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2022 CEO Statement on Electronic Cigarettes: Plain-English Summary

The CEO Statement provides public health advice on the safety and impacts of electronic cigarettes (e-cigarettes) based on review of the current evidence.

ABOUT E-CIGARETTES

- E-cigarettes[1] heat liquid containing chemicals (e-liquids) that users breathe in. Using an e-cigarette is also known as vaping.
- There are many different types of e-cigarettes. The way e-cigarettes are made and used varies. This variability makes it hard to know if they are safe or if they can harm your health.

PRODUCT SAFETY

- E-liquids can contain nicotine (even when labelled 'nicotine-free') and many other chemicals. More than 200 chemicals have been detected in e-liquids.
- E-cigarettes can be harmful. All e-cigarette users are exposed to chemicals and toxins that can harm your health.
- Use of e-cigarettes can result in serious burns and injuries. In some cases, these burns and injuries have resulted in death.

HEALTH EFFECTS

- Use of e-cigarettes can result in seizures in some users.
- Exposure to e-liquids that contain nicotine can result in poisoning for some users which, although it may not happen to everyone, can be severe and cause death.
- E-cigarette-related calls to Australian Poisons Information Centres have increased over the last 5 years. Most poisonings occur in toddlers and adults.
- Use of e-cigarettes can result in a serious and sometimes fatal lung condition known as E-cigarette or Vaping Associated Lung Injury (EVALI) in some users. Most cases of EVALI are linked to cannabis oils and vitamin E acetate but other chemicals may also contribute to this condition.
- Use of e-cigarettes that contain nicotine probably results in throat irritation, cough, dizziness, headaches and nausea.
- There is not enough information from human research studies to know about the potential impacts of e-cigarette use on conditions such as cancer and cardiovascular disease, reproductive health, respiratory conditions (e.g. asthma) and mental illness.
- Lack of information does not mean that e-cigarettes are safe. More information is needed to know if long-term e-cigarette use is safe or if it harms your health.

Specific health effects by tobacco smoking status

In addition to the health effects listed above:

If you **have never smoked tobacco cigarettes** and you use or are thinking of using e-cigarettes

- There are no health benefits of using e-cigarettes if you do not currently smoke tobacco cigarettes.
- You can become addicted if you use e-cigarettes that contain nicotine.

[1] Electronic cigarettes are also known as e-cigarettes, e-cigs, electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENNDS), alternative nicotine delivery systems, personal vaporisers, e-hookahs, vape pens or vapes.

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If you are a **current tobacco smoker** and you use or are thinking of using e-cigarettes

- You will probably experience immediate increases in heart and blood pressure and stiffening of the arteries if you use e-cigarettes.
- You may become addicted to e-cigarettes if they contain nicotine and you may use e-cigarettes in excess.

If you are a **former tobacco smoker** and you use or are thinking of using e-cigarettes

- You may experience a decrease in blood pressure after you have switched.

E-CIGARETTE USE AND UPTAKE

- E-cigarette use has increased in Australia since 2016. This increase has been reported across most age groups, especially among youth and young adults.
- Teenagers are more likely to try e-cigarettes if they are exposed to e-cigarettes on social media.
- More information is needed on what makes e-cigarettes appealing, such as flavours, packaging and price.

E-CIGARETTE USE AND TOBACCO SMOKING

Tobacco smoking uptake

If you **have never smoked tobacco cigarettes** and you use or are thinking of using e-cigarettes

- You are more likely to try tobacco smoking if you use e-cigarettes.
- You are more likely to become a tobacco smoker if you use e-cigarettes.

Tobacco smoking cessation

If you are a **current tobacco smoker** and you use or are thinking of using e-cigarettes

- There are other proven safe and effective options to help you quit smoking. E-cigarettes are not proven safe and effective smoking cessation aids.
- Short-term e-cigarette use may benefit you if you are able to quit smoking and have been previously unsuccessful with other smoking cessation aids. However, not everyone finds e-cigarettes helpful for quitting.
- Research studies have found that it was more common for smokers to become dual users (using both e-cigarettes and tobacco products at the same time) than quit if they used nicotine e-cigarettes.
- For some smokers, using nicotine e-cigarettes may assist them to quit; however, more research is needed to confirm the harms and benefits of using them for this purpose.
- For additional assistance to quit tobacco smoking or quit e-cigarettes you are encouraged to seek further information from reliable sources, such as your healthcare practitioner or quit services.

Relapse to tobacco smoking

If you are a **former tobacco smoker** and you use or are thinking of using e-cigarettes

- Using an e-cigarette may increase your chance of smoking relapse.

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NHMRC e-cigarette infographics

April 2022 | Final concept

Concept A — primary campaign graphic

Concept A — infographic

Concept A — social media tiles

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BMJ Open

E-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis

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ABSTRACT

Objective To review and summarise the current evidence on the uptake of combustible cigarette smoking following e-cigarette use in non-smokers—including never-smokers, people not currently smoking and past smokers—through an umbrella review, systematic review and meta-analysis.

Design Umbrella review, systematic review and meta-analysis.

Data sources PubMed, Scopus, Web of Science, PsychINFO (Ovid), Medline (Ovid) and Wiley Cochrane Library up to April 2020.

Results Of 6225 results, 25 studies of non-smokers—never, not current and former smokers—with a baseline measure of e-cigarette use and an outcome measure of combustible smoking uptake were included. All 25 studies found increased risk of smoking uptake with e-cigarette exposure, although magnitude varied substantially. Using a random-effects model, comparing e-cigarette users versus non-e-cigarette users, among never-smokers at baseline the OR for smoking initiation was 3.25 (95% CI 2.61 to 4.05, I^2 85.7%) and among non-smokers at baseline the OR for current smoking was 2.87 (95% CI 1.97 to 4.19, I^2 90.1%). Among former smokers, smoking relapse was higher in e-cigarette users versus non-users (OR=2.40, 95% CI 1.50 to 3.83, I^2 12.3%).

Conclusions Across multiple settings, non-smokers who use e-cigarettes are consistently more likely than those avoiding e-cigarettes to initiate combustible cigarette smoking and become current smokers. The magnitude of this risk varied, with an average of around three times the odds. Former smokers using e-cigarettes have over twice the odds of relapse as non-e-cigarettes users. This study is the first to our knowledge to review and pool data on the latter topic.

PROSPERO registration number CRD42020168596.

Strengths and limitations of this study

- Comprehensive and systematic literature search with pooled evidence from 25 published studies reviewed according to a prespecified protocol.
- Inclusion of studies investigating all ages and types of non-smokers (never, not current and former).
- Independent corroboration of results from previous studies, reviews and meta-analyses, while adding evidence on smoking uptake with e-cigarette exposure among former smokers.
- The evidence is largely reliant on self-reported product use and the studies reviewed were observational in nature as it is not ethical or appropriate to randomise non-smokers to e-cigarette exposure.
- While all studies reported significantly higher uptake of tobacco smoking among non-smokers exposed to e-cigarettes, compared with those not exposed, there was significant variation in the magnitude of the observed increase in risk; the results of the meta-analyses should therefore be considered to be an average of the published studies.

INTRODUCTION

Globally, combustible tobacco smoking results in over 8 million deaths each year.[1] Due to vigorous public health interventions, smoking prevalence in Australia has declined substantially over the last 50 years.[2] Nevertheless, 9.3% of the total disease burden (in disability-adjusted life years) was attributable to combustible tobacco use in 2015.[3]

E-cigarettes are a diverse group of battery-operated or rechargeable devices that heat a liquid ('e-liquid' or 'e-juice') to produce a vapour that users inhale. Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol and flavouring agents and are commonly used to deliver nicotine.[4] The labelling of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) is not always accurate, with reports of nicotine found in products labelled ENNDS.[4 5]

Studies indicate that in many countries, e-cigarette use among never-smoking youth is increasing.[6–11] In Australia, the proportion of non-smokers aged 14 years or older who had ever used e-cigarettes increased from 4.9% in 2016 to 6.9% in 2019.[12] The increase was particularly notable in young adults, with 20% of 18–24years old non-smokers reporting e-cigarette use.[12] E-cigarette use among youth is predominantly driven by curiosity and experimentation rather than smoking cessation.[13–15] Evidence also suggests that most people who report ever e-cigarette do not graduate to regular e-cigarette use.[15 16] Although the identification of risk factors for initiation of e-cigarette use is complex, it appears as though many are similar to those for smoking initiation.[17 18]

There are concerns that the use of e-cigarettes in never-smokers may increase the probability that they will try combustible tobacco cigarettes and go on to become regular smokers, particularly among youth and young adults.[19 20] Furthermore, use of e-cigarettes could conceivably lead to combustible tobacco smoking relapse in former smokers. If e-cigarette use leads to more people smoking combustible cigarettes, compared with the number of people who have smoked in the absence of e-cigarettes, this would be a source of considerable public health harm.[21] Thus, our primary research question is: among never smokers, current non-smokers and former smokers, how does e-cigarette use affect the subsequent risk of initiating use, current use and relapse to combustible tobacco cigarettes? This review aims to systematically update global contemporary population-level evidence on the relationship of e-cigarette use to smoking uptake.

METHODS

This summary of the global evidence comprises an umbrella review of systematic reviews and a top-up systematic review of primary research not included in the systematic reviews of the umbrella review. The protocol was published online through PROSPERO.

Search strategy

The Population, Intervention, Comparison, Outcome (PICO) format was used to structure the search (online supplemental table 1). Studies investigating the association between ENDS or ENNDS use among non-tobacco smokers and uptake of combustible cigarette smoking were included. E-cigarette use, cigarette smoking and uptake related search terms and keywords were used (online supplemental table 2). For both the umbrella review and the top-up systematic review, six databases (PubMed, Scopus, Web of Science, PsycINFO (Ovid), MEDLINE (Ovid) and Cochrane) were searched on 1 April 2020 (online supplemental table 3).

Inclusion and exclusion criteria

Systematic reviews and meta-analyses of prospective cohort studies or randomised or non-randomised controlled trials (RCTs) examining the exposure (e-cigarette use) and outcome (smoking uptake in current non-smokers) of interest were included in the umbrella review. For the top-up systematic review, individual prospective cohort studies or randomised or non-RCTs identified in the search and not included in the umbrella review studies, were included. Cross-sectional studies were excluded due to difficulties in establishing the temporal relationship between e-cigarette exposure and smoking uptake. Studies with a follow-up of less than 6 months or with abstracts not published in English were excluded. The full inclusion and exclusion criteria can be found in online supplemental table 1.

Data screening and extraction

EndNote and Covidence software were used for review management. Two authors of this review (ONB and LF) undertook initial screening, study selection, risk of bias assessment and data extraction. Titles and abstracts identified in the searches were screened using a checklist, followed by full-text screening. A forward and backward reference search using Scopus was performed from the final included articles. After removing duplicates, titles, abstracts and then full texts were screened for any studies fulfilling the inclusion and exclusion criteria. Data were independently extracted from the included systematic reviews and cohort studies using a prespecified 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 also extracted. Studies were considered separately if they received funding from the tobacco or nicotine industry.

Risk of bias assessment

Risk of bias for each study included was independently assessed using the AMSTAR 2[22] for the systematic reviews and meta-analyses included in the umbrella reviews, and the Newcastle-Ottawa Scale (NOS)[23] for the studies in the top-up systematic review. For meta-analyses with at least 10 studies, risk of bias across studies was assessed and interpreted using the symmetry of funnel plots and superimposed 95% confidence limits.[24]

Summary measures and synthesis of results

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 top-up systematic review were then considered in an integrated systematic review. Where appropriate, ORs from the studies in the integrated systematic review were combined using a random-effects model. Heterogeneity of study effect estimates were assessed by an I^2 statistic. All analyses were conducted using Stata V.16.1.

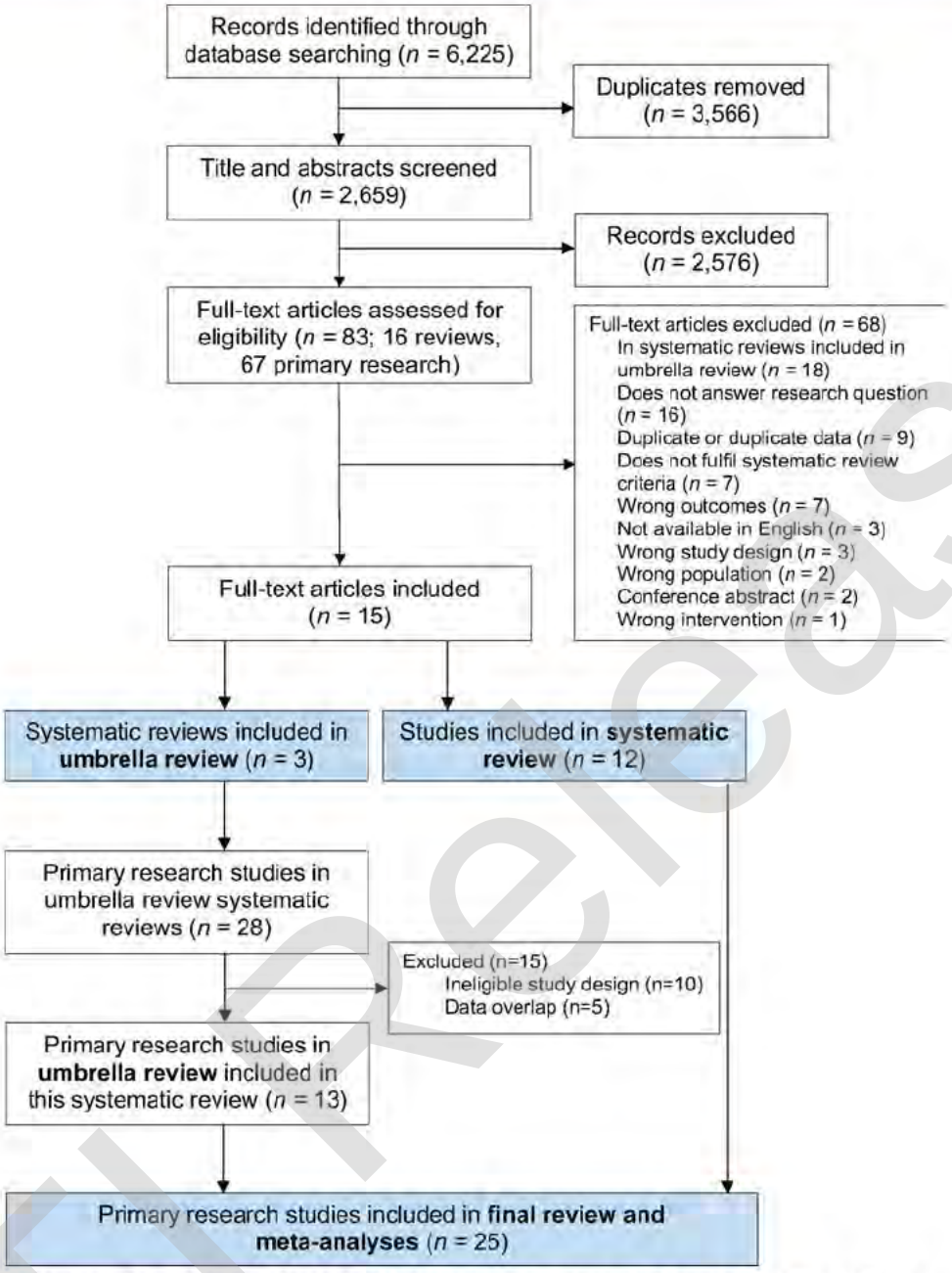

Figure 1 Flow chart for selection of studies for inclusion in umbrella review and top-up systematic review.

Patient and public involvement

No patient involved.

RESULTS

Study selection

Study selection for this umbrella review and top-up systematic review are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart in figure 1. A total of 6225 studies were identified for title and abstract screening; 2659 remained after exclusion of duplicates. After title and abstract screening, 83 articles were identified for full-text screening. Fifteen papers were identified for inclusion; three were systematic reviews that were included in the umbrella review and 12 were primary research studies included in the top-up systematic review. Ten of the latter studies were prospective observational studies and two were secondary analyses of RCTs.

From the three systematic review papers included in the umbrella review, 28 primary research studies were identified after removing duplicates. For our meta-analyses, we excluded 15 studies due to ineligible study design (n=10) or data overlap (n=5). No studies were excluded based on their quality assessment scores. The meta-analyses were thus based on 13 primary research studies identified from the prior systematic reviews, and 12 studies from our top-up systematic review, that is, a total of 25 primary research studies on e-cigarette use and smoking uptake (figure 1).

Table 1 ORs and adjusted ORs of the association between e-cigarette use and combustible cigarette smoking from systematic reviews and meta-analyses included in the umbrella review

Authors/year	Studies included (n=total population)	OR (95% CI)	Adjusted OR (95% CI) and heterogeneity (I^2)
Khouja *et al*[43]	17 (n=105 448)	4.59 (3.60 to 5.85)	2.92 (2.30 to 3.71) I^2: 84.5%
Aladeokin and Haighton[44]	8 (n=73 076)	5.55 (3.94 to 1.82)	3.86 (2.18 to 6.82) I^2: 74%
Soneji *et al*[21]	9 (n=17 389)	Initiation: 3.83 (3.74 to 3.91) Past 30-day: 5.68 (3.49 to 9.24)	Initiation: 3.50 (2.38 to 5.16) I^2: 56% Past 30-day: 4.28 (2.52 to 7.27) I^2: 0%

No potential competing interests were identified in the included studies themselves, or by the authors, based on the disclosure statements from the publications. Although one[25] primary research study identified during screening in the top-up systematic review was found to have potential competing interests, as it was funded by the tobacco industry, it was previously excluded due to a large overlap with data presented in a more recent paper by Berry *et al*.[26]

There is considerable uncertainty regarding the chemical constituents of the e-liquids delivered by the e-cigarettes in the studies included in the review. Where evidence on nicotine content was available, it indicated that a substantial majority of e-cigarettes in those studies delivered nicotine.[27–30] Many publications noted considerable uncertainty regarding nicotine content, including apparent mislabelling, and the need for greater clarity and reliability on this point.

