 Device malfunction: 2 Device physical property issue: 1 Fear: 1 Headache: 1 Insomnia: 1 Lung disorder: 1 Malaise: 1 Migraine: 1 Pain: 2 Product label issue: 1 Productive cough: 1 Panic reaction: 1 Sensation of heaviness: 1 VIIth nerve paralysis: 1	Not stated	Not stated	Low methodological quality Very small study size Conflicts of interest Author is an employee of Micron Inc (technology company) Funding Japan Society for the Promotion of Science

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.16 Optical health

Main conclusions from the synthesised evidence on the optical effects of e-cigarette use

- There is no available evidence on the relation of e-cigarette use to clinical optical outcomes.
- There is insufficient evidence on the relation of e-cigarette use to corneal epithelial thickness or pre-corneal tear film stability and no evidence on other optical outcomes.

Table 4.16-1: Overview of studies of optical health outcomes identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Optical health				1 0 / 1			1 0 / 1		

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM; the second small number is the count of studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Macular degeneration, cataracts, uveitis, retinal detachment, glaucoma, diabetic retinopathy, dry eye syndrome, and corneal disease.
- **Other optical outcomes**: Optical symptoms and markers such as eye pain, blurred vision, tearing including pre-corneal tearing film, eye redness, sensitivity to light, corneal epithelial thickness.

Effects of optical application of nicotine e-liquids are considered in the poisons section.

4.16.1 Findings from previous reviews

The NASEM,[3] Public Health England,[11] CSIRO,[14] SCHEER,[4] and USPSTF[16] reviews did not include optical health as a main outcome and no optical health studies were identified nor discussed elsewhere.

Although also not included as a main outcome, the Irish Health Research Board literature map[15] identified one cross-sectional survey[713] on optical outcomes (included in other outcomes). This study was identified in our top-up review and is considered below.

4.16.2 Summary of conclusions from previous reviews

No studies on optical health outcomes were identified in any review.

4.16.3 Top-up review

Search results

Overall, two articles were located in the top-up systematic literature search. One was cross-sectional,[713] and did not meet the eligibility criteria of our top-up review and no further description of the study has been included. Therefore, one study[714] was included in the evidence synthesis (Table 4.17-1).

Optical health: clinical outcomes

No studies examining clinical outcomes related to clinical optical health were identified.

Optical health: other outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to other optical health outcomes were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to other optical health outcomes were located.

Cohort studies

No cohort studies reporting on the relationship of e-cigarette use to other optical health outcomes were located.

Non-randomised intervention studies

One non-randomised intervention study[714] on the relationship of e-cigarette use to other optical health outcomes was located. The South African study included 64 young e-cigarette naïve participants (smoking status unknown), 43 were male and 21 were female, with an average age of 21 years. All participants were exposed to 10 puffs of e-cigarettes containing 8mg/mL of nicotine, with a total consumption of 0.05mL of e-liquid.

There was no significant difference in central, superior, inferior, nasal and temporal corneal epithelial thicknesses after e-cigarette use (all p-values<0.05).[714] There was a non-significant increase in tear break-up time (measure of tear film stability) of 1.40 seconds (pre-exposure: 12.72 seconds; post-exposure 14.12 seconds; p=0.089).

The study was of moderate quality using the Joanna Briggs Institute's quality appraisal checklist and no conflicts of interest were declared (Table 4.16.2).

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to other optical health outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to subclinical optical health outcomes

One cross-sectional survey[713] reporting on the relationship of e-cigarette use to other optical health outcomes of dry eye and tear film quality was located. Due to difficulties attributing causality, this study is not discussed further and cross-sectional surveys are not included in the evidence synthesis.

4.16.4 Summary of findings from top-up review

No studies on the relationship of e-cigarette use to clinical optical health outcomes were identified. Hence:

- There is no available evidence on the relationship of e-cigarettes to clinical optical health outcomes.

There was one small non-randomised intervention study with smoking status unknown, reporting on other optical outcomes, finding:

- Acute exposure to nicotine e-cigarettes does not change corneal epithelial thickness or pre-corneal tear film stability. Hence:
  - There is insufficient evidence on the relation of e-cigarette use to corneal epithelial thickness or pre-corneal tear film stability and no evidence on other optical outcomes.
- Due to the study types available, the GRADE approach was not applied and the certainty of evidence is automatically rated as very low.

4.16.5 Summary of findings integrating evidence from previous reviews and top-up review

As no additional evidence was sourced from other reviews, please see findings from the top-up review for the summary.

4.16.6 Main conclusions from the synthesised evidence on the optical health effects of e-cigarette use

- There is no evidence on the relationship of e-cigarette use to clinical optical outcomes.
- There is insufficient evidence on the relationship of e-cigarette use to corneal epithelial thickness or pre-corneal tear film stability and no evidence on other optical outcomes.

Table 4.16-2. Study details: optical health – non-randomised intervention studies

Study details (author, year, location, study design)	Sample characteristics	Exposure/ Comparison groups	Outcome measure	Results	Quality assessment study size, conflict of interest, funding
Munsamy et al., 2019[714] South Africa Non-randomised, pre- and post-study Study date not reported	Study size 64 enrolled, 58 analysed Sample E-cigarette naïve subjects Gender – n (%) Male: 43 (67.2) Female: 21 (32.8) Age mean (years) 21 Setting Designated smoker area (4.67m by 2.25m), air-conditioning turned off	Exposure - dose 0.05mL of 8mg/mL nicotine containing e-liquid Comparator Within subject Materials Not specified Pattern of use 10 puffs	Corneal epithelial thickness (microns) of the 5 zones: central, superior, inferior, nasal and temporal Tear film stability (seconds) measured by Non-Invasive Keratograph Break-up Time (NIKBUT)	Mean change for corneal epithelial thickness, n=58 (microns) Central: Pre 52.44, Post 52.76, Mean change -0.3448, SD ±1.5955, p 0.105 Superior: Pre 52.38, Post 52.56, Mean change -0.2414, SD ±1.5138, p 0.230 Inferior: Pre 52.97, Post 53.19, Mean change -0.2931, SD ±1.6005, p 0.169 Nasal: Pre 52.63, Post 52.81, Mean change -0.2069, SD ±1.4112, p 0.269 Temporal: Pre 51.64, Post 51.87, Mean change -0.2759, SD ±1.3218, p 0.117 All the mean changes for corneal epithelial thickness were statistically insignificant Tear film stability, n=57 (seconds) Pre Post: Pre 12.72, Post 14.12, Mean change -1.40, SD ±6.11, p 0.089 Negative reading implies an increase, therefore non-significant increase in tear film stability	Moderate methodological quality Very small study size Conflicts of interest None declared Funding Not stated

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.17 Wound healing

Main conclusions from the synthesised evidence on wound healing and e-cigarette use

- There is no available evidence as to the effect of e-cigarette use on clinical or subclinical wound healing outcomes.

Table 4.17-1: Overview of studies of wound healing outcomes identified in the systematic review, by study design

Health outcome	Meta-analysis	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Wound healing									2 0 / 2

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Failure of wound healing, delayed wound healing, and tissue necrosis.
- **Subclinical outcomes**: Oxygen tissue perfusion, compromised free flap reconstruction.

4.17.1 Findings from previous major international reviews

The NASEM review[3] did not include wound healing as a health outcome in their review, and as such, no articles on the effects of e-cigarettes on wound healing were identified.

The Irish Health Research Board literature map[15] identified three case reports[715-717] describing the effects of e-cigarettes on wound healing, two of which were also included in the top-up review[715,716] and one that was published before the date limit of the top-up review and was not included in the NASEM review.[717] Case reports were not considered suitable evidence for this outcome and have not been discussed further.

The CSIRO review[14] identified two case reports[715,716] describing the negative effects of e-cigarettes on post-surgery wound healing, both of which were included in the literature map by the Irish Health Research Board.

The Public Health England,[11] SCHEER[4] and USPSTF[16] reviews did not identify any articles on the effects of e-cigarettes on wound healing.

4.17.2 Summary of conclusions from previous reviews

The Irish Health Research Board literature map[15] did not provide any summative conclusions on the relationship between e-cigarettes and wound healing.

The CSIRO review[14] concluded that:

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

4.17.3 Top-up review

Search results

Overall, two articles[715,716] were located in the top-up systematic literature search. As these studies were case reports, they did not meet eligibility criteria and no articles were available for the top-up synthesis of evidence (Table 4.18-1).

One systematic review with findings on wound healing outcomes related to e-cigarette was identified in the database search. Tzortzi et al. identified two case reports,[715,716] both of which were included in the top-up review.[267]

Wound healing: clinical outcomes

Meta-analyses
No meta-analyses of the relationship of e-cigarette use to wound healing were located.

Randomised controlled trials
No randomised controlled trials reporting on the relationship of e-cigarette use to wound healing were located.

Cohort studies
No cohort studies reporting on the relationship of e-cigarette use to wound healing were located.

Non-randomised intervention studies
No non-randomised intervention studies reporting on the relationship of e-cigarette use to wound healing were located.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to wound healing were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to wound healing
One case report, Fracol et al.,[716] was identified in the top-up review. In this context, case reports are not considered suitable evidence and no further description of the study has been included.

Wound healing: subclinical outcomes

No studies examining subclinical outcomes related to wound healing were identified.

Meta-analyses
No meta-analyses of the relationship of e-cigarette use to wound healing were located.

Randomised controlled trials
No randomised controlled trials reporting on the relationship of e-cigarette use to wound healing were located.

Cohort studies
No cohort studies reporting on the relationship of e-cigarette use to wound healing were located.

Non-randomised intervention studies
No non-randomised intervention studies reporting on the relationship of e-cigarette use to wound healing were located.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to wound healing were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to wound healing
One case report, Agochukwu et al.,[715] was identified in the top-up review. In this context, case reports are not considered suitable evidence and no further description of the study has been included.

4.17.4 Summary of findings from top-up review

No studies on the relationship of e-cigarette use to wound healing outcomes were identified.

4.17.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence from the top-up systematic review with the evidence from previous reviews:

- No studies on the relationship of e-cigarette use to clinical or subclinical wound healing outcomes were identified.

4.17.6 Main conclusions from the synthesised evidence on wound healing in relation to e-cigarette use

- There is no available evidence as to the effect of e-cigarette use on clinical or subclinical wound healing outcomes.

4.18 Olfactory outcomes

Main conclusions from the synthesised evidence on the olfactory effects of e-cigarette use

- There is no available evidence on the effect of e-cigarette use on clinical olfactory outcomes.
- There is insufficient evidence on the relationship between use of e-cigarettes and subclinical olfactory measures.

Table 4.18-1: Overview of studies of olfactory outcomes identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Olfactory outcomes							1 0 / 1		

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use and outcomes such as bad or irritating smell, desirability of smell, etc.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Diminished smell function (anosmia, hyposmia), qualitative olfactory impairment (e.g. parosmia, phantosmia).
- **Subclinical outcomes**: Odour perception measures, olfactory functioning changes not meeting clinical disease criteria.

4.18.1 Findings from previous reviews

The NASEM,[3] Public Health England,[11] CSIRO,[14] SCHEER[4] and USPSTF[16] reviews did not include olfactory health as a primary outcome and no additional olfactory health studies were identified and discussed elsewhere.

Although also not included as an individual outcome, the Irish Health Research Board literature map[15] identified one cross-sectional survey[677] on changes in olfactory sensation, reported under other health outcomes. This study was not included in the top-up review as the comparator was not relevant.

4.18.2 Summary of conclusions from previous reviews

The Irish Health Research Board literature map[15] did not provide any summative conclusions on how e-cigarette use affects olfactory health outcomes.

4.18.3 Top-up review

Search results

Overall, one article was located in the top-up systematic literature search. This study was cross-sectional and was considered eligible evidence for this outcome and is therefore included in the evidence synthesis (Table 4.19-1).[718]

Olfactory disease: clinical outcomes

No studies were identified on the relation of e-cigarette use to clinical olfactory outcomes.

Olfactory disease: subclinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to subclinical olfactory health outcomes were located.

Randomised controlled trials

No randomised controlled trials on the relationship of e-cigarette use to subclinical olfactory health outcomes were located.

Cohort studies
No cohort studies on the relationship of e-cigarette use to subclinical olfactory health outcomes were located.

Non-randomised intervention studies
Case-control studies
No case-control studies on the relationship of e-cigarette use to subclinical olfactory health outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to subclinical olfactory health outcomes
One cross-sectional survey[718] in non-smokers on e-cigarette use and changes to olfactory function was located (Table 4.18.2). Although this study could technically be considered cross-sectional and would not generally be considered further, it is less plausible that olfactory outcomes could influence the exposure than for other cross-sectional surveys and hence findings are outlined here.

The Austrian study included 181 participants: 70 never smokers, 66 smokers and 45 exclusive e-cigarette users (former smokers, abstinent for a minimum of two years). On average, e-cigarette users consumed 10.8mL of nicotine e-liquid per day for 2.3 years. Participants ranged from 18-46 years of age, and there was an equal split of male and female participants (50%).

Participant's olfactory perception was assessed with the Threshold Discrimination and Identification (TDI) test. The test includes an odour threshold test (detection of one n-butanol odour pen out of 48), a discrimination test (determination of one unique odour out of three identical odours) and an identification test (identification of 16 common odours). The highest score for each test was 16 points, thus the combined maximum score (the TDI-score) is 48 points with 30 or over considered normal function.

Compared to non-smokers, exclusive e-cigarette users were significantly less able to correctly discriminate ($p \leq 0.001$) and identify ($p=0.033$) odours. No significant difference between groups was found in the threshold test results ($p=0.349$). Combining the three test results, the mean TDI-score in the exclusive e-cigarette users was significantly lower than that of non-smokers (ENDS: 33.20 ± 2.23 and non-smokers: 34.74 ± 3.60; $p<0.05$), however, both groups were considered to have normal olfactory function.

Compared to smokers, exclusive e-cigarette users scored significantly higher on the threshold test ($p \leq 0.001$), the discrimination test ($p \leq 0.001$), and the identification test ($p=0.001$). The mean TDI-score in exclusive e-cigarette users was significantly higher than that of smokers (ENDS: 33.20 ± 2.23 and smokers: 25.83 ± 2.26; $p<0.05$) who were considered to have decreased olfactory function (TDI-score <30).

Years using e-cigarettes was significantly correlated to odour threshold and combined TDI-scores ($p<0.05$), but not discrimination or identification, and e-liquid volume was not significantly correlated to any outcome.

The study was assessed as moderate quality using the Joanna Briggs Institute's critical appraisal checklist, and no conflicts of interest were declared.

4.18.4 Summary of findings from top-up review
No studies on the relationship of e-cigarette use to clinical olfactory outcomes were identified. Hence:
- No evidence on how the use of e-cigarettes affects clinical olfactory outcomes.

There was one very small cross-sectional survey in exclusive e-cigarette users reporting on subclinical olfactory outcomes, finding:
- Compared to non-smokers, exclusive e-cigarette users have lessened olfactory functioning, however, they are still considered to have normal functioning. Hence:
  - There is insufficient evidence on how the use of e-cigarettes affects subclinical olfactory measures.
- The GRADE rating was very low certainty.

4.18.5 Summary of findings integrating evidence from previous reviews and top-up review
As no additional evidence was sourced from other reviews, please see findings from the top-up review for the summary.

4.18.6 Main conclusions from the synthesised evidence on the olfactory effects of e-cigarette use
- There is no available evidence on the effect of e-cigarette use on clinical olfactory outcomes.

- There is insufficient evidence on the relationship between use of e-cigarettes and subclinical olfactory measures.

Table 4.18-2. Study details: olfactory outcomes – cross-sectional surveys

Study details (author, year, study design, time frame [data source])	Sample characteristics	Exposure/ Comparison groups	Outcome measure	Results	Quality assessment, study size, conflict of interest, funding
Majchrzak et al., 2020[718] Austria Cross-sectional July-October 2017 Students of the University of Vienna, Vienna University of Economics and Business, vapour bars – recruited via social media, personal contacts	Study size 181 participants total Never smokers: 70 Smokers: 66 Exclusive EC: 45 Sample Never smokers: non-smokers that never smoked Smokers: no definition Exclusive EC: ex-smokers abstinent from smoking for approximately 2 years Age – mean (SD) percent - Never smokers: 25.2 (5.4) - Smokers: 27.2 (5.7) - EC: 26.8 (6.3) Gender – n - Never smokers: 40 females, 30 males - Smokers: 32 females, 34 males - EC: 18 females, 27 males	Exposure - dose Average 10.8mL liquid/day for an average of 2.3 years Comparators Never smokers Materials Not specified Follow-up Used e-cigarettes approximately 2 years	Olfactory sensitivity 1. Threshold test (score out of 16) 2. Discrimination test (score out of 16) 3. Identification test (score out of 16) 4. Olfactory test result – TDI (score out of 48)	Exclusive e-cigarette users and never smokers Exclusive e-cigarette users Mean (SD) / Never smokers Mean (SD) / P-value Threshold test: 10.19 ± 1.76 / 9.96 ± 2.03 / 0.349 Pearson correlation Years of e-cigarette use: r = −0.099 / 0.517 Volume consumed (mL): r = −0.204 / 0.180 Discrimination test: 11.67 ± 1.38 / 12.73 ± 1.46 / **≤0.001** Pearson correlation Years of e-cigarette use: r = 0.091 / 0.553 Volume consumed (mL): r = −0.013 / 0.932 Identification test: 11.34 ± 1.44 / 12.06 ± 1.82 / **0.033** Pearson correlation Years of e-cigarette use: r = −0.075 / 0.626 Volume consumed (mL): r = −0.038, / 0.803 TDI-score: 33.20 ± 2.23 / 34.74 ± 3.60 / **< 0.05** Exclusive e-cigarette users and smokers Exclusive e-cigarette users Mean (SD) / Smokers Mean (SD) / P-value Threshold test: 10.19 ± 1.76 / 6.07 ± 1.36 / **≤0.001** Discrimination test: 11.67 ± 1.38 / 9.23 ± 1.38 / **≤0.001** Identification test: 11.34 ± 1.44 / 10.53 ± 1.38 / **0.001** TDI-score: 33.20 ± 2.23 / 25.83 ± 2.26 / **<0.05**	Moderate methodological quality Small study size Conflicts of interest None declared Funding No specific funding

Notes: EC: e-cigarette, nicotine content not specified; ENDS: nicotine e-cigarette; ENNDS: non-nicotine e-cigarette

4.19 Endocrine outcomes

Main conclusions from the synthesised evidence on how e-cigarette use affects endocrine outcomes

- There is no available evidence on the relationship of e-cigarette use to clinical endocrine outcomes and insufficient evidence regarding subclinical endocrine outcomes of prediabetes and insulin resistance.

Table 4.19-1: Overview of studies of endocrine outcomes identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Endocrine outcomes							2 0 / 2		

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Diabetes mellitus, thyroid diseases such as hyperthyroidism, hypothyroidism, growth disorders, sexual dysfunction, and other hormone-related disorders.
- **Subclinical outcomes**: Glycosylated haemoglobin levels (HbA1c), insulin resistance, and prediabetes.

4.19.1 Findings from previous reviews

The NASEM,[3] CSIRO,[14] SCHEER[4] and USPSTF[16] reviews did not include endocrine outcomes as a main health outcome and no articles on endocrine outcomes were identified and discussed elsewhere.

Although also not included as a main health outcome, the Irish Health Research Board literature map[15] identified two cross-sectional surveys[719,720] on the effects of e-cigarettes on endocrine outcomes. One[719] was included in the top-up review and the other[720] did not meet inclusion criteria.

The Public Health England review[12] also did not include endocrine outcomes as a main outcome and no articles were identified and discussed elsewhere. However, the review mentions that there was one unspecified endocrine disorder (1 out of 86 cases) reported via the UK Medicines and Healthcare Products Regulatory Agency Yellow Card Scheme between 2016 and 2020, but no details are provided.

4.19.2 Summary of conclusions from previous reviews

The Irish Health Research Board literature map[15] did not provide any summative conclusion on how e-cigarette use affects endocrine outcomes.

4.19.3 Top-up review

Search results

Overall, two articles[105,719] were located in the top-up systematic literature search.

Endocrine: clinical outcomes

No studies on clinical endocrine outcomes were identified.

Endocrine: subclinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to subclinical endocrine outcomes were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to subclinical endocrine outcomes were located.

Cohort studies
No cohort studies reporting on the relationship of e-cigarette use to subclinical endocrine outcomes were located.

Non-randomised intervention studies
No non-randomised intervention studies reporting on the relationship of e-cigarette use to subclinical endocrine outcomes were located.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to subclinical endocrine outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to endocrine outcomes
Two cross-sectional surveys[105,719] on the relationship between e-cigarette use and subclinical endocrine health outcomes were located.

Atuegwu et al.[719] used the Behavioral Risk Factor Surveillance System (BRFSS) survey to compare the risk of self-reported prediabetes between never e-cigarette users (n=143,952), current e-cigarette users (n=1,339) and former e-cigarette users (n=7,625) all of whom were never smokers. There were between 43.1%-68.8% males across the three groups and the age distribution for each group varied with the majority of participants aged 55 years and over among never users (33.3%), 18-24 years among current users (67.3%) and former users (52.0%). Compared to never users, current e-cigarette users had a significantly increased risk of prediabetes (odds ratio: 1.97; 95% CI 1.25-3.10) while there was no difference for former e-cigarette users (odds ratio: 1.07; 95% CI 0.84-1.37).

The study by Orimoloye et al.[105] used data from the 2013–2014 and 2015–2016 cycles of the National Health and Nutrition Examination Survey (NHANES) in the US to compare insulin resistance (using the homeostatic model assessment of insulin resistance (HOMA-IR) and glucose tolerance tests (GTT)) across non-users of e-cigarettes or cigarettes (n=3,415), and exclusive e-cigarette users (n=30). In the whole sample, there were 50% females, and the majority of participants (32%) were aged 45-65 years. There was no significant difference in insulin resistance between exclusive e-cigarette users and non-users (HOMA-IR: β=0.20; 95% CI -0.09-0.49 and GTT: β=-0.05; 95% CI -0.21-0.11).

Both studies were of moderate methodological quality and no conflicts of interest were reported.

4.19.4 Summary of findings from top-up review
There were no studies identified with findings on the relationship of e-cigarettes to clinical endocrine outcomes. Hence:

- There is no available evidence on the relation of e-cigarette use to clinical endocrine outcomes.

There were two cross-sectional surveys with findings on subclinical endocrine outcomes.

- Among non-smokers, a significantly increased prediabetes risk was found in current e-cigarette users compared to never users in one study, and there was no difference in insulin resistance between exclusive e-cigarette users and non-users in another study. Hence:
    - There is insufficient evidence on the relationship of e-cigarette use to subclinical endocrine outcomes of prediabetes and insulin resistance.
- The GRADE rating was very low certainty.

4.19.5 Summary of findings integrating evidence from previous reviews and top-up review
As no additional evidence was sourced from other reviews, please see findings from the top-up review for the summary.

4.19.6 Main conclusions from the synthesised evidence on the endocrine effects of e-cigarette use

- There is no available evidence on the relationship of e-cigarette use to clinical endocrine outcomes and insufficient evidence regarding subclinical endocrine outcomes of prediabetes and insulin resistance.