Umbrella review: quality assessment

All three systematic reviews from the selected articles rated moderate in the AMSTAR 2[22] assessment. Information was lacking regarding study exclusion criteria, stated sources of funding and detail on data extraction (online supplemental table 4).

Umbrella review

Table 1 summarises the results of the three systematic reviews included in the umbrella review. All three systematic reviews excluded studies with participants over 30 years of age. Sample sizes for the individual studies varied considerably, ranging from 298 to 17 318. Of the 13 included longitudinal primary research studies (detailed in online supplemental table 5), 9[20 31–38] were based in the USA, 2[39 40] in the UK and 1 each in Mexico,[41] and the Netherlands.[42] Each of the three systematic reviews conducted meta-analyses and found the odds of smoking initiation were increased for youth and young adult e-cigarette users compared with non-e-cigarette users; these results are summarised in table 1.

The Khouja *et al* systematic review and meta-analysis included 17 studies published up to November 2018.[43] The study found that the risk of later smoking in people aged <30 years who had ever used or currently use e-cigarettes was strong; an almost threefold the odds compared with never users after adjustment for covariates (see table 1). However, there were high levels of heterogeneity in the summary estimates (adjusted OR I^2=84.5%), which remained high in adjusted analysis subgrouping by age, ever smoking, risk of bias and location of study. Heterogeneity was reduced when the adjusted ORs were grouped into those examining the relationship between ever e-cigarette use and current smoking (adjusted OR 2.21; 95% CI 1.72 to 2.84, I^2=5%) and those assessing the relationship of current e-cigarette use to ever smoking (adjusted OR 2.33; 95% CI 1.84 to 2.96, I^2=5%).

Aladeokin and Haighton aimed to systematically review the evidence on e-cigarette use and initiation of cigarette smoking in adolescents (aged 10–19 years old) in the UK and included eight studies.[44] Their meta-analysis showed e-cigarette users were much more likely than non-users to go on to smoke combustible cigarettes, even after adjusting for covariates (see table 1); the substantial heterogeneity in the summary estimate should be noted.

The Soneji *et al* systematic review and meta-analysis included nine longitudinal studies of US participants ≤30 years of age.[21] Seven of the included studies assessed the association of baseline ever e-cigarette use with subsequent ever combustible cigarette use at follow-up among baseline never smokers. Soneji *et al* also identified two studies that assessed baseline past 30-day e-cigarette use with subsequent past 30-day combustible cigarette use among those reporting no past 30-day use of cigarettes at baseline. The meta-analysis showed a markedly higher odds of combustible cigarette use in those who had used e-cigarettes (table 1).

Top-up systematic review: quality assessment

The quality of the included studies was evaluated using the NOS.[23] Of the 12 studies, the NOS totals (out of 10 stars) ranged from 5 to 8 (online supplemental table 6). Only one[45] study rated 5, five[28–30 46 47] rated 6, two[9 48] rated 7 and four[26 49–51] rated 8. No studies received a star for assessment of outcome. The main areas impacting the NOS scores were ascertainment of exposure and adequacy of follow-up of cohorts (studies with less than 30% loss to follow-up were considered adequate).

Top-up systematic review and integration with primary research studies from the umbrella review

A total of 12 studies published in 2018, 2019 and 2020 were newly identified for the top-up systematic review (table 2; online supplemental table 7). Among the 12 included, 6 were from the USA, 2 from the UK and 1

Table 2 ORs and adjusted ORs of the association between e-cigarette use and subsequent combustible cigarette use for: (1) never-smokers at baseline, (2) non-smokers* (never or no current use) at baseline and (3) former smokers at baseline

Authors/year	Country	Baseline cigarette use	E-cigarette use	Follow-up cigarette use	OR (95% CI)	Adjusted OR (95% CI)
Initiation in never smokers at baseline						
Berry *et al*[26]	USA	Never	Ever	Ever		4.09 (2.97 to 5.63)
Chien *et al*[27]	Taiwan	Never	Ever	Ever	2.44 (1.94 to 3.09)	2.14 (1.66 to 2.75)
Conner *et al*[47]	UK (England)	Never	Ever	Ever	4.03 (3.33 to 4.88)	2.78 (2.20 to 3.51)
McMillen *et al*[50]	USA	Never	Current†	Ever	16.4 (9.8 to 27.5)	6.6 (3.7 to 11.8)
Pénzes *et al*[46]	Romania	Never	Ever	Ever	2.75 (1.52 to 4.96)	3.57 (1.96 to 6.49)
Current use in non-smokers at baseline						
Aleyan *et al*[28]	Canada	Non-smokers*	Current†	Current†		Wave 1–2: 1.54 (1.37 to 1.74) Wave 2–3: 1.18 (1.08 to 1.29)
Barrington-Trimis *et al*[48]	USA	Never	Current†	Current†		*NHW to dual use*: 7.44 (3.63 to 15.3) *HW to dual use:* 3.64 (1.62 to 8.18)
Bold *et al*[45]	USA	No current*	Current†	Current†		Wave 1–2: 7.08 (2.34 to 21.42) Wave 2–3: 3.87 (1.86 to 8.06)
Conner *et al*[47]	UK (England)	Never	Ever	Current† Regular‡	3.38 (2.72 to 4.21) 3.60 (2.35 to 5.51)	2.17 (1.76 to 2.69) 1.27 (1.17 to 1.39)
Kinnunen *et al*[29]	Finland	Never	Ever nicotine-containing Ever non-nicotine containing	Daily	11.52 (4.91 to 27.01) 1.88 (0.25 to 14.45)	8.50 (2.14 to 29.19) With school clustering: 2.92 (1.09 to 7.85) 2.50 (0.25 to 12.05) With school clustering: 0.94 (0.22 to 4.08)
McMillen *et al*[50]	USA	Never	Ever (not current) Current†	Established§	5.9 (1.7 to 20.7) 25.5 (10.6 to 61.4)	2.5 (0.6 to 10.9) 8.0 (2.8 to 22.7)
Osibogun *et al*[49]	USA	Non-smokers*	Current†	Regular‡	Year 1: 16.4 (7.8 to 34.5) Year 2: 11.1 (3.5 to 35.2)	Year 1: 5.0 (1.9 to 12.8) Year 2: 3.4 (1.0 to 11.5)
Relapse in former smokers at baseline						
Brose *et al*[30]	UK	≥2-month ex-smokers	Ever Non-daily	Ever	1.52 (0.88 to 2.62) 3.32 (1.23 to 8.96)	1.13 (0.61 to 2.07) 2.45 (0.85 to 7.08)
Dai and Leventhal[51]	USA	>12-month ex-smokers	Current† Occasional Prior	Ever	6.36 (4.49 to 9.00) 5.79 (1.50 to 22.33) 9.68 (4.74 to 19.75)	2.00 (1.25 to 3.20) 1.56 (0.34 to 7.14) 3.77 (1.48 to 9.65)
McMillen *et al*[50]	USA	≥5 years ex-smokers	Ever (not current†) Current†	Ever	5.4 (2.9 to 10.2) 7.6 (3.0 to 19.4)	3.3 (1.6 to 6.7) 5.2 (1.6 to 16.3)

*Non-smokers defined as never or no current (past 30-day) use.
†Current defined as past 30-day use.
‡Regular defined as ≥20 days/30 days.
§Established defined as ≥100 combustible cigarettes and currently smokes every day or some.
HW, Hispanic white; NHW, non-Hispanic white.

each from Romania, Finland, Taiwan and Canada. Study sample sizes varied considerably, ranging from 374 to 14 623.

Of the six newly identified studies based on US participants, four[26 49–51] used Population Assessment of Tobacco and Health (PATH) data from a US nationally representative longitudinal study. Of these, two[50 51] looked at adult (≥18 years old) former smokers, one[49] looked at youth (12–17 years old) and one[26] at a more restricted youth group (12–15 years old). Even though these four studies have the same data source, they were all included in this review as they had different outcome or exposure variables, different populations and included the most recent data.

Of the 12 newly identified studies, five[26 27 46 47 50] had outcomes assessing ever smoking among never smokers at baseline, seven[28 29 45 47–50] had outcomes assessing current smoking among non-smokers (never or not

current smoking) at baseline and three[30 50 51] assessed the odds of relapse in former smokers. Results were separated based on these three categories and combined with the 13 primary research studies identified in the umbrella review. Twelve of the seventeen studies in Khouja *et al* were included,[20 31 33–42] three were excluded due to data overlap.[52–54] one was excluded as it used retrospective data[55] and one was excluded as it was cross-sectional.[56] Of the eight studies in Aladeokin and Haighton, two were included[39 40]; five were excluded for cross-sectional design[57–61] and one for data overlap.[54] From the nine studies identified in Soneji *et al* six were included[31–34 36 37] after two were excluded as they were abstracts and one excluded for data overlap.[62]

Cigarette smoking initiation among never smokers at baseline

Five[26 27 46 47 50] of the newly identified studies investigated smoking initiation among never smokers, of which Berry *et al*[26] and McMillen *et al*[50] used PATH data, focusing on youth (12–15 years old) and adults (≥18 years old), respectively (table 2). Chien *et al* examined the association between ever e-cigarette and subsequent combustible smoking initiation in 12954 youth enrolled in schools in Taiwan between 2014 and 2016.[27] Conner *et al* investigated the association of e-cigarette use at baseline and smoking in adolescents (13–14 years old) between waves 3 and 5 (2014–2016) of a cluster RCT in 20 schools in England.[47] Pénzes *et al* conducted secondary data analysis from 1369 ninth grade students in the Romanian ASPIRA RCT. Details of the studies are given in online supplemental table 7.[46].

All newly identified studies found that people who used e-cigarettes were significantly more likely than non-users to initiate smoking of combustible cigarettes, with ORs varying substantially from 2.1 to 6.6 (I^2=81%; figure 2).

Considering these newly identified studies along with 12 studies from the umbrella review, all found significantly increased risk of initiating smoking of combustible cigarettes in people who had used e-cigarettes, compared with those who had not (figure 2). Combining the studies from the umbrella review with the newly identified

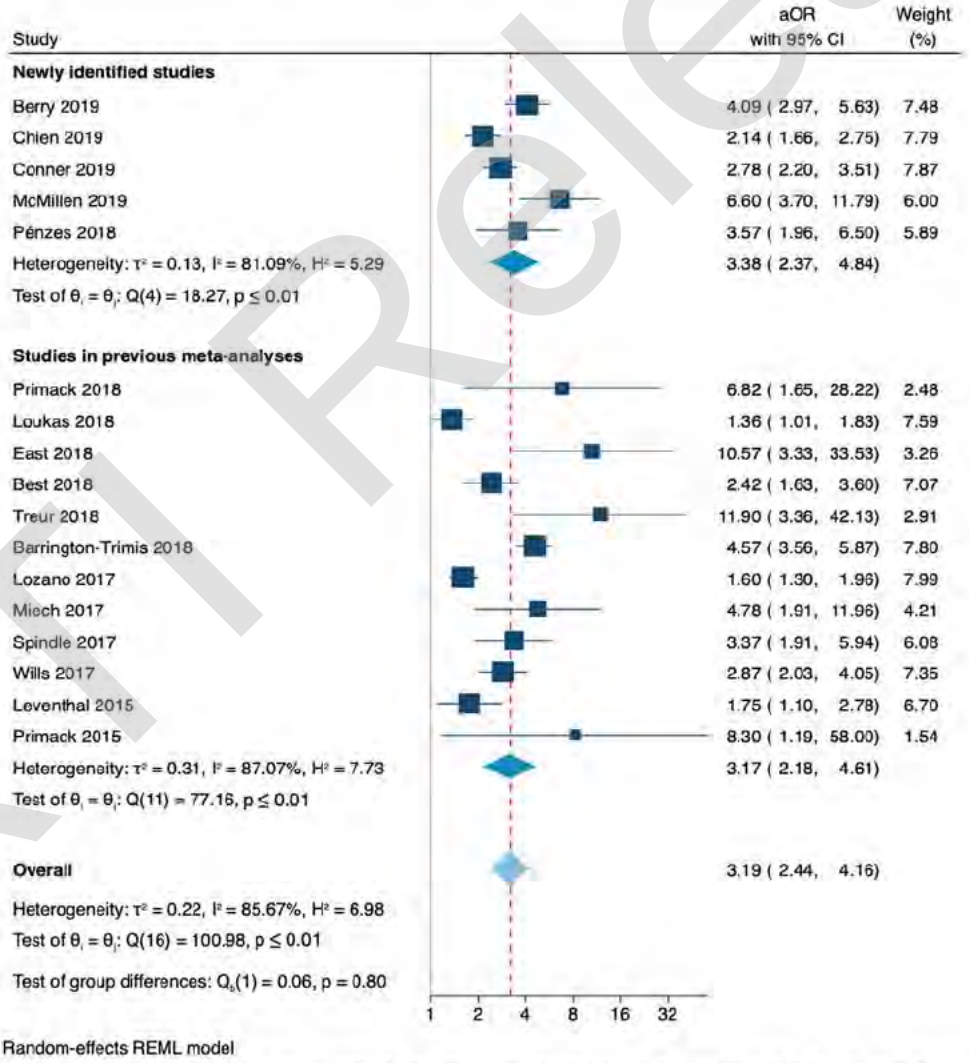

Figure 2 Forest plot and random-effects meta-analysis for the adjusted odds of smoking initiation at follow-up among never smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline. aOR, adjusted OR; REML, Restricted Maximum Likelihood

studies, people exposed to e-cigarettes more likely to take up smoking of combustible cigarettes than people who were not exposed to e-cigarettes (pooled adjusted OR 3.19 (95% CI 2.44 to 4.16)).

Current (past 30-day) cigarette smoking among non-smokers (never smokers or no current use at baseline)

Seven[28 29 45 47–50] of the newly identified primary research studies investigated current (past 30-day) use of combustible cigarettes following the use of e-cigarettes (table 2). Four[29 47 48 50] of these studies looked at never smokers at baseline, while three[28 45 49] looked at non-smokers (either never or no current use).

Two[49 50] of the included studies were based on PATH data. McMillen *et al*[50] used data on adult (≥18 years old) never smokers from waves 1 to 2 of the PATH study and Osibogun *et al*[49] used data on youth (12–17 years old) non-smokers from waves 1 to 3. A further two[45 48] of the newly identified studies used data from the USA. Bold *et al* surveyed 808 high school students across three waves (2013–2015) in Connecticut.[45] Barrington-Trimis *et al* collated data on 6258 youth from three US school-based studies between 2013 and 2015: the Children's Health Study; the Happiness and Health Study and the Yale Adolescent Survey Study.[48] This study separated results based on ethnicity and found the adjusted odds of dual use at follow-up was considerably higher in non-Hispanic whites compared with Hispanic whites (see table 2), although with considerable overlap in the CIs.

The remaining three[28 29 47] newly identified studies used data from Canada, the UK and Finland. Aleyan *et al* examined the association between current e-cigarette use and subsequent current smoking among 6729 Canadian school students using data from a school-based longitudinal cohort study, COMPASS.[28] Conner *et al* investigated the association of e-cigarette use at baseline and smoking between waves 3 and 5 (2014–2016) of a cluster RCT assessing a self-regulation anti-smoking intervention from 20 schools in England.[47] Kinnunen *et al* used MEtLoFIN a school-based longitudinal cohort dataset in 3474 Finnish adolescents between 2014 and 2016.[29] Kinnunen *et al* separated the use of e-cigarettes based on their nicotine delivery and found among baseline never-smokers, ever use of nicotine-delivering e-cigarettes was associated with a nearly threefold increase in the odds of uptake of daily smoking (see table 2) and found no increase in risk associated with use of non-nicotine delivering e-cigarettes.

All of the newly identified studies, and the one relevant study from the umbrella review,[32] found a significant increase in the risk of transitioning from being a non-smoker to a current smoker in people who had used e-cigarettes compared with not using e-cigarettes, but with considerable heterogeneity in the estimates (I^2=91%; figure 3).

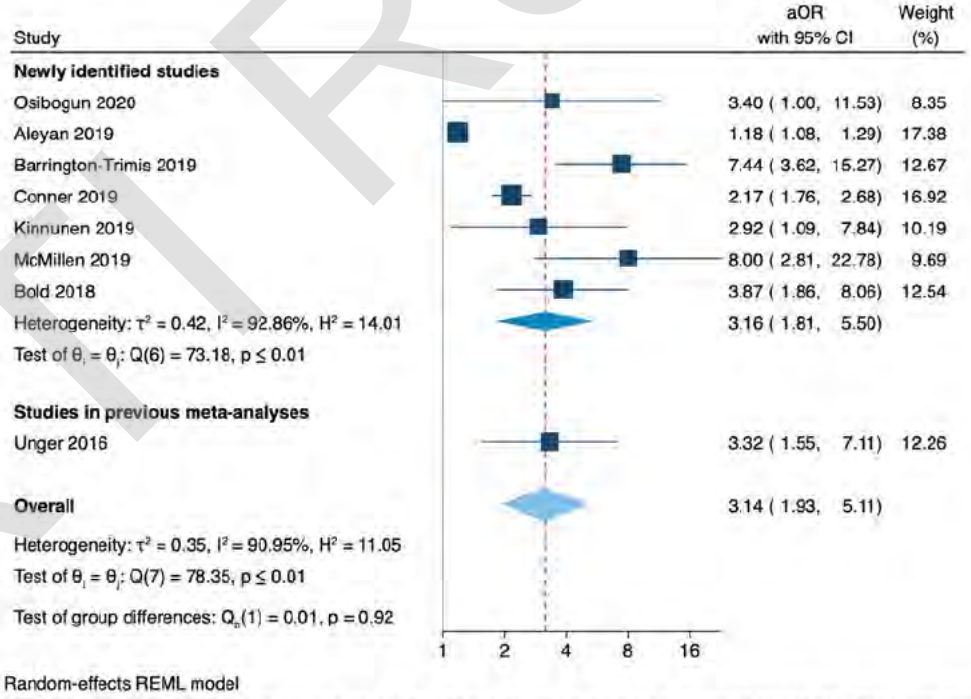

Figure 3 Forest plot and random-effects meta-analysis for the adjusted odds of current (past 30-day) smoking at follow-up among non-current smokers and current e-cigarette users at baseline compared with non-current e-cigarette users at baseline. **aOR, adjusted OR; REML, Restricted Maximum Likelihood**

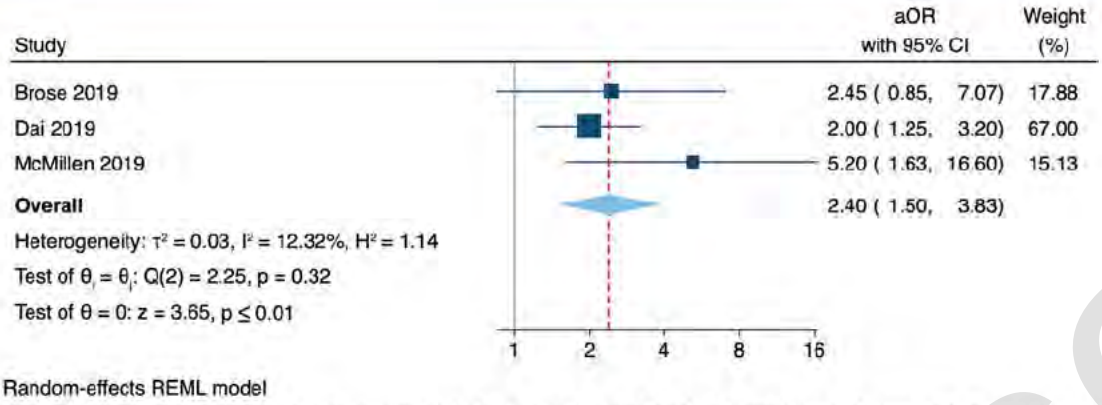

Figure 4 Forest plot and random-effects meta-analysis for the adjusted odds of smoking relapse at follow-up among former smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline. aOR, adjusted OR; REML, Restricted Maximum Likelihood

Cigarette smoking relapse among former smokers (at least 2 months since quit date)

Three[30 50 51] newly identified studies in this review investigated the odds of relapse to combustible cigarette smoking following the use of e-cigarettes in adults aged ≥18 years (table 2). None of the three previously conducted systematic reviews investigated this relationship, so no additional studies from the umbrella review were included. Brose *et al* used data from 371 adults who quit ≥2 months prior to baseline in 2016 from a national web-based survey in the UK.[30] The other two studies used PATH data. Dai and Leventhal looked at 3210 ex-smokers, who had not smoked for >12 months.[51] McMillen *et al* looked at data relating to 8108 adults who had quit ≥5 years prior to baseline; subanalyses from this study were included in the previous two sections, as the study also provided data on never smokers.[50]

All three included studies found the odds of ever relapse was higher among ever e-cigarette users, compared with never e-cigarette users (figure 4). With respect to more detailed findings, in addition to the prespecified meta-analyes, Brose *et al* reported lower odds of relapse among recent ex-smokers who vaped daily versus those who vaped non-daily, while Dai and Leventhal and McMillen *et al* showed past 30-day regular e-cigarette use had greater odds of relapse than non-current use.[30 50 51] Within the Dai and Leventhal study, regular e-cigarette use in recent smokers (quit ≤12 months) was not associated with smoking relapse.[51] However, regular e-cigarette use in those who had ceased smoking for more than 12 months was associated with a significant increase in the odds of relapse. A meta-analysis of the three newly identified studies found former smokers who used e-cigarettes had 2.4 times greater odds of relapse when compared with those who did not use e-cigarettes, with similar magnitudes of this relationship between studies (I^2=12%) (figure 4).

Risk of bias across studies

Funnel plots corresponding to the studies included in the meta-analyses are presented in online supplemental figure 1. The plot for the 17 smoking initiation studies of never-smokers is somewhat asymmetrical and seven points lie outside the 95% confidence region, suggesting there may be some selection bias across included studies, publication bias or possible heterogeneity (as supported by the I^2 statistic; 86%). With less than ten studies investigating current smoking in non-smokers[28 29 32 45 47–49] and relapse in former smokers,[30 50 51] test for funnel plot asymmetry was not used as the power of the test would be too low for it to be a reliable indicator of publication bias.[24]

DISCUSSION

Our umbrella and systematic review, along with an updated meta-analysis using data from primary studies, shows strong and consistent evidence 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 become regular tobacco smokers. We found that, on average, non-smokers who used e-cigarettes have around threefold the odds of either initiating smoking or currently smoking combustible cigarettes compared with non-smokers who have not used e-cigarettes. The limited available evidence indicates that former smokers who report current e-cigarette use within the previous 30-days have more than twice the odds of relapse and resumption of current smoking compared with former smokers who have not used e-cigarettes.

This review builds on and has findings consistent with earlier systematic reviews and meta-analyses in the peer-reviewed and grey literature.[11 21 43 44 63 64] A 2018 review by the National Academies of Sciences, Engineering, and Medicine on the public health consequences of e-cigarettes concludes that there is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes, and moderate evidence that e-cigarette use increases the frequency and intensity of subsequent combustible tobacco smoking, among youth and young adults.[64] Previous systematic reviews have focused on evidence in those 30 years of age or less, whereas our review included data on adults and former smokers. This is the first systematic review to examine whether e-cigarette use is associated with smoking relapse.

The use of e-cigarettes may represent a risk factor for cigarette smoking initiation, current smoking and relapse to cigarette smoking for several behavioural and physiological reasons. For those who use nicotine-delivering e-cigarettes, a resulting addiction to nicotine may leave users at risk of seeking other forms of inhalable nicotine, such as combustible cigarettes.[65 66] Additionally, as e-cigarettes can mimic behavioural (eg, hand-mouth) and sensory (eg, taste) aspects of smoking, associated e-cigarette habits and movements may make the transition to combustible smoking more natural.[67 68] Further studies should examine potential mediators to better understand possible mechanisms for the association between e-cigarette use and subsequent cigarette use. Although one study showed that an intervention designed to reduce smoking initiation in adolescents through self-regulatory implementation intentions attenuated the odds of smoking uptake in never smokers who used e-cigarettes, a statistically significant increased odds remained.[47]

Although studies in this review were consistent in finding increased risks of smoking uptake in non-smokers exposed to e-cigarettes, the magnitude of this increased risk varied substantially between studies. The reason for this variation is unclear, but may relate to the different products, populations and policy environments. In addition, it is challenging to estimate the overall effect of e-cigarettes on smoking initiation due to the variety of ways in which devices (eg, e-cigarettes, JUULs, pods, vape pens) and users (eg, never-users, ever-users, current-users, former users) are classified. The high heterogeneity in most of the results from the meta-analyses suggests that pooled ORs should be interpreted as an average of disparate results, rather than a reflection of the true underlying effect.

A limitation in this review is that included studies were limited to those written in English. While emerging results from this review and similar studies provide evidence regarding the association between e-cigarette and combustible cigarette use, the evidence is heavily weighted towards US and UK data. Only nine countries were included in this analysis, with a notable lack of data from the Asia-Pacific, Africa and the Middle East. Furthermore, the studies were reliant on self-reported product use, which is likely to be subject to self-reporting bias. All three systematic reviews rated moderate in the AMSTAR 2 risk of bias assessment and the 12 newly identified studies rated between 5 and 8 on the NOS. Although the consistency of findings across multiple studies and settings supports the likelihood of a causal relationship, given the observational nature of many of the included studies, the findings may be potentially influenced by confounding factors, including socioeconomic status and the tendency for risk behaviours to occur together. As the ability to adjust for such confounding factors varied according to study, the possibility of residual confounding cannot be excluded.

CONCLUSION

This review found consistent evidence that use of e-cigarettes, largely nicotine-delivering, is associated with increased risk of subsequent combustible smoking initiation, current combustible smoking and smoking relapse after accounting for known demographic, psychosocial and behavioural risk factors. This is the first review to examine associations between e-cigarette use and cigarette use across the whole population, including youth, adults and former smokers. Intervention efforts and policies surrounding e-cigarettes are needed to reduce the potential of furthering combustible tobacco use in Australia and beyond.

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Supporting Information

Supplementary Table 1: Inclusion and exclusion criteria for umbrella review (of systematic reviews) and systematic review (of primary research)

PICO	Inclusion Criteria	Exclusion Criteria
Population	Non tobacco smokers nc udes never, former or ever users (th s nc udes pr or users who have tr ed smok ng but have not used n the past 30 days) Humans, any age (youth, young adu ts and adu ts)	Current tobacco smokers (use w th n the past 30 days) An ma stud es, n v tro stud es
Intervention	N cot ne conta n ng or non n cot ne conta n ng e c garettes or e qu d dev ces (a so referred to as vap ng products)	Stud es w th a focus on heat not burn or tobacco conta n ng dev ces Stud es w th a focus on the uptake of mar juana, other c t drugs and harmfu substances (as n the CSIRO report [58])
Comparison	No n cot ne conta n ng or non n cot ne conta n ng e c garettes or e qu d dev ces	
Outcomes	Ever smok ng combust b e tobacco c garettes	Stud es where smok ng c garettes s not the pr mary outcome var ab e
Study	Pub shed, peer rev ewed terature For umbre a rev ew - Systemat c rev ews and meta ana yses of random sed/non random sed contro ed tr a s, c n ca tr a s and prospect ve cohort stud es (f a systemat c rev ew/meta ana ys s nc udes study des gns other than cohort and random sed/ non random sed contro ed tr a s, the rev ew w on y be nc uded f the ana ys s and/ or resu ts are separated by study des gn) For systemat c rev ew - Random sed/ non random sed contro ed tr a s, c n ca tr a s (a though ntervent ona stud es are not expected) - Prospect ve cohort stud es	Systemat c rev ews that are superseded by a ater rev ew wh ch nc ude a stud es from the ear er rev ew. - Non systemat c terature rev ews - Intervent on tr a w th no comparator (e.g. before and after study) - Qua tat ve stud es - Retrospect ve cohort stud es - Case contro stud es - Cross sect ona (nc ud ng repeated cross sect ona) - Case stud es - Grey terature, conference abstracts, etters, ed tor a s, correspondence, op n on p eces, government reports, pos t on statements *Systematic reviews and meta analyses will be excluded if they include only the above study designs.*
Follow-up	M n mum 6 months	
Setting	Any country	
Time period	A years	No exc us on
Other	- Eng sh - Fu text ava ab ty	- Not ava ab e n Eng sh - Dup cated data

Supplementary Appendix: Search strategy

MEDLINE, PyschINFO, PubMed, Scopus, Web of Science and Cochrane Library were searched. Papers were imported into an Endnote library, exported to Covidence and duplicates removed. The titles and abstracts were screened by two reviewers (OB and LF) to isolate relevant publications. Full texts were then identified for the relevant publications by two reviewers (OB and LF) and independently assessed the publications against the selection criteria. Any conflicts were discussed and if no consensus was reached the publication was reviewed by a third reviewer (MH).

A forward and backward reference search was performed on the final articles completed using Web of Science and Scopus. After removing duplicates, titles, abstracts and then full texts were screened for any randomised controlled trials fulfilling our inclusion and exclusion criteria by two reviewers (OB and LF).

Data were systematically extracted from the publications using data extraction templates. The quality of the included studies was assessed independently by two reviewers (OB and LF), with discrepancies resolved by discussion and by adjudication of a third reviewer (EB). E-cigarette, cigarette smoking and uptake search terms will be combined with the Boolean operator 'AND' for the final search.

Supplementary Table 2: Search terms

E-cigarette re ated search terms (comb ned w th Boo ean operator OR)	Combust b e **cigarette smoking** re ated search terms (comb ned w th Boo ean operator OR)	**Uptake** re ated search terms (comb ned w th Boo ean operator OR)
Keywords 1. E ectron c c garette* 2. E-c garette* 3. E ectron c n cot ne de very system* 4. E ectron c n cot ne de* 5. E ectron c non-n cot ne de* 6. Vape 7. Vap ng 8. Vapo* 9. E-hookah 10. E ectron c nha ant dev ce 11. E- qu d MeSH terms 1. E ectron c N cot ne De very Systems (ENDS)	Keywords 1. Combust b e c garette 2. Tobacco smok ng 3. Smok ng 4. C garette MeSH terms 1. Smokers 2. Non-smokers	Keywords 1. In t at* 2. Uptak* 3. Subsequent* 4. Pred ct* 5. Onset

Supplementary Table 3: Search histories

Database	Search	Studies and search date
PubMed	(((E ectron c c garette* or E c garette* or E ectron c n cot ne de very systems[Mesh] or E ectron c non n cot ne de very* or E ectron c n cot ne dev ce* or E ectron c non n cot ne dev ce* or Vape or Vap ng or Vapo* or E hookah or E ectron c nha ant dev ce or E qu d)) AND (Smoker*[Mesh] or non smoker*[Mesh] or ex smoker*[Mesh] or Combust b e c garette or Tobacco smok ng or Smok ng or C garette or C garette smok ng or C gar smok ng)) AND (In t at* OR Uptak* OR Subsequent* OR Pred ct* OR Onset)	1187 (01/04/2020)
Scopus	(TITLE ABS KEY (("E ectron c c garette*" OR "E c garette*" OR "E ectron c n cot ne de very system*" OR "E ectron c non n cot ne de very*" OR "E ectron c n cot ne dev ce*" OR "E ectron c non n cot ne dev ce*" OR "Vape" OR "Vap ng" OR "Vapo*" OR "E hookah")) AND TITLE ABS KEY (("Smoker*" OR "non smoker*" OR "ex smoker*" OR "Combust b e c garette" OR "Tobacco smok ng" OR "Smok ng" OR "C garette" OR "C garette smok ng" OR "C gar smok ng")) AND TITLE ABS KEY (("In t at*" OR "Uptak*" OR "Subsequent*" OR "Pred ct*" OR "Onset")))	1289 (01/04/2020)
Web of Science	**ALL FIELDS:** (("E ectron c c garette*" OR E c garette* OR "E ectron c n cot ne de very system*" OR "E ectron c non n cot ne de very*" OR "E ectron c n cot ne dev ce*" OR "E ectron c non n cot ne dev ce*" OR Vape OR Vap ng OR Vapo* OR E hookah OR "E ectron c nha ant dev ce")) *AND* **ALL FIELDS:** ((Smoker* OR non smoker* OR ex smoker* OR "Combust b e c garette" OR "Tobacco smok ng" OR Smok ng OR C garette OR "C garette smok ng" OR "C gar smok ng")) *AND* **ALL FIELDS:** ((In t at* OR Uptak* OR Subsequent* OR Pred ct* OR Onset))	1488 (01/04/2020)
PsychINFO (Ovid)	1. (E ectron c c garette* or E c garette* or E ectron c n cot ne de very system* or E ectron c non n cot ne de very* or E ectron c n cot ne dev ce* or E ectron c non n cot ne dev ce* or Vape or Vap ng or Vapo* or E hookah or E ectron c nha ant dev ce or E qu d).af. 2. (Smoker* or non smoker* or ex smoker* or Combust b e c garette or Tobacco smok ng or Smok ng or C garette or C garette smok ng or C gar smok ng).af. 3. (In t at* or Uptak* or Subsequent* or Pred ct* or Onset).af. 4. 1 and 2 and 3	874 (01/04/2020)
Medline (Ovid)	1 (E ectron c c garette* or E c garette* or E ectron c n cot ne de very system* or E ectron c non n cot ne de very* or E ectron c n cot ne dev ce* or E ectron c non n cot ne dev ce* or Vape or Vap ng or Vapo* or E hookah or E ectron c nha ant dev ce or E qu d).af. 2 (Smoker* or non smoker* or ex smoker* or Combust b e c garette or Tobacco smok ng or Smok ng or C garette or C garette smok ng or C gar smok ng).af. 3 (In t at* or Uptak* or Subsequent* or Pred ct* or Onset).af. 4 1 and 2 and 3	1168 (04/02/2020)
Cochrane	1. MeSH descr ptor: [E ectron c N cot ne De very Systems] exp ode a trees 2. ("E ectron c c garette" OR E c garette OR Vape OR Vap ng OR E hookah OR "E ectron c nha ant dev ce" OR E qu d OR "E ectron c N cot ne De very Systems"):t ,ab,kw 3. #1 OR #2 4. (Smoker* or non smoker* or ex smoker* or Combust b e c garette or Tobacco smok ng or Smok ng or C garette or C garette smok ng or C gar smok ng):t ,ab,kw 5. #4 OR #5 6. (In t at* OR Uptak* OR Subsequent* OR Progress* OR Pred ct* OR Durat on OR Intens* OR Frequen* OR Onset):t ,ab,kw 7. #3 AND #6 AND #7	219 (01/04/2020)

Supplementary Table 4: AMSTAR2[17] rating of included systematic review studies

Criteria	A adeok n & Ha ghton 2019[39]	Sone et a . 2017[16]	Khou a et a . 2020[38]
1. D d the research quest ons and nc us on cr ter a for the rev ew nc ude the components of PICO?	Yes	Yes	Yes
2. D d the report of the rev ew conta n an exp c t statement that the rev ew methods were estab shed pr or to the conduct of the rev ew and d d the report just fy any s gn f cant dev at ons from the protoco ?	Yes	No	Part a Yes
3. D d the rev ew authors exp a n the r se ect on of the study des gns for nc us on n the rev ew?	Yes	Yes	Yes
4. D d the rev ew authors use a comprehens ve terature search strategy?	Part a Yes	Part a Yes	Part a Yes
5. D d the rev ew authors perform study se ect on n dup cate?	Yes	Yes	Yes
6. D d the rev ew authors perform data extract on n dup cate?	No	No	Yes
7. D d the rev ew authors prov de a st of exc uded stud es and ust fy the exc us ons?	No	No	No
8. D d the rev ew authors descr be the nc uded stud es n adequate deta ?	Yes	Yes	Yes
9. D d the rev ew authors use a sat sfactory techn que for assess ng the r sk of b as (RoB) n nd v dua stud es that were nc uded n the rev ew?	Yes	Yes	Yes
10. D d the rev ew authors report on the sources of fund ng for the stud es nc uded n the rev ew?	No	No	No
11. If meta ana ys s was performed d d the rev ew authors use appropr ate methods for stat st ca comb nat on of resu ts?	Yes	Yes	Yes
12. If meta ana ys s was performed, d d the rev ew authors assess the potent a mpact of RoB n nd v dua stud es on the resu ts of the meta ana ys s or other ev dence synthes s?	Yes	Yes	Yes
13. D d the rev ew authors account for RoB n nd v dua stud es when nterpret ng/d scuss ng the resu ts of the rev ew?	Yes	Yes	Yes
14. D d the rev ew authors prov de a sat sfactory exp anat on for, and d scuss on of, any heterogene ty observed n the resu ts of the rev ew?	Yes	Yes	Yes
15. If they performed quant tat ve synthes s d d the rev ew authors carry out an adequate nvest gat on of pub cat on b as (sma study b as) and d scuss ts ke y mpact on the resu ts of the rev ew?	No	Yes	Yes
16. D d the rev ew authors perform study se ect on n dup cate?	Yes	Yes	Yes
Rating overall confidence in the results of the review	Moderate	Moderate	Moderate