Table 4.19-2. Study details: endocrine outcomes – cross-sectional surveys

<table>
<tr><th>Study details (author, year, location, data source, time frame)</th><th>Sample characteristics</th><th>Exposure/Comparison groups</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflict of interest, funding</th></tr>
<tr>
<td>Atuegwu et al., 2019[719]

US

Behavioral Risk Factor Surveillance System (BRFSS) survey

2017</td>
<td>Study size
Never smokers: 154,404
Never e-cigarette users: 143,952
Current e-cigarette users: 1,339
Former e-cigarette users: 7,625

Sample
Never e-cigarette users: no ever e-cigarette use
Current e-cigarette users: currently using e-cigarettes every day or some days
Former e-cigarette users: ever using an e-cigarette but not currently using e-cigarettes

Age – % (years)
<table>
<tr><th></th><th>Never</th><th>Current</th><th>Former</th></tr>
<tr><td>18-24</td><td>14</td><td>67.3</td><td>52.0</td></tr>
<tr><td>25-34</td><td>17.3</td><td>21.2</td><td>28.3</td></tr>
<tr><td>35-44</td><td>16.9</td><td>6.9</td><td>9.8</td></tr>
<tr><td>45-54</td><td>18.4</td><td>2.5</td><td>5.6</td></tr>
<tr><td>55+</td><td>33.3</td><td>2.2</td><td>4.3</td></tr>
</table>
Gender - %
<table>
<tr><th></th><th>Never</th><th>Current</th><th>Former</th></tr>
<tr><td>Male</td><td>43.1</td><td>68.8</td><td>56.6</td></tr>
<tr><td>Female</td><td>56.9</td><td>31.2</td><td>43.4</td></tr>
</table>
</td>
<td>Exposure
Former or current e-cigarette use

Comparators
Never e-cigarette users

Materials
Not specified</td>
<td>Self-reported prediabetes</td>
<td>Self-reported prediabetes - OR (95% CI)
<table>
<tr><th></th><th>All</th><th>Males</th><th>Females</th></tr>
<tr><td>Never e-cigarette users</td><td>Ref</td><td>Ref</td><td>Ref</td></tr>
<tr><td>Current e-cigarette users</td><td>1.97 (1.25-3.10)</td><td>2.36 (1.26-4.40)</td><td>1.88 (1.00-3.53)</td></tr>
<tr><td>Former e-cigarette users</td><td>1.07 (0.84-1.37)</td><td>1.22 (0.86-1.74)</td><td>1.00 (0.71-1.40)</td></tr>
</table>
Self-reported prediabetes for those that had a blood sugar test in past 3 years - OR (95% CI)
<table>
<tr><th></th><th>All</th><th>Males</th><th>Females</th></tr>
<tr><td>Never e-cigarette users</td><td>Ref</td><td>Ref</td><td>Ref</td></tr>
<tr><td>Current e-cigarette users</td><td>1.96 (1.13-3.40)</td><td>2.34 (1.13-4.86)</td><td>1.76 (0.79-3.92)</td></tr>
<tr><td>Former e-cigarette users</td><td>1.20 (0.91-1.58)</td><td>1.39 (0.92-2.10)</td><td>1.11 (0.77-1.59)</td></tr>
</table>
</td>
<td>Moderate methodological quality

Moderate study size

Conflicts of interest
None declared

Funding
Supported by NCI and NIH</td>
</tr>
</table>

<table>
<tr><th>Study details (author, year, location, data source, time frame)</th><th>Sample characteristics</th><th>Exposure/Comparison groups</th><th>Outcome measure</th><th>Results</th><th>Quality assessment, study size, conflict of interest, funding</th></tr>
<tr>
<td>Orimoloye et al., 2019[105]

US

National Health and Nutrition Examination Survey (NHANES)

2013-2016</td>
<td><u>Study size</u>
2,666 participants

<u>Sample</u>
Non-users: never smokers or former cigarette smokers who do not use e-cigarettes
Exclusive (‘sole’) e-cigarette users:
never smokers or former cigarette smokers with history of recent e-cigarette (past 5 days) use

<u>Age – % (years)</u>
<table>
<tr><th></th><th>Non-user</th><th>Sole user</th></tr>
<tr><td>18-30</td><td>23.2</td><td>36.7</td></tr>
<tr><td>30-45</td><td>24.9</td><td>30.0</td></tr>
<tr><td>45-65</td><td>29.9</td><td>30.0</td></tr>
<tr><td>65+</td><td>22.2</td><td>3.3</td></tr>
</table>
<u>Gender - %</u>
<table>
<tr><th></th><th>Non-user</th><th>Sole user</th></tr>
<tr><td>Male</td><td>47.3</td><td>60.0</td></tr>
<tr><td>Female</td><td>52.7</td><td>40.0</td></tr>
</table>
</td>
<td><u>Exposure (n=30)</u>
Exclusive (‘sole’) e-cigarette use

<u>Comparators (n=2,636)</u>
Non users

<u>Materials</u>
Not specified</td>
<td><u>Insulin resistance</u>

Homeostatic model assessment of insulin resistance (HOMA-IR)

Glucose tolerance tests (GTT)</td>
<td><u>Multivariable-adjusted association between product use categories and log-transformed-β-coefficient (95% CI)</u>
<table>
<tr><th></th><th>HOMA-IR</th><th>GTT</th></tr>
<tr><td>Non e-cigarette users</td><td>Ref</td><td>Ref</td></tr>
<tr><td>Sole e-cigarette users</td><td>0.20 (-0.09-0.49)</td><td>-0.05 (-0.21-0.11)</td></tr>
</table>
Models were adjusted for age, sex, race, physical activity, body mass index, and heavy drinking</td>
<td>Moderate methodological quality

Small study size

<u>Conflicts of interest</u>
None declared

<u>Funding</u>
Supported by NIH</td>
</tr>
</table>

4.20 Allergic diseases

Main conclusions from the synthesised evidence on the relation of e-cigarette use to allergic diseases

- There is limited evidence that e-cigarette use can lead to contact dermatitis and no available evidence on other clinical allergy outcomes.

Table 4.20-1: Overview of studies of allergic diseases identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Allergic diseases							2 0 / 2	1 0 / 1	3 2 / 1

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Allergic conditions such as allergic rhinitis (hay fever), dermatitis and anaphylaxis.

4.20.1 Findings from previous reviews

The NASEM review[3] identified two case reports[721,722] describing nickel-induced contact allergic dermatitis related to e-cigarette use.

One study described the case of a 37-year-old woman who presented with erythematous, and scaly dermatitis, slightly lichenified on the thumb and index finger after experiencing several episodes over the past six months. She had a several-year history of mild hand dermatitis and a self-reported allergy to nickel. The patient's e-cigarette was tested using a dimethylglyoxime nickel spot test, revealing a positive result. Following two months of avoidance of this device, the patient's dermatitis improved.[722]

The other study described a 52-year-old woman who presented with itchy erythematous dermatitis on the right hand which had started eight-months previously. She had a history of contact allergy and a positive patch test reaction to nickel. The patient's e-cigarette was tested using a dimethylglyoxime nickel spot test which revealed a positive result. The patient was advised to use a nickel-free device and in doing so the dermatitis cleared two months later.[721]

The Irish Health Research Board literature map[15] identified four studies - three case reports[721-723] and one case series[724] - on the effects of e-cigarette use on allergic diseases included in the discussion of e-cigarette toxins. Of the four studies, two[721,722] were included in the NASEM review and two were included in the top-up review[723,724].

The Public Health England,[11] SCHEER[4] and USPSTF[16] reviews did not include allergic diseases as a main health outcome and no studies were identified and discussed elsewhere.

The CSIRO review[14] identified one case series[724] describing two cases of contact allergic dermatitis due to nickel exposure from e-cigarette use. It has been included in the top-up review.

4.20.2 Summary of conclusions from previous reviews

The NASEM review[3] concluded that:

- ... nickel-induced allergic dermatitis is related to e-cigarette use.

The Irish Health Board Review literature map[15] and the CSIRO review[14] did not provide summative conclusions on the relationship of e-cigarettes to allergic diseases.

4.20.3 Top-up review

Search results

Overall, four articles were located in the top-up systematic literature search. Two were cross-sectional[379,725] and did not meet eligibility criteria, thus, two studies[723,724] were included in the top-up synthesis of evidence (Table 4.20-1).

One systematic review with findings on allergic disease was identified in the database search. Tzortzi et al.,[267] identified four studies, three case reports and one case series. Of the four studies, two were included in the NASEM review[721,722], one[724] was included in the top-up review, and one[726] was excluded due to being a poor quality case report.

Allergic disease: Clinical outcomes

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to allergic diseases were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to allergic diseases were located.

Cohort studies

No cohort studies reporting on the relationship of e-cigarette use to allergic diseases were located.

Non-randomised intervention studies

No non-randomised intervention studies reporting on the relationship of e-cigarette use to allergic diseases were located.

Case-control studies

No case-control studies reporting on the relationship of e-cigarette use to allergic diseases were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to allergic diseases

Four studies, one case report, one case series and two cross-sectional surveys on the relationship of e-cigarette use to clinical allergy outcomes were located. The two cross-sectional surveys[379,725], one on asthma, allergic rhinitis and atopic dermatitis and the other on asthma and allergic rhinitis, were not included due to the difficulty of attributing causality, and are not discussed further.

Case series

The case series[724] presents two cases of allergic contact dermatitis due to nickel exposure from e-cigarettes in the UK. The first patient, a 50-year-old male with no known allergy to nickel and a two-year history of intermittent dermatitis, presented with erythematous scaly patches under the nose and chin. The patient had been using an e-cigarette for the past six years and attributed his symptoms to his e-cigarette device. After a patch test, the patient was strongly positive for nickel and positive for mercaptobenzothiazole (although this was not considered to be of current relevance by the authors). A dimethylglyoxime nickel spot test was performed on his device and returned a positive result. He was advised to cease using his device, after which his symptoms resolved. The other case, a 38-year-old female e-cigarette user, with no history of a nickel allergy or dermatitis, presented with ill-defined erythematous patches on the right hand. A patch test was conducted and was positive for nickel. A dimethylglyoxime nickel spot test was performed on her device returning a positive result. The patient was advised to avoid her device and in doing so reported significant improvement in her symptoms within three months.

Case reports

The case report by Azevedo et al.[723] described a 38-year-old female patient presenting with erythematous and scaly dermatitis with lichenification on both hands. She had been experiencing symptoms for the past six months and reported using an e-cigarette around the time of onset. The patient was not known to have an allergy to nickel, however, a patch test (Portuguese baseline series of contact allergens) revealed a positive reaction to nickel (5% pet). The e-cigarette device returned a negative result for nickel using a dimethylglyoxime nickel spot test. After further discussion with the patient, it was revealed that e-liquid had been spilled over her hands prior to presentation. A spot test with the e-liquid (Cigavapor) returned a strong positive response. After spot testing for some of the ingredients in the e-liquid, the patient responded strongly to menthol, thus the authors suggested menthol was the causative agent.

4.20.4 Summary of findings from top-up review

There were two studies, one case report and one case series, on the relationship of e-cigarette use to clinical allergy outcomes, finding:

- E-cigarettes can cause clinical allergic reactions, primarily contact dermatitis, due to nickel exposure from e-cigarettes or potentially menthol within e-liquid. Hence:
    - There is limited evidence that e-cigarette use can lead to contact dermatitis and no available evidence on other clinical allergy outcomes.

4.20.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence from the top-up systematic review with the evidence from previous reviews:

- Four studies, three case reports and one case series, on the relationship of e-cigarette use to allergic diseases were identified.
- E-cigarettes can cause clinical allergic reactions, primarily contact dermatitis, due to nickel exposure from e-cigarettes or potentially menthol within e-liquid. Hence:
    - There is limited evidence that e-cigarette use can lead to contact dermatitis and no available evidence on other clinical allergy outcomes.
- GRADE was not applied.

4.20.6 Main conclusions from the synthesised evidence on the allergic diseases effects of e-cigarette use

- There is limited evidence that e-cigarette use can lead to contact dermatitis and no available evidence on other clinical allergy outcomes.

Table 4.9-3. Study details: allergic diseases – case reports and case series

Study details (author, year, location, [time frame], data source)	Demographics and medical history	Exposure (location of device, circumstance	Presentation	Treatment	Outcome	Quality assessment, conflicts of interest
Case series						
Shim et al., 2018[724] UK No time frame reported Hospital department	Case 1 Male 50 years Childhood eczema and no known allergy to nickel Case 2 Female 38 years No intolerance to jewelry an no personal or familial history of atopy	Case 1 E-cigarette use for 6 years Case 2 Vapouriser	Case 1 Erythematous scaly patches under the nose and chin Case 2 Ill-defined erythematous patches on the palm of right hand	Case 1 Patch tested, strongly positive to nickel Dimethylglyoxime (DMG) test – positive reaction to the metal compartment on the e-cigarette and the batteries Advised to avoid device Case 2 Patch tested, positive to nickel Dimethylglyoxime (DMG) test – positive to vapouriser pen Advised to avoid device	Case 1 Subsequently reported clear of hand and facial dermatitis Case 2 Patient reported significant improvement of hand dermatitis within 3 months	Low methodological quality Conflicts of interest None declared Funding None received
Case reports						
Azevedo et al., 2019[723] Portugal Hospital department	Female 38 years No known nickel allergy, no personal or familial history of atopy	Patient reported using e-cigarette device around the time of onset of hand dermatitis Cigavapor e-liquid	Erythematous, scaly dermatitis, with lichenification on both hands for previous 6 months	Positive reaction (++) was seen to nickel 5% pet E-cigarette device tested with a dimethylglyoxime (DMG) nickel spot – negative result A positive reaction (+++) was seen only to vaping liquid. The patient reacted strongly (+++) to menthol Treatment not reported	Not reported	Low methodological quality Conflicts of interest Not reported Funding Not reported

4.21 Haematological outcomes

Main conclusions from the synthesised evidence on haematological outcomes of e-cigarette use

- There is no available evidence on the relationship of e-cigarette use to haematological outcomes.

Table 4.21-1 Overview of studies of haematological outcomes identified in the systematic review, by study design

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Haematological outcomes									2 0 / 2

Notes:
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Outcomes

- **Clinical outcomes**: Anaemias, bone marrow failure syndromes, bleeding disorders, polycythaemia, methaemoglobinaemia.

4.21.1 Findings from previous reviews

The NASEM,[3] Public Health England,[11] CSIRO,[14] SCHEER,[4] and USPSTF[16] reviews did not include haematological outcomes as a primary health outcome and no studies were identified and discussed elsewhere.

The Irish Health Research Board literature map[15] identified one case report on haematological outcomes, specifically methaemoglobinaemia, although this was reported under respiratory disease.[337] This case report was also identified in the top-up review.

4.21.2 Summary of conclusions from previous reviews

The Irish Health Research Board literature map[15] did not provide any summative conclusions on the relationship of e-cigarettes to haematological outcomes.

4.21.3 Top-up review

Search results

Overall, two articles were located in the top-up systematic literature search.[337,727] As these studies were case reports, they did not meet eligibility criteria and thus no articles were available for the top-up synthesis of evidence (Table 4.21-1).

One systematic review with findings on haematological outcomes related to e-cigarette use was located in the database search. Tzortzi et al. identified one case report[727] which was also included in the top-up review.[267]

Haematological: clinical outcomes

Two case reports on haematological outcomes were identified. No articles on how e-cigarette use affects clinical haematological outcomes were included in the evidence synthesis.

Meta-analyses

No meta-analyses of the relationship of e-cigarette use to haematological outcomes were located.

Randomised controlled trials

No randomised controlled trials reporting on the relationship of e-cigarette use to clinical haematological outcomes were located.

Cohort studies
No cohort studies reporting on the relationship of e-cigarette use to clinical haematological outcomes were located.

Non-randomised intervention studies
No non-randomised intervention studies reporting on the relationship of e-cigarette use to clinical haematological outcomes were located.

Case-control studies
No case-control studies reporting on the relationship of e-cigarette use to clinical haematological outcomes were located.

Other study types with limited contribution to assessment of the likely causal relationship of e-cigarette use to haematological outcomes
No cross-sectional surveys reporting on the relationship of e-cigarette use to clinical haematological outcomes were located.

Two case reports were identified in the top-up review. Okuni-Watanabe et al.[727] reported on polycythaemia observed in an e-cigarette user and Twohig et al.[337] reported on a case of methaemoglobinaemia in an e-cigarette user. Given the difficulty of attributing causality from individual case reports, these studies are not described further and do not form part of the evidence synthesis.

4.21.4 Summary of findings from top-up review
No studies on the relationship of e-cigarette use to clinical haematological outcomes were identified for evidence synthesis.

4.21.5 Summary of findings integrating evidence from previous reviews and top-up review
Combining evidence from the top-up systematic review with the evidence from previous reviews:

- No studies on the relationship of e-cigarette use to clinical haematological outcomes were identified.

4.21.6 Main conclusions from the synthesised evidence on the haematological health effects of e-cigarette use
- There is no available evidence on the relationship of e-cigarette use to haematological outcomes.

5 Smoking behaviour - smoking uptake and smoking cessation

Main conclusions from the synthesised evidence on the effects of e-cigarette use on smoking uptake and smoking cessation

- There is strong evidence that never smokers who use e-cigarettes are on average around three times as likely than those who do not use e-cigarettes to initiate cigarette smoking.
- There is strong evidence that non-smokers who use e-cigarettes are also around three times as likely as those who do not use e-cigarettes to become current cigarette smokers.
- There is limited evidence that former smokers who use e-cigarettes are more likely to relapse and resume current smoking than former smokers who have not used e-cigarettes.
- There is limited evidence that, in the clinical context, freebase nicotine e-cigarettes may be more efficacious for smoking cessation than existing NRT, and that nicotine e-cigarettes may be more efficacious than no intervention or usual care.
- Trials demonstrating efficacy were limited to products with freebase nicotine concentrations ≤20mg/mL. There is no evidence that nicotine salt products are efficacious for smoking cessation.
- There is insufficient evidence that freebase nicotine e-cigarettes are efficacious for smoking cessation, compared to non-nicotine e-cigarettes or that non-nicotine e-cigarettes are efficacious for smoking cessation compared to counselling or approved NRT.
- There is insufficient evidence that freebase nicotine e-cigarettes are efficacious outside the clinical setting.
- No evidence on nicotine salt products was located and their efficacy for smoking cessation is unknown.
- There is limited evidence that use of nicotine e-cigarettes for smoking cessation results in greater ongoing exposure to nicotine than approved NRT, through ongoing exclusive e-cigarette use or dual use if smoking continues.

5.1 Smoking uptake

This section summarises findings from previous international reviews and a review conducted by The Australian National University, which has been reported previously.[8] Details of the methods are included in the original report.

Outcomes

- **Primary outcomes**: Cigarette smoking initiation in never smokers, cigarette smoking relapse among former smokers.

5.1.1 Findings from previous reviews

The NASEM review reported on 10 observational studies that consistently found a positive association between e-cigarette use and a transition from never to ever combustible cigarette smokers. Four papers were also identified relating to e-cigarette use to combustible smoking frequency.[728-731] Apparent or suggestive dose-response associations were found for most analyses indicating a positive association between more frequent e-cigarette use and increasing smoking frequency and number of cigarettes smoked per day in non-smokers.[3]

The 2018 Public Health England review examined two longitudinal studies on youth and young adult never smokers finding e-cigarette users at baseline were significantly more likely to subsequently try cigarettes. The Public Health England review suggests caution when interpreting findings, due to the observational nature of the data.

The CSIRO review[14] examined 22 studies: eight cohort and 14 cross-sectional surveys. Evidence from the cohort studies demonstrated e-cigarette use was consistently associated with subsequent initiation and/or regular use of conventional cigarettes among teenagers and young adults.[732-739] Evidence from cross-sectional surveys supported this finding, however, adjustment for confounding was omitted in original studies such that findings should be interpreted with caution.[740-752] This pattern was also observed for non-nicotine e-cigarettes albeit with a weaker association. A dose-response relationship was observed such that the probability of smoking initiation increased with higher e-cigarette nicotine concentrations.[14] The CSIRO review also noted the observational nature of the data.

The Irish Health Research Board's systematic review[753] on the effects of e-cigarette use in adolescents on subsequent cigarette smoking included 21 longitudinal cohort studies published between 1 January 2005 and 2 October 2019. The majority of the 21 studies, of which 14 were unique and seven undertook

secondary analyses of existing study data, reported a significant positive association between ever e-cigarette use at baseline and ever cigarette smoking at follow-up. Results from a pairwise meta-analysis found that ever e-cigarette use was associated with smoking initiation at 4-24-month follow-up (OR 4.06; 95% CI 3.00-5.48; moderate to high heterogeneity; nine studies) with all included studies reporting significant positive associations. The evidence was of moderate certainty. Similarly, past-30-day e-cigarette use at baseline was positively associated with initiation of cigarette use (OR 2.14; 95% CI 1.75-2.62; three studies).

The SCHEER review considered four systematic reviews (three of which conducted meta-analyses)[754-756] including prospective cohort evidence. All indicated use of e-cigarettes in non-smokers is associated with subsequent tobacco use. [754 755-757]

The USPSTF review[16] did not examine smoking uptake.

5.1.2 Summary of conclusions from previous reviews

The NASEM review concluded that:

- There is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults.
- 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.
- 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.

The 2018 Public Health England review concluded that:

- E-cigarette use is associated with subsequent smoking in young people.

The 2020 Irish Health Board review[758] concluded that:

- There is evidence of an association between ever using e-cigarettes and the initiation of smoking tobacco cigarettes among adolescents.
- There is moderate confidence in these results using GRADE.

The CSIRO review concluded that:

- There is consistent evidence for a strong relationship between e-cigarette use and subsequent cigarette smoking amongst youth.

The SCHEER review concluded that:

- There is moderate evidence that e-cigarettes are a gateway to smoking for young people.

5.1.3 Umbrella and top-up review, reproduced from Baenziger et al.[8]

Search results

A total of 6,225 studies were identified for title and abstract screening of which 15 studies were included; three[754,755,759] systematic reviews in the umbrella review and 12[149,739,760-767] primary research studies in the top-up review. This led to a total of 25 primary research studies on e-cigarette use and smoking uptake (see original report for PRISMA diagram). No potential competing interests were identified in any study.

Umbrella review

After duplicates were removed, there were 28 primary research articles identified from the three[754,755,759] systematic reviews included in the umbrella review.

Khouja et al.[759] included 17 studies and found a statistically significant increase in the risk of later smoking in ever and current e-cigarette users compared to never users in people aged <30 years (adjusted OR 2.92 (95% CI 2.30 – 3.71). Combining results from three studies in adolescents (aged 10-19) in the UK, Aladeokin and Haighton[755] found e-cigarettes users were markedly more likely to go on to smoke combustible cigarettes (aOR 3.86; 95% CI 2.18 – 6.82, I^2=74). Soneji et al.[754] included nine US longitudinal studies in populations <30 years. Incorporating evidence from seven studies, ever e-cigarette use significantly increased the risk of combustible cigarette smoking in baseline never smokers (OR: 3.83; 95% CI 3.74–3.91; I^2=56%). Combining results from two studies, baseline past 30-day e-cigarette use significantly increased the risk of past 30-day combustible cigarette use at follow-up among those reporting no past 30-day use of cigarettes at baseline (aOR = 4.28; 95% CI 2.52 – 7.27, I^2=0%).