Supplementary Table 5: Primary research studies included in systematic reviews in the umbrella review that were included in the top-up systematic review

Authors/ Year	Title	Systematic review(s) included in	Country and data source(s)	Baseline cigarette use	E-cigarette use	Follow up cigarette use	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Barr ngton Tr m s et a ., 2018[33]	E-cigarette Use and Subsequent Smoking Frequency Among Adolescents	Khou a et a ., 2020	US (CA, CT): CHS, HH, YASS	Never	Ever	Ever	3.80 (3.10 4.66)	4.57 (3.56 5.87)
Best et a ., 2018[35]	Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents a cohort study	A adeok n & Ha ghton 2019 Khou a et a ., 2020	Scot and (UK): Schoo based	Never	Ever	Ever	4.62 (3.34 6.38)	2.42 (1.63 3.60)
East et a ., 2018[34]	The Association Between Smoking and Electronic Cigarette Use in a Cohort of Young People	A adeok n & Ha ghton 2019 Khou a et a ., 2020	Eng and (UK): AOSHGB	Never	Ever	Ever	12.31 (5.06 29.94)	10.57 (3.33 33.50)
Leventha et a ., 2015[32]	Association of Electronic Cigarette Use With nitiation of Combustible Tobacco Product Smoking in Early Adolescence	Khou a et a ., 2020 Sonej et a ., 2017	US (LA): YBRS Schoo based	Never	Ever	Ever	2.95 (1.74 4.99)	1.75 (1.10 2.77)
Loukas et a ., 2018[14]	Exclusive e-cigarette use predicts cigarette initiation among college students	Khou a et a ., 2020	US (TX): M PACT	Never	Ever	Ever	2.72 (2.10 3.53)	1.36 (1.01 1.83)
Lozano et a ., 2017[36]	A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents	Khouja et a ., 2020	Mex co: Schoo based	Never	Ever	Ever	2.46 (1.85 3.26)	1.60 (1.31 1.97)
M ech et a ., 2017[31]	E-cigarette use as a predictor of cigarette smoking results from a 1-year follow-up of a national sample of 12th grade students	Khou a et a ., 2020 Sonej et a ., 2017	US: MTD 2014 2015	Never	Ever	Ever	6.32 (1.73 23.10)	6.58 (2.04 57.88)†
Pr mack et a ., 2015[29]	Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults	Khou a et a ., 2020 Sonej et a ., 2017	US: Dartmouth med a survey 2012 2014	Never	Ever	Ever	5.66 (1.99 16.07)	8.3 (1.2 58.6)
Pr mack et a ., 2018[30]	nitiation of Traditional Cigarette Smoking after Electronic Cigarette Use Among Tobacco-Naive US Young Adults	Khou a et a ., 2020	US: Growth from Know edge 2013 2014	Never	Ever	Ever	6.06 (2.15 17.10)	6.82 (1.65 28.25)
Sp nd e et a ., 2017[28]	Electronic cigarette use and uptake of cigarette smoking A longitudinal examination of U S college students	Khou a et a ., 2020 Sonej et a ., 2017	US: M d At ant c un vers ty (S4S pro ect)	Never	Ever	Ever	3.50 (2.41 5.09)	3.37 (1.91 5.94)
Treur et a ., 2018[37]	E-cigarette and waterpipe use in two adolescent cohorts cross-sectional and longitudinal associations with conventional cigarette smoking	Khou a et a ., 2020	Nether ands	Never	Ever**	Ever	10.83 (8.87 13.22)	11.9 (3.36 42.11)

Unger et a ., 2016[27]	E-cigarette use and subsequent cigarette and marijuana use among Hispanic young adults	Sonej et a ., 2017	US (LA): Project RED	No current[a]	Current[a]	Current[a]	4.71 (2.27	9.77)	3.32 (1.55	7.11)
W s et a ., 2017[26]	Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii	Khou a et a ., 2020 Sonej et a ., 2017	US (HI): Schoo based	Never	Ever	Ever	4.25 (2.74	6.61)	2.87 (2.03	4.05)

Supplementary Table 6: Newcastle Ottawa Scale[18] (NOS) rating of newly-identified primary research studies

Study	Selection				Comparability	Outcome			Total
	Representativeness o the Exposed Cohort (★)	Selection o the Non-Exposed Cohort (★)	Ascertainment o Exposure (★)	Demonstration hat Outcome o nterest Was Not Present at Start o Study (★)	Comparability o Cohorts on the Basis o the Design or Analysis (★★)	Assessment o Outcome (★)	Was Follow-Up Long Enough or Outcomes to Occur (★) *	Adequacy o Follow Up o Cohorts (★)	
Aleyan et al 2019 [23]	★	★		★	★★		★		6
Barrington-Trimis et al 2019 [43]	★	★		★	★★		★	★	7
Berry et al 2019 [21]	★	★	★	★	★★		★	★	8
Bold et al 2018 [40]	★	★		★	★		★		5
Brose et al 2019 [25]	★	★		★	★★		★		6
Chien et al 2019 [22]	★	★		★	★★		★	★	7
Conner et al 2019 [42]	★	★		★	★★		★		6
Dai et al 2019 [46]	★	★	★	★	★★		★	★	8
Kinnunen et al 2019 [24]	★	★		★	★★		★		6
McMillen et al 2019 [45]	★	★	★	★	★★		★	★	8
Osibogun et al 2020[44]	★	★	★	★	★★		★	★	8
Pénzes et al 2018 [41]	★	★		★	★★		★		6

* 6 months considered adequate follow-up time
‡ Studies with less than 30% loss to follow-up considered adequate

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Supplementary Table 7: Study characteristics from newly-identified studies for the top-up systematic review

Study	Country and data source	Study design	Duration (follow up and date range)	Study population size baseline age/ grade % female	Considerations of confounding	NOS[1] score
Aleyan et al 2019 [23]	Canada (COMPASS Waves 1-3)	Longitudinal cohort	36 months (2014 to 2017)	- 6 729 - 9th or 10th grade - 54 2% female	Gender grade ethnicity friends that smoke weekly spending money current cannabis use and current binge drinking at each wave	6
Barrington-Trimis et al 2019 [43]	US (CT and CA) CHS HH YASS[1]	Longitudinal cohort	12 months (2013 to 2015)	- 6 258 - Grades 9 to 12 - 53 5% female	Gender grade and cohort (CHS H&H YASS) school (H&H/YASS) or community (CHS)	7
Berry et al 2019 [21]	US (PATH[3] Waves 1-3)	Longitudinal cohort	24 months (2013 to 2016)	- 6 123 - 12-15 years old mean 13 4 years (SD 1 2) - 49 5% female	Age gender income race and ethnicity parental education urban residence living with a tobacco user frequency of noticing health warnings on cigarette packages and ability to recall a favourite tobacco advertisement Risk-taking behaviours sensation-seeking personality traits and cigarette susceptibility	8
Bold et al 2018 [40]	US (CT)	Longitudinal cohort	36 months (2013 to 2015)	- 808 - Mean 15 04 years (SD 0 90) - 53% female	School sociodemographic characteristics (sex race/ethnicity SES) and use of other tobacco products	5
Brose et al 2019 [25]	UK (National web-based survey 2012-2017)	Longitudinal cohort	12 months (2016 to 2017)	- 374 - Mean 49 2 years (SD 14 1) - 44% female	Time quit smoking vaping status gender income and NRT use	6
Chien et al 2019 [22]	Taiwan (TAALS[4] Waves 1-2)	Longitudinal cohort	24 months (2014 to 2016)	- 12 954 - 36 9% ever smokers female 58 1% never smokers female	Smoking susceptibility at baseline socio-demographic profile psychological status and peer support	7
Conner et al 2019 [42]	UK (England) RCT Waves 3 and 5	Post-hoc analysis of a cluster RCT	24 months (2014 2016)	- 3 994 - 13 to 14 years old - 52 3% female	Sociodemographic (gender ethnicity family affluence percentage of children per school eligible for free school meals) friends' smoking status family smoking impulsiveness	6
Dai et al 2019 [46]	US (PATH[3] Waves 1-2)	Longitudinal cohort	12 months (2013 to 2015)	- 4 094 - Adults (≥18 years) - 45 9% female	Sociodemographic (age sex race education poverty level region and health insurance) and tobacco use characteristics (smoking chronicity typical number of combustible cigarettes smoked per day during the period of regular smoking and length of time since quit smoking)	8
Kinnunen et al 2019 [24]	Finland MetLoF N[5] (school-based)	Longitudinal cohort	18 months (2014 to 2016)	- 3 474 - Grade 9 (ages 15 to 16 years) - 51 8% female	Gender socioeconomic background parents' education other tobacco product and drug use school clustering Crude and adjusted logistic regressions were also conducted with the Firth's bias-reduced logistic regression	6
McMillen et al 2019 [45]	US (PATH[3] Waves 1-2)	Longitudinal cohort	12 months (2013 to 2015)	- 8 108 - Adults (≥18 years) - 54 4% distant former smoker female 40 0% never smoker female	Sociodemographic (race/ethnicity sex age education) psychosocial predictors of combustible cigarette smoking risk (household smoking rules and living with someone who smokes)	8
Osibogun et al 2020[44]	US (PATH[3] Waves 1-3)	Longitudinal cohort	36 months (2013 to 2016)	- 14 623 - Ages 12-17 years - 48% female	Sociodemographic and tobacco-related factors	8
Pénzes et al 2018 [41]	Romania (ASP RA[6] RCT)	Secondary analysis from data in cluster RCT	6 months (2014 to 2015)	- 1 369 - Grade 9 mean 14 88 (SD 0 48)	ntervention/control condition gender age the design effect due to the cluster sampling and used schools as cluster units	6

[1] NOS Newcastle-Ottawa Scale (out of a total of 10)
[2] CHS Children's Health Study HH Happiness & Health Study YASS Yale Adolescent Survey Study
[3] PATH Population Assessment of Tobacco and Health Study
[4] TAALS The Taiwan Adolescent to Adult Longitudinal Study
[5] MetLoF N Metropolitan Longitudinal Finland
[6] ASP RA A Smoking Prevention nteractive Experience [Roman acronym for translation of ASP RE]

Supplementary Figure 1: Funnel plots to assess the risk of bias across studies

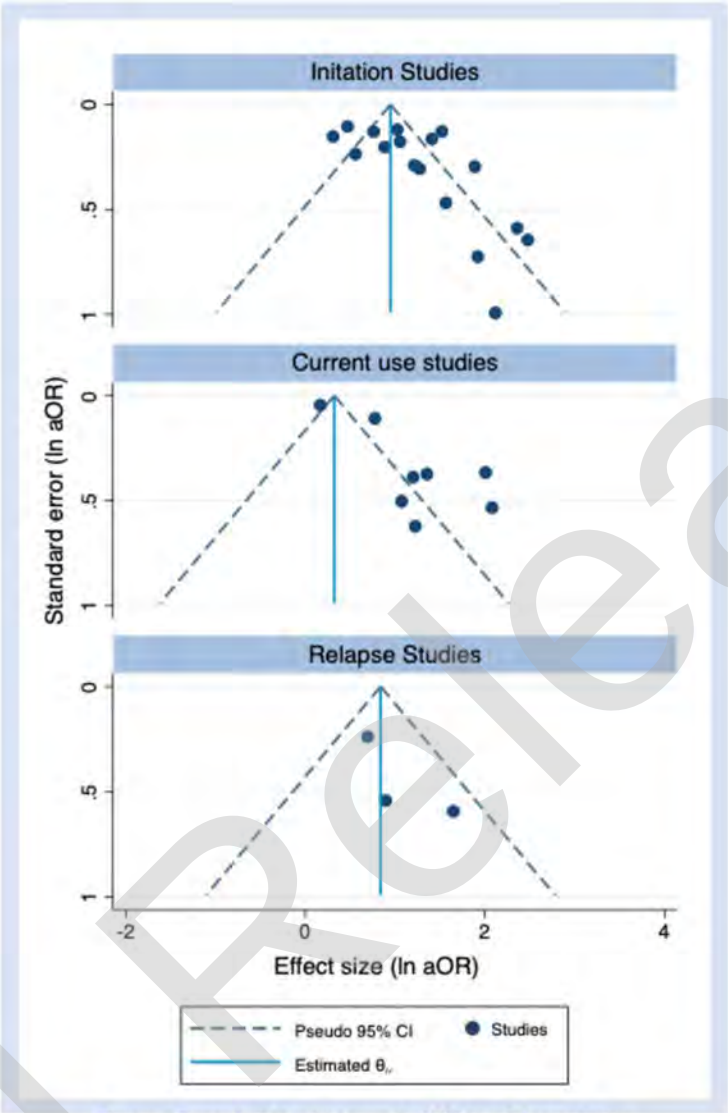

Figure: Funnel plots with pseudo 95% confidence limits

Australian National University

Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review

Final report prepared for the Australian Government Department of Health: online version

14 September 2021

Amelia Yazidjoglou, Laura Ford, Olivia Baenziger, Sinan Brown, Melonie Martin, Tehzeeb Zulfiqar, Grace Joshy, Katie Beckwith, Emily Banks

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Executive Summary

Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review

Amelia Yazidjoglou, Laura Ford, Olivia Baenziger, Sinan Brown, Melonie Martin, Tehzeeb Zulfiqar, Grace Joshy, Katie Beckwith, and Emily Banks

Background

E-cigarettes are a diverse group of battery-powered devices that create an aerosol from a liquid (e-liquid). Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol, glycerine and flavouring agents; it commonly contains nicotine in freebase or salt form.

Tobacco smoking is the leading preventable cause of death and disability globally, causing over eight million deaths each year.[1] It is the leading cause of burden of disease in Australia[2] and is responsible for over one-third of all deaths in Aboriginal and Torres Strait Islander people.[3] In many countries, e-cigarettes are marketed as aids to smoking cessation – explicitly or implicitly – and, among e-cigarette users, smoking cessation is a commonly reported reason for use. However, no e-cigarette products have been approved by the Australian Therapeutic Goods Administration as smoking cessation aids; the situation is similar in many other countries.

A scheduling decision announced by the Australian Therapeutic Goods Administration in December 2020 clarified that consumers will require a valid Australian medical prescription to access nicotine e-cigarettes and certain other nicotine products from 1 October 2021. Appropriate prescribing will require suitable guidance for health professionals regarding e-cigarettes, including up-to-date evidence on their efficacy as an aid for sustained cessation of combustible tobacco smoking. In order to support this, the Australian Government Department of Health commissioned this updated report, which will feed into the process of the development of guidelines on e-cigarettes from the Royal Australian College of General Practitioners. The Department also requested consideration of the effects of nicotine concentrations in e-liquids likely to be used in the therapeutic setting, as well as non-inferiority in interpretation of trial results.

Aims and methods

This systematic review and meta-analysis aims to summarise the current published peer-reviewed randomised control trial (RCT) evidence on the efficacy of e-cigarettes – nicotine and non-nicotine – for the sustained cessation of combustible tobacco cigarette smoking and for the cessation of ongoing exposure to nicotine. The review also considers the evidence in the light of potential competing interests.

Key findings

Findings from the systematic review of the current evidence on the efficacy of e-cigarettes as a smoking cessation aid:

- Reliable evidence on the efficacy of interventions – such as e-cigarettes for smoking cessation – requires large-scale, independent randomised controlled trial evidence from multiple studies.
- The evidence on the efficacy of nicotine e-cigarettes and non-nicotine e-cigarettes for smoking cessation was limited. From 6,555 titles identified, eleven RCTs were identified; 347 of 5,901 smokers randomised achieved smoking cessation. RCTs were of nicotine in freebase form; no trials of nicotine salt products were identified.
- RCTs were generally small, short term (maximum 1 year), employed a wide range of study designs and the majority had methodological issues indicating a high risk of bias. The overall certainty of the evidence was rated as very low.

- Summary measures were influenced by the inclusion or non-inclusion of individual studies and by choice of meta-analytic method. Both random- and fixed-effects methods have limitations in the e-cigarette context.
- 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.
- 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 nicotine-replacement therapy. 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, where data were available, mean nicotine concentrations of 18mg/mL, 12mg/mL and 8mg/mL at 4, 26 and 52 weeks, respectively, and the smaller trial reported median nicotine concentrations of 10mg/mL at commencement and 6mg/mL at 6 month follow up.
- 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.
- Trial participants randomised to ENDS utilising freebase nicotine had significantly greater quit rates than participants randomised to no intervention or usual care, based on very low certainty evidence. The difference was 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 ENNDS versus approved NRT or ENNDS plus counselling versus counselling only. The certainty of the evidence for this comparison 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.
- 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.

Conclusions

There is limited evidence that, in the clinical context in combination with best-practice counselling and supportive care, 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. There is insufficient evidence that 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. There is also 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. The certainty of the evidence is low or very low and additional high-quality large-scale RCTs are needed. Trials demonstrating efficacy were limited to products with nicotine concentrations ≤20mg/mL. Use of nicotine e-cigarettes is likely to result in prolonged exposure to nicotine, including through dual e-cigarette use and combustible smoking. The balance of safety and efficacy of e-cigarettes needs to be considered in clinical decision making about their use for smoking cessation.

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Background

E-cigarettes are a diverse group of battery-powered devices that create an aerosol from a liquid (e-liquid). Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol, glycerine and flavouring agents. E-cigarettes commonly contain nicotine, in either freebase form or, more recently, nicotine salt form.