All three[754,755,759] systematic reviews were rated moderate using the AMSTAR2 assessment. Information was lacking in reasoning for excluded studies, stating sources of funding and data extraction.

Top-up review

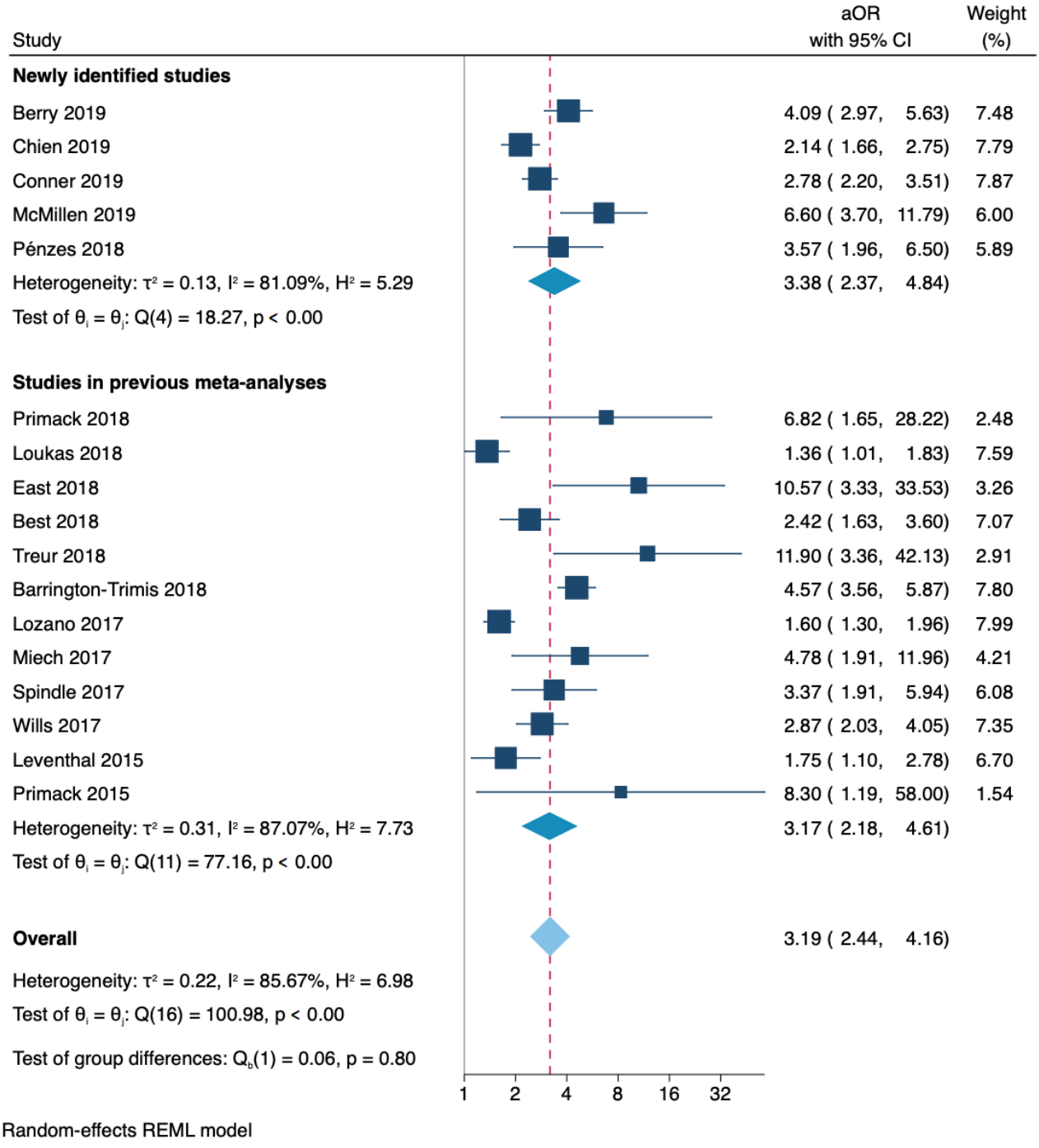
There were 12 studies[149,739,760-769], 10 prospective observational studies and two secondary analyses of randomised controlled trials, identified in the top-up review. Of the 28 studies identified from the three systematic reviews in the umbrella review, 13[730,731,733,735,737,770-777] of these were included in the meta-analyses after 15 studies were excluded due to ineligible study design (n=10) or data overlap (n=5). Therefore, a total of 25 studies have been included in the top-up review meta-analyses.

Cigarette smoking initiation among never smokers at baseline, in relation to e-cigarette use

All five newly-identified studies in the top-up review assessed the association between ever-use of e-cigarettes and ever smoking combustible tobacco cigarettes among never smokers at baseline, except for one[149] which assessed the association between current e-cigarette use and ever smoking combustible tobacco cigarettes among never smokers at baseline. People who used e-cigarettes were significantly more likely than non-users to initiate smoking of combustible cigarettes in all studies, with odds ratios varying substantially from 2.1 to 6.6. The pooled adjusted odds ratios (using a random-effects model) found that e-cigarette use significantly increased the odds of ever smoking combustible cigarettes in never smokers (OR: 3.38; 95% CI 2.37-4.84).

Combining studies from the top-up and umbrella review, people exposed to e-cigarettes were around three times as likely to take up smoking of combustible cigarettes than people who were not exposed to e-cigarettes (aOR: 3.19; 95% CI 2.44 – 4.16; 17 studies) (Figure 5.1-1).

Figure 5.1-1 Forest plot and random-effects meta-analysis for the adjusted odds of smoking initiation at follow-up among never smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline. aOR, adjusted OR; REML, Restricted Maximum Likelihood

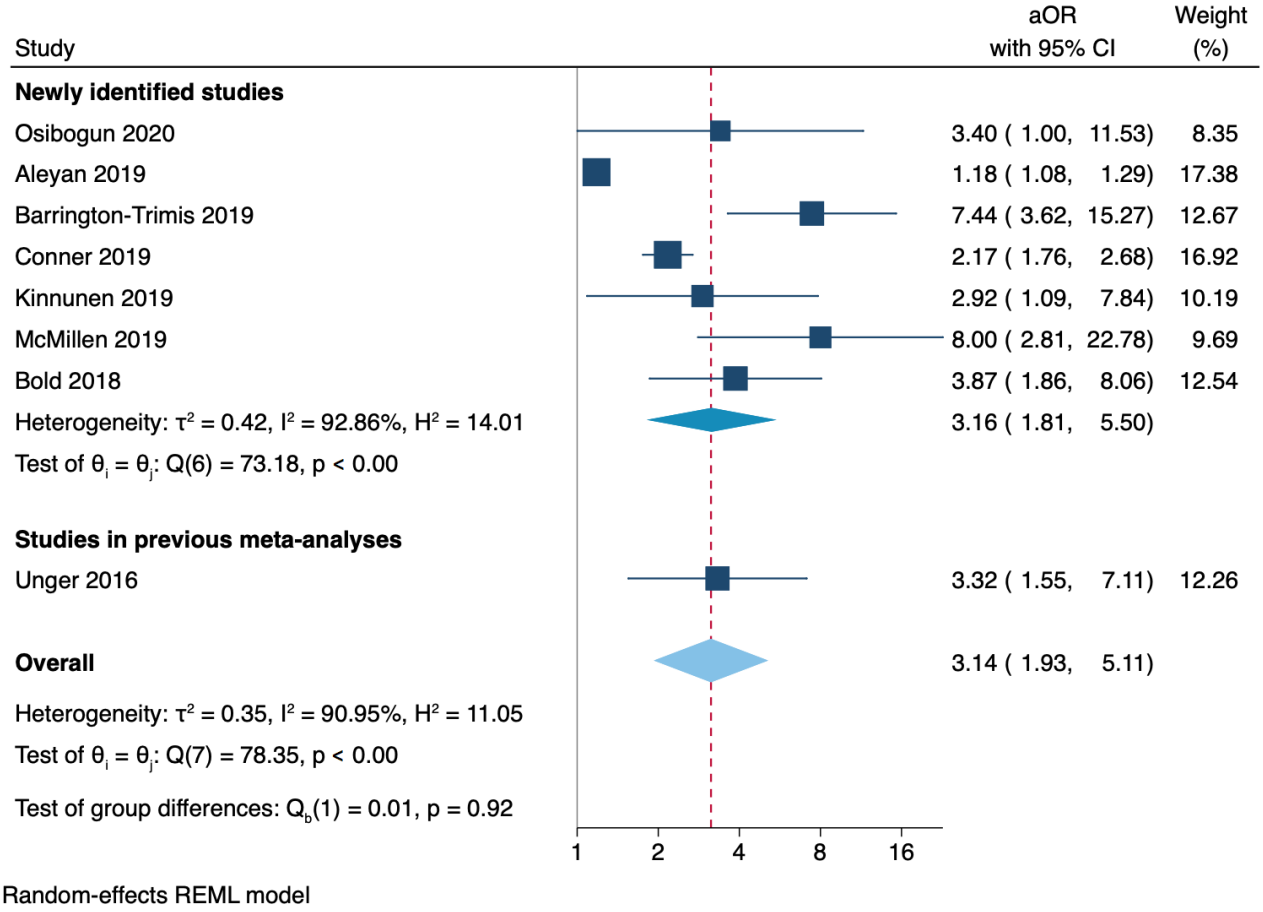


Current (past 30-day) cigarette smoking among non-smokers (never smokers or no past 30-day-use) at baseline, in relation to e-cigarette use

All seven studies newly-identified in the top-up review found e-cigarette users were significantly more likely than non-users (never smokers or no past 30-day use) to initiate current (past 30-day) cigarette smoking of combustible cigarettes, with odds ratios varying substantially from 1.18 to 8.00. The pooled adjusted odds ratios found around a three-fold increase in the odds of current smoking in non-smokers using e-cigarettes compared to non-users (OR: 3.16; 95% CI 1.81-5.50; I^2=93%).

Combining results from the seven newly-identified studies and the one[776] relevant study from the umbrella review, the risk of current smoking in e-cigarette users was around three times larger than those who had not used e-cigarettes in baseline non-smokers (aOR: 3.14; 95% CI 1.93 – 5.11; I^2=91%; eight studies) (Figure 5.1-2).

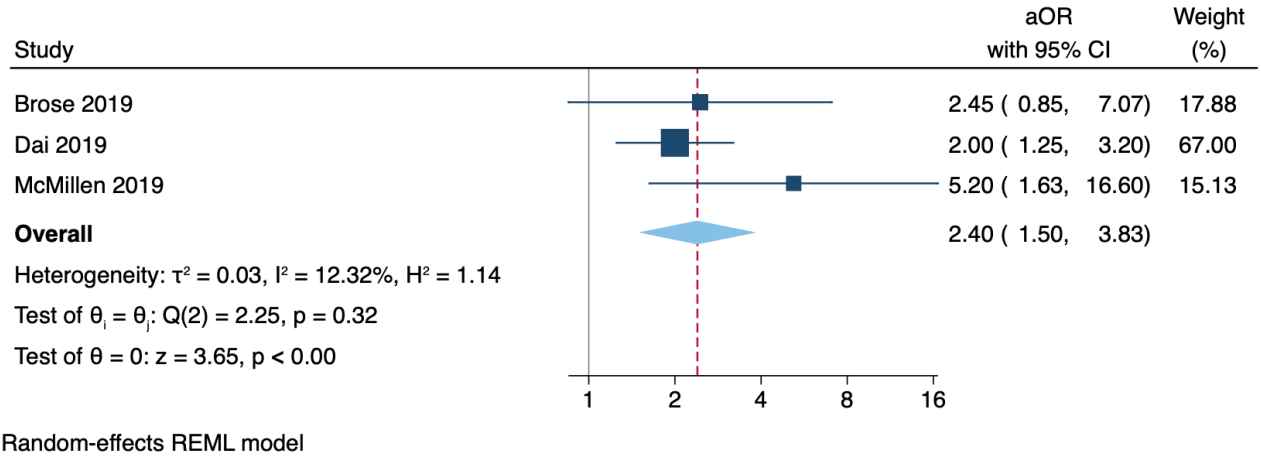
Figure 5.1-2 Forest plot and random-effects meta-analysis for the adjusted odds of current (past 30-day) smoking at follow-up among non-current smokers and current e-cigarette users at baseline compared with non-current e-cigarette users at baseline. AOR, adjusted OR; REML, Restricted Maximum Likelihood



Cigarette smoking relapse among former smokers at baseline, in relation to e-cigarette use

Three[149,768,769] newly-identified studies in the top-up review and none from the umbrella review investigated the odds of relapse to combustible cigarette smoking following the use of e-cigarettes in adult former smokers aged at least 18 years. All found the odd ratios of ever relapse was higher among ever e-cigarette users, compared to never e-cigarette users and varied from 2.00 to 5.20. Additionally, the odds of ever relapse were higher among current e-cigarette users than non-current e-cigarette users. The pooled adjusted odds ratios (using a random-effects model) found that e-cigarette use significantly increased the odds of cigarette smoking relapse in former smokers compared to non-users (OR 2.40; 95% CI 1.50-3.83; I^2=12%; three studies) (Figure 5.1-3).

Figure 5.1-3 Forest plot and random-effects meta-analysis for the adjusted odds of smoking relapse at follow-up among former smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline. aOR, adjusted OR; REML, Restricted Maximum Likelihood



Quality assessment

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale.[778] Of the 12 studies included, totals (out of 10 stars) ranged from 5 to 8. Only one[765] study rated 5, five[739,760,762,766,768] rated 6, two[763,764] rated 7 and four[149,761,767,769] rated 8. No studies received a star for assessment of outcome. The main areas impacting quality assessment scores were ascertainment of exposure and adequacy of follow-up of cohorts (studies with less than 30% loss to follow-up were considered adequate).

5.1.4 Summary of findings from umbrella and top-up review

There were 17 observational studies on smoking initiation among never smokers, finding:

- A three-fold increase in the odds of initiating cigarette smoking in baseline never smokers that use e-cigarettes compared to non-e-cigarette users.

There were eight observational studies on current smoking uptake among non-smokers (never and no past 30-day-use), finding:

- A three-fold increase in the odds of current cigarette smoking in baseline non-smokers that use e-cigarettes compared to non-e-cigarette users.

There were three observational studies on cigarette smoking relapse among former smokers, finding:

- A two-fold increase in the odds of cigarette smoking relapse in former smokers that use e-cigarettes compared to non-e-cigarette users.

Hence:

- There is strong evidence that never smokers who use e-cigarettes are more likely than those who do not use e-cigarettes to initiate cigarette smoking.
- There is strong evidence that non-smokers who use e-cigarettes are more likely than those who do not use e-cigarettes to become current cigarette smokers.
- There is limited evidence that former smokers who have used e-cigarettes are more likely to relapse and resume current smoking than former smokers who have not used e-cigarettes.

5.1.5 Summary of findings integrating evidence from previous reviews and umbrella and top-up review

The following can be concluded from this systematic review of the worldwide evidence on the relationship of e-cigarette use to uptake of smoking of combustible tobacco:

- There is substantial and consistent evidence from observational studies that never smokers who have used e-cigarettes are more likely than those who have not used e-cigarettes to try smoking conventional cigarettes and to transition to becoming regular tobacco smokers.
- On average, the current evidence indicates that never smokers who have used e-cigarettes have around three times the odds of becoming a smoker of combustible cigarettes compared to never smokers who have not used e-cigarettes. Studies consistently observe increased risks of smoking uptake with e-cigarette use, the magnitude of which varies substantially between studies.
- The limited available evidence indicates that former smokers who have used e-cigarettes are more likely to relapse and resume current smoking than former smokers who have not used e-cigarettes.

5.1.6 Main conclusions from the synthesised evidence on the effect of e-cigarette use on smoking uptake

- Based on strong evidence, never smokers who use e-cigarettes are on average around three times as likely as those who do not use e-cigarettes to initiate cigarette smoking.
- There is strong evidence that non-smokers who use e-cigarettes are also around three times as likely as those who do not use e-cigarettes to become current cigarette smokers.
- There is limited evidence that former smokers who have used e-cigarettes are more likely to relapse and resume current smoking than former smokers who have not used e-cigarettes.

5.2 Smoking and nicotine cessation

This section summarises findings from previous international reviews and a review conducted by The Australian National University, which has been reported previously.[10] Details of the methods are included in Appendix 1.

Outcomes

- **Primary outcomes**: Biologically confirmed smoking abstinence after at least four months follow-up, biologically confirmed nicotine cessation.

5.2.1 Findings from previous reviews

The 2018 NASEM review[3] considered evidence published until August 2017 on the effectiveness of e-cigarettes as smoking cessation aids from previous systematic reviews.[3] The review did not examine cessation of nicotine exposure as an outcome. Included systematic reviews used evidence from randomised controlled trials (RCTs), non-randomised intervention studies, cohort and repeated cross-sectional surveys. Of the 17 systematic reviews included, six conducted a formal meta-analysis. The reviews consistently agreed that the available evidence-base was insufficient to definitively answer the question of whether e-cigarettes helped smokers to quit.

The 2018 Public Health England review[11] identified 14 systematic reviews of e-cigarettes for smoking cessation and/or reduction, seven of which included a meta-analysis. Two meta-analyses found a positive effect on cessation for e-cigarette use, four found an inconclusive effect for cessation and one found a negative effect. The 2021 Public Health England review[13] examined evidence published since the 2018 evidence review, and consisted of six systematic reviews and meta-analyses, four RCTs and 13 non-randomised intervention studies. Of the six systematic reviews, three found e-cigarette products containing nicotine were significantly more effective for smoking cessation than NRT (also supported by two non-randomised intervention studies). However, findings of meta-analyses of RCTs were inconclusive regardless of comparator (ENNDS or behavioural support) although when studies of high risk of bias were omitted, pooled results of RCTs indicated that ENDS were more effective.

The 2018 CSIRO review[14] identified four randomised controlled trials, one uncontrolled trial, 10 longitudinal studies and 10 cross-sectional surveys on smoking cessation. The review specifically reviewed Australian evidence, but it was found to be lacking, only citing one Australian observational study.

The 2020 Irish Health Research Board network meta-analysis[753] (based on seven RCTs) found that there was no evidence of a difference in effect in smoking cessation for ENDS (RR 1.17; 95% Credible Interval: 0.61–1.99) or ENNDS (RR 0.65; 95% Credible Interval 0.24-1.42) compared to NRTs.[753] The evidence was low certainty for cessation at 24 or 26 weeks and very low certainty at 52 weeks, driven by small numbers of cessation events and high loss to follow-up.[753]

The 2020 US Surgeon General review[779] also supported NASEM's findings and concluded that there is inadequate evidence on the efficacy of ENDS for smoking cessation and that the rapid evolution of ENDS products and the small number of studies over various contexts introduces uncertainty to the evidence. They also consider the evidence suggestive but insufficient regarding the efficacy of ENDS compared to ENNDS.[779]

The USPSTF published its latest report on smoking cessation in January 2021, concluding that "the evidence on the use of e-cigarettes for tobacco smoking cessation in adults, including pregnant persons, is insufficient, and the balance of benefits and harms cannot be determined."[16,780] This was based on the consideration of five RCTs investigating the effectiveness of e-cigarettes to aid in stop smoking or reduce smoking compared with placebo or NRT.[16,780]

The 2021 SCHEER review[4] considered three previous systematic reviews and a meta-analysis, and two RCTs,[419,679,684,781,782] concluding that there was weak evidence that e-cigarettes were efficacious as an aid for smoking cessation.[4]

The most recent update from the Cochrane systematic review[686] found that ENDS were more efficacious than NRT (RR 1.69; 95% CI 1.25-2.27; I^2= 0.0%; three studies), ENNDS (RR 1.70; 95% CI 1.03-2.81; I^2=0.0%; four studies) and behavioural support (RR 2.70; 95% CI 1.39-5.26; I^2=0.0%; five studies) for smoking cessation using a fixed-effect meta-analysis. Evidence was rated as being of moderate certainty for both the ENDS versus NRT, and ENDS versus ENNDS analyses but low certainty for ENDS versus behavioural support, largely driven by concerns over imprecision.[686]

In their random-effects meta-analysis, Grabovac et al. found ENDS were more efficacious than ENNDS (RR 1.71; 95% CI 1.02–2.84; five studies) and NRTs (RR 1.69; 95% CI 1.25–2.27; three studies), with no significant difference observed for ENDS versus counselling only (RR 2.04; 95% CI 0.90–4.64; two studies).[783] The evidence for ENDS compared to ENNDS was judged to be of moderate certainty and for ENDS compared to NRT or behavioural support it was rated as low certainty.[783] Using a network meta-analysis, Chan et al. found that participants randomised to ENDS were more likely to achieve abstinence than those randomised to NRTs (RR 1.49; 95% CI 1.09-2.04; four studies) and to ENNDS and/or usual care (RR 2.09; 95% CI 1.46-2.99; five studies).[784] When comparing the efficacy of ENDS to conventional therapy (NRTs and usual care) across nine RCTs using a random-effects meta-analysis, Wang et al. found participants receiving free ENDS were 1.55 times as likely to achieve smoking abstinence (95% CI 1.173-2.061).[785] Zhang et al. conducted a random-effects meta-analysis and reported that ENDS may be superior to NRTs and/or placebo for smoking cessation (RR=1.55; 95% CI 1.00–2.40; I^2=57.6%; 5 studies) although evidence was low certainty.[756]

5.2.2 Summary of conclusions from previous reviews

The NASEM review,[3] including randomised controlled trials and observational studies, concluded that:

- Overall, there is limited evidence that e-cigarettes may be effective aids to promote smoking cessation.
- There is moderate evidence from randomised controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation.
- There is insufficient evidence from randomised 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.
- 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 an increased likelihood of cessation.

The 2018 Public Health England review[11] concluded that:

- No conclusion regarding the efficacy of e-cigarettes for smoking cessation was provided.

The 2021 Public Health England review[13] concluded that:

- There is stronger evidence, since the previous report that nicotine vaping products are an effective aid to cessation and reduction.

The CSIRO review[14] concluded that:

- The effectiveness of this method [e-cigarettes] compared with other smoking cessation methods is not known.

The Irish Health Research Board[753] meta-analysis concluded that:

- There is no evidence of a difference in effect [between electronic nicotine delivery systems (e-cigarettes) and therapies usually given for smoking cessation] on incidences of smoking cessation. There is a low-level of certainty in these results.

The SCHEER review[4] concluded that:

- There is weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit.

The USPSTF review[16,780] concluded that:

- The evidence on the use of e-cigarettes for tobacco smoking cessation in adults, including pregnant persons, is insufficient, and the balance of benefits and harms cannot be determined.