For clarity, in this review "ENDS" or "nicotine e-cigarettes" will be used to refer to e-cigarettes delivering nicotine, "ENNDS" or "non-nicotine e-cigarettes" will be used to refer to e-cigarettes without nicotine, and "e-cigarettes" will be used as a general term for the devices. The term "Nicotine Replacement Therapy" or "NRT" refers to a therapy that delivers nicotine in a way that aims to "replace" that delivered by tobacco smoking and in this review refers to therapeutically approved or standard NRT only, to the exclusion of ENDS.

Tobacco smoking is the leading preventable cause of death and disability globally, causing over eight million deaths each year.[1] It is the leading cause of burden of disease in Australia[2] and is responsible for over one-third of all deaths in Aboriginal and Torres Strait Islander people[3]. In many countries, e-cigarettes are explicitly or implicitly marketed as aids to smoking cessation, and among e-cigarette users, smoking cessation is a commonly reported reason for use. ENDS deliver nicotine, so it is plausible that they would support cessation in ways similar to other products that deliver nicotine. It has been proposed that e-cigarettes may have advantages over approved NRTs. They involve certain behavioural and sensory aspects of smoking, such as hand-mouth movement, and can rapidly and directly deliver nicotine to the user at relatively high doses. Hence, they have greater similarity to the combustible cigarette experience, which may increase efficacy for cessation, as well as the risk of abuse and long-term use.[4-7] At the same time, use of ENDS may potentially support continuing smoking and dual use of combustible tobacco cigarettes and e-cigarettes is one of the most common patterns of observed use.[8-10] High cost, limitations on places where smoking is allowed, bans on advertising, clear health warnings and reduced social acceptability are all important elements in comprehensive tobacco control.[11] Smokers may be able to mitigate some of these impacts through dual use with ENDS, thereby prolonging smoking. ENDS are generally cheaper than cigarette smoking, are often able to be used in settings where combustible cigarettes are prohibited, their health impacts are less clear, and they are often more socially acceptable. No e-cigarette products have been approved by the Australian Therapeutic Goods Administration, nor have they been approved for this purpose by many other healthcare product regulatory authorities outside Australia.

If ENDS are used as a cessation tool, and use continues following tobacco smoking cessation, there is ongoing exposure to nicotine, as well as inhalational exposure to particulates and other chemicals. Nicotine is a highly addictive drug,[12] which has been shown to harm brain development and increase risk of cardiovascular,

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respiratory and gastrointestinal disorders.[13,14] More recently introduced "pod" ENDS products contain nicotine in the form of nicotine salts, delivering nicotine more rapidly and allowing inhalation of high levels of nicotine more easily and with less throat irritation than freebase nicotine.[13] Differences between freebase nicotine and nicotine salts, including in their pharmacokinetic profiles,[15] mean that they are not bioequivalent.[16] High concentrations of nicotine from ENDS can result in acute toxicity (sometimes termed being 'nic-sick' or 'nic'd out').[17] The Australian Government Department of Health has requested consideration of cessation of nicotine as an outcome in this review, as well as cessation of smoking of combustible cigarettes.

A scheduling decision announced by the Australian Therapeutic Goods Administration in December 2020 clarified that consumers will require a valid Australian medical prescription to access nicotine e-cigarettes and certain other nicotine products from 1 October 2021. Appropriate prescribing will require suitable guidance to health professionals regarding e-cigarettes, including up-to-date evidence on their efficacy as an aid for sustained cessation of combustible tobacco smoking. In order to support this, the Australian Government Department of Health commissioned this updated report, to inform the development of guidelines on e-cigarettes by the Royal Australian College of General Practitioners. In addition, to ensure it is fit for purpose, the review emphasises evidence that is independent of competing interests, includes non-inferiority as well as superiority considerations where comparators are consistent with standard care and considers doses of nicotine likely to be used in the clinical setting.

Aim

This systematic review and meta-analysis aims to summarise the current published peer-reviewed randomised control trial (RCT) evidence on the efficacy of e-cigarettes – nicotine and non-nicotine – for the sustained cessation of combustible tobacco cigarette smoking and for the cessation of ongoing exposure to nicotine. The review also considers the evidence in light of potential competing interests.

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.[18] Six databases (PubMed, Scopus, Web of Science, PsycINFO (Ovid), MEDLINE (Ovid), and Cochrane) were initially searched between 5 February and 2 March 2020 (Appendix 1). An additional search was conducted on the 27th of 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 RCTs, as defined by the Cochrane Community,[19] in which current smokers were randomised to intervention groups of e-cigarettes, no cigarettes, or other smoking cessation treatments (e.g. approved NRT, behavioural therapy, combination), or to a placebo control group. The outcomes included were

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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.[18 20 21] All other study designs or populations were excluded.

Papers were imported into an EndNote library, exported to Covidence[22] 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. After removing duplicates, titles, abstracts, and then full-texts were screened for any studies fulfilling the inclusion and exclusion criteria by two reviewers. One reviewer assessed each RCT to determine whether it met the definition of an RCT as defined by the Cochrane Community.[19] Full inclusion and exclusion criteria and the RCT definition can be found in Appendix 2.

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 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.[23] 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

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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[24] 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 trials.[25] The certainty of the body of evidence for smoking cessation was evaluated using the GRADE approach.[26 27] 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 (Appendix 3). 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,[18] Public Health England 2018,[28] CSIRO 2018, the US Surgeon General,[29] the US Preventive Services Task Force[30] and the European Union Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)[15 31]) 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.[32 33] 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[34] and menopausal hormone therapy and coronary heart disease.[35] 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.

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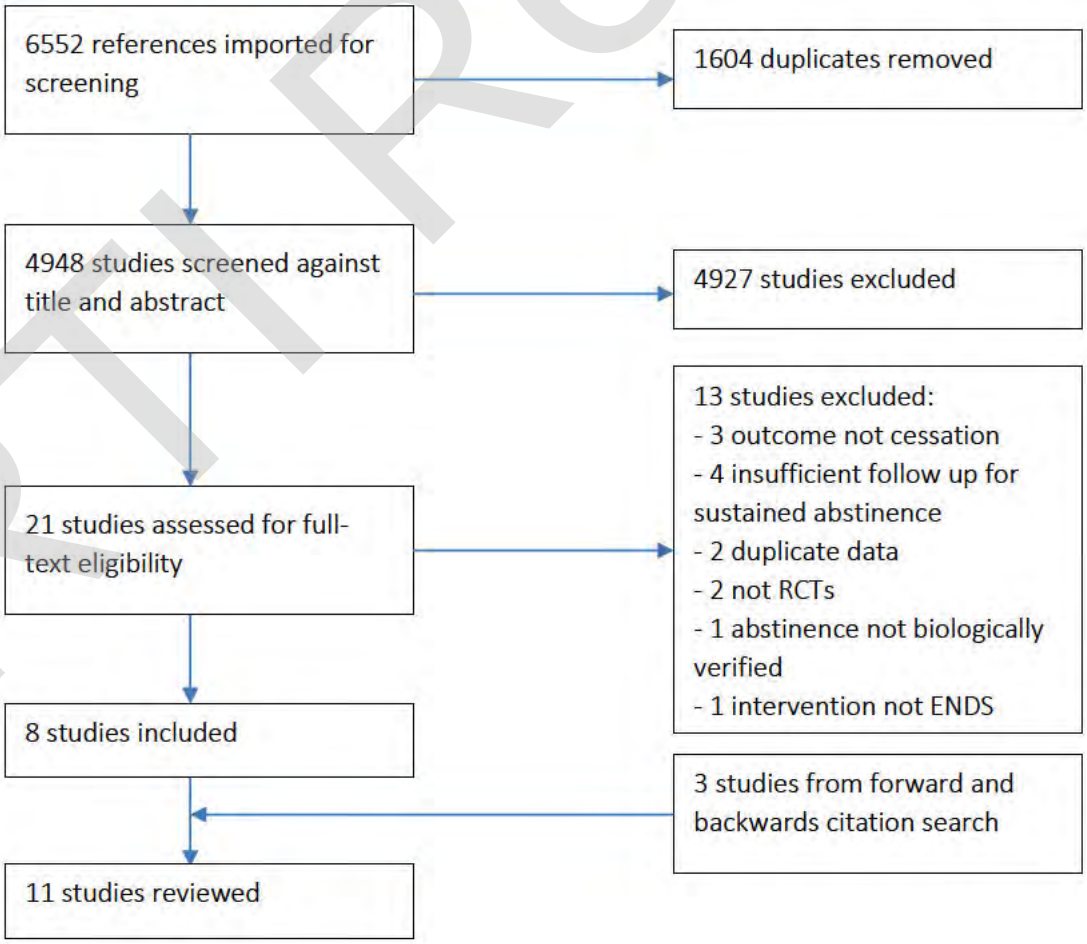
Furthermore, the Therapeutic Goods Administration of Australia can only provide approval for a product as a therapeutic tool if it has clear, unequivocal evidence that the product is beneficial, and that the balance of safety and efficacy is appropriate. It is upon the evidence of clinical trials that a product receives approval as a therapeutic good in Australia.[36 37] It is by these standards that the decision was made to approve NRT products.

Findings

Search outcomes and study characteristics

Of the 6,552 titles identified for screening, eleven RCTs of ENDS and three RCTs of ENNDS were identified that examined smoking cessation as an outcome (Figure 1). 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: 3,005 randomised to ENDS and 2,896 to comparison groups. Two systematic reviews or meta-analyses[38 39] meeting the inclusion criteria and published after the NASEM review search date (August 31, 2017) were systematically identified from the database search at the time of searching and a further three were identified subsequently.[40-42] Additional major reports identified include those from Public Health England,[28] CSIRO,[31] the Irish Health Research Board,[43] the US Surgeon General,[29] the US Preventive Services Task Force[30] and SCHEER.[15]

Figure 1: E-cigarette and smoking cessation review flowchart.



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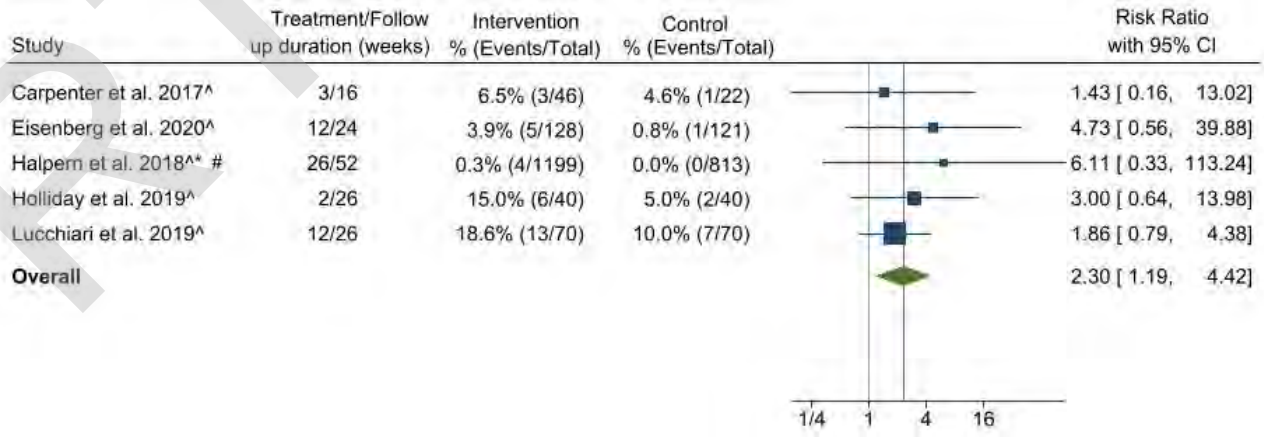
Experimental interventions included the use of ENDS and ENNDS. All ENDS were freebase products, according to the interventions listed in the study publications (Table 2) or according to the dates covered by the study intervention period, noting that nicotine salt products were introduced to European markets in mid-2018 to early 2019[15]. Five studies included some degree of behavioural support or counselling in conjunction with the ENDS or ENNDS intervention.[23 44-47] Two studies included approved NRT in combination with the ENDS intervention,[44 48] one of these also offering behavioural support.[44] Control interventions consisted of approved NRT in five studies,[23 44 48-50] behavioural support in five studies[44-47 51] ENNDS in two studies[44 52] and no intervention in another study.[53] One study incorporated multiple interventions (ENNDS, approved NRT and behavioural support).[44] The most common treatment duration was six months,[45-49 51] however, 16[53] and 24[50] weeks, and one year [23 51 52] were also used.

Nicotine e-cigarettes versus no intervention or usual care

Five RCTs compared ENDS to no intervention or usual care (Table 2 and Appendix 4).[45-47 51 53] These studies randomised a total of 2,549 participants, of whom 42 achieved sustained smoking cessation (Figure 2). 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.[51]

In their pilot RCT, Carpenter et al. recruited 68 community-dwelling US smokers via media outlets who were not specifically seeking treatment.[53] Participants were randomised to control or to three weeks of ENDS and attended multiple laboratory visits for follow-up. At four-month follow-up, 4.0% of the 16mg and 9.5% of the 24mg nicotine ENDS groups versus 4.6% of the control (no intervention) respectively, achieved biochemically verified seven-day point prevalent abstinence (RR ENDS versus control 1.43; 95% CI 0.16-13.02); this difference was not statistically significant.

Figure 2: 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

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of the 2x2 table)
Total cessation events: 31/1483 (2.1%) in intervention group, 11/1066 (1.0%) in control group; absolute difference 10.6 more per 1,000 (2.0 more to 35.3 more)
Heterogeneity: Tau2=0.00; Chi2= 1.40, df=4, p = 0.84; I2 =0.0%; Test for overall effect: Z=2.49, p=0.01
For study weights, see Appendix 5

Also in the US, the web-based RCT of Halpern et al. included 6,006 smokers from employees and their spouses from companies that utilised Vitality wellness programs – 2,012 in study arms comparing ENDS and usual care.[51] Participants were contacted by email and accessed study interventions and reported outcomes via a web portal; no contact was assumed to represent continuing smoking and cessation outcomes were verified biochemically only in those reporting cessation. At six-month follow-up, 12 of 1,199 participants (1.0%; 95% CI 0.4%-1.6%) in the ENDS arm and one of 813 participants in the usual care arm (0.1%; 95% CI 0.0%-0.3%) were verified as having ceased smoking. After accounting for multiple testing, there was no statistically significant difference in outcomes between these groups.[51] At 12-month follow-up, four of 1,199 participants (0.3%; 95% CI 0.0%-0.7%) in the ENDS arm and none of 813 participants in the usual care arm were verified as having ceased smoking.

In a study recruiting smokers from an Italian screening program for lung cancer and including clinic-based follow-up and telephone smoking cessation counselling, Lucchiari et al. found 19.0% of 70 smokers randomised to three months of ENDS and 10.0% of 70 smokers randomised to control achieved continuous biochemically verified abstinence at six-month follow-up (RR 1.86; 95% CI 0.79-4.38).[47]

In the Canadian RCT, Eisenberg et al.[45] included smokers motivated to quit recruited from outpatient, smoking cessation, and/or walk in clinics, and through community advertising. Participants were followed up via the telephone and clinic visits. At 24-week follow-up, 3.9% (five out of 128) of participants randomised to ENDS and 0.8% (one out of 121) randomised to usual care achieved continuous abstinence (RR 4.73; 95% CI 0.56-39.88). Using a non-continuous measure of cessation, 17.2% randomised to ENDS and 9.9% randomised to usual care reported biochemically confirmed 7-day point prevalence abstinence at 24-week follow-up.[45]

In their pilot RCT, Holliday et al.[46] recruited smokers with periodontitis from Dental Hospital clinics and primary care practices in the UK. Participants were followed up in the clinic in line with their normal periodontal treatment and received smoking cessation advice. At six-month follow-up, six out of 40 (15%) participants randomised to ENDS and two out of 40 (5%) randomised to usual care achieved biochemically confirmed abstinence (RR 3.00; 95% CI 0.64-13.98).[46]

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 2) and at six-month follow-up (RR 2.40; 95% CI 1.21-4.78) (Figure

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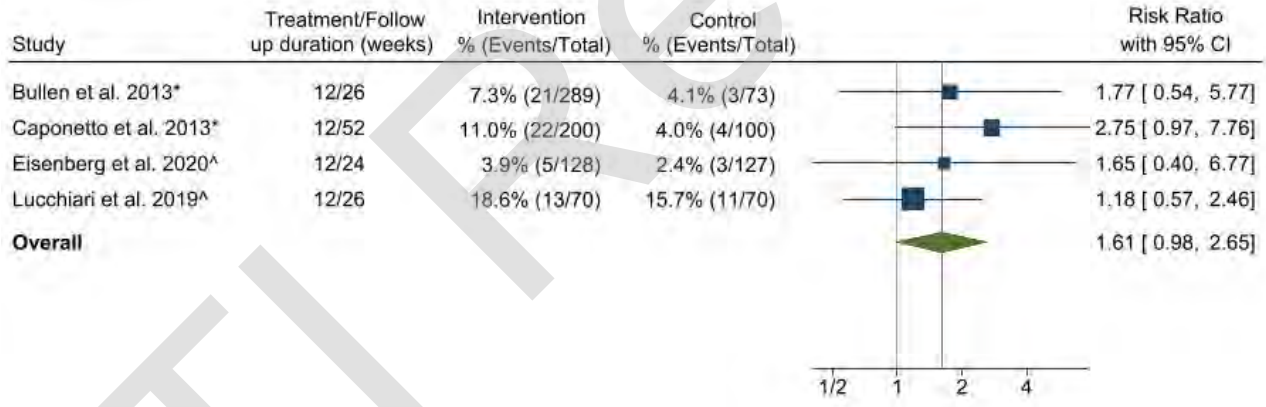
11). This conclusion did not change materially when a fixed-effects model was used (RR 2.46, 95%CI 1.28-4.71) (Appendix 5). Nor did it change substantively when the random-effects meta-analysis was restricted to studies with no noted potential competing interests (RR 2.18; 95%CI 1.11-4.27; I^2 = 0.0%), although evidence was even more limited, with 27 of 284 participants ceasing smoking (Figure 8). 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[53] and the other three judged high risk for missing outcome data.[45 46 51] One study was found to have concerns in two domains – deviations from intended intervention and missing data (Appendix 6).[47] The GRADE rating for this comparison was very low (Appendix 7).