The US Surgeon General review[779] concluded that:

- The evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation. However, the evidence is suggestive but not sufficient to infer that the use of e-cigarettes containing nicotine is associated with increased smoking cessation compared with the use of e-cigarettes not containing nicotine.

5.2.3 Findings from the systematic review

Search results

Of the 6,552 titles identified for screening, 11 RCTs of ENDS and three RCTs of ENNDS were identified that examined smoking cessation as an outcome (see original report for PRISMA diagram).[10] There were no RCTs that examined nicotine cessation as their primary outcome. A total of 5,901 smokers were randomised in studies conducted from 2013-2020; 347 achieved smoking cessation at follow-up. RCTs were of nicotine in freebase form; no trials of nicotine salt products were identified.

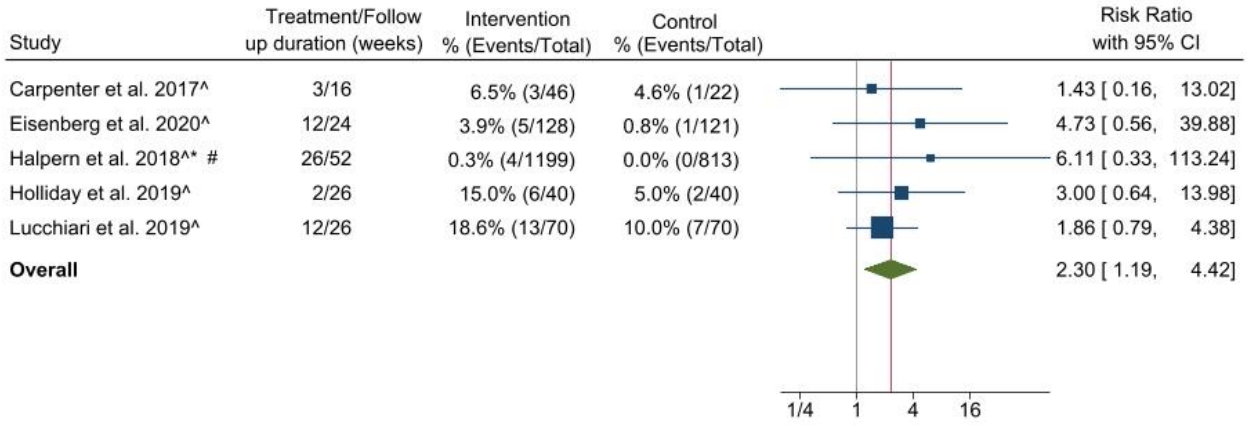
One analysis, nicotine e-cigarettes plus NRT versus other comparators which included two studies,[684,692] was not reproduced in this report and can be located in the original report[10].

Nicotine e-cigarettes versus no intervention or usual care

Five RCTs compared ENDS to no intervention or usual care.[681,695,698,712,786] These studies randomised a total of 2,549 participants, of whom 42 achieved sustained smoking cessation. None were funded directly by the tobacco or e-cigarette industry, nor were there any reported potential competing interests for the authors of the studies. Halpern et al. reported receiving e-cigarettes donated by an e-cigarette company.[786]

No individual study reported a significant difference in cessation outcomes between randomised groups. Results from the random-effects meta-analysis found a significant difference at four-to-12-month follow-up (RR 2.30; 95% CI 1.19-4.42; I^2=0.0%) (Figure 5.2-1) and at six-month follow-up (RR 2.40; 95% CI 1.21-4.78). This conclusion did not change materially when a fixed-effects model was used (RR 2.46, 95% CI 1.28-4.71). Nor did it change substantively when the random-effects meta-analysis was restricted to studies with no noted potential competing interests (RR 2.18; 95% CI 1.11-4.27; I^2=0.0%), although evidence was even more limited, with 27 of 284 participants ceasing smoking. Four of the included studies were assessed as having a high risk of bias, one was judged to be at high risk for measurement of the outcome[681] and the other three judged high risk for missing outcome data.[698,712,786] One study was found to have concerns in two domains – deviations from intended intervention and missing data.[695] The GRADE rating for this comparison was very low.

Figure 5.2-1 Biochemically verified sustained smoking cessation in smokers randomised to nicotine e-cigarettes versus no intervention or usual care: random-effects meta-analysis



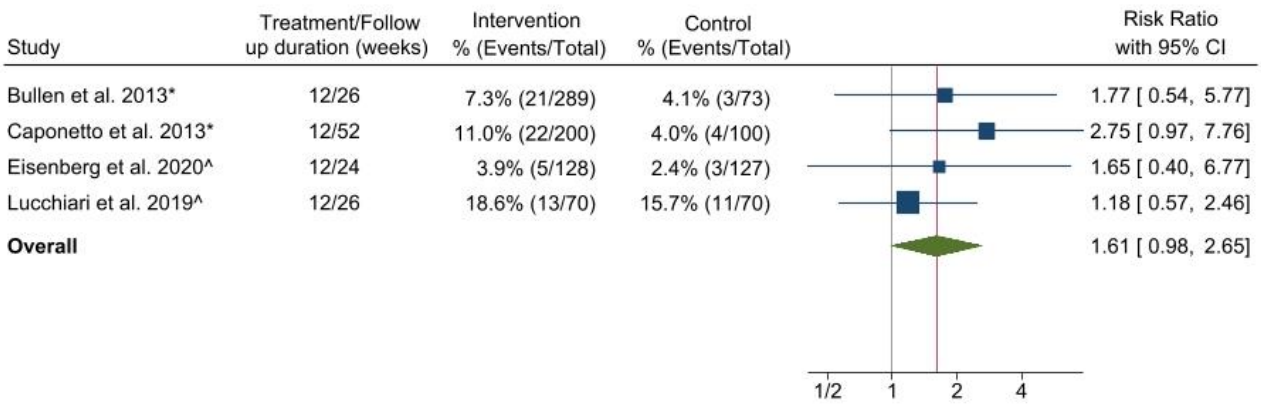
* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
# RR is undefined due to zero events in the control group. RR estimated by applying the continuity correction (adding 0.5 to each cell of the 2x2 table)
Total cessation events: 31/1483 in intervention group, 11/1066 in control group
Heterogeneity: Tau^2=0.00; Chi^2= 1.40, df=4, p = 0.84; I^2 =0.0%; Test for overall effect: Z=2.49, p=0.01

Nicotine e-cigarettes versus e-cigarettes which do not deliver nicotine

Four RCTs compared smoking cessation outcomes in participants randomised to ENDS and ENNDS (considered a placebo).[147,680,695,712] These trials reported a total of 82 participants ceasing smoking out of 1,057 randomised. No studies were directly funded by the tobacco or e-cigarette industry. Bullen et al.[680] had a study author who reported previously receiving research funding from an e-cigarette manufacturer and Caponnetto et al.[147] had a study author who had received funding from the tobacco industry.[787] Both studies reported using e-cigarettes donated by an e-cigarette company.[147,680]

No statistically significant difference between ENDS and ENNDS was found in any study. The random-effects summary rate ratio for smoking cessation at six-to-12-month follow-up in those randomised to ENDS versus ENNDS was 1.61, with no statistically significant difference between the groups (95% CI 0.98-2.65; I^2=0.0%) (Figure 5.2-2). The finding became significant using fixed-effects meta-analysis (RR 1.70, 95 % CI 1.03-2.81) but did not change materially when restricted to six-month follow-up only (RR 1.56; 95% CI 0.96-2.53). Two of the included studies were assessed as having a high risk of bias due to missing outcome data[681,712] and the remaining two were considered to raise "some concerns" due to deviations from the intended intervention and missing outcome data. [680,695] The GRADE rating for this comparison was very low. Restricting the evidence to that without known potential competing interests, two studies remained with a summary RR of 1.27 (95% CI 0.66-2.43) for cessation in smokers randomised to ENDS versus ENNDS, based on 395 participants, 32 of whom quit successfully.[695,712]

Figure 5.2-2 Biochemically verified sustained smoking cessation in smokers randomised to nicotine e-cigarettes versus non-nicotine-e-cigarettes: random-effects meta-analysis



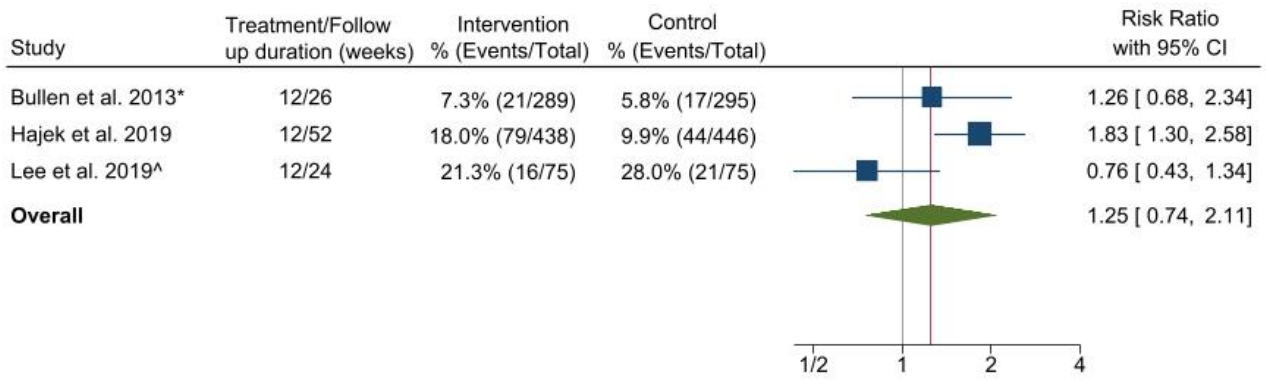
* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total events: 61/687 in intervention group, 21/370 in control group
Heterogeneity: Tau^2=0.00; Chi^2= 1.73, df=3, p = 0.63; I^2 =0.00%; Test for overall effect: Z=1.87, p=0.06

Nicotine e-cigarettes versus other nicotine replacement therapy

Three RCTs were identified that compared ENDS to approved NRT.[419,680,682] They included a total of 1,618 participants, all of whom were smokers motivated to quit and were randomised to 12-week treatment programs; 198 achieved smoking cessation at greater than four-month follow-up. Bullen et al.[680] had the potential competing interests noted above; no other studies had reported competing interests.

Of the three studies, two reported no statistically significant difference between ENDS and approved NRT[680,689] and the other found significantly greater cessation in those randomised to ENDS[419]. Results from the random-effects meta-analysis found that there was no statistically significant difference in the efficacy of ENDS compared to approved NRT for smoking cessation at six-to-12-month follow-up, with substantial variation in these results (RR 1.25; 95% CI 0.74-2.11; I^2=69.0%) Figure 5.2-3). This finding was statistically significant using fixed-effects meta-analysis (RR 1.44; 95% CI 1.10-1.87). The conclusion from the random-effects model did not substantially change when the meta-analysis was limited to studies with no noted potential competing interests (RR 1.22; 95% CI 0.52-2.86; I^2=85.1%), although evidence was even more limited, with 160 of 1,034 participants ceasing smoking. The summary rate ratio at six-month follow-up was similar to that incorporating 12-month results (RR 1.18; 95% CI 0.82-1.70). One study was judged to be at a low risk of bias across all domains,[419] one was judged to have some concerns due to deviations from the intended interventions[680] and the last was judged high risk due to missing outcome data.[682] The GRADE rating for this comparison was very low.

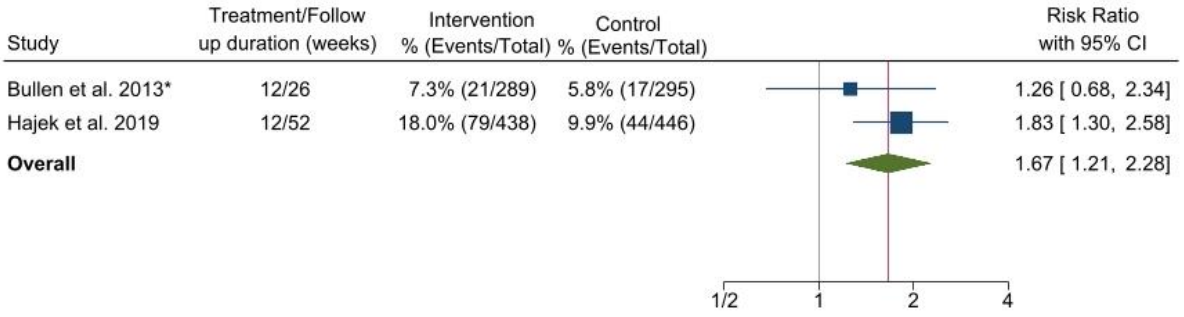
Figure 5.2-3 Biochemically verified sustained smoking cessation in smokers randomised to nicotine e-cigarettes versus other nicotine-replacement therapy: random-effects meta-analysis



* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total events: 116/802 in intervention group, 82/816 in control group
Heterogeneity: Tau2=0.15; Chi2= 6.85, df=2, p = 0.03; I2 =69.0%; Test for overall effect: Z=0.85, p=0.4

Following the *a priori* protocol, e-cigarettes were considered ENDS if they contained any amount of nicotine. However, an analysis was conducted restricted to studies with e-cigarettes delivering a dose of nicotine comparable that of other NRT to support smoking cessation. When ENDS nicotine concentration was considered, two studies[419,680] remained comparing the efficacy of ENDS to NRT. The results from the random-effects meta-analysis found that a statistically significant difference in the efficacy of ENDS compared to NRTs (RR 1.67; 95% CI 1.21-2.28; I^2=5.48%)(Figure 5.2-4) derived from 161 of 1,468 participants ceasing smoking. This finding did not substantially change when limited to six-month follow-up (RR 1.39; 95% CI 1.15-1.69). When the meta-analysis was limited to studies with no potential competing interests, only one study[419] remained, reporting a statistically significant difference in the efficacy of ENDS compared to NRT (RR 1.83; 95% CI 1.30-2.58). The summary risk ratio did not change materially using a fixed-effect meta-analysis (RR 1.67; 95% CI 1.24-2.25). One of the studies was judged to be at a low risk of bias[419] and the other to have some concerns.[680] The GRADE rating for this comparison was low.

Figure 5.2-4 Biochemically verified sustained smoking cessation in smokers randomised to nicotine e-cigarettes (nicotine concentration >0.01 mg/mL) versus other nicotine-replacement therapy: random-effects meta-analysis



* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total events: 100/727 in intervention group, 61/741 in control group
Heterogeneity: Tau^2=0.00; Chi^2= 1.06, df=1, p = 0.30; I^2 =5.48%; Test for overall effect: Z=3.17, p=0.00

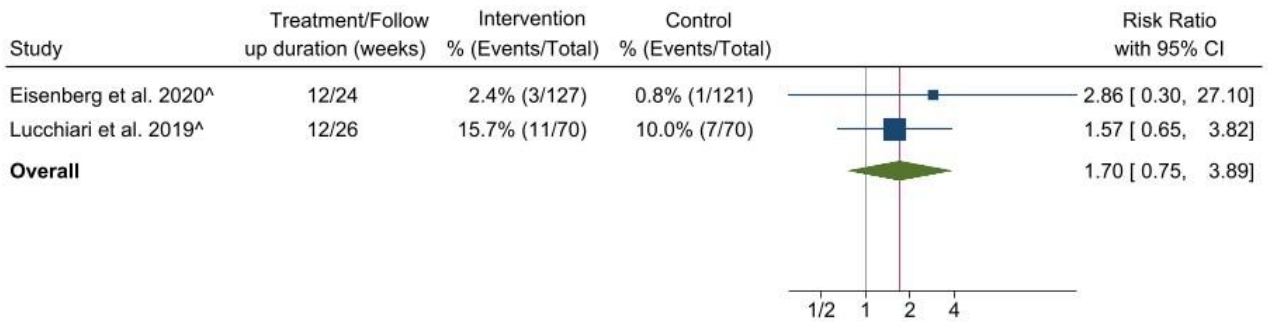
Non-nicotine e-cigarettes plus counselling versus counselling alone

Two RCTs were identified that compared ENNDS plus counselling to counselling alone.[695,712] The studies were conducted between 2019 and 2020 in Italy and in Canada. There was a total of 388 participants, all of whom received a 12-week treatment program and were followed for six months; 22 achieved smoking cessation at greater than four-month follow-up. Neither study had any potential competing interests.

No statistically significant difference between ENNDS and counselling only was found in either study at 24-26-week follow-up. The random-effects summary rate ratio for smoking cessation at six-month follow-up in those randomised to ENNDS versus counselling only was 1.70, with no statistically significant difference between the groups (95% CI 0.75-3.89; I^2=0.0%) (Figure 5.2-5). The result did not change materially using a fixed-effects model (RR 1.74; 95% CI 0.76-3.96). One was judged to be at high[712] risk of

bias and the other was judged to have some concerns[695] driven by missing outcome data in both studies. The GRADE rating for this comparison was very low.

Figure 5.2-5 Verified smoking cessation in smokers randomised to non-nicotine e-cigarettes compared to counselling alone



^ RRs are calculated from number of events or percentages reported in the published study Total events: 14/197 (7.11%) in intervention group, 8/191 (4.12%) in control group; absolute difference 29.2 more per 1,000 (10.5 less to 121.0 more) Heterogeneity: Tau2=0.00; Chi2= 0.24, df=1, p = 0.63; I2 =0.00%; Test for overall effect: Z=1.26, p=0.21

Non-nicotine e-cigarettes versus other nicotine replacement therapy

One study was identified that compared ENNDS to approved NRT. In the previously mentioned RCT from New Zealand, Bullen et al. found 4.12% (3/73) randomised to ENNDS and 5.76% (17/295) randomised to patches achieved smoking cessation at six-month follow-up (RR 0.71; 95% CI 0.21-2.37).[680] This study had potential competing interests and was judged to have some concerns in the risk of bias assessment. The GRADE rating for this comparison was very low.

Use of ENDS and nicotine cessation

There was limited evidence on the efficacy of ENDS as an aid to nicotine cessation, with no RCTs including this as an *a priori* outcome. Five RCTs contained data on nicotine cessation: two with[680,684] and three without[419,681,692] competing interests noted. These RCTs involved 2,773 smokers, 232 of whom quit during the follow-up period. Considering the data that are available, smokers using e-cigarettes were substantially more likely to be using nicotine in any form (combustible cigarettes, ENDS or approved NRT) at six-to-12-month follow-up, or to be using ENDS or NRT, than smokers who used approved forms of NRT. There were insufficient data to compare ENDS and no intervention. Restricting data to studies without potential competing interests had no material effect on the conclusions.

Quality assessment

Eight of the 11 studies were found to have a high risk of bias,[147,681,682,684,692,698,712,786] two raised some concerns,[680,695] and one was found to have a low risk of bias.[419] Risk of bias did not appear to vary according to whether or not the study had noted potential competing interests. The quality of the evidence using GRADE was rated as very low in six comparisons, driven by concerns in risk of bias and imprecision. Only ENDS (nicotine concentration <0.01mg/mL) versus NRT was rated low. The overall GRADE rating was very low.

Additional evidence identified post-search

An additional small RCT was identified after completion of the search and meta-analyses, comparing nicotine e-cigarettes to NRT within a single UK National Health Service stop-smoking service. This trial recruited 135 smokers attending the service or via social media who had not managed to quit using routine treatment. After six months, 19.1% (13) of those in the e-cigarette arm and 3.0% (2) of those in the NRT arm had validated smoking cessation (RR=6.4, 95% CI 1.5-27.3, p=0.01). Participants in the e-cigarette arm were free to use devices and nicotine concentrations of their choosing, up to the EU limit of 20mg/mL, with a median concentration of 10mg/mL at one-week follow-up, reducing to 6mg/mL at six months. At six month follow-up, 47% of ENDS users and 10% of NRT users were still using their allocated products.[711]

5.2.4 Summary of findings from systematic review

There were five RCTs comparing freebase ENDS to no intervention or usual care, finding:

- No statistical difference in cessation outcomes between the groups.

There were four RCTs comparing freebase ENDS to ENNDS (placebo), finding:

- No statistical difference in cessation outcomes between the groups.

There were three RCTs comparing freebase ENDS to no intervention or usual care, finding:

- No statistical difference in cessation outcomes between the groups.

- When restricted to studies with a nicotine concentration >0.01mg/mL, a statistically significant difference in smoking cessation with randomisation to freebase ENDS compared to NRT.

There were two RCTs comparing ENNDS plus counselling to counselling alone, finding:

- No statistical difference in cessation outcomes between the groups.

There was one RCT comparing ENNDS to NRT, finding:

- No statistical difference in cessation outcomes between the groups.

There were five RCTs with evidence on use of freebase ENDS and nicotine cessation, finding:

- Smokers using e-cigarettes were substantially more likely to be using nicotine in any form (combustible cigarettes, ENDS or approved NRT) at six-to-12-month follow-up, or to be using ENDS or NRT, than smokers who used approved forms of NRT.

Hence:

- There is limited evidence that freebase nicotine e-cigarettes may be more efficacious for smoking cessation than existing NRT, in the clinical context, and that nicotine e-cigarettes may be more efficacious than no intervention or usual care.
- There is insufficient evidence that nicotine e-cigarettes are efficacious for smoking cessation, compared to non-nicotine e-cigarettes.
- There is insufficient evidence that non-nicotine e-cigarettes are efficacious for smoking cessation, compared to counselling or approved NRT.

5.2.5 Summary of findings integrating evidence from previous reviews and top-up review

Combining evidence from the top-up systematic review with the evidence from previous reviews:

- The evidence on the efficacy of nicotine e-cigarettes and non-nicotine e-cigarettes for smoking cessation was limited.
- Based on random-effects meta-analyses of the current limited evidence, no significant benefit for smoking cessation of freebase electronic nicotine delivery systems (ENDS) versus electronic non-nicotine delivery systems (ENNDS) or approved nicotine replacement therapy (NRT) was detected. Significantly greater quit rates in smokers randomised to freebase ENDS versus ENNDS and approved NRT were found using a fixed-effects meta-analysis. The certainty of the evidence for these comparisons was rated as very low.
- Based on low certainty evidence, e-cigarettes delivering freebase nicotine at doses likely to be used in the clinical setting were significantly more efficacious than standard NRT for smoking cessation.
- The one RCT rated as having a low risk of bias was conducted within clinical smoking cessation services and found a significant benefit of freebase ENDS for smoking cessation compared to approved NRT. An additional smaller trial, in the same setting and published after the search date, also found a significant benefit. These two trials were limited to nicotine concentrations ≤20mg/mL. The larger trial reported that, where data were available, mean nicotine concentrations were 18mg/mL, 12mg/mL and 8mg/mL at 4, 26 and 52 weeks, respectively, and the smaller trial reported use of median nicotine concentrations of 10mg/mL at commencement and 6mg/mL at six-month follow-up.
- Trial participants randomised to ENDS had significantly greater quit rates than participants randomised to no intervention or usual care, based on very low certainty evidence. The difference remained statistically significant in both the random-effects and fixed-effects meta-analyses.
- Studies on the efficacy of non-nicotine e-cigarettes for smoking cessation found no statistically significant benefit of ENDS versus approved NRT or ENNDS plus counselling versus counselling only. The certainty of this evidence was rated as very low.
- Considering the very limited available data, smokers using nicotine e-cigarettes were substantially more likely to be using nicotine in any form at six-to-12-month follow-up than smokers who used approved forms of NRT. In smokers randomised to ENDS, dual ENDS use and combustible smoking was more common than quitting, at trial completion.
- The overall certainty of the evidence was rated as very low.
- Considering only studies without potential competing interests and those with at least six months of follow-up further limited evidence but did not materially change conclusions.