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) (Table 2 and Appendix 4).[45 47 49 52] These trials reported a total of 82 participants ceasing smoking out of 1,057 randomised (Figure 3). No studies were directly funded by the tobacco or e-cigarette industry. Bullen et al.[49] had a study author who reported previously receiving research funding from an e-cigarette manufacturer and Caponetto et al.[52] had a study author who had received funding from the tobacco industry.[54] Both studies reported using e-cigarettes donated by an e-cigarette company.[49 52]

Figure 3: 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 (8.9%) in intervention group, 21/370 (5.7%) in control group; absolute difference 32.0 more per 1,000 (1.1 less to 93.6 more)
Heterogeneity: Tau2=0.00; Chi2= 1.73, df=3, p = 0.63; I2 =0.00%; Test for overall effect: Z=1.87, p=0.06
For study weights, see Appendix 5

In their Italian pilot RCT published in 2013, Caponnetto et al. recruited 300 smokers not intending to quit via newspaper advertisements inviting them to try e-cigarettes "to reduce the risk of tobacco smoking".[52] The study protocol included nine visits held at a smoking cessation clinic and participants received a 12-week supply of e-cigarettes at baseline. At one-year follow-up 11.0% (22/200) of participants randomised to ENDS and 4.0% (4/100) of participants randomised to ENNDS achieved cessation (RR 2.75; 95% CI 0.97-7.76).

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In the New Zealand superiority RCT of Bullen et al.,[49] community-dwelling smokers who were motivated to quit were recruited through community newspapers. Participants telephoned a screening clinic and received interventions via courier (e-cigarettes); 289 were randomised to 12 weeks of 16mg nicotine e-cigarettes and 73 were randomised to 12 weeks of ENNDS. At six-month follow-up 7.3% (21/289) of smokers randomised to ENDS and 4.1% (3/73) randomised to ENNDS had verified smoking abstinence (RR 1.77; 95% CI 0.54-5.77).[49]

The Italian study of Lucchiari et al., outlined above, reported that 19.0% of smokers randomised to ENDS and 16.0% randomised to ENNDS achieved continuous abstinence at six-month follow-up (RR 1.18; 95% CI 0.57-2.46).[47]

Eisenberg et al., the Canadian study mentioned previously, found that 3.9% of smokers randomised to ENDS and 2.4% randomised to ENNDS achieved biochemically verified continuous abstinence at 24-weeks follow-up (RR 1.65; 95% CI 0.40-6.77). When using biologically verified seven-day-point prevalence abstinence, 17.2% of smokers randomised to ENDS and 20.5% randomised to ENNDS achieved smoking abstinence.[45]

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 3). The finding became significant using fixed-effects meta-analysis (RR 1.70, 95% CI 1.03-2.81) (Appendix 5) but did not change materially when restricted to six-month follow-up only (RR 1.56; 95%CI 0.96-2.53) (Figure 12). Two of the included studies were assessed as having a high risk of bias due to missing outcome data[45 53] and the remaining two were considered to raise "some concerns" due to deviations from the intended intervention and missing outcome data [47 49] (Appendix 6). The GRADE rating for this comparison was very low (Appendix 7). 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 (Figure 9).[45 47]

Nicotine e-cigarettes versus other nicotine replacement therapy

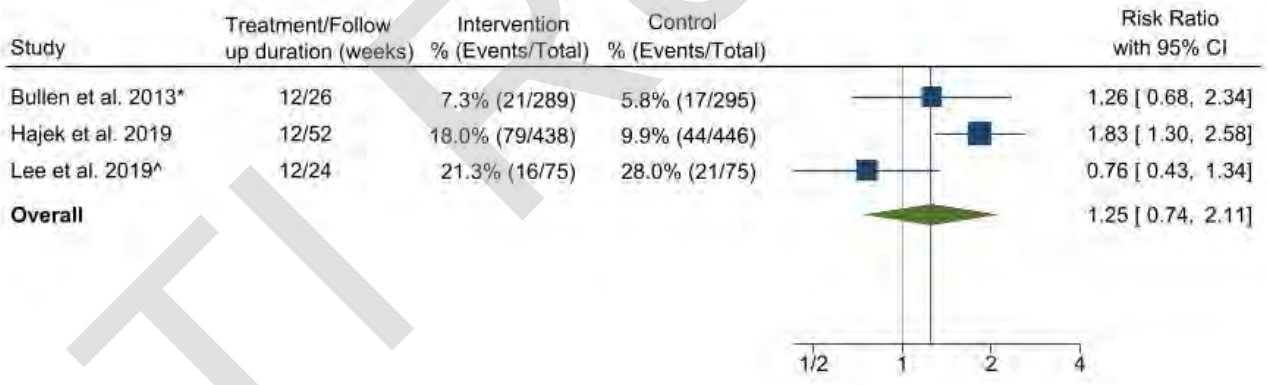
Three RCTs were identified that compared ENDS to approved NRT (Table 2 and Appendix 4).[23 49 50] The studies were conducted between 2013 and 2019. They included a total of 1,618 participants, all of whom were smokers motivated to quit and were randomised to 12-week treatment programs; 198 achieved smoking cessation at greater than four-month follow-up. Bullen et al.[49] had the potential competing interests noted above; no other studies had reported competing interests.

In the previously mentioned New Zealand RCT, smoking cessation at six months was achieved by 7.3% (21/289) of those randomised to ENDS and 5.8% (17/295) of those randomised to nicotine patches (RR 1.26; 95% CI 0.68-2.34).[49]

In a study of patients attending the UK National Health Service smoking cessation program, Hajek et al. randomised smokers to ENDS or to a range of approved NRT products as the comparator (patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs), encouraging participants in the NRT group to combine and/or switch products.[23] Behavioural therapy was provided to all participants, including weekly one-on-one sessions with local clinicians for at least four weeks after the quit date.[23] Among 162 ENDS arm participants who provided information on nicotine strength of their e-liquid at all time points the mean nicotine content was 18mg/mL, 12mg/mL and 8mg/mL at 4, 26 and 52 weeks, respectively (Friedman test=255.6, p<.001). This study found that 18.0% (79/438) of those randomised to ENDS and 9.9% (44/446) of those randomised to approved NRT achieved one-year sustained abstinence from smoking (RR 1.83; 95% CI 1.30-2.58).

Lee et al. randomised male smoking employees at a motor company in Korea to either very low dose ENDS or nicotine gum; all participants received an education session and four weekly visits to a medical office for evaluation and counselling by an independent medical practitioner.[50] At 24-week follow-up, 21.3% (16/75) of the ENDS and 28.0% (21/75) of the nicotine gum groups achieved continued smoking abstinence (adjusted p=0.291; RR 0.76; 95% CI 0.43-1.34).

Figure 4: 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 (14.5%) in intervention group, 82/816 (10.0%) in control group; absolute difference 44.1 more per 1,000 (25.1 less to 110.5 more)
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
For study weights, see Appendix 5

In summary, of the three studies, two reported no statistically significant difference between ENDS and approved NRT[49 55] and the other found significantly greater cessation in those randomised to ENDS[23]. 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 4). This finding was

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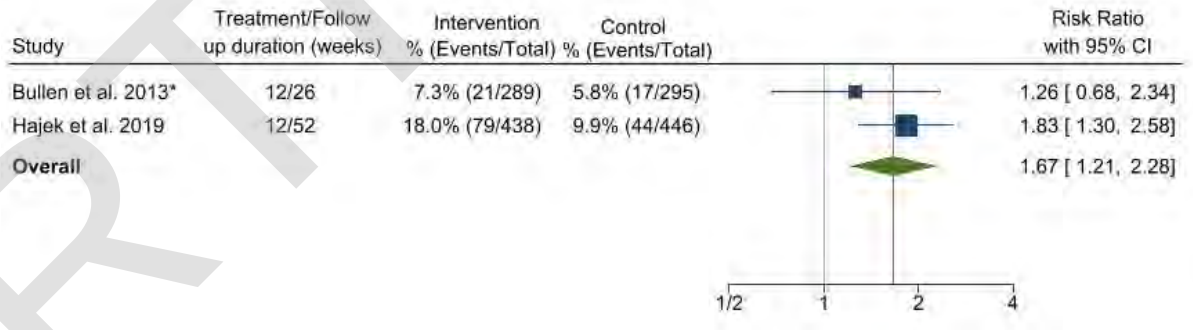
statistically significant using fixed-effects meta-analysis (RR 1.44; 95%CI 1.10-1.87) (Appendix 5). The conclusion from the random-effects model did not substantially change when the meta-analysis was limited to studies with no noted potential competing interests (RR 1.22; 95% CI 0.52-2.86; I^2 = 85.1%), although evidence was even more limited, with 160 of 1,034 participants ceasing smoking (Figure 10). 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) (Figure 13). One study was judged to be at a low risk of bias across all domains[23], one was judged to have some concerns due to deviations from the intended interventions[49] and the last was judged high risk due to missing outcome data[50] (Appendix 6). The GRADE rating for this comparison was very low (Appendix 7).

Following the a priori protocol for this review, e-cigarettes were considered ENDS if they contain any amount of nicotine. However, to inform the Royal Australian College of General Practitioners guidelines 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[23 49] 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%) derived from 161 of 1,468 participants ceasing smoking (Figure 5). This finding did not substantially change when limited to six-month follow-up (RR 1.39; 95% CI 1.15-1.69) (Figure 14). When the meta-analysis was limited to studies with no potential competing interests, only one study[23] 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[23] and the other to have some concerns[49]. The GRADE rating for this comparison was low (Appendix 7).

Figure 5: 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 (13.8%) in intervention group, 61/741 (8.2%) in control group; absolute difference 55.2 more per 1,000 (17.3 more to 105.4 more)
Heterogeneity: Tau2=0.00; Chi2= 1.06, df=1, p = 0.30; I2 =5.48%; Test for overall effect: Z=3.17, p=0.00

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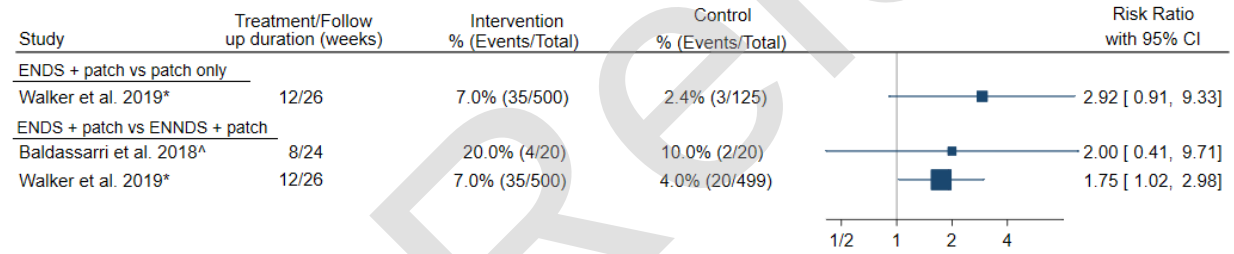
Nicotine e-cigarettes plus NRT versus other comparators

Two studies examined quitting in smokers randomised to ENDS and ENNDS, with all study participants receiving nicotine patches (Table 2 and Figure 6).[44 48] One study had potential competing interests identified.[48] Both were judged to be at high risk of bias due to missing outcome data. The GRADE rating for these comparisons was very low (Appendix 7).

In their US pilot RCT of 40 smokers willing to quit who were attending clinics and smoking cessation services, Baldassarri et al. found that 20.0% randomised to ENDS and nicotine patches and 10.0% randomised to ENNDS and patches achieved seven-day point prevalence abstinence at 24 weeks (RR 2.00; 95% CI 0.41-9.71).[44] Walker et al. found that among New Zealand community-dwelling smokers, 7.0% (35/500) of motivated smokers randomised to 14 weeks of ENDS combined with nicotine patches achieved cessation at six months, compared to 2.4% (3/125) of those randomised to patches alone (RR 2.92; 95% CI 0.91-9.33) (Figure 6).[48] Cessation was 4% (20/499) in smokers randomised to ENNDS plus nicotine patch (RR compared to patch only 1.75; 95% CI 1.02-2.98).

Figure 6: Biochemically verified smoking cessation in smokers using patches, randomised to nicotine e-cigarettes, non-nicotine e-cigarettes or no additional intervention



* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study

Non-nicotine e-cigarettes plus counselling versus counselling alone

Two RCTs were identified that compared ENNDS plus counselling to counselling alone (Table 2 and Appendix 4).[45 47] The studies were conducted between 2019-2020 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.

In the previously mentioned study by Lucchiari et al., smoking cessation at six-month follow-up was achieved by 15.7% (11/70) randomised to ENNDS and 10.0% (7/70) randomised to counselling only (RR 1.57; 95% CI 0.65-3.82).[47]

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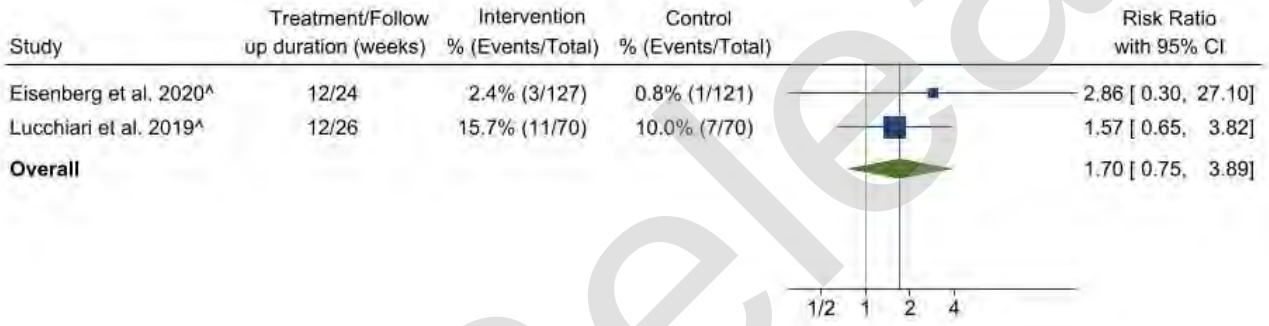
The Canadian study previously mentioned found continuous smoking abstinence at six-month follow-up was achieved by 2.4% (3/127) randomised to ENNDS and 0.8% (1/121) randomised to counselling only (RR 2.86; 95% CI 0.30-27.10).[45]

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 7). 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[45] risk of bias and the other was judged to have some concerns[47] driven by missing outcome data in both studies. The GRADE rating for this comparison was very low (Appendix 7).

Figure 7: Biochemically 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: Tau^2=0.00; Chi^2= 0.24, df=1, p = 0.63; I^2 =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).[49] 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 (Appendix 7).

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 (Table 3). Five RCTs contained data on nicotine cessation: two with[48 49] and three without[23 44 53] competing interests noted. These RCTs involved 2,773 smokers, 232 of whom quit during the follow-up period.

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One study contained sufficient data to compare cessation of any nicotine exposure between participants randomised to ENDS or approved NRT.[23] Data from Hajek et al. indicate that 3.7% (16/438) of participants randomised to ENDS and 9.0% (40/446) of participants randomised to NRT had ceased all nicotine exposure (combustible cigarettes, ENDS or NRT) at 52-week follow-up (RR for ceasing any nicotine exposure=0.41; 95% CI 0.23-0.72).[23]

At 52-week follow-up in Hajek et al., 39.5% (173/438) of smokers randomised to ENDS were using nicotine-delivering products (ENDS or approved NRT) compared to 4.3% (19/446) of the NRT group, meaning smokers randomised to ENDS were 9.27 times (95% CI 5.88-14.61) as likely than those randomised to NRT to be using any nicotine-delivering products.[23] Restricting the data to smokers who quit successfully, 79.8% (63/79) of quitters randomised to ENDS and 9.1% (4/44) of quitters in the NRT group were using nicotine-delivering products at 52 weeks (RR 8.77; 95% CI 3.42-22.48).[23] Continuing smokers in the ENDS group were also much more likely to be using nicotine-delivering products at follow-up compared to those in the approved NRT group (RR 8.21; 95% CI 4.88-13.82).[23]

In their New Zealand study published in 2013, Bullen et al.[49] found that participants in the ENDS group were 4.26 times (95% CI 2.58-7.06) as likely to be using any nicotine-delivering products at six-month follow-up compared with those randomised to approved NRT. In the ENDS group, 38% (8/21) of combustible tobacco quitters were still using ENDS at follow-up. The number of participants still using approved NRT in the approved NRT group was not reported.

Data from the US pilot study conducted by Carpenter et al.[53] indicate that in the week preceding the final study visit (Week 16), 32.0% of participants in the 16mg ENDS group, 60.0% of participants in the 24mg ENDS group and 13.0% of participants in the control (no intervention) group were using ENDS.[53]

In the small Italian pilot study of Baldassarri et al.[44] at 24-week follow-up, 90.0% (18/20) of smokers randomised to ENDS and nicotine patch and 95.0% (19/20) randomised to ENNDS and nicotine patch were using nicotine in any form (combustible cigarettes, ENDS or approved NRT) (RR for having ceased nicotine in any form for ENDS + patch versus ENNDS + patch 2.00; 95% CI 0.20-20.33).[44] Among quitters, 50.0% (2/4) of the ENDS plus patch group and 50.0% (1/2) of the ENNDS plus patch were using NRT or e-cigarettes at follow-up (RR 1.00; 95% CI 0.18-5.46).[44] Walker et al.[48] found that intervention groups that included e-cigarettes were more likely to be using NRT products – including ENDS and other products – at six-month follow-up, compared with the patch-only control group (ENDS + patch versus patch only RR 1.53; 95% CI 1.05-2.22; ENNDS + patch versus patch only RR 1.52; 95% CI 1.05-2.21).

In summary, the evidence regarding e-cigarette use in smokers and nicotine cessation is very limited. Considering the data that are available, smokers using e-cigarettes are 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.