5.2.6 Main conclusions from the synthesised evidence on the effects of e-cigarette use on smoking behaviour

- There is limited evidence that, in the clinical context, freebase nicotine e-cigarettes may be more efficacious for smoking cessation than existing NRT, and that nicotine e-cigarettes may be more efficacious than no intervention or usual care.

- Trials demonstrating efficacy were limited to products with freebase nicotine concentrations ≤20mg/mL. There is no evidence that nicotine salt products are efficacious for smoking cessation.
- There is insufficient evidence that nicotine e-cigarettes are efficacious for smoking cessation, compared to non-nicotine e-cigarettes.
- There is insufficient evidence that non-nicotine e-cigarettes are efficacious for smoking cessation compared to counselling or approved NRT.
- There is insufficient evidence that nicotine e-cigarettes are efficacious outside the clinical setting.
- No evidence on nicotine salt products was located and their efficacy for smoking cessation is unknown.
- There is limited evidence that use of nicotine e-cigarettes for smoking cessation results in greater ongoing exposure to nicotine than approved NRT, through ongoing exclusive e-cigarette use or dual use if smoking continues.
- The overall certainty of the evidence was rated as very low and more reliable, large-scale randomised evidence is needed.

6 Discussion

6.1 Overview of main findings

The current worldwide evidence indicates that use of electronic cigarettes (e-cigarettes) increases the risk of certain adverse health outcomes. There is conclusive evidence that nicotine e-cigarettes and their constituents can cause poisoning, injuries and burns, and immediate toxicity through inhalation, including seizures, and moderate evidence they cause less serious adverse events, such as throat irritation and nausea. There is conclusive evidence that e-cigarettes cause acute lung injury (EVALI), largely linked to e-liquids containing THC and vitamin E acetate, although around 1 in 8 cases in the largest study to date were from reported use of nicotine-only products. Their environmental impacts include waste, fires and indoor airborne particulate matter, which, in turn, are likely to have adverse health impacts, the extent of which cannot be determined.

Nicotine is highly addictive and there is clear evidence of widespread use and addiction, particularly among youth, in many countries.

There is insufficient evidence regarding ceasing smoking and switching completely to e-cigarettes with respect to exacerbations of respiratory disease or changes in respiratory symptoms, lung function and other respiratory measures. There is limited or insufficient evidence that use of ENDS in non-smokers leads to acute reductions in lung function and other respiratory measures. Among smokers, there is moderate evidence that use of ENDS increases heart rate, systolic blood pressure, diastolic blood pressure and arterial stiffness acutely after use.

As summarised in our previous reviews, there is strong evidence that e-cigarettes increase the uptake of combustible smoking in non-smokers, particularly youth, and limited evidence that freebase nicotine e-cigarettes are efficacious in the clinical setting as an aid to smoking cessation.[8,10,788] There is limited evidence that ex-smokers who use e-cigarettes have around double the likelihood of relapse to resuming smoking than ex-smokers who do not use e-cigarettes.

A central finding of this systematic review is the paucity of evidence regarding health outcomes from e-cigarette use. While certain more immediate risks can be identified from the current evidence, the impact of nicotine e-cigarettes on a wide range of important health outcomes – including cancer, cardiovascular, metabolic, mental health, developmental, reproductive and neurological outcomes other than seizures – is not known, as reliable evidence is lacking. The evidence that is available relates largely to common health outcomes discernible within months or years of commencing use – such as effects on smoking behaviour – and acute outcomes where causality between exposure to e-cigarettes and the health event is apparent at the individual or group level – such as poisonings, burns, nicotine toxicity and EVALI. The health impacts of dual smoking and e-cigarette use – the commonest pattern of use – are not known.

Reliable evidence relating to common clinical health outcomes such as cancer, cardiovascular disease and mental health problems requires high-quality large-scale short and long-term studies and statistical comparisons between those exposed and not exposed to e-cigarettes. It also requires studies where the effects of e-cigarettes can be reliably distinguished from those of tobacco smoking and that are independent of competing interests. Studies must also relate directly to the outcomes of interest and be capable of providing evidence relevant to causality. Overall, across 20 outcomes groups, there were 143 studies relating to primary clinical disease outcomes (Appendix 5). Studies were generally small and short-term and did not permit reliable conclusions to be drawn regarding the relationship of e-cigarette use to these outcomes. In this review, we have also included commentary on physiological and other outcome types and other study types for completeness. However, these should not be interpreted as providing reliable evidence on the causal relationship of e-cigarettes to clinical disease outcomes.

6.2 Safety considerations

Establishing safety requires large-scale studies capable of both detecting and, crucially, excluding risks of public health importance. Considering the scale of exposure to e-cigarettes, relative increases in risks of important clinical outcomes outlined above in users versus non-users of the order of 10-20% need to be detectable – or able to be excluded – to establish safety. The current evidence falls short of this by a wide margin. It is therefore not possible to characterise the safety of e-cigarettes with respect to a wide range of important short- and long-term health outcomes and hence it is not possible to reliably determine their overall safety with respect to health. Given the relatively widespread global use of e-cigarettes in children and adolescents, and among women of childbearing age, the lack of evidence regarding developmental and reproductive outcomes is particularly problematic.

6.3 Mechanisms

ENDS deliver nicotine, along with a range of other compounds – including propylene glycol, vegetable glycerine, flavours, tobacco-specific nitrosamines, volatile organic compounds, phenolic compounds, flavourings, tobacco alkaloids, aldehydes, free radicals, reactive oxygen species, furans and metals[4] – to the lungs and mucosa of the respiratory tract and, via these, to the bloodstream and organs throughout the body. There are multiple mechanisms likely to contribute to the adverse outcomes linked to use of e-cigarettes. Poisoning, addiction, toxicity from inhalation and certain cardiovascular effects are likely to be chiefly caused by nicotine. Trauma, burns and fires are largely attributable to malfunctioning lithium batteries. Environmental effects relate to multiple aspects of e-cigarette devices and other paraphernalia. Toxicological data suggest that multiple other chemicals are likely to contribute to health effects, but the extent and nature of these effects are currently unknown.

Nicotine is one of the most addictive substances known[789] and there is currently substantial evidence that e-cigarettes are capable of causing dependency in non-smokers and that they increase smoking uptake by an average of around three-fold. It should be noted that the evidence relates to products available at the time of the studies and largely predates those delivering higher doses of nicotine more rapidly, such as nicotine salt products. Nicotine is also highly toxic, with a potentially lethal dose of 5mg per kilogram.[789] Accidental and intentional poisoning from nicotine in e-cigarette e-liquids is an identified risk of these products, which is increased with increasing nicotine concentrations and "at home" preparation of e-liquids.[97] They have also been demonstrated to cause immediate toxicity through inhalation – such as seizures. Children are particularly vulnerable to poisoning. In discussing a case-report of poisoning, the authors note:

> "Although nicotine toxicity is not a new phenomenon, the emergence of electronic cigarettes has spawned a market for highly concentrated liquid nicotine. This phenomenon has resulted in unprecedented access to potentially toxic doses of nicotine and other harmful compounds in the home."[622]

There is conclusive evidence that use of e-cigarettes can cause acute lung injury (EVALI). Such illness appears to be largely the result of inhalation of aerosolised e-liquids containing THC with or without vitamin E acetate – identified in 82% of cases reported to the US CDC. However, 14% of cases of EVALI reported use of nicotine products only,[363] so such adverse events from other e-liquid components are also likely. Recently, a case report of EVALI in Australia was published, relating to a 15-year-old reporting use of a prefilled e-cigarette device just prior to becoming ill. The e-liquid in this device was found on analysis to contain glycerol, nicotine and flavouring agents ethyl-maltol and menthol; no THC or vitamin E acetate was detected.[445] The exact mechanism underlying EVALI is unclear, with suggestions that it may be the result of airway-centred chemical pneumonitis.[341,790] There is insufficient evidence that use of e-cigarettes may be associated with an increased risk of other respiratory illnesses, such as asthma and bronchitis and, although toxicological and other data would support a link, methodological issues – particularly separating e-cigarette impacts from those of smoking – hamper the interpretation of these findings.

6.4 Implications for public health, clinical practice and research

Tobacco smoking is exceptionally harmful to health and quitting brings commensurate benefits. The goal of smoking cessation is complete abstinence. Even so-called "light smoking" – including smoking fewer than 10 cigarettes per day – carries large health risks. This includes a doubling in cardiovascular mortality and over nine-fold risks of lung cancer compared to never smoking.[20,21] The commonest pattern of use of e-cigarettes is dual use in combination with smoking. Evidence on the direct health effects of dual use is lacking. In terms of indirect effects, such use appears to help smokers to offset important tobacco control measures – for example, by being cheaper and more socially acceptable than smoking, by permitting use where smoking is banned and by being perceived as less harmful to health (see Section 3.5). Reducing the number of cigarettes smoked is also a common reason given for e-cigarette use among smokers. If dual use results in prolongation of smoking, the net impact may well be harmful, even if the number of cigarettes smoked per day is reduced, as noted by the WHO:

> "…modest prolongation of duration of use may overwhelm the effect of a substantial reduction in intensity of exposure in determining the risk for individual smokers. Therefore, a product with lower levels of toxic emissions (e.g., smokeless product) which enabled a person to continue his or her use of a more toxic product (e.g., cigarette) may result in increased harm if cessation of the more toxic product is delayed." [791]

Effective tobacco control relies on a framework approach, incorporating population-level measures such as taxation, restrictions on advertising, avoidance of tobacco company interference in government and elsewhere, limitations on places where people can smoke, mass media and health warnings, as well as

measures supporting individuals to quit.[792] Increasingly, low smoking prevalence is driven by lack of smoking uptake, especially among youth.[109] The substantial majority of smokers – around two-thirds to three-quarters – who quit successfully do so unaided;[793-796] a minority will seek health professional support. Among those seeking additional support, a range of evidence-based interventions are available, including those based on registered therapeutic goods, which do not share the harms and uncertainties of e-cigarettes. The findings from our previous review indicate limited evidence that e-cigarettes are efficacious as an aid to smoking cessation. The evidence that is available is in the clinical environment – it does not support widespread use of e-cigarettes as a consumer product. The review also found evidence that use of nicotine e-cigarettes results in more prolonged exposure to nicotine than use of approved nicotine replacement therapies. For example, in the highest quality randomised controlled trial of e-cigarettes versus nicotine replacement therapy, among participants who had abstained from tobacco smoking for one year, 80% of those in the nicotine e-cigarette group were continuing to use nicotine e-cigarettes while 9% of those in the approved nicotine replacement group were continuing to use nicotine replacement.[419]

Evidence on the balance of risks and benefits of an exposure is fundamental to determining appropriate regulatory measures, including use in consumer or therapeutic settings. The balance of risks and benefits of e-cigarettes, and regulatory options, will be explored more fully in our forthcoming *Public Health Assessment of Electronic Cigarettes;* they are considered briefly below.

A number of risks and no direct benefits of e-cigarettes were identified. While many of the risks related to e-cigarettes apply broadly to those using them, the population, comparator and nature of use will influence the absolute balance of harms and benefit relating to e-cigarettes. Furthermore, exposure to nicotine from e-cigarettes is highly variable, according to device and e-liquid characteristics, as well as user behaviour and characteristics. The risks identified in this summary of worldwide evidence apply to the general population – regardless of smoking status – apart from increased risk of combustible smoking uptake in non-smoking e-cigarette users and dual use in smokers. There is also virtually complete uncertainty about a range of important outcomes.

Among non-smokers, there is strong evidence that use of e-cigarettes is harmful to health overall in that multiple health harms and no health benefits were identified in this population. Given the evidence regarding the direct health risks of e-cigarette use, the evidence that they generate new tobacco smokers – with established high levels of harm – the uncertainty about major health outcomes, and the importance of low smoking uptake as a driver of progress against tobacco, use of e-cigarettes in non-smokers, especially youth, represents a serious public health risk.

These risks are reinforced by the fact that use by children and adolescents is increasing rapidly in many parts of the world.[38,96] Youth is the time when risk behaviours – including long-term tobacco use – are established, as well as being a period of rapid brain development and vulnerability. Current global patterns of e-cigarette use cause, and are the consequence of, large-scale nicotine addiction in young people – a negative outcome in itself – with contextual evidence for this review indicating likely effects on future addiction and brain functioning, including impacts on anxiety, concentration and memory (see Section 3.5). In 2018, the US Surgeon General declared the large-scale use of e-cigarettes among youth to be an "epidemic"[797] and the Secretary of the US Department of Health and Human Services, noted recently "the United States has never seen an epidemic of substance use arise as quickly as our current epidemic of youth use of e-cigarettes".[798]

In common with non-smokers, direct health impacts of e-cigarette use in ex-smokers will be reduced if use is avoided, compared to ex-smokers who do not use e-cigarettes. Based on limited evidence, the risk of relapse and resumption of smoking is increased in ex-smokers who use e-cigarettes, compared to ex-smokers who do not use them.[8]

Smokers are vulnerable to the direct adverse health consequences of e-cigarettes identified here. While some of the risks of e-cigarette use will accrue to these individuals, others – such as poisoning, environmental impacts, use by non-smokers and increased smoking uptake in non-smokers – will also affect other community members. Those affected can also include family members of smokers using e-cigarettes – as was seen with the poisoning death of "Baby J" in Australia in 2018.[799] Based on the current limited evidence, freebase nicotine e-cigarettes may be efficacious in supporting smoking cessation when used in the clinical setting. Appropriate use of a product in this context relates not only to efficacy, but also to safety and quality. Since multiple direct risks of nicotine e-cigarettes have been identified here and their long-term effects are unknown, the balance of safety and efficacy of the use of e-cigarettes in smokers is unclear. This issue underpins the US Preventive Services Task Force conclusions in its 2021 recommendations regarding tobacco smoking cessation that "the evidence on the use of e-cigarettes for tobacco smoking cessation in adults, including pregnant persons, is insufficient, and the

balance of benefits and harms cannot be determined."[16,780] This conclusion is consistent with the current status of e-cigarettes in the US, EU, Australia and elsewhere in that they are not registered therapeutic goods and, as such, their quality, safety and efficacy with respect to smoking cessation have not been established. Given the extreme harms of smoking, the balance of probabilities may be that e-cigarettes are beneficial in some smokers who use them and rapidly cease smoking entirely, bearing in mind the current inability to determine the overall balance of harms and benefits in smokers. As noted above, the most common pattern of e-cigarette use in many countries, including Australia, is dual tobacco smoking and e-cigarette use which may increase risks. The most recent review from the World Health Organization states:

> "Although the consequences for long-term effects on morbidity and mortality have not yet been studied sufficiently, ENDS and ENNDS are not safe for young people, pregnant women and adults who have never smoked. While it is expected that use of ENDS and ENNDS in these groups might increase their health risks, non-pregnant adult smokers who completely and promptly switch from combustible tobacco cigarettes to use of unadulterated and appropriately regulated ENDS and ENNDS alone might reduce their health risks."[92]

The main comparator for exposure to e-cigarettes applied in this review, supported by the NHMRC E-cigarettes Working Committee, was using neither e-cigarettes nor other tobacco products. A claim that is often made, particularly by industry seeking to promote e-cigarettes, that e-cigarette use is "safer than smoking tobacco". It is important to consider these claims in the light of the evidence, and its limitations. Acknowledging the extreme harms of tobacco smoking:

- the comparison with tobacco is only relevant to the smoking population. As stated by the WHO, use of e-cigarettes by non-smokers cannot be considered a harm reduction measure.[791]
- for certain outcomes, including poisoning, immediate toxicity from inhalation, trauma from exploding batteries and EVALI, the current evidence is that e-cigarettes are likely to be more harmful than conventional tobacco smoking.
- for the vast majority of important health outcomes, the impact of e-cigarettes is not known. It is therefore not possible to establish with certainty whether use of e-cigarettes is safer than tobacco smoking or not.[9,10]
- globally and nationally, tobacco smoking is the most harmful exogenous exposure, responsible for around eight million deaths annually[38] and the leading exogenous cause of burden of disease.[800,801] Even if e-cigarettes were found to be safer than this highly harmful exposure, this would not constitute evidence of safety in absolute terms.
- there is strong evidence that use of e-cigarettes by non-smokers increases the risk of taking up tobacco smoking an average of three-fold.[8] The generation of new smokers is not safe from the point of view of the affected individuals or population-level tobacco control.
- the majority of smokers who use e-cigarettes continue to smoke and there is evidence that e-cigarettes may allow smokers to offset some of the main ways in which tobacco control measures work, hence supporting ongoing smoking, rather than quitting.[10]
- most smokers quit unaided[9,10] and for those requiring support, there are other means of quitting smoking that have established safety and efficacy.[16]
- considering all of the above, as well as the evidence reviewed in this report, as stated previously the balance of probabilities may be that e-cigarettes are beneficial in some smokers who use them and cease smoking promptly and entirely, with caveats about ongoing uncertainty.

The findings reported here underpin the increasing need to consider e-cigarette use in clinical practice. This includes assessing use, particularly among youth, to support cessation of e-cigarettes, as well as to inform the diagnosis and management of symptoms, signs and conditions potentially caused or exacerbated by e-cigarettes – such as seizures, lung injury and behavioural/mental health issues. In Australia, and elsewhere, e-cigarettes are not registered as an aid for smoking cessation, but practitioners may be advised to consider their use in specific circumstances.[802]

The major uncertainties regarding the health effects of e-cigarettes highlight the importance of research. More evidence is needed on the direct effect of e-cigarettes on health, particularly on clinical outcomes and in never smokers. Given widespread use among youth, research on effects in this group is particularly important. Research on the effects of dual tobacco smoking and e-cigarettes is also required, although differentiation between the overwhelming effects of tobacco on health make this work difficult. Given the challenges faced by regulators and policymakers nationally and internationally, research that informs effective e-cigarette regulation to maximise population health is central to progress. Research and monitoring must also keep pace with industry developments, including examining effects of high concentration nicotine salt products.

6.5 Factors influencing the health effects of e-cigarettes

High nicotine intake increases risks via many different pathways and nicotine delivery is highly varied according to device and device modification.[803] As nicotine concentrations increase, so does risk of severe poisoning outcomes[4,97] and immediate nicotine toxicity through inhalation.[803] This is particularly dangerous for children when lethal quantities can be consumed in a single swallow.[600] For example, a 10kg toddler would experience potentially lethal effects with ingestion of as little as 0.5mL of 100mg/mL nicotine e-liquid. Fatal poisonings have been reported with concentrations likely to be used directly in e-cigarettes (e.g. 10mg/mL)[580] as well as high concentrations requiring dilution at home,[573] including the case of "Baby J" in Australia.[636] Although crucial to evaluate risk, nicotine concentration data is limited in e-liquids related poisonings with poisonings occurring at nicotine concentrations ranging from 6mg/mL to 990mg/mL. Higher nicotine concentrations also increase the risk of addiction[4] and uptake and long-term use of e-cigarettes, especially nicotine salt products[804] in non-smokers.

Freebase e-liquids over about 20mg/mL generally cannot be used directly in devices[97] and require "at home" dilution. Dilutions of high nicotine containing e-liquids can be complex and may lead to titration errors. In contexts where e-cigarettes are banned or available on prescription, illicit use or diversion through dilution and distribution of products obtained on prescription is more likely with high concentration nicotine products.

Anything that increases the likelihood of nicotine e-cigarette use in the broader community, including among youth and non-smokers, will also increase e-cigarette related risks. There is strong evidence that flavours are an important factor in the attractiveness of use of e-cigarettes and initiation, with adolescents considering flavouring the most important factor in trying and initiating e-cigarettes.[4] As evidence supporting plans to prohibit sugars and sweeteners in e-cigarette products and limit flavourings to tobacco, mint and menthol to reduce their appeal to youth, Health Canada states that "flavours other than tobacco, as well as the presence of sugars and sweeteners, are associated with increased product appeal, decreased perception of harm, and increased intention to try or use these products."[804] Other factors likely to increase use include: widespread availability, including as a consumer good; advertising/promotion; low cost; lack of enforcement of policies and legislation; public and private sector influence of the nicotine industry; misinformation about health impacts; and high concentration nicotine salt products.

Other aspects likely to increase risks related to e-cigarettes include: availability of large volumes of e-liquid; the addition of THC, vitamin E acetate and other adulteration; inadequate or inaccurate labelling; and packaging which is not child-resistant.

The safety issues are also likely to disproportionately affect certain priority populations. Risks related to poisoning – unintentional and as part of self-harm – are likely to be greater in Aboriginal and Torres Strait Islander populations because of multigenerational households, overcrowding, higher mental health risks; lack of suitable storage facilities and limited resources and lower health literacy and numeracy for "at home" preparation. High concentration nicotine salt products may also threaten the excellent progress that has been seen with reductions in Aboriginal and Torres Strait Islander youth smoking.[111]

6.6 Considerations when interpreting the findings of this review

This systematic review was conducted according to current best practice, based on a pre-specified, published protocol.[805] It considers the worldwide evidence to date from major reviews and individual published studies on human health across 20 health areas. Its findings add to and accord with those of previous major reviews, including the paucity of evidence and the conclusion that direct health impacts of e-cigarettes on clinical disease outcomes are largely unknown. While mentioned in the section on exposure, evidence from toxicological, *in vitro* and animal studies are largely considered elsewhere and were not included in the systematic review. This evidence is useful in considering the potential impacts of an exposure, particularly where epidemiological evidence is lacking.

The remit of the review was to summarise evidence on the health effects of nicotine and non-nicotine e-cigarettes, excluding e-liquids containing THC and other illicit substances where possible. However, studies did not generally collect or present this information so it was not possible to reliably report separately on these two types of exposure. Moreover, e-cigarette labelling has been shown to be problematic so, even if collected, these data may have validity issues.[4] Since the vast bulk of e-cigarette use relates to nicotine-delivering products,[112] consistent with nicotine being the primary driver of addiction and hence ongoing use, the health effects observed were considered to apply to nicotine e-cigarettes, unless specified otherwise, and those known to relate to THC were excluded. Although it remains possible that a small proportion of the use in the studies conducted was of non-nicotine e-

cigarettes, this issue would be likely to bias results that relate to nicotine effects towards the null and would hence lead to conservative findings.

E-cigarettes include thousands of products and chemical combinations and variations are being introduced on an ongoing basis. Certain risks are likely to vary according to device and product type as well as other factors, including user behaviour and characteristics. For example, risks of severe poisoning increase with increasing nicotine concentration in e-liquids[799] and the risks of high prevalences of use in children and youth are particularly great for high concentration nicotine salt products.[806] The EVALI epidemic further illustrates the importance of rapid monitoring of and responses to the health impacts of new products. A key limitation of this review, and the evidence it is based on, includes that it relates to the products in use at the time the constituent studies were conducted. Future work evaluating the effects of e-cigarettes on health must take into account product diversity and changes over time. In the meantime, the identified risks related to nicotine e-cigarette use should be assumed to apply more generally unless there is appropriate evidence that they do not apply to specific products. The review also relates to the broader health context at the time and, for example, largely predates the COVID-19 pandemic. Concerns have been raised that e-cigarette use may increase the risk of contracting COVID[807] and future work should ensure evaluation of risk considers appropriate contemporary health outcomes.

Research on e-cigarettes is emerging rapidly, including over the time of conducting this review and following the pre-specified search dates. It is important that reviews of the evidence remain current to inform decision-making and understanding, through regular updating and/or through "living reviews" approaches.[808]

Across all health outcomes in which GRADE was applied, both clinical and subclinical outcomes were rated as very low certainty evidence. This finding is largely reflective of limitations with the scale of included studies, limitations in study designs and the overall paucity of evidence. Issues regarding small study sizes were apparent in consistent serious or very serious judgments in imprecision. The majority of evidence identified in the review was from non-randomised studies and as per the GRADE approach, is automatically considered low certainty. No non-randomised study was rated up due to deductions in at least one GRADE criteria. The paucity of evidence raised serious or very serious concerns in inconsistency, imprecision and indirectness. The most common missing data relate to study dates and demographic factors, which are unlikely to substantially impact results. Publication bias was consistently assessed as undetected, however this was not statistically analysed and the lack of evidence limited the accuracy of the judgment. Due to severe concerns in the other GRADE domains, the inability to appropriately judge publication bias is unlikely to have materially impacted the certainty of the evidence and the interpretation of findings. Where possible, risk of bias included both the judgements from the Joanna Briggs Institute's critical appraisal checklists and consideration of any potential conflicts of interest such as any author affiliation or financial support from the tobacco industry or pharmaceutical companies. Deductions in GRADE risk of bias was primarily driven by concerns in methodological quality. While no formal analysis was conducted, 31 of the 189 studies identified in evidence synthesis of the top-up review had noted potential competing interests, thus their exclusion is unlikely to largely impact GRADE risk of bias judgments. Though, concerns with risk of bias were consistently noted across health outcomes, these in isolation are not likely to have materially impacted the overall certainty of evidence or the interpretation of findings due to significant concerns in other domains.

The conclusions that can be drawn from the findings of this review are necessarily constrained by the paucity of high-quality evidence. In addition to the central issue of the paucity of evidence, there are major issues in disentangling the likely effects of cigarettes from those of combustible tobacco use.

This systematic review prioritises evidence that is most informative for assessment of the likely causal relationship of e-cigarettes to clinical health outcomes, including randomised controlled trials, cohort and case-control studies. There was insufficient evidence to conduct meta-analyses for outcomes other than tobacco smoking uptake and cessation, due to the small number and diversity of the located studies. For outcomes where the disease event has been attributed directly to e-cigarette exposure – such as burns, poisonings, injuries and EVALI - case reports, case series and surveillance reports also provide useful evidence. While previous reviews, including the NASEM review, have also incorporated evidence from cross-sectional surveys, this report has largely avoided using such evidence, due to difficulties reliably attributing causality.

Considering all of the above, there were severe limitations in study power and quality, meaning it was not possible to detect or exclude most of the potential health effects of e-cigarettes, resulting in major uncertainty about their impact on important clinical conditions. A key implication is that the absence of evidence documented here should not be interpreted as evidence of safety. Situations with uncertainty about the effects of an exposure, where serious adverse effects are scientifically plausible, particularly

those affecting future generations, are not benign and generally invoke the precautionary principle.[809] This means avoiding the exposure and focusing on gathering further evidence. E-cigarettes combine uncertainty about health effects with widespread exposure in many countries, particularly among youth. This is a high-risk situation and the rationale for recent comments from the WHO: "ENDS should be strictly regulated for maximum protection of public health." Monitoring of e-cigarette use and effects, with vigilance regarding signals of potential harm, is a critical part of this.

7 Conclusions

There is strong or conclusive evidence that nicotine e-cigarettes can be harmful to health and uncertainty regarding their impacts on a range of important health and disease outcomes. Based on the current worldwide evidence, use of nicotine e-cigarettes increases the risk of a range of adverse health outcomes, including poisoning, toxicity from inhalation (such as seizures), addiction, trauma and burns, lung injury and smoking uptake, particularly in youth. Their effects on most other clinical outcomes are unknown, including those related to cardiovascular disease, cancer, respiratory conditions other than lung injury, mental health, development in children and adolescents, reproduction, sleep, wound healing, neurological conditions other than seizures and endocrine, olfactory, optical, allergic and haematological conditions. Nicotine e-cigarettes are highly addictive, underpinning increasing and widespread use among children and adolescents in many settings. Less direct evidence indicates adverse effects of e-cigarettes on cardiovascular health markers, including blood pressure and heart rate, lung function and adolescent brain development and function. Environmental impacts include indoor air pollution, waste and fires. The commonest pattern of e-cigarette use is dual e-cigarette use and tobacco smoking, which is generally considered an adverse outcome. There is limited evidence of efficacy of freebase nicotine e-cigarettes as an aid to smoking cessation in the clinical setting. Given the extreme harms of smoking, e-cigarettes may be beneficial in some smokers who use them to quit smoking completely and promptly, bearing in mind uncertainties about their long-term effects. The current evidence supports national and international efforts to avoid e-cigarette use in the general population, particularly in non-smokers and youth. Better evidence is needed regarding the overall balance of quality, safety and efficacy of e-cigarettes as a potential aid for smoking cessation, as well as regarding the most effective regulatory options.

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Appendix 1: Smoking behaviour methods

Smoking uptake

Methods

The summary of the global contemporary evidence comprises an umbrella review of systematic reviews, a top-up systematic review of primary research not included in the systematic reviews of the umbrella review, and a summary of the main findings in the three recent major reports on e-cigarettes and smoking behaviour: reviews from NASEM;[3] Public Health England 2018;[11] and the CSIRO.[14]

For both the umbrella review and the top-up systematic review, six databases (PubMed, Scopus, Web of Science, PsycINFO (Ovid), MEDLINE (Ovid), Cochrane) were searched on 1 April 2020. EndNote and Covidence software were used for review management. Two authors of this review independently screened all titles and abstracts identified in the searches, followed by full text screening. A forward and backward reference search using Scopus was performed from the final included articles. After removing duplicates, screening was performed by two review authors, first by title and abstract, and then full text, for any studies fulfilling the inclusion and exclusion criteria. There was no date limit on the search and only studies with abstracts published in English were included. The systematic review protocol was published on PROSPERO (CRD42020168596).

In the umbrella review, systematic reviews and meta-analyses of studies examining the association between e-cigarette (nicotine or non-nicotine) use among non-tobacco smokers and uptake of combustible tobacco cigarette smoking were included.

Cross-sectional surveys were excluded due to difficulties in establishing the temporal relationship between e-cigarette exposure and smoking uptake. Cohort studies and randomised/non-randomised controlled trials or clinical trials were eligible. Studies with a follow-up duration less than six months were excluded.

Two authors of this review independently extracted data from the included systematic reviews and cohort studies using a pre-specified data extraction template. As it is important to consider whether authors of the studies under review hold any conflicts of interest that could potentially bias their findings, or whether the research was funded by an organisation with a financial interest in the outcomes, information on the source of research sponsorship or external involvement was extracted. Studies were considered separately if they were funded and/or received contributions in kind by the tobacco or e-cigarette industry, or if their authors currently or previously received funding from the tobacco or e-cigarette industry.

Two authors of this review also independently assessed the risk of bias for each study included. AMSTAR 2 was used to assess the methodological quality of the systematic reviews and meta-analyses included in the umbrella reviews. The Newcastle Ottawa Scale (NOS) was used to assess the quality of non-randomised intervention studies in the systematic review.

Findings from the umbrella review and the top-up systematic review were synthesised separately in narrative summaries. Individual prospective primary research studies identified from both the umbrella review and the top-up systematic review were considered in an integrated systematic review. Where appropriate, adjusted odds ratios from the studies in the integrated systematic review were combined using a random-effects model in STATA version 16.1, to calculate pooled odds ratios. Heterogeneity of study effect estimates are indicated by an I-squared statistic.

Inclusion and exclusion criteria

Inclusion criteria:

Study designs: Published, peer-reviewed literature.

For the umbrella review:

- Systematic reviews and meta-analyses of randomised/non-randomised controlled trials, clinical trials and prospective cohort studies.

For the systematic review:

- Randomised/non-randomised controlled trials, clinical trials (although intervention studies are not expected)
- Prospective cohort studies.

Population: Non-tobacco smokers – includes never, former or ever users (this includes prior users who have tried smoking but have not used in the past 30 days). Humans, any age (youth, young adults and adults).

Intervention: Nicotine- or non-nicotine-e-cigarettes or e-liquid devices.

Comparison: No nicotine- or non-nicotine-e-cigarettes or e-liquid devices.

Outcome: Ever smoking combustible tobacco cigarettes.

Follow-up: Minimum six months (as per the NASEM review).

Timing: All years.

Setting: Any country.

Language: Articles reported in English.

Exclusion criteria:

Study designs: Systematic reviews that are superseded by a later review which include all studies from the earlier review. Non-systematic literature reviews, intervention trials with no comparator (e.g. before and after study), qualitative studies, retrospective cohort studies, case-control studies, cross-sectional (including repeated cross-sectional) surveys, case reports, grey literature, conference abstracts, letters, editorials, correspondence, opinion pieces, government reports, position statements.

Population: Current tobacco smokers (use within the past 30 days), *in vitro* studies or animal studies.

Intervention: Heat-not-burn and tobacco containing products, studies with a focus on the uptake of marijuana, other illicit drugs and harmful substances.

Outcome: Studies where smoking cigarettes is not the primary outcome variable.

Timing: No exclusion criteria.

Setting: No exclusion criteria.

Language: Articles not published or translated to English.

Other: Duplicated data, unavailable full text.

Search terms

MEDLINE search terms:

1. (Electronic cigarette* or E-cigarette* or Electronic nicotine delivery system* or Electronic non-nicotine delivery* or Electronic nicotine device* or Electronic non-nicotine device* or Vape or Vaping or Vapo* or E-hookah or Electronic inhalant device or E-liquid).af.
2. (Smoker* or non-smoker* or ex-smoker* or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking).af.
3. (Initiat* or Uptak* or Subsequent* or Predict* or Onset).af.
4. 1 and 2 and 3

Results: 1,168

PsychINFO search terms:

1. (Electronic cigarette* or E-cigarette* or Electronic nicotine delivery system* or Electronic non-nicotine delivery* or Electronic nicotine device* or Electronic non-nicotine device* or Vape or Vaping or Vapo* or E-hookah or Electronic inhalant device or E-liquid).af.
2. (Smoker* or non-smoker* or ex-smoker* or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking).af.
3. (Initiat* or Uptak* or Subsequent* or Predict* or Onset).af.
4. 1 and 2 and 3

Results: 847

PubMed search terms:

1. (((Electronic cigarette* or E-cigarette* or Electronic nicotine delivery systems[Mesh] or Electronic non-nicotine delivery* or Electronic nicotine device* or Electronic non-nicotine device* or Vape or Vaping or Vapo* or E-hookah or Electronic inhalant device or E-liquid)) AND (Smoker*[Mesh] or non-smoker*[Mesh] or ex-smoker*[Mesh] or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking)) AND (Initiat* OR Uptak* OR Subsequent* OR Predict* OR Onset)

Results: 1,187

Scopus search terms:

1. (TITLE-ABS-KEY (("Electronic cigarette*" OR "E-cigarette*" OR "Electronic nicotine delivery system*" OR "Electronic non-nicotine delivery*" OR "Electronic nicotine device*" OR "Electronic non-nicotine device*" OR "Vape" OR "Vaping" OR "Vapo*" OR "E-hookah")) AND TITLE-ABS-KEY (("Smoker*" OR "non-smoker*" OR "ex-smoker*" OR "Combustible cigarette" OR "Tobacco smoking" OR "Smoking" OR "Cigarette" OR "Cigarette smoking" OR "Cigar smoking")) AND TITLE-ABS-KEY (("Initiat*" OR "Uptak*" OR "Subsequent*" OR "Predict*" OR "Onset")))

Results: 1,289

Web of Science search terms:

1. ALL FIELDS: (("Electronic cigarette*" OR E-cigarette* OR "Electronic nicotine delivery system*" OR "Electronic non-nicotine delivery*" OR "Electronic nicotine device*" OR "Electronic non-nicotine device*" OR Vape OR Vaping OR Vapo* OR E-hookah OR "Electronic inhalant device")) AND ALL FIELDS: ((Smoker* OR non-smoker* OR ex-smoker* OR "Combustible cigarette" OR "Tobacco smoking" OR Smoking OR Cigarette OR "Cigarette smoking" OR "Cigar smoking")) AND ALL FIELDS: ((Initiat* OR Uptak* OR Subsequent* OR Predict* OR Onset))

Results: 1,488

Cochrane search terms:

1. MeSH descriptor: [Electronic Nicotine Delivery Systems] explode all trees
2. ("Electronic cigarette" OR E-cigarette OR Vape OR Vaping OR E-hookah OR "Electronic inhalant device" OR E-liquid OR "Electronic Nicotine Delivery Systems"):ti,ab,kw
3. #1 OR #2
4. (Smoker* or non-smoker* or ex-smoker* or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking):ti,ab,kw
5. #4 OR #5
6. (Initiat* OR Uptak* OR Subsequent* OR Progress* OR Predict* OR Duration OR Intens* OR Frequen* OR Onset):ti,ab,kw
7. #3 AND #6 AND #7

Results: 219

Smoking cessation

Methods

A systematic review was undertaken to examine the efficacy of e-cigarettes as a smoking cessation aid and methods were consistent with those used in a recent national US report.[3] Six databases (PubMed, Scopus, Web of Science, PsycINFO (Ovid), MEDLINE (Ovid), Cochrane) were initially searched between 5 February and 2 March 2020. An additional search was conducted on 27 April 2021 to retrieve papers published since the initial search. There was no date limit on the search prior to this and only studies with abstracts published in English were included. The systematic review protocol was published on PROSPERO (CRD42020170692).

This review included randomised controlled trials (RCTs), as defined by the Cochrane Community,[810] in which current smokers were randomised to intervention groups of e-cigarettes, no cigarettes, other smoking cessation treatments (e.g., approved NRT, behavioural therapy, combination), or to a placebo control group. The outcomes included were biochemically verified sustained cessation of combustible tobacco smoking and, separately, nicotine cessation (i.e., cessation of combustible tobacco smoking, ENDS or approved NRT). Studies with cessation outcomes measured earlier than four months after their quit date were excluded in accordance with standard measures of sustained abstinence, and outcomes at the latest follow-up date were included.[3,679,811] All other study designs or populations were excluded.

Papers were imported into an EndNote library, exported to Covidence[812] and duplicates were removed. Two authors of this review independently screened all titles and abstracts identified in the searches, followed by full text screening. A forward and backward reference search using ANU Library, Web of Science and Scopus was performed from the final included articles. One review author assessed each RCT to determine whether it met the definition of an RCT as defined by the Cochrane Community.[810]

Two authors of this review independently extracted data from the included RCTs using a pre-specified data extraction template. Relative risks and 95% confidence intervals – by intention-to-treat – were extracted from each paper or, when possible, calculated from the number of events or percentages reported in the published study. Available data on cessation of nicotine in any form (e.g., combustible tobacco, ENDS, approved NRT); and use of approved NRT, behavioural therapy, ENDS or ENNDS, among all participants, quitters, and among those who do not quit, were extracted.

In RCTs, end-expired carbon monoxide (CO) is the main biochemical validation of smoking abstinence used.[419] Salivary cotinine can also be used to biochemically validate nicotine cessation. Where biochemical data were not available or appropriate to determine nicotine cessation for NRT, this review used discontinuation of nicotine-containing products at follow-up as an indicator of nicotine cessation.

This review aims to summarise the available high-quality, reliable evidence on the efficacy of e-cigarettes for smoking cessation. Avoiding the potential influence of competing interests on research findings is central to this. Research funding and author conflict of interest information was extracted from each study and studies were considered separately if they were funded and/or received contributions in kind by the tobacco or e-cigarette industry, or if their authors currently or previously received funding from the tobacco or e-cigarette industry.

Where appropriate, relative risks from studies were combined using meta-analyses to assess the efficacy of ENDS for smoking cessation compared to the efficacy of no intervention (or usual care), placebo (ENNDS) or approved NRT and other comparators. Following data extraction, but prior to any meta-analyses, we assessed whether random- or fixed-effect models were most appropriate. Due to the likelihood that the interventions and the target populations in the different studies differed materially, a random-effects REML model was used for the primary analyses. The I-squared statistic was used to evaluate statistical heterogeneity between studies. Because the small number of studies for each outcome made random-effects modelling less suitable, we conducted sensitivity analyses using fixed-effects modelling. Other sensitivity analyses included repeating the analyses restricted to studies without noted potential competing interests, restriction to trials of e-cigarettes likely to deliver doses of nicotine comparable to, or greater than, that of approved NRT[813] and, separately, examining outcomes at the most consistent sustained follow-up time available (i.e., 24-26 weeks). All analyses were conducted using STATA version 16.1.

The risk of bias for each included RCT was assessed independently by two review authors using the Cochrane Collaboration's tool for assessing risk of bias in randomised controlled trials.[814] The certainty of the body of evidence for smoking cessation was evaluated using the GRADE approach.[34,815] The authors then applied an evidence to recommendation framework, mapping the risk of bias and quality of evidence

findings to stated conclusions, drawing on the US National Academies of Science, Engineering and Medicine (NASEM) review. No studies were excluded based on their quality assessment scores.

Separate to the systematic review, the main findings on the efficacy of e-cigarettes as a smoking cessation tool from previously published major reviews (NASEM,[3] Public Health England 2018,[11] CSIRO 2018, the US Surgeon General,[779] the US Preventive Services Task Force[16] and the European Union Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)[4,14]) were summarised. In addition, a supplementary search was undertaken to identify systematic reviews/meta-analyses published since the NASEM review to identify RCTs that were not identified through the systematic review search and to compare their findings and interpretation with those of the systematic review in this report.

This systematic review includes only RCTs and excludes evidence from observational studies. RCTs present the only reliable evidence on the efficacy of a therapeutic tool.[816,817] Observational data do not provide reliable evidence on the effect of interventions on their intended therapeutic endpoints, largely because people exposed to specific agents tend to differ from those not exposed in ways that cannot be accounted for using this study type. A potential exception to this is where the observed effect is very large. There are many instances where observational data have been wrongly interpreted as indicating efficacy, with high profile examples including those relating to vitamins and mortality[818] and menopausal hormone therapy and coronary heart disease.[819] Smokers who do and do not use e-cigarettes differ in multiple and complex ways, including in their likely commitment to quitting, health, risk appetites and other health behaviours. This review aims to summarise the reliable global evidence on the efficacy of e-cigarettes for smoking cessation and hence includes only RCTs.

Furthermore, the Therapeutic Goods Administration of Australia can only provide approval for a product as a therapeutic tool if it has clear, unequivocal evidence that the product is beneficial, and that the balance of safety and efficacy is appropriate. It is upon the evidence of clinical trials that a product receives approval as a therapeutic good in Australia.[820,821] It is by these standards that the decision was made to approve NRT products.

Inclusion and exclusion criteria

Inclusion criteria:

Study designs:	Published, peer-reviewed randomised control trials (RCTs).
Population:	Current tobacco smokers, humans, any age, no limit on smoking status (duration, cigarettes per day etc.), smokers motivated or unmotivated to quit.
Intervention:	Nicotine- or non-nicotine-e-cigarettes or e-liquids.
Comparison:	No e-cigarettes, placebo. Standard smoking cessation treatment/aids such as nicotine replacement therapies (e.g., patch, gum, inhalers), behavioural and/or pharmacological cessation aids (e.g., bupropion & varenicline), and combination of e-cigarettes and treatments. Any other treatments or aids intended to assist with cessation.
Outcome:	Primary or secondary outcome variable is combustible tobacco smoking cessation. RCT contains outcome data on cessation of nicotine exposure in any form and cessation of non-nicotine e-cigarettes. Abstinence must be biochemically verified at a minimum four-month follow-up.
Timing:	All years.
Setting:	Any country.
Language:	Articles reported in English.

Exclusion criteria:

Study designs:	Systematic reviews and meta-analyses, non-systematic reviews – literature reviews, non-randomised clinical trials, intervention trials with no comparator (e.g., before and after study), qualitative studies, prospective cohort studies/crossover trials, retrospective cohort studies, cross-sectional surveys, case-control studies, case reports, grey literature, conference abstracts, letters, editorials, correspondence, opinion pieces, government reports, position statements.

Population:	*In vitro* studies or animal studies.
Intervention:	Heat-not-burn and tobacco containing products.
Outcome:	Studies where smoking, or nicotine, cessation is not the primary or secondary outcome variable.
Timing:	No exclusion criteria.
Setting:	No exclusion criteria.
Language:	Articles not published or translated to English.
Other:	Duplicated data, unavailable full text.