Non-inferiority considerations

When considering the potential use of ENDS for smoking cessation, the trials that have been conducted to date have been designed to assess superiority of ENDS versus other comparators for smoking cessation. However, it is also worth considering whether or not ENDS has non-inferior efficacy, particularly with respect to comparators such as existing NRT. The recommended approach when assessing non-inferiority is to compare the estimated 95% confidence interval of the new treatment versus the active comparator from the non-inferiority trial to a predefined margin.[56-60] The pre-defined non-inferiority margin is the largest clinically acceptable difference between the two products. Historical evidence from RCTs comparing the active comparator against placebo is considered; the margin is defined either based on such pooled estimate or based on the limit of the 95% CI that is the closest to the null effect (in this case, the lower limit of RR for smoking cessation, say M_1). Based on clinical judgement, the fraction of M_1 that must be preserved by the new drug is defined as the non-inferiority margin.[61] In this case, no such non-inferiority margin was pre-defined, and it is not possible to formally quantitatively assess non-inferiority.

Considering non-inferiority less formally, since the evidence to date indicate e-cigarettes delivering nicotine >0.01mg/mL may be superior to NRT and to usual care/no intervention, it is by definition likely to be non-inferior to both of these. The ENDS versus ENNDS comparison is less relevant as ENNDS does not represent current standard of care. Moreover, the evidence to date gives a RR for smoking cessation for ENDS versus ENNDS of 1.61 (0.98-2.65); given the above requirements, and in the absence of reliable data on the efficacy of ENNDS versus usual care for smoking cessation, it is not feasible to meaningfully calculate a non-inferiority margin for the ENDS versus ENNDS comparison.

Quality assessment

Eight of the eleven studies were found to have a high risk of bias,[44-46 48 50-53] two raised some concerns,[47 49] and one was found to have a low risk of bias[23] (Appendix 6). 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 (Appendix 7). Only ENDS (nicotine concentration <0.01mg/mL) versus NRT was rated low. The overall GRADE rating was very low.

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Main findings of major international reports and meta-analyses

The 2018 NASEM review analysed evidence published until August 2017 on the effectiveness of e-cigarettes as smoking cessation aids.[18] The review did not examine cessation of nicotine exposure as an outcome. The evidence was derived from RCTs, non-randomised trials, cohort and repeated cross-sectional studies. As stated in the NASEM review,[18] the authors concluded:

1. Overall, there is limited evidence that e-cigarettes may be effective aids to promote smoking cessation.
2. There is moderate evidence from randomised controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation.
3. 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.
4. While the overall evidence from observational trials is mixed, there is moderate evidence from observational studies that more frequent use of e-cigarettes is associated with an increased likelihood of cessation.

The 2018 Public Health England review and the CSIRO review supported the conclusions of the NASEM review on smoking cessation.[28 31] The 2018 CSIRO review specifically reviewed Australian evidence on e-cigarettes "to identify any potential for e-cigarettes to reduce rates of smoking in Australia", but found that there was a lack of Australian evidence, only citing one Australian observational study in their chapter on the use of e-cigarettes for smoking cessation. The 2020 US Surgeon General review[29] also supported NASEMS 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 introduce uncertainty to the evidence. They also consider the evidence suggestive but insufficient regarding the efficacy of ENDS compared to ENNDS.[29] The US Preventive Services Task Force 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."[30] The 2021 SCHEER report concluded that there was weak evidence that e-cigarettes were efficacious as an aid for smoking cessation.[15]

Table 1: Summary of findings from major international reviews

International Review	Conclusion
European Union Scientific Committee on Health, Environmental and Emerging Risks (April 2021)[15]	There is **weak evidence** for the support of electronic cigarettes' effectiveness in helping smokers to quit.
The US Preventive Services Task Force (Jan 2021)[62]	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.

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US Surgeon General (2020)[29]	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.
Irish Research Board (June 2020)[43]	The systematic review and network meta-analysis of electronic nicotine delivery systems (e-cigarettes) versus therapies usually given for smoking cessation showed that there is **no evidence** of a difference in effect on incidences of smoking cessation. There is a low-level of certainty in these results.
National Academies of Science, Engineering and Medicine (2018)[18]	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.
Australian Commonwealth Scientific and Industrial Research Organisation (2018)[31]	The effectiveness of this method compared with other smoking cessation methods is **not known.**

Since the NASEM review, several meta-analysis reporting on the efficacy of ENDS for smoking cessation have been published. Combined, these meta-analyses suggest that ENDS may be more efficacious than NRTs, ENNDS, and usual care for smoking cessation. However, certainty of the evidence was moderate to very low and the largest analysis consisted of only seven studies.

The most recent update from the Cochrane systematic review[41] found that ENDS were more efficacious than NRTs (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.[41]

The 2020 Irish Health Research Board network meta-analysis (based on seven RCTs) found that there is 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.[43] The evidence was in 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 lost to follow-up.[43]

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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).[38] 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.[38] 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).[40] 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 time as likely to achieve smoking abstinence (95% CI 1.173, 2.061).[39] Zhang et al. conducted a random-effect 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 trials) although evidence was low certainty.[42]

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 6 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 6 months. The intervention period predates nicotine salt introduction to EU markets[15], so ENDS used in the trial are assumed to be freebase products. At 6 month follow up, 47% of ENDS users and 10% of NRT users were still using their allocated products.[63]

Interpretation

The following summary points can be drawn from this systematic review and meta-analysis of the current evidence on the efficacy of nicotine e-cigarettes as a smoking cessation aid:

- Reliable evidence on the efficacy of interventions – such as e-cigarettes for smoking cessation – requires large-scale, independent RCT evidence from multiple studies.
- The evidence on the efficacy of nicotine e-cigarettes and non-nicotine e-cigarettes for smoking cessation was limited.
- From 6,552 titles identified, eleven RCTs were identified; 347 of 5,901 randomised smokers achieved smoking cessation. RCTs were generally small, of short duration (maximum one year) employed a wide range of study designs and the majority had methodological issues indicating a high risk of bias.
- RCTs were of nicotine in freebase form; no trials of nicotine salt products were identified.

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- Summary measures were influenced by the inclusion or non-inclusion of individual studies and by choice of meta-analytic method. Both random- and fixed-effects methods have limitations in the e-cigarette context.
- Based on random-effects meta-analyses of the current limited evidence, and including all studies, no significant benefit of nicotine e-cigarettes was demonstrated when compared to ENNDS or approved NRT. A significant difference between ENDS compared to NRT and ENNDS was found using fixed-effects meta-analysis. The certainty of the evidence for these comparisons was rated as very low.
- 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 nicotine-replacement therapy. 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 6 month follow up.
- Based on low certainty evidence, e-cigarettes delivering nicotine at doses likely to be used in the clinical setting were significantly more efficacious than standard NRT for smoking cessation.
- 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.

In conclusion:

- There is limited evidence that 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.
- 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.

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- 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.
- The trial evidence indicates 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.

Discussion

Around two-thirds to three-quarters of smokers who quit successfully do so unaided.[64-69] This indicates that, although NRT and other pharmacotherapies improve the probability of quitting, and there is a general impression that they are necessary for smoking cessation,[70] they are not essential for most smokers.

Robust evidence on the efficacy of e-cigarettes as an aid to smoking cessation is limited, particularly when the scale of exposure – often justified on this basis – is considered. Overall, we identified eleven RCTs world-wide meeting the eligibility criteria, including relating to at least four months of biochemically verified smoking cessation. Most of the trials were small and had methodological issues; the overall quality of the evidence was rated as low. Overall, there is limited evidence that, in the supervised clinical context, e-cigarettes delivering potentially therapeutic doses of freebase nicotine 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. There is insufficient evidence that nicotine e-cigarettes are efficacious for smoking cessation, compared to non-nicotine e-cigarettes. Similarly, there is insufficient evidence that non-nicotine e-cigarettes are efficacious for smoking cessation compared to counselling or approved NRT. There is also insufficient evidence that nicotine e-cigarettes are efficacious outside the clinical setting. No trial evidence on nicotine salt products was located. The findings regarding nicotine e-cigarettes versus NRT are largely driven by the results of a single trial in UK therapeutic smoking cessation services.[23] The additional small trial published post-completion of the review, also in the UK therapeutic setting, reinforces this. Hence, the evidence is not robust but is promising that ENDS may help with cessation, supporting the need for additional high-quality large-scale RCTs.

Studies of NRT receiving funding from industry, and sponsored device and drug studies more broadly, tend to find more favourable results than those without such funding.[71 72] When the review and meta-analyses were restricted to studies with no apparent potential competing interests, evidence on e-cigarettes and smoking cessation became even more limited, although the general direction of the findings did not change materially. Given the data issues, there was limited ability to detect a difference between findings according to whether

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or not a potential competing interest was present. Hence, the impact of potential competing interests on the findings will need to continue to be reviewed as evidence emerges.

If ENDS are used as a tobacco cessation tool, and use continues following cessation, there is ongoing exposure to nicotine, a highly addictive drug.[12-14] There are concerns that nicotine addiction itself is problematic and that, although ENDS use would generally be considered better than continuing to smoke, quitting nicotine altogether is preferable. The use of nicotine e-cigarettes tends to result in more prolonged exposure to nicotine than use of approved NRT. In an RCT based in the UK National Health Service, almost 80% of combustible tobacco smoking quitters randomised to ENDS were still using them one year following their quit date, and were almost nine times more likely to be using any nicotine-delivering product at follow-up compared to quitters in the NRT arm.[23] Findings were similar in participants who continued to smoke.[23] A letter to the editor about this RCT notes, "For every 100 participants who used the e-cigarette strategy, 18 quit smoking, but 14 of those participants became e-cigarette users. An additional 25 participants who did not quit smoking became dual users, so the e-cigarette strategy created more dual users than quitters, and most participants who quit smoking transitioned to vaping".[73] Hence, the US Surgeon General's report noted that there is a greater likelihood of complete abstinence from all products in the long term with use of standard NRT than with e-cigarette use.[29]

Evidence on e-cigarettes is evolving rapidly and this updated review includes two additional trials since our last review: one that was published in 2020[45] and one in a clinical population that was reconsidered for inclusion.[46] The additional trial published post-completion of the review should also be noted. Our findings regarding the efficacy of e-cigarettes for smoking and nicotine cessation are broadly consistent with those of earlier major reviews[18 20 21 28 31] and more contemporary systematic reviews and meta-analyses,[15 29 38 39 41-43] noting the overall paucity and general uncertainty of the evidence. Of the eight most recent systematic reviews and meta-analyses, four – including the US Preventive Services Task Force, the US Surgeon-General's report and the Irish Health Research Board's independent network meta-analysis – state that the current evidence is insufficient to conclude that e-cigarettes are efficacious for smoking cessation,[29 38 43] two considered the evidence to be of low certainty that e-cigarettes appear to be potentially effective for smoking cessation[40 42] and two – including the most recent Cochrane review[41] – considered the evidence that ENDS was more efficacious for smoking cessation than ENNDS or NRT was moderate-certainty. However, the Cochrane review included one study which did not have verified outcomes at six months,[55] included some unpublished non-peer-reviewed data and gave overall higher quality ratings than this review. This review is independent of the trials conducted to date, whereas three of the Cochrane review authors were authors of three of the 11 main trials included in the review and two of the three comparing ENDS and NRT. A major consideration here is the limited numbers of events in the studies; GRADE recommends calculating the optimal information size or deferring to a minimum of 300 events in each of the randomised comparisons examined.[26 27] If the optimal

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information size criterion is not met, the imprecision criterion should be rated down.[26] As such, the small numbers of events within the included RCTs for each comparator led to a loss of one point, for all comparisons considered. A second point deduction is recommended when the confidence intervals are wide and include both appreciable benefits and harm[26] and hence four comparisons incurred a second point deduction leading to a judgement of very serious concerns for imprecision. Deductions for imprecision and other assessment parameters lead to the necessary conclusion of very low certainty evidence overall and for each specific randomised comparison, apart from the comparison between nicotine e-cigarettes (nicotine concentration >0.01mg/mL) and other nicotine-replacement therapy, which was rated as low certainty.

Effective tobacco control relies on a framework approach, incorporating population-level measures such as taxation, mass media campaigns, health warnings, bans on advertising and limitations on places where people can smoke, as well as measures targeting individual smokers to quit. Increasingly, low smoking prevalence in Australia is driven by lack of smoking uptake, especially among youth. For individuals considering quitting, the substantial majority do so unaided, as noted above, and a minority will seek health professional support. Reflecting the differing needs of smokers trying to quit, clinical support for smoking cessation tends to follow a cascade of intervention, commencing with brief interventions and behavioural support and progressing to pharmaceutical interventions. Comparison between nicotine e-cigarettes and NRT, in the context of comprehensive and regular face-to-face behavioural support therefore represents the most intensive end of the spectrum, accounting for an important but relatively small minority of those who quit smoking.

While there is limited evidence of the potential for e-cigarettes to support cessation as part of clinically supervised intervention, the World Health Organization has concluded that there is even less evidence available to support the role of ENDS as an intervention at the population scale. Moreover, clinical interventions must consider safety – which is beyond the scope of this review – as well as efficacy. As Wang et al. state in their recent review "E-cigarettes may warrant consideration as a prescription drug to be used as part of a clinically supervised smoking cessation intervention, provided that the associated risks are commensurate with the benefit."[39] Accordingly, in their January 2021 recommendations on Interventions for Tobacco Smoking Cessation, the US Preventive Services Task Force concluded "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."[62] The limited evidence base for ENDS is important to consider when there are other smoking cessation tools available that have a large evidence base demonstrating their safety and efficacy, along with public health and education measures with a track record of proven success, and which have no evidence of associated increases in the likelihood of tobacco smoking initiation among non-smokers.[22 74 75] Indeed, such measures generally reduce tobacco smoking uptake, including among youth, while there is strong evidence that non-smokers who use e-cigarettes are more likely than others to go on to take up combustible tobacco smoking.[76]

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This report provides a comprehensive overview of contemporary evidence on the relationship of e-cigarette use to smoking cessation. This report followed best-practice methods, including search terms and databases used in the NASEM review. Distinctive features of this report include:

- Updated evidence reviews to start of May 2021.
- The review examining the evidence for the efficacy of e-cigarettes as a smoking cessation tool only included RCTs as they provide reliable evidence on the efficacy of interventions.[32]
- The primary outcome for the smoking cessation review was limited to cessation only. Reduction in smoking frequency as an outcome was excluded because smoking cessation is the end goal for cessation aids,[77 78] and there is evidence of significant morbidity even with low smoking frequency.[79] Seven RCTs were excluded during screening that had data on the efficacy of e-cigarettes as a smoking cessation aid because smoking cessation was not the primary outcome, and may not have been measured directly.
- Use of random- and fixed-effects meta-analyses.
- As nicotine is an addictive substance that can result in poisoning and contribute to adverse health outcomes this review included a secondary outcome of cessation of nicotine exposure, which aligns with one of the Australian Government Department of Health's requirements for this body of work, to minimise risks of nicotine addiction.

The available evidence on e-cigarettes and smoking cessation is affected by significant methodological issues. Many of the trials are small, with four explicitly termed pilot studies, designed more to test future study feasibility than the efficacy of e-cigarettes for cessation. The overall number of smokers quitting is also small: 208 in those randomised to ENDS and 139 in those randomised to comparators. This contributes to the lack of statistical power for the body of evidence as a whole to both detect and exclude an effect. It also makes publication and other types of bias more probable, including the fact that researchers may be more likely to choose not to publish negative findings from small studies.[80] The small number of relevant RCTs means tests for funnel plot asymmetry are not appropriate to investigate the potential for publication bias.[81] Loss to follow-up and issues with ascertainment of cessation are also issues, especially for trials involving minimal contact with participants. The RCT including the largest number of participants, randomising employees at multiple US companies, recorded that none of the 813 smokers in the control arm had quit over a 12-month period. As well as being relatively statistically unstable, this is not consistent with the background 12-month quit rate in the general US population.[82] In this web-based study, participants needed to actively log on to record smoking outcomes – no activity was taken to indicate continuing smoking – as well as to access intervention e-cigarettes. It is therefore likely that cessation events were missed and possible that those in the ENDS intervention arm had greater engagement and reporting of outcomes than smokers in the control arm.

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We decided, a priori, to use random-effects meta-analysis as our primary method of quantitatively combining results, since we considered that the included studies were likely to be of differing underlying populations. However, random-effects models are less suitable when there are few trials – hence, we also conducted fixed-effects meta-analyses and present both sets of results. We consider it is not possible to conclude which summary result is "correct" or "incorrect" but rather that the limitations of the evidence mean that the summary results are not robust to the choice of analytic method. Furthermore, they are influenced by the inclusion and non-inclusion of individual studies. This contributed to our overall rating of the evidence as "limited".

The generalisability of the RCT evidence is also problematic. E-cigarettes are highly heterogeneous, with many thousands of variants in the devices and e-liquids used, including the dose and nature of the nicotine delivered.[1] The 2020 report of the US Surgeon-General reports that "E-cigarettes, a continually changing and heterogeneous group of products, are used in a variety of ways. Consequently, it is difficult to make generalisations about efficacy for cessation based on clinical trials involving a particular e-cigarette, and there is presently inadequate evidence to conclude that e-cigarettes, in general, increase smoking cessation."[29] The trials used freebase nicotine in concentrations ranging from 0.01mg/mL to 24mg/mL, with the two trials demonstrating significant efficacy – including the trial published after the search date cut off – conducted within UK National Health Services smoking cessation clinics.[23] In the one of these trials, participants randomised to ENDS received a starter pack including 18mg/mL freebase nicotine e-liquid and were instructed to use a nicotine concentration of their choice subsequently, up to the statutory limit of 20mg/mL; where data were available, mean concentrations were 18mg/mL, 12mg/mL and 8mg/mL at 4, 26 and 52 weeks, respectively.[23] In the other trial, with an intervention period prior to the introduction of nicotine salts onto the EU market, participants randomised to ENDS chose their own nicotine concentration, up to 20mg/mL, and used a median of 10mg/mL initially, and 6mg/mL at 6 month follow up.

Bioequivalence is defined by the United States Food and Drug Administration as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[16] Nicotine salt products deliver nicotine more rapidly than freebase products and have other differences in pharmacokinetic properties.[15 83] Hence, they are not bioequivalent to freebase nicotine and their efficacy for smoking cessation is unknown.