Search terms

MEDLINE search terms:

1. Smoker.mp
2. Smokers.mp
3. Ex-Smokers.mp
4. Ex-Smokers.mp
5. Exp Smokers/
6. Exp Ex-smokers/
7. 1 or 2 or 3 or 4 or 5 or 6
8. E-cigarette.mp
9. E-cigarettes.mp
10. “electronic cigarette”.mp
11. “electronic cigarettes”.mp
12. “electronic nicotine de*”.mp
13. “electronic nicotine delivery system”.mp
14. Vape.mp
15. Vaping.mp
16. Vapo*.mp
17. E-liquid.mp
18. E-hookah.mp
19. “Electronic inhalant device”.mp
20. Exp “Electronic nicotine delivery systems”/
21. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. “Smoking cessation”.mp
23. Cessation.mp
24. Quit.mp
25. Abstinence.mp
26. Exp “smoking cessation”/
27. Exp “tobacco use cessation devices”/
28. Exp “smoking cessation agents”/
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 7 and 21 and 29
31. Limit 30 to randomized controlled trials

Results: 96

PsychINFO search terms:

1. Smoker.mp
2. Smokers.mp
3. Ex-Smokers.mp
4. Ex-Smokers.mp
5. Smokers.mh
6. Ex-smokers.mh
7. 1 or 2 or 3 or 4 or 5 or 6
8. E-cigarette.mp
9. E-cigarettes.mp
10. “electronic cigarette”.mp
11. “electronic cigarettes”.mp
12. “electronic nicotine de*”.mp
13. “electronic nicotine delivery system”.mp
14. Vape.mp
15. Vaping.mp
16. Vapo*.mp
17. E-liquid.mp
18. E-hookah.mp
19. “Electronic inhalant device”.mp
20. “Electronic nicotine delivery systems”.mh
21. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. “Smoking cessation”.mp
23. Cessation.mp
24. Quit.mp
25. Abstinence.mp
26. “Smoking cessation”.mh
27. “Tobacco use cessation devices”.mh
28. “Smoking cessation agents”.mh
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 7 and 21 and 29
31. Limit 30 to “0300 clinical trial”

Results: 13

PubMed search terms:

1. ((("smoking cessation" OR Cessation OR quit OR Abstinence OR "smoking cessation" [MeSH Terms] OR "tobacco use cessation devices"[MeSH Terms] OR "smoking cessation agents"[MeSH Terms]) AND (E-cigarette OR E-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "Electronic nicotine delivery system" OR Vape OR Vaping OR E-liquid OR Vapo* OR E-hookah OR "Electronic inhalant device" OR "Electronic nicotine delivery systems"[MeSH Terms]) AND (Smoker OR Smokers OR Ex-smoker OR Ex smokers OR Smokers[MeSH Terms] OR Exsmokers[MeSH Terms]))) AND Randomized Controlled Trial[ptyp]

Results: 87

Scopus search terms:

1. TITLE-ABS-KEY (("smoking cessation" OR Cessation OR quit OR Abstinence OR "tobacco use cessation devices" OR "smoking cessation agents") AND (E-cigarette OR E-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "Electronic nicotine delivery system" OR Vape OR Vaping OR E-liquid OR Vapo* OR E-hookah OR "Electronic inhalant device") AND (Smoker OR Smokers OR Ex-smoker OR Ex-smokers) AND (LIMIT-TO (DOCTYPE, “ar”)))

Results: 3,759

Web of Science search terms:

2. TS=("smoking cessation" OR Cessation OR quit OR Abstinence) AND TS=(E-cigarette OR E cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "Electronic nicotine delivery system" OR Vape OR Vaping OR E-liquid OR Vapo* OR E-hookah OR "Electronic inhalant device") AND TS=(Smoker OR Smokers OR Ex-smoker OR Ex-smokers)) AND DOCUMENT TYPES: (Article)

   Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Results: 930

Cochrane search terms:

1. (Smoker):ti,ab,kw OR (Smokers):ti,ab,kw OR (Exsmoker): ti,ab,kw OR (Ex-smokers):ti,ab,kw
2. MeSH descriptor: [Smokers] explode all trees
3. MeSH descriptor: [Ex-Smokers] explode all trees
4. #1 OR #2 OR #3
5. E-cigarette OR E-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "Electronic nicotine delivery system" OR Vape OR Vaping OR E liquid OR Vapo* OR E-hookah OR "Electronic inhalant device"
6. MeSH descriptor: [Electronic Nicotine Delivery Systems] explode all trees
7. #5 OR #6
8. "smoking cessation" OR Cessation OR quit OR Abstinence
9. MeSH descriptor: [Smoking Cessation] explode all trees
10. MeSH descriptor: [Tobacco Use Cessation Devices] explode all trees
11. MeSH descriptor: [Smoking Cessation Agents] explode all trees
12. #8 OR #9 OR #10 OR #11
13. #4 AND #7 AND #12
14. #13 in trials

Results: 246

Cochrane criteria for randomised control trials (RCTs)

The Cochrane Community Glossary[810] defines randomised controlled trials (RCTs) as:

An experiment in which two or more interventions, possibly including a control or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body).

Therefore, this systematic review of RCTs will use the following criteria for an RCT:

1. Does the article describe an experiment with two or more interventions (one may be a control intervention or no intervention)?
2. Are the interventions being compared by being randomly allocated to participants?

Appendix 2: Search terms

General Search

Date: 22 July 2020

PubMed

e-cigarette OR e-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR e-liquid OR "Electronic nicotine delivery system" OR vape OR vaping OR "Electronic inhalant device" OR "Electronic Nicotine Delivery Systems"[Mesh] AND ((humans[Filter]) AND (2017:2020[pdat])) AND (humans[Filter]) Filters: Humans

Results: 2,930

Scopus

TITLE-ABS-KEY ((e-cigarette) OR (e-cigarettes) OR (Electronic cigarette) OR (Electronic cigarettes) OR "Electronic nicotine de*" OR (Electronic nicotine delivery system) OR vape OR vaping OR (Electronic inhalant device)) AND NOT TITLE-ABS-KEY (animal OR animals OR mice OR mouse OR rat OR rats) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re") OR LIMIT-TO (DOCTYPE , "er")) AND (LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017))

Results 3,574

MEDLINE

1. "electronic nicotine delivery".ti,ab.
2. "electronic nicotine device".ti,ab.
3. vape.ti,ab.
4. vaping.ti,ab.
5. "electronic delivery system".ti,ab.
6. e-liquid.ti,ab.
7. e-cigarette.ti,ab.
8. e-cigarettes.ti,ab.
9. "electronic cigarette".ti,ab.
10. "electronic cigarettes".ti,ab.
11. "electronic inhalant device".ti,ab.
12. exp electronic nicotine delivery system/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. limit 13 to (humans and yr="2017 -Current")
15. limit 14 to (case reports or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or "corrected and republished article" or evaluation study or historical article or introductory journal article or journal article or meta-analysis or multicenter study or observational study or pragmatic clinical trial or published erratum or randomized controlled trial or "review" or "scientific integrity review" or "systematic review" or technical report or twin study or validation study)

Results: 1,971

PsycINFO

1. "electronic nicotine delivery".ti,ab.
2. "electronic nicotine device".ti,ab.
3. vape.ti,ab.
4. vaping.ti,ab.
5. "electronic delivery system".ti,ab.
6. e-liquid.ti,ab.
7. e-cigarette.ti,ab.
8. e-cigarettes.ti,ab.
9. "electronic cigarette".ti,ab.
10. "electronic cigarettes".ti,ab.
11. "electronic inhalant device".ti,ab.

12. exp electronic nicotine delivery system/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. limit 13 to (humans and yr="2017 -Current")
15. limit 14 to ("0100 journal" or "0110 peer-reviewed journal")

Results: 1,025

Web of Science

(TS=("e-cigarette" OR "e-cigarettes" OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "e-liquid" OR "Electronic nicotine delivery system" OR "vape" OR "vaping" OR “Electronic inhalant device”) NOT TS=(animal OR animals OR mice OR mouse OR rat OR rats)) AND DOCUMENT TYPES: (Article)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC
Timespan=2017-2020

Results: 2,838

Cochrane

1. e-cigarette OR e-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR e-liquid OR "Electronic nicotine delivery system" OR vape OR vaping OR "Electronic inhalant device"
2. MeSH descriptor [Electronic Nicotine Delivery Systems] explode all trees
3. #1 OR #2
4. #3 limit with Cochrane Library publications from Jun 2017 to Aug 2020

Results: 538

Note: two “special collection” citations could not be exported.

Search Terms: Dependence

Date: 24 July 2020

PubMed

(e-cigarette OR e-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "Electronic nicotine delivery system" OR vape OR vaping OR e-liquid OR "Electronic inhalant device" OR "Electronic Nicotine Delivery Systems"[Mesh]) AND ("Tobacco Use Disorder" [MeSH] OR "Substance Withdrawal Syndrome" [MeSH] OR "Craving" [MeSH] OR dependence or withdrawal or craving OR appeal or addiction OR "abuse liability" OR "subjective effects" OR "smoking urge" OR "urge to smoke" OR "smoking desire" OR "desire to smoke") Filters: from 2017 – 2020

Results: 1,504

Scopus

TITLE-ABS-KEY ((e-cigarette) OR (e-cigarettes) OR (Electronic cigarette) OR (Electronic cigarettes) OR "Electronic nicotine de*" OR (Electronic nicotine delivery system) OR vape OR vaping OR (Electronic inhalant device)) AND TITLE-ABS- KEY (dependence OR withdrawal OR craving OR appeal OR addiction OR "abuse liability" OR "subjective effects" OR "smok* w/3 urge" OR "smok* w/3 desire") AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT- TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017))

Results: 1,079

MEDLINE

1. "electronic nicotine delivery".ti,ab.
2. "electronic nicotine device".ti,ab.
3. vape.ti,ab.
4. vaping.ti,ab.
5. "electronic delivery system".ti,ab.
6. e-liquid.ti,ab.
7. e-cigarette.ti,ab.
8. e-cigarettes.ti,ab.
9. "electronic cigarette".ti,ab.
10. "electronic cigarettes".ti,ab.
11. "electronic inhalant device".ti,ab.
12. exp electronic nicotine delivery system/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp "tobacco use disorder"/
15. exp "substance withdrawal syndrome"/
16. exp craving/
17. dependence.ti,ab.
18. withdrawal.ti,ab.
19. craving.ti,ab.
20. appeal.ti,ab.
21. (smok* adj3 urge).ti,ab.
22. (smok* adj3 desire).ti,ab.
23. "abuse liability".ti,ab.
24. "subjective effects".ti,ab.
25. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 13 and 25
27. limit 26 to yr="2017 -Current"

Results: 525

PsycINFO

1. "electronic nicotine delivery".ti,ab.
2. "electronic nicotine device".ti,ab.
3. vape.ti,ab.
4. vaping.ti,ab.
5. "electronic delivery system".ti,ab.
6. e-liquid.ti,ab.

7. e-cigarette.ti,ab.
8. e-cigarettes.ti,ab.
9. "electronic cigarette".ti,ab.
10. "electronic cigarettes".ti,ab.
11. "electronic inhalant device".ti,ab.
12. exp electronic nicotine delivery system/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp "tobacco use disorder"/
15. exp "substance withdrawal syndrome"/
16. exp craving/
17. dependence.ti,ab.
18. withdrawal.ti,ab.
19. craving.ti,ab.
20. appeal.ti,ab.
21. (smok* adj3 urge).ti,ab.
22. (smok* adj3 desire).ti,ab.
23. "abuse liability".ti,ab.
24. "subjective effects".ti,ab.
25. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 13 and 25
27. limit 26 to yr="2017 -Current"

Results: 261

Web of Science

(TS= ("e-cigarette" OR "e-cigarettes" OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "Electronic nicotine delivery system" OR vape OR vaping OR e-liquid OR "Electronic inhalantdevice") AND TS=(dependence or withdrawal or craving or appeal or addiction OR "abuse liability" OR "subjective effects" OR "smok* NEAR/3 urge" OR "smok* NEAR/3 desire")) AND DOCUMENT TYPES: (Article Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2017-2020

Results: 607

Cochrane

1. e-cigarette OR e-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR e-liquid OR "Electronic nicotine delivery system" OR vape OR vaping OR "Electronic inhalant device"
2. MeSH descriptor [Electronic Nicotine Delivery Systems] explode all trees
3. #1 OR #2
4. dependence or withdrawal or craving or appeal or addiction OR "abuse liability" OR "subjective effects" OR "smok* NEAR/3 urge" OR "smok* NEAR/3 desire”
5. MeSH descriptor [Tobacco Use Disorder] explode all trees
6. MeSH descriptor [Substance Withdrawal Syndrome] explode all trees
7. MeSH descriptor [Craving] explode all trees
8. #4 or #5 OR #6 OR #7
9. #3 AND #8
10. #9 limit with Cochrane Library publications from Jun 2017 to Aug 2020

Results: 235

Search Terms: Injuries, burns, poisoning

Date: 24 July 2020

PubMed

(e-cigarette OR e-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "Electronic nicotine delivery system" OR vape OR vaping OR e-liquid OR "Electronic inhalant device" OR "Electronic Nicotine Delivery Systems"[Mesh]) AND ("Poisoning"[MeSH] OR dermal OR injury OR injuries OR explosi* OR explod* OR ingestion OR poison OR poisoning OR ingest OR burn*) AND (2017:2020[pdat])

Results: 616

Scopus

TITLE-ABS-KEY((e-cigarette) OR (e-cigarettes) OR (Electronic cigarette) OR (Electronic cigarettes) OR "Electronic nicotine de*" OR (Electronic nicotine delivery system) OR vape OR vaping OR (Electronic inhalant device)) AND TITLE-ABS-KEY (dermal OR injury OR injuries OR explos* OR explod* OR ingestion OR poison OR poisoning OR ingest OR burn*) AND (LIMIT-TO (PUBYEAR,2020) OR LIMIT-TO (PUBYEAR,2019) OR LIMIT-TO (PUBYEAR,2018) OR LIMIT-TO (PUBYEAR,2017))

Results: 536

MEDLINE

1. "electronic nicotine delivery".ti,ab.
2. "electronic nicotine device".ti,ab.
3. vape.ti,ab.
4. vaping.ti,ab.
5. "electronic delivery system".ti,ab.
6. e-liquid.ti,ab.
7. e-cigarette.ti,ab.
8. e-cigarettes.ti,ab.
9. "electronic cigarette".ti,ab.
10. "electronic cigarettes".ti,ab.
11. "electronic inhalant device".ti,ab.
12. exp electronic nicotine delivery system/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp poisoning/
15. dermal.ti,ab.
16. injury.ti,ab.
17. injuries.ti,ab.
18. Burn*.ti,ab.
19. ingestion.ti,ab.
20. poison.ti,ab.
21. poisoning.ti,ab.
22. ingest.ti,ab.
23. Explod*.ti,ab.
24. Explos*.ti,ab.
25. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
26. 13 and 38
27. limit 39 to yr="2017 -Current"

Results: 440

PsycINFO

1. "electronic nicotine delivery".ti,ab.
2. "electronic nicotine device".ti,ab.
3. vape.ti,ab.
4. vaping.ti,ab.
5. "electronic delivery system".ti,ab.
6. e-liquid.ti,ab.
7. e-cigarette.ti,ab.
8. e-cigarettes.ti,ab.
9. "electronic cigarette".ti,ab.

10. "electronic cigarettes".ti,ab.
11. "electronic inhalant device".ti,ab.
12. exp electronic nicotine delivery system/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp poisoning/
15. dermal.ti,ab.
16. injury.ti,ab.
17. injuries.ti,ab.
18. Burn*.ti,ab.
19. ingestion.ti,ab.
20. poison.ti,ab.
21. poisoning.ti,ab.
22. ingest.ti,ab.
23. Explod*.ti,ab.
24. Explos*.ti,ab.
25. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
26. 13 and 38
27. limit 39 to yr="2017 -Current"

Results: 36

Web of Science

(TS= ("e-cigarette" OR "e-cigarettes" OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "Electronic nicotine delivery system" OR vape OR vaping OR e-liquid OR "Electronic inhalant device") AND TS=(dermal OR injury OR injuries OR explos* OR explod* OR ingestion OR poison OR poisoning OR ingest OR burn*)) AND DOCUMENT TYPES: (Article)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Results: 341

Cochrane

1. e-cigarette OR e-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR e-liquid OR "Electronic nicotine delivery system" OR vape OR vaping OR "Electronic inhalant device"
2. MeSH descriptor [Electronic Nicotine Delivery Systems] explode all trees
3. #1 OR #2
4. dermal OR injury OR injuries OR explos* OR explod* OR ingestion OR poison OR poisoning OR ingest OR burn*
5. MeSH descriptor [Poisoning] in al MeSH products
6. #4 OR #5
7. #3 AND #6
8. #7 limit with Cochrane Library publications from Jun 2017 to Aug 2020

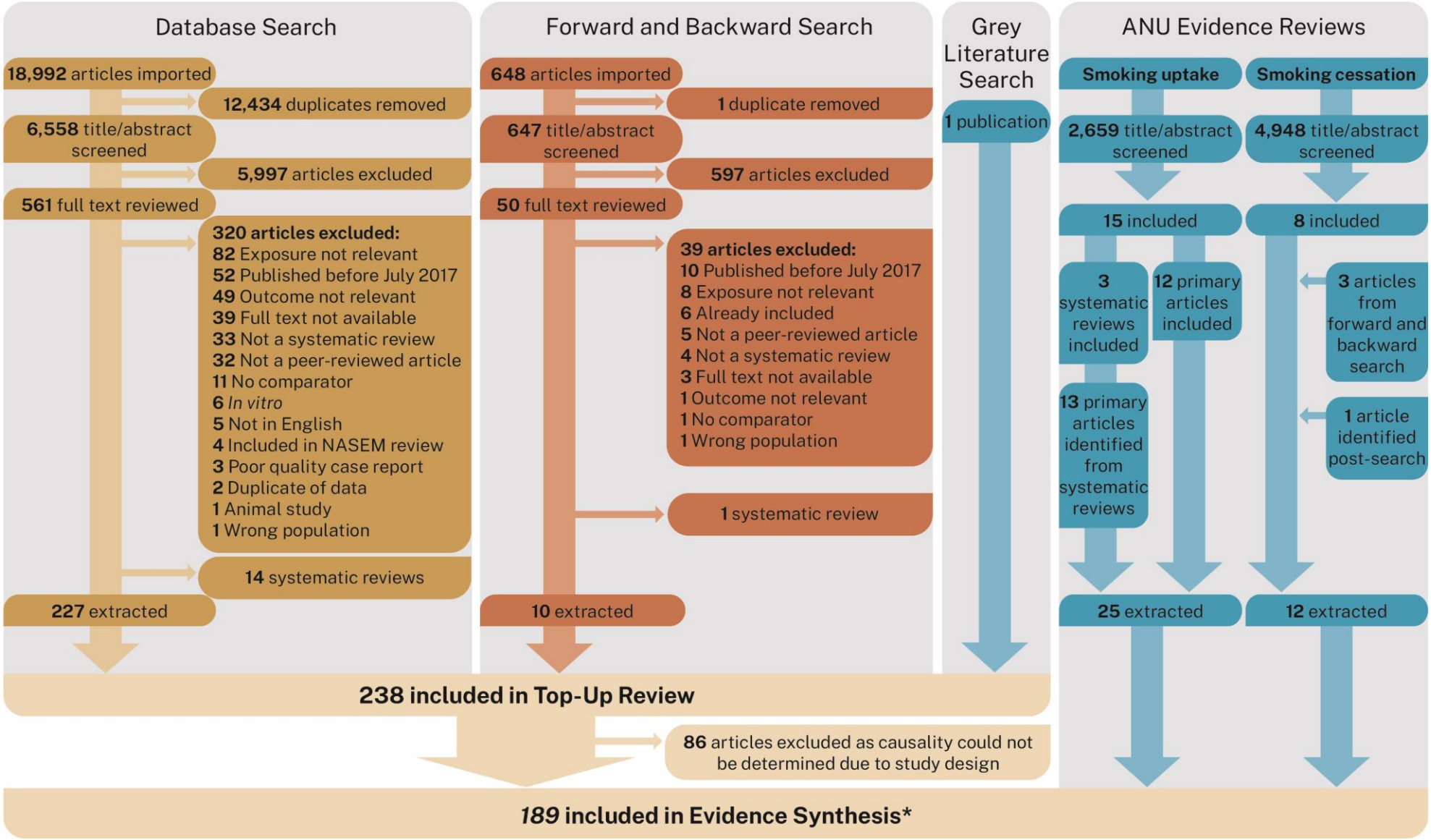
Results: 50

Appendix 3: Inclusion and exclusion criteria

PICO	Inclusion Criteria	Exclusion Criteria
Population	General population Priority subgroups: - Non-smoking populations - Children and youth - Aboriginal and Torres Strait Islander communities - Current smokers	Animals *In vitro*
Intervention	Exposure to nicotine- or non-nicotine- e-cigarettes or e-liquids	Heat-not-burn and other tobacco products Passive exposure or second- or third- hand exposure
Comparison	Never smokers (e-cigarette or combustible tobacco products), or Former smokers (former e-cigarette smoker or former combustible tobacco smoker/dual user). For some outcomes where no other comparator is possible, smoker populations will be considered	Current combustible tobacco smokers Dual users
Outcomes	Primary outcomes are clinical disease endpoints, such as myocardial infarction, stroke and cancer. Measures of physiological response or biological effect – such as intermediate markers of disease or health outcome (e.g., atherosclerosis, high blood pressure, lung damage), will be considered if they are likely to be specifically informative. Health outcomes include: Dependence Abuse liability Cardiovascular disease Cancer Respiratory disease Oral disease Development and reproductive effects Injuries, burns and poisonings Mental health Environmental impacts relevant to human health e.g., fire Any other health outcomes derived from the search (e.g., neurological, sleep, adverse events, optical health, wound healing, olfactory, endocrine, allergic diseases and haematological)	Studies that measure the suppression of withdrawal and craving related to combustible tobacco smoking only
Study type	Human studies Published, peer-reviewed original research The highest quality data will be prioritised, in the following order and dependent on the health outcome under investigation: - Randomised controlled trials (including randomised crossover trials) - Prospective cohort studies - Case-control studies - Non-randomised intervention studies (with comparison group or compared to baseline) For health outcomes where epidemiological studies are not available or are not relevant, and where these types of evidence are likely to be informative, other forms of evidence listed below will be considered: - Cross-sectional surveys	Primary evidence included in the NASEM review, Public Health England review and CSIRO review Qualitative studies Conference abstracts, letters, editorials, correspondence, opinion pieces, position statements Case reports/series of poor quality

	- Case reports and case series (particularly for exposure-dependent health outcomes, e.g., burns/injuries, poisonings) - Grey literature/reports from passive surveillance systems	
Follow-up period	No restrictions	
Setting	Any country	No exclusion criteria
Time period	From 2017 to July 2020 (date of search). As searches cannot be limited by month of year, studies published prior to July 2017 will be manually excluded.	Published before July 2017 and included in the NASEM review
Language	English only	Not available in English
Other		Duplicated data Unavailable full text Focus on e-cigarette ingredients/ toxicology (with no health outcome) Focus on factors associated with e-cigarette uptake, not health outcomes Prevalence study on e-cigarette use Focus on perceptions of e-cigarette safety Focus on e-cigarette particle distribution Studies otherwise inappropriate for this section

Appendix 4: PRISMA



* Numbers will not add up to other counts as some articles addressed more than one outcome.

Appendix 5: Overview of study papers with clinical outcomes included in the top-up review by health outcomes category and study design table

Health outcome	Meta-analyses	Randomised controlled trial	Cohort study	Non-randomised intervention study	Case-control study	Surveillance report	Cross-sectional survey	Case series	Case report
Dependence		1 0 / 1	1 0 / 1	8 4 / 4			20 11 / 9		
Cardiovascular health outcomes							5 0 / 5		
Cancer			1 1 / 0						1 0 / 1
Respiratory health outcomes			4 2 / 2			18 0 / 18	12 2 / 10	7 0 / 7	8 0 / 8
Oral health			2 1 / 1	2 2 / 0			3 0 / 3		1 0 / 1
Developmental and reproductive effects			2 0 / 2				1 0 / 1		
Burns and injuries						7 1 / 6		24 14 / 10	16 5 / 11
Poisoning						25 13 / 12		4 2 / 2	23 14 / 9
Mental health effects							3 0 / 3		
Environmental hazards with health implications*				17 9 / 8		2 0 / 2		5 0 / 5	
Neurological outcomes						3 0 / 3		2 0 / 2	7 1 / 6
Sleep outcomes							4 0 / 4		
Less serious adverse events		11 3 / 8	3 1 / 2	2 2 / 0		1 0 / 1	3 0 / 3		
Optical health									
Wound healing									1 0 / 1
Olfactory outcomes									
Endocrine outcomes									
Allergic diseases							2 0 / 2	1 0 / 1	3 2 / 1
Haematological outcomes									0 0 / 2

Notes:
* Characterisation of studies in environmental differs from other outcomes. Those included in non-randomised intervention studies are controlled experimental studies and those included in case series are natural experiments.
- The top large number is the combined count of studies from the NASEM review and the top-up review; the first small number is the count of studies from the NASEM review; the second small number is the count of additional studies from the top-up review.
- Numbers in green relate to evidence most relevant to the assessment of causation; numbers in red relate to evidence of generally limited contribution to the assessment of causation.
- Study counts exclude studies from the NASEM review that are outside our eligibility criteria, e.g., THC e-cigarette use, biomarker outcomes.
- In a small number of cases, indicated study design may be different to the design as stated by individual study authors.

Appendix 6: GRADE table

Outcome	Risk of bias[1]	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the evidence[2]
Clinical outcomes						
Randomised controlled trials						
Dependence 1 study	Serious concerns	Serious concerns	Not applicable	Very serious concerns	Not detected	Very low
Cardiovascular health outcomes	No studies identified					
Cancer	No studies identified					
Respiratory health outcomes	No studies identified					
Oral health	No studies identified					
Developmental and reproductive effects	No studies identified					
Burns and injuries	GRADE was not applied					
Poisoning	GRADE was not applied					
Mental health effects	No studies identified					
Environmental hazards with health implications	No studies identified					
Neurological outcomes	No studies identified					
Sleep outcomes	No studies identified					
Less serious adverse events 33 studies	Very serious concerns	Very serious concerns	Very serious concerns	Very serious concerns	Not detected	Very low
Optical health	No studies identified					
Wound healing	No studies identified					
Olfactory outcomes	No studies identified					
Endocrine outcomes	No studies identified					
Allergic diseases	No studies identified					
Haematological outcomes	No studies identified					
Smoking uptake	Not applicable					
Smoking cessation (Overall GRADE)	Very serious concerns[3]	No concerns	No concerns	Very serious concerns	Undetected	Very low
Non-randomised studies[4]						
Dependence (1 cohort, 8 non-randomised intervention, 21 cross-sectional)	Very serious concerns	Very serious concerns	No concerns	Serious concerns	Not detected	Very low

Outcome	Risk of bias[1]	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the evidence[2]
Cardiovascular health outcomes	No studies identified					
Cancer 1 study (1 cohort)	Very serious concerns	Serious concerns	Not applicable	Serious concerns	Not detected	Very low
Respiratory health outcomes 4 studies (4 cohort)	Serious concerns	Very serious concerns	No concerns	Serious concerns	Not detected	Very low
Oral health 3 studies (2 cohort, 1 non-randomised intervention)	No concerns	Serious concerns	Serious concerns	Serious concerns	Not detected	Very low
Developmental and reproductive effects 3 studies (2 cohort, 1 cross-sectional)	No concerns	Serious concerns	Serious concerns	Very serious concerns	Not detected	Very low
Burns and injuries	GRADE was not applied					
Poisoning	GRADE was not applied					
Mental health effects	No studies identified					
Environmental hazards with health implications 22 studies (17 controlled, 5 natural experiment)	Serious concerns	Serious concerns	Very serious concerns	Very serious concerns	Not detected	Very low
Neurological outcomes	GRADE was not applied					
Sleep outcomes	No studies identified					
Less serious adverse events 21 studies (4 non-randomised intervention, 17 cohort)	Very serious concerns	Serious concerns	Serious concerns	Very serious concerns	Not detected	Very low
Optical health	No studies identified					
Wound healing	No studies identified					
Olfactory outcomes	No studies identified					
Endocrine outcomes	No studies identified					
Allergic diseases	No studies identified					
Haematological outcomes	No studies identified					
Smoking uptake	GRADE was not applied					
Smoking cessation	Not applicable					
Subclinical/intermediate outcomes						
Randomised controlled trials						
Abuse liability 13 studies	Very serious concerns	Very serious concerns	Very serious concerns	Very serious concerns	Not detected	Very low

Outcome	Risk of bias[1]	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the evidence[2]
Cardiovascular health outcomes	No studies identified					
Cancer	No studies identified					
Respiratory health outcomes 9 studies	Serious concerns	Very serious concerns	Very serious concerns	Very serious concerns	Not detected	Very low
Oral health	No studies identified					
Developmental and reproductive effects	No studies identified					
Burns and injuries	GRADE was not applied					
Poisoning	GRADE was not applied					
Mental health effects	No studies identified					
Environmental hazards with health implications	No studies identified					
Neurological outcomes	Not applicable					
Sleep outcomes	Not applicable					
Less serious adverse events	Not applicable					
Optical health	No studies identified					
Wound healing	No studies identified					
Olfactory outcomes	No studies identified					
Endocrine outcomes	No studies identified					
Allergic diseases	Not applicable					
Haematological outcomes	Not applicable					
Smoking uptake	Not applicable					
Smoking cessation	Not applicable					
Non-randomised studies[4]						
Abuse liability 16 studies (15 non-randomised intervention, 1 cross-sectional)	Serious concerns	Serious concerns	Very serious concerns	Very serious concerns	Not detected	Very low
Cardiovascular health outcomes	No studies identified					
Cancer	No studies identified					
Respiratory health outcomes 9 studies (4 cohort, 8 non-randomised intervention)	Very serious concerns	Very serious concerns	Very serious concerns	Very serious concerns	Not detected	Very low
Oral health 2 studies (1 cohort, 1 non-randomised intervention)	No concerns	Very serious concerns	Very serious concerns	Very serious concerns	Not detected	Very low

Outcome	Risk of bias[1]	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the evidence[2]
Developmental and reproductive effects	No studies identified					
Burns and injuries	GRADE was not applied					
Poisoning	GRADE was not applied					
Mental health effects 3 studies (3 cohort)	Very serious concerns	Very serious concerns	Very serious concerns	Serious concerns	Not detected	Very low
Environmental hazards with health implications	No studies identified					
Neurological outcomes	Not applicable					
Sleep outcomes	Not applicable					
Less serious adverse events	Not applicable					
Optical health 1 study (1 non-randomised intervention)	Serious concerns	Very serious concerns	Not applicable	Very serious concerns	Not detected	Very low
Wound healing	No studies identified					
Olfactory outcomes 1 study (1 non-randomised intervention)	Serious concerns	Serious concerns	Not applicable	Very serious concerns	Not detected	Very low
Endocrine outcomes 2 studies (2 cross-sectional)	Serious concerns	Serious concerns	Very serious concerns	Serious concerns	Not detected	Very low
Allergic diseases	Not applicable					
Haematological outcomes	Not applicable					
Smoking uptake	Not applicable					
Smoking cessation	Not applicable					

[1]Risk of bias assessments (using the Joanna Briggs Institute's (JBI) critical appraisal checklists) were only available for studies included in the top-up review. Rating should be interpreted with caution.
[2]Certainty of evidence should be interpreted with caution as risk of bias was available only for studies in the top-up review.
[3]Risk of bias assessments were conducted using the Cochrane risk-of-bias tool for randomised controlled trials.[814]
[4]No studies were eligible for upgrading-criteria not presented in table.

Appendix 7: Additional materials identified after database searches and not included in major international reviews

These materials were considered relevant to the review but were published after the search was completed. The articles were identified non-systematically and were not included in the evidence synthesis.

1. Chan BS, Kiss A, McIntosh N, Sheppeard V, Dawson AH. E-cigarette or vaping product use-associated lung injury in an adolescent. *Medical Journal of Australia* 2021; 215: 313-314.e1. https://doi: 10.5694/mja2.51244.

   In September 2020, a Sydney public health unit was notified of the admission to a tertiary paediatric hospital intensive care unit of a 15-year-old girl with suspected e-cigarette or vaping product use-associated lung injury (EVALI). The girl had presented to another Sydney hospital with a four-day history of dysuria, urinary frequency and back pain followed by two days of vomiting and rigors.

   She reported vaping nicotine two to three times weekly for the previous seven months. Her drug history subsequently revealed that she had vaped 300 puffs from a prefilled nicotine vaping device (5% nicotine concentration; 20-pack equivalent) every three weeks for about seven months. She had also used tetrahydrocannabinoids (THC) via a water pipe in the previous four months. She last used THC more than a week before presentation to hospital but had never used THC via a vape device. She admitted to also smoking cigarettes for the past seven months. Her urine drug screen result on the day of admission was positive for cannabinoids and benzodiazepines.

   The patient had a similar presentation to other reported EVALI cases and fulfilled the Centers for Disease Control and Prevention (CDC) case definition of EVALI as she used e-cigarettes within 90 days of her symptom onset, had bilateral pulmonary infiltrates on chest x-ray and computed tomography, and there was an absence of pulmonary infection. The patient was discharged after a seven-day admission.

   The patient gave environmental health officers a flavoured vape device that she had used just before becoming ill. The device was submitted to the NSW Forensic and Analytical Science Service, which found that the vape fluid contained glycerol, nicotine, flavouring agents ethyl-maltol and menthol. THC and vitamin E acetate were not detected.

2. Bendel GS, Hiller HM, Ralston A. Nicotine toxicity secondary to aftermarket modifications to a vaping device. *Military Medicine* 2021; usab223. https://doi.org/10.1093/milmed/usab223.

   Electronic cigarettes continue to rise in popularity as a reportedly safe alternative to standard cigarette smoking. Their use has become common in our society and specifically in our young active duty population. This cigarette smoking alternative has come under recent scrutiny with the discovery of e-cigarette or vaping product use-associated lung injury. However, there is another potential risk associated with vaping: the relative ease at which vaping devices can be modified has allowed a growing community of users to invent novel ways of delivering higher concentrations of nicotine. Here, we describe two cases of active duty patients who presented to an emergency department with clinical nicotine toxicity after using a heavily modified e-cigarette.

3. Froggatt S, Reissland N, Covey J. The effects of prenatal cigarette and e-cigarette exposure on infant neurobehaviour: A comparison to a control group. *EClinicalMedicine* 2020; 28: 100602. https://doi.org/10.1016/j.eclinm.2020.100602.

   Background: Infant neurobehaviour provides an insight into the development of the central nervous system during infancy, with behavioural abnormalities highlighting a cause for concern. Research has demonstrated that prenatal exposure to cigarettes leads to deficits within neurobehavioural development, along with negative birth outcomes detrimental to subsequent development. With the growing use of e-cigarettes amongst pregnant women, this study explores how prenatal e-cigarette exposure compares to prenatal cigarette exposure.

   Methods: Eighty-three infants were involved in the study, either exposed prenatally to cigarettes or e-cigarettes or not exposed to either. Differences were assessed between these three groups

for birth outcomes and scores on the Neonatal Behavioural Assessment Scale (NBAS) at one month of age.

Findings: Both cigarette and e-cigarette exposed infants had a significantly greater number of abnormal reflexes (p=.001; p=.002). For both self-regulation and motor maturity, cigarette exposed infants performed significantly worse (p=.010; p=.002), with e-cigarette exposed infants having decreased motor maturity (p=.036) abilities and marginally decreased for self-regulation (p=.057). Birth outcomes, namely birthweight, gestation and head circumference, did not differ for e-cigarette exposed infants compared with infants who were not prenatally exposed to nicotine. Cigarette exposed infants had a significantly lower birthweight (p=.021) and reduced head circumference (p=.008) in comparison to non-exposed infants.

Interpretation: To our knowledge, this is the first research study assessing a neurological outcome as a result of e-cigarette exposure. Findings of this have potentially important implications for public health policies regarding the safety and use of e-cigarettes throughout pregnancy.

4. Regan AK, Bombard JM, O'Hegarty MM, Smith RA, Tong VT. Adverse birth outcomes associated with prepregnancy and prenatal electronic cigarette use. *Obstetrics & Gynecology* 2021; 138(1): 85 – 94. https://doi.org/10.1097/AOG.0000000000004432.

   Objective: To evaluate the risk of adverse birth outcomes among adults who use electronic cigarettes (e-cigarettes) before and during pregnancy.

   Methods: Data from the 2016–2018 PRAMS (Pregnancy Risk Assessment Monitoring System) were used to assess the association between e-cigarette use during the 3 months before and last 3 months of pregnancy among 79,176 individuals with a recent live birth and the following birth outcomes: preterm birth, small for gestational age, and low birth weight (LBW). Adjusted prevalence ratios were generated using average marginal predictions from multivariable logistic regression models. Models were stratified by prenatal combustible cigarette smoking and frequency of e-cigarette use (daily or less than daily use).

   Results: In the 3 months before pregnancy, 2.7% (95% CI 2.6–2.9%) of respondents used e-cigarettes; 1.1% (95% CI 1.0–1.2%) used e-cigarettes during the last 3 months of pregnancy. Electronic cigarette use before pregnancy was not associated with adverse birth outcomes. Electronic cigarette use during pregnancy was associated with increased prevalence of LBW compared with nonuse (8.1% vs. 6.1%; adjusted prevalence ratio 1.33; 95% CI 1.06–1.66). Among respondents who did not also smoke combustible cigarettes during pregnancy (n=572,256), e-cigarette use was associated with higher prevalence of LBW (10.6%; adjusted prevalence ratio 1.88; 95% CI 1.38–2.57) and preterm birth (12.4%; adjusted prevalence ratio 1.69; 95% CI 1.20–2.39). When further stratified by frequency of e-cigarette use, associations were seen only for daily users.

   Conclusion: E-cigarette use during pregnancy, particularly when used daily by individuals who do not also smoke combustible cigarettes, is associated with adverse birth outcomes.

5. The Coroners Court of Victoria. (2019). Inquest into the Death of BABY J (File No. COR 2018 2773) https://www.coronerscourt.vic.gov.au/sites/default/files/2019-07/Baby%20J_277318.pdf.

   Coroner Phillip Byrne "investigated the death of baby J and having held an inquest in relation to his death on 8 July 2019 at The Coroners Court of Victoria" found Baby J died from 1(a) hypoxic ischaemic encephalopathy post cardiac arrest 1(b) nicotine toxicity.

   A Victorian Institute of Forensic Medicine (VIFM) Toxicology Report advised that Baby J's death was due to: 1(a) Hypoxic Ischaemic Encephalopathy Post Cardia Arrest 1(b) Nicotine toxicity.

   Finding: "Baby J died at the Royal Children's Hospital, Parkville on 10 June 2018 as a result of him ingesting an unknown quantity of concentrated liquid nicotine; his untimely death was due to a tragic accident."

   Recommendation: "the Department of Health and Human Services conduct a public awareness campaign in relation to liquid nicotine per se, not the broad issues surrounding e-cigarettes, and nicotine free liquids utilised in vaping."

6. Center for Tobacco Products – Special Announcement Some E-cigarette Users Are Having Seizures, Most Reports Involving Youth and Young Adults. https://www.fda.gov/tobacco-

products/ctp-newsroom/some-e-cigarette-users-are-having-seizures-most-reports-involving-youth-and-young-adults

Since June 2018, the Food and Drug Administration (FDA) observed a slight but noticeable increase in reports of seizures. After examining poison control centers' reports between 2010 and early 2019, the FDA determined that, between the poison control centers and the FDA, there were a total of 35 reported cases of seizures mentioning use of e-cigarettes within that time frame.

Seizures have been reported among first-time e-cigarette users and experienced users. In a few situations, e-cigarette users reported a prior history of seizure diagnosis. A few reported cases indicated seizures in association with use of other substances such as marijuana or amphetamines. Seizures have been reported as occurring after a few puffs or up to one day after use. Most of the self-reported data that the FDA has received does not contain any specific brand or sub-brand information about the e-cigarette.

While detailed information is currently limited, the FDA is alerting the public to this important and potentially serious health issue.

- Healthcare providers should be aware that seizures may be associated with e-cigarette use—redacted reports of past incidents (/media/122794/download) are available on the FDA website and may assist medical evaluations of seizures.
- Consumers should recognize the wide range of symptoms that may be associated with e-cigarette use and the importance of reporting new or unexpected seizures to their doctor or clinic.
- Parents, teachers, and other concerned adults should be aware that many youth are using e-cigarettes that closely resemble a USB flash drive, have high levels of nicotine and emissions that are hard to see.
- Youth and young adult users should also be aware that some e-cigarettes (also called vapes) can contain high levels of nicotine, even as much nicotine as a pack of regular cigarettes. Teens who vape may end up addicted to nicotine faster than teens who smoke. Vapes may be used more frequently because they are easier to hide and may expose users to more nicotine. There are no safe tobacco products.

7. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Fanshawe TR, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2021, Issue 4. Art. No.: CD010216. https://doi.org/10.1002/14651858.CD010216.pub5.

   Background: Electronic cigarettes (ECs) are handheld electronic vaping devices which produce an aerosol formed by heating an e-liquid. Some people who smoke use ECs to stop or reduce smoking, but some organizations, advocacy groups and policymakers have discouraged this, citing lack of evidence of efficacy and safety. People who smoke, healthcare providers and regulators want to know if ECs can help people quit and if they are safe to use for this purpose. This is an update of a review first published in 2014.

   Objectives: To examine the effectiveness, tolerability, and safety of using electronic cigarettes (ECs) to help people who smoke achieve long-term smoking abstinence.

   Search methods: We searched the Cochrane Tobacco Addiction Group's Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and PsycINFO to 1 February 2021, together with reference-checking and contact with study authors.

   Selection criteria: We included randomised controlled trials (RCTs) and randomised cross-over trials in which people who smoke were randomised to an EC or control condition. We also included uncontrolled intervention studies in which all participants received an EC intervention. To be included, studies had to report abstinence from cigarettes at six months or longer and/or data on adverse events (AEs) or other markers of safety at one week or longer.

   Data collection and analysis: We followed standard Cochrane methods for screening and data extraction. Our primary outcome measures were abstinence from smoking after at least six months follow-up, adverse events (AEs), and serious adverse events (SAEs). Secondary outcomes included changes in carbon monoxide, blood pressure, heart rate, blood oxygen saturation, lung function, and levels of known carcinogens/toxicants. We used a fixed-effect Mantel-Haenszel model to calculate the risk ratio (RR) with a 95% confidence interval (CI) for dichotomous

outcomes. For continuous outcomes, we calculated mean differences. Where appropriate, we pooled data from these studies in meta-analyses.

Main results: We included 56 completed studies, representing 12,804 participants, of which 29 were RCTs. Six of the 56 included studies were new to this review update. Of the included studies, we rated five (all contributing to our main comparisons) at low risk of bias overall, 41 at high risk overall (including the 25 non-randomised studies), and the remainder at unclear risk.

There was moderate-certainty evidence, limited by imprecision, that quit rates were higher in people randomised to nicotine EC than in those randomised to nicotine replacement therapy (NRT) (risk ratio (RR) 1.69, 95% confidence interval (CI) 1.25 to 2.27; I^2=0%; 3 studies, 1498 participants). In absolute terms, this might translate to an additional four successful quitters per 100 (95% CI 2 to 8). There was low certainty evidence (limited by very serious imprecision) that the rate of occurrence of AEs was similar) (RR 0.98, 95% CI 0.80 to 1.19; I^2=0%; 2 studies, 485 participants). SAEs occurred rarely, with no evidence that their frequency differed between nicotine EC and NRT, but very serious imprecision led to low certainty in this finding (RR 1.37, 95% CI 0.77 to 2.41: I^2=n/a; 2 studies, 727 participants).

There was moderate certainty evidence, again limited by imprecision, that quit rates were higher in people randomised to nicotine EC than to non-nicotine EC (RR 1.70, 95% CI 1.03 to 2.81; I^2=0%; 4 studies, 1057 participants). In absolute terms, this might again lead to an additional four successful quitters per 100 (95% CI 0 to 11). These trials mainly used older EC with relatively low nicotine delivery. There was moderate-certainty evidence of no difference in the rate of AEs between these groups (RR 1.01, 95% CI 0.91 to 1.11; I^2=0%; 3 studies, 601 participants). There was insufficient evidence to determine whether rates of SAEs differed between groups, due to very serious imprecision (RR 0.60, 95% CI 0.15 to 2.44; I^2=n/a; 4 studies, 494 participants).

Compared to behavioral support only/no support, quit rates were higher for participants randomised to nicotine EC (RR 2.70, 95% CI 1.39 to 5.26; I^2=0%; 5 studies, 2561 participants). In absolute terms this represents an increase of seven per 100 (95% CI 2 to 17). However, this finding was of very low certainty, due to issues with imprecision and risk of bias. There was no evidence that the rate of SAEs differed, but some evidence that non-serious AEs were more common in people randomised to nicotine EC (AEs: RR 1.22, 95% CI 1.12 to 1.32; I^2=41%, low certainty; 4 studies, 765 participants; SAEs: RR 1.17, 95% CI 0.33 to 4.09; I^2=5%; 6 studies, 1011 participants, very low certainty).

Data from non-randomised studies were consistent with RCT data. The most commonly reported AEs were throat/mouth irritation, headache, cough, and nausea, which tended to dissipate with continued use. Very few studies reported data on other outcomes or comparisons and hence evidence for these is limited, with confidence intervals often encompassing clinically significant harm and benefit.

Author's conclusions: There is moderate certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain. More studies are needed to confirm the size of effect, particularly when using modern EC products. Confidence intervals were for the most part wide for data on AEs, SAEs and other safety markers, though evidence indicated no difference in AEs between nicotine and non-nicotine ECs. Overall incidence of SAEs was low across all study arms. We did not detect any clear evidence of harm from nicotine EC, but longest follow-up was two years and the overall number of studies was small. The evidence is limited mainly by imprecision due to the small number of RCTs, often with low event rates. Further RCTs are underway. To ensure the review continues to provide up-to-date information, this review is now a living systematic review. We run searches monthly, with the review updated when relevant new evidence becomes available. Please refer to the Cochrane Database of Systematic Reviews for the review's current status.

Appendix 8. EVALI definition – Centers for Disease Control and Prevention (CDC)

Confirmed case

1. Using an e-cigarette ("vaping") or dabbing* in 90 days prior to symptom onset.
   AND
2. Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT.
   AND
3. Absence of pulmonary infection on initial work-up. Minimum criteria are:
   (a) A negative respiratory viral panel.
   AND
   (b) A negative influenza PCR or rapid test, if local epidemiology supports influenza testing.
   AND
4. All other clinically-indicated respiratory infectious disease testing (e.g., urine Antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture if productive cough, bronchoalveolar lavage (BAL) culture if done, blood culture, HIV-related opportunistic respiratory infections if appropriate) are negative.
   AND
5. No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process).

Probable case

1. Using an e-cigarette ("vaping") or dabbing* in 90 days prior to symptom onset.
   AND
2. Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT.
   AND
3. Infection identified via culture or PCR, but clinical team** believes this infection is not the sole cause of the underlying lung injury **OR minimum criteria** to rule out pulmonary infection not met (testing not performed) and clinical team** believes infection is not the sole cause of the underlying lung injury.
   AND
4. No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process).

*Using an electronic device (e.g., electronic nicotine delivery system (ENDS), electronic cigarette, e-cigarette, vaporizer, vape(s), vape pen, dab pen, or other device) or dabbing to inhale substances (e.g., nicotine, marijuana, THC, THC concentrates, CBD, synthetic cannabinoids, flavourings, or other substances).

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