There was also major variation in the settings and participants of the included RCTs, ranging from minimal contact telephone- and web-based studies of smokers with or without specific plans to quit to the RCT receiving the highest quality rating, based within smoking cessation services, involving smokers motivated to quit and incorporating comprehensive face-to-face behavioural therapy. In accordance with this variation, the

proportion of smokers quitting successfully differed markedly between trials. The generalisability of the RCT results across community, workplace and clinical contexts is unclear. It is likely that ENDS will be used differently by smokers who intend to quit and those who do not. Furthermore, the impact of any form of nicotine replacement is likely to differ according to whether or not it is used in conjunction with behavioural therapy and other support from smoking cessation services.[84]

This review provides a comprehensive and up-to-date quantitative overview of evidence from RCTs and major reviews on the efficacy of e-cigarettes as a smoking cessation tool. It includes only published studies with biochemically verified evidence of sustained smoking abstinence. It explicitly and quantitatively considers evidence independent of and with potential competing interests. This is the first review to our knowledge to examine the efficacy of e-cigarettes for nicotine cessation, finding limited evidence available. Nicotine cessation was not the primary or secondary outcome in any RCT and biochemical methods to validate nicotine cessation are still being developed.[85-87] It includes only RCTs; while observational data provide useful evidence on some elements of e-cigarette use and their health impacts, smokers who do and do not use e-cigarettes differ in ways likely to affect their underlying propensity to quit, including in their commitment to quitting, health and health behaviours.

Conclusions

There is limited evidence that, in the clinical context in combination with best-practice counselling and supportive care, 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. There is insufficient evidence that 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. There is also 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. The certainty of the evidence is low or very low and additional high-quality large-scale RCTs are needed. Trials demonstrating efficacy were limited to products with nicotine concentrations ≤20mg/mL. Use of nicotine e-cigarettes is likely to result in prolonged exposure to nicotine, including through dual e-cigarette use and combustible smoking. The balance of safety and efficacy of e-cigarettes needs to be considered in clinical decision making about their use for smoking cessation.

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Table 2: Details from identified RCTs of nicotine electronic cigarettes for smoking cessation

Authors, year, country and participants	Duration (treatment and follow-up)	Experimental intervention	Control intervention	Participants ceasing tobacco smoking at follow-up
Bullen et al., 2013[49]* New Zealand Smokers from the general community intending to quit responding to media invitation	Treatment 12 weeks supply received via courier or mailed voucher, enrolment by phone Follow-up 1 and 3 months via telephone and 6-month laboratory visit in those self-reporting abstinence	Intervention 1 (n=289) Electronic nicotine delivery system (ENDS), 16 mg nicotine Intervention 2 (n=73) Electronic non-nicotine delivery system (ENNDS)	Nicotine patches (n=295) 21 mg nicotine patch, one daily accessed via exchanging a voucher received in mail for patches at a community pharmacy	6-month verified abstinence ENDS: 7.3% (21/289) Patches: 5.8% (17/295) ENNDS: 4.1% (3/73)
Caponnetto et al., 2013[52]* Italy Smokers not intending to quit invited via newspaper advertisements to "try e-cigarettes to reduce the risk of tobacco smoking"	Treatment 12 weeks dispensed at baseline visit held at smoking cessation clinic Follow-up 2, 4, 6, 8, 10, 12, 24, 52 week visits to study clinic	Group A (n=100) ENDS, 7.2 mg nicotine Group B (n=100) ENDS, 7.2 mg nicotine for 6 weeks and 5.4 mg nicotine ENDS for 6 weeks	Group C (n=100) ENNDS	Week-52 complete abstinence Group A: 13.0% (13/100) Group B: 9.0% (9/100) Group C: 4.0% (4/100) Group A & B: 11.0% (22/200) Group A & B vs Group C (p = 0.04)
Carpenter et al., 2017[53] United States Non-treatment seeking smokers from the community recruited via media	Treatment 3 weeks, laboratory visits at 2,3,4 weeks Follow-up Laboratory visits at 8, 12, 16 weeks	Intervention 1 (n=25) ENDS, 16 mg/mL nicotine Intervention 2 (n=21) ENDS, 24 mg/mL nicotine	No intervention (n=22)	7-day point prevalence abstinence at 16 weeks Control: 4.6% (1/22) 16mg ENDS: 4.0% (1/25) 24mg ENDS: 9.5% (2/21)
Baldassarri et al. 2018[44] United States Motivated smoking patients from hospital outpatient pulmonary and primary care clinics, tobacco treatment service, and medical provider referrals	Treatment 8 weeks, laboratory visits at 2,4,6,8 weeks Follow-up Laboratory visit at 24 weeks	Intervention (n=20) ENDS, 24 mg/mL nicotine, nicotine patch and counselling	Control (n=20) ENNDS, nicotine patch and counselling	7-day point prevalence abstinence at 24 weeks ENNDS + patch: 2 (10%) ENDS + patch: 4 (20%) 95%CI=0.36-14.0 p=0.66
Halpern et al., 2018[51]* United States Employees and their spouses who were smokers from 54 companies that used Vitality wellness programs	Treatment 6 months, supply ordered over the web Follow-up Web-based opt-in survey with laboratory visit for those reporting cessation, at 12 months	Intervention (n=1199) Invitation to register via web-based system to receive free ENDS with up to 20 chambers of 1.0-1.5% nicotine content per week in participants' chosen flavours	Usual Care (n=813) Invitation to register for web-based smoking cessation program, including information	Sustained abstinence at 6 months (95%CI) Usual care: (1/813); 0.1% (0-0.3) ENDS: (12/1199); 1.0% (0.4-1.6) 12 months, (95%CI) Usual care: (0/813) ENDS: (4/1199); 0.3% (0.0-0.7)

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Hajek et al., 2019[23] United Kingdom Adults attending U.K. National Health Service stop-smoking services	Treatment 12 weeks, trial visit at enrolment and week 4 Follow-up 52 weeks, phone call at 26 and 52 weeks and trial visit at 52 weeks	Intervention (n=438) ENDS, nicotine 18 mg/mL. Behavioural support including weekly one-on-one session with local clinicians.	Nicotine-replacement (n=446) Preferred product from range of NRT (patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs). Behavioural support including weekly one-on-one session with local clinicians.	Abstinence at 52 weeks ENDS: 18.0% (79/438) NRT: 9.9% (44/446)
Holliday et al., 2019[46] United Kingdom Adult smokers with periodontitis attending the Newcastle Dental Hospital or primary care practitioners in North England	Treatment 2 weeks Follow-up 6 months, clinic visits at 4 weeks and 3 and 6 months	Intervention (n=40) ENDS, choice of nicotine concentration (0 mg/mL, 6 mg/mL, 12 mg/mL and 18 mg/mL) and behavioural counselling. No participants selected a nicotine concentration of 0 mg/mL	Control (n=40) Counselling only	Smoking abstinence at 6 months ENDS: 15.0% (6/40) Control: 5.0% (2/40)
Lee et al., 2019[50] Korea Male smokers from a motor company who were motivated to quit	Treatment 12 weeks, enrolment at medical office. Follow-up 24 weeks at medical office	Intervention (n=75) ENDS, nicotine 0.01 mg/mL	Nicotine gum (n=75) 12 weeks supply of nicotine gum	Continuous abstinence at 9-24 weeks ENDS: 21.3% (16/75) Nicotine gum: 28.0% (21/71) Adj p-value*: 0.291 7-day Point Prevalence abstinence - 24 weeks ENDS: 22.7% (17/75) Nicotine gum: 29.3% (22/75) Adjusted p-value: 0.365
Lucchiari et al. 2019[47] Italy Smoking COSMOS II lung cancer screening participants at the European Institute of Oncology Hospital	Treatment 12 weeks, enrolment at clinic Follow-up 26 weeks at clinic; pulmonary health also assessed	Intervention 1 (n=70) ENDS with 12 10mL liquid cartridges (8 mg/mL concentration of nicotine), telephone counselling Intervention 2 (n=70) ENNDS, telephone counselling	Usual care (n=70) Antismoking telephone counselling including phone interviews at weeks 1,4, 8, 12	Continuous smoking abstinence at 6 months follow-up ENNDS: 11/70 (16%) ENDS: 13/70 (19%) Control: 7/70 (10%) Total: 31/210 (10%)
Walker et al., 2019[48]* New Zealand	Treatment 12 weeks, 14-week supply delivered by courier, enrolment by phone	Intervention 1 (n=500) E-cigarette with 0mg nicotine plus 21 mg, 24 h nicotine patch	Nicotine patch only (n=125): A 21 mg, 24 h nicotine patch	CO-verified quit rate at 6 months Patch + END: 7% (35/500) Patch + ENNDS: 4% (20/499)

Smokers from the community who were motivated to quit, recruited through media	Follow-up Phone call 1, 3, 6 months after quit date, clinic visit at 6 and 12 months in those reporting cessation.	Intervention 2 (n=499) ENDS, 18 mg/mL nicotine and a 21 mg, 24 h nicotine patch		Patch: 2% (3/125)
Eisenberg et al., 2020[45] Canada Smokers motivated to quit from outpatient, smoking cessation, and/or walk in clinics, and/or through advertising in city/community hardcopy and online newspapers	Treatment 12 weeks Follow-up Telephone call at weeks 1, 2, 8 and 18. Laboratory visit at weeks 4, 12, and 24	Intervention 1 (n= 128) ENDS, 15 mg/mL nicotine, and behavioural counselling Intervention 2 (n= 127) ENNDS, 0 mg/mL nicotine, and behavioural counselling	Control (n=121) Counselling only	7-day point prevalence abstinence at 24 weeks Control: 9.9% (12/121) ENDS: 17.2% (22/128) ENNDS: 20.5% (26/127) Continuous abstinence at 24 weeks Control: 0.8% (1/121) ENDS: 3.9% (5/128) ENNDS: 2.4% (3/127)

* Potential competing interest noted for study author(s)

Table 3: Details of RCTs of e-cigarettes for smoking cessation, with data on nicotine use at follow- up

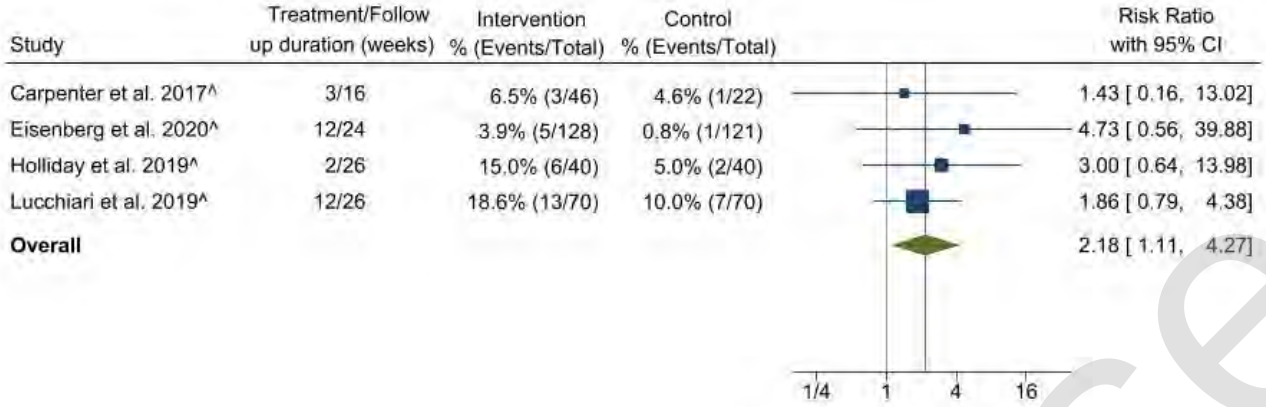
Authors, year, country and participants	Duration (treatment and follow-up)	Experimental intervention (n= randomised participants)	Control intervention (n= randomised participants)	Participants not using any nicotine at follow-up: ENDS, NRT or conventional cigarettes	Participants using NRT or ENDS at follow-up	Quitters using NRT or ENDS at follow-up	Non-quitters using NRT or ENDS at follow-up
Bullen et al., 2013[49]* New Zealand Smokers from the general community intending to quit, responding to media invitation	Treatment 12-week supply received via courier or mailed voucher Follow-up 1, 3, 6 months via telephone and 6-month laboratory visit for those reporting cessation	Intervention 1 (n=289) Electronic nicotine delivery system (ENDS), 16 mg nicotine from 1 week before until 12 weeks after quit day Intervention 2 (n=73) Electronic non-nicotine delivery system (ENNDS) from 1 week before until 12 weeks after quit day	Nicotine patches (n=295) 21 mg nicotine patch, one daily accessed via exchanging a voucher received in mail for patches at a community pharmacy	ENDS: 4.5% (12/289) Patches: Not stated ENNDS: 4.1% (3/73)*	Adherence at 6 months ENDS: 24.6% (71/289) Patches: 5.8% (17/295) Relative Risk (95% CI)** ENDS vs patches 4.26 (2.58-7.06) Reported in the paper per protocol ENDS: 29% (71/241) Patches: 8% (12/215)	ENDS: 38% (8/21) Patches: Not stated	ENDS: 29% (63/220) Patches: Not stated (NB: Unclear whether ENDS or ENNDS)
Caponnetto et al., 2013[52]* Italy Smokers not intending to quit invited via newspaper advertisements to "try e-cigarettes to reduce the risk of tobacco smoking."	Treatment 12 weeks dispensed at baseline visit held at smoking cessation clinic Follow-up 2, 4, 6, 8, 10, 12, 24 and 52 week visits	Group A (n=100) E-cigarette loaded with 7.2 mg for 12 weeks Group B (n=100) E-cigarette with 7.2 mg nicotine cartridge for 6 weeks and 5.4 mg nicotine cartridges for 6 weeks	Group C (n=100) E-cigarettes with 12-week supply of non-nicotine cartridges	Not stated	Not stated	Group A, B & C: 26.9% (7/26) (NB: Unclear whether ENDS or ENNDS)	Not stated

	to study clinic						
Carpenter et al., 2017[53] United States Non-treatment seeking smokers from the community, recruited via media	Treatment 3 weeks, laboratory visits at 2, 3 and 4 weeks Follow-up Laboratory visits at 8, 12, and 16 weeks	Intervention 1 (n=25) E-cigarette with 16 mg/mL nicotine Intervention 2 (n=21) E-cigarette with 24 mg/mL nicotine	No intervention (n=22)	Not stated	**ENDS use at week 16** Intervention 1 32% (8/25) Intervention 2 60% (13/21) Control 13% (3/22)	Not stated	Not stated
Baldassarri et al. 2018[44] United States Motivated smoking patients from hospital outpatient pulmonary and primary care clinics, tobacco treatment service, and medical provider referrals	Treatment 8 weeks, laboratory visits at 2, 4, 6, and 8 weeks Follow-up Laboratory visit at 24 weeks	Intervention (n=20) E-cigarettes with 8-week supply of 24 mg/mL nicotine containing e-liquid, nicotine patch and counselling	Control (n=20) E-cigarette with 8-week supply of 0 mg/ml nicotine containing e-liquid, nicotine patch and counselling	ENNDS + patch: 5% (1/20) ENDS + patch: 10% (2/20) **Relative Risk (95% CI)**** ENDS + patch vs ENNDS + patch 2.00 (0.20-20.33)	Not stated	ENNDS + patch: 50% (1/2) ENDS + patch: 50% (2/4) **Relative Risk (95% CI)**** ENDS + patch vs ENNDS + patch 1.00 (0.18-5.46)	Not stated
Hajek et al., 2019[23] United Kingdom Adults attending UK National Health Service stop-smoking services	Treatment 12 weeks, trial visit at enrolment and week 4 Follow-up 52 weeks, phone call at 26 and	Intervention (n=438) One 30mL bottle containing 18 mg/mL nicotine. Behavioural support including weekly one-on-one sessions with local clinicians	Nicotine-replacement (n=446) Range of NRT products (patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs) and preferred product selected. Use of combinations was	ENDS: 3.65% (16/438) NRT: 8.97% (40/446) **Relative Risk (95% CI)**** ENDS vs approved NRT 0.41 (0.23-0.72)	**Adherence at 52 weeks** ENDS: 39.5% (173/438) NRT: 4.3% (19/446) **Relative Risk (95% CI)**** ENDS vs approved NRT 9.27 (5.88-14.61)	ENDS: 80% (63/79) NRT: 9% (4/44) **Relative Risk (95% CI)**** ENDS vs approved NRT 8.77 (3.42-22.48)	ENDS: 30.6% (110/359) NRT: 3.7% (15/402) **Relative Risk (95% CI)**** ENDS vs approved NRT 8.21 (4.88-13.82)

	52 weeks and trial visit at 52 weeks		encouraged and participants were free to switch products. Behavioural support including weekly one-on-one sessions with local clinicians				
Walker et al., 2019[48]* New Zealand Smokers from the community who were motivated to quit, recruited through media	Treatment 12 weeks, 14-week supply delivered by courier Follow-up 6 months after quit date, phone call at 1, 3, and 6 months, clinic visit at 6 months for those reporting cessation	Intervention 1 (n=500) ENDS (60:40 propylene glycol to vegetable glycerin ratio), a masked nicotine content of 0 mg/mL and a 21 mg, 24 h nicotine patch Intervention 2 (n=499) ENDS (60:40 propylene glycol to vegetable glycerin ratio), a masked nicotine content of 18 mg/mL and a 21 mg, 24 h nicotine patch	Nicotine patch only (n=125) 21 mg, 24 h nicotine patch	Not stated	**Adherence at 6 months** Control: 21/52 (40%) Intervention 1 Both: 41/308 (13%) ENNDS only: 111/308 (36%) Patch only 88/308 (29%) Intervention 2 Both: 36/317 (11%) ENDS only: 143/317 (45%) Patch only: 70/317 (22%) **Relative Risk (95% CI)**** Patch + ENDS vs Patch only 1.53 (1.05-2.22) Patch + ENNDS vs Patch only 1.52 (1.05-2.21) Patch + ENDS vs Patch + ENNDS 1.00 (0.88-1.15)	Not stated	Not stated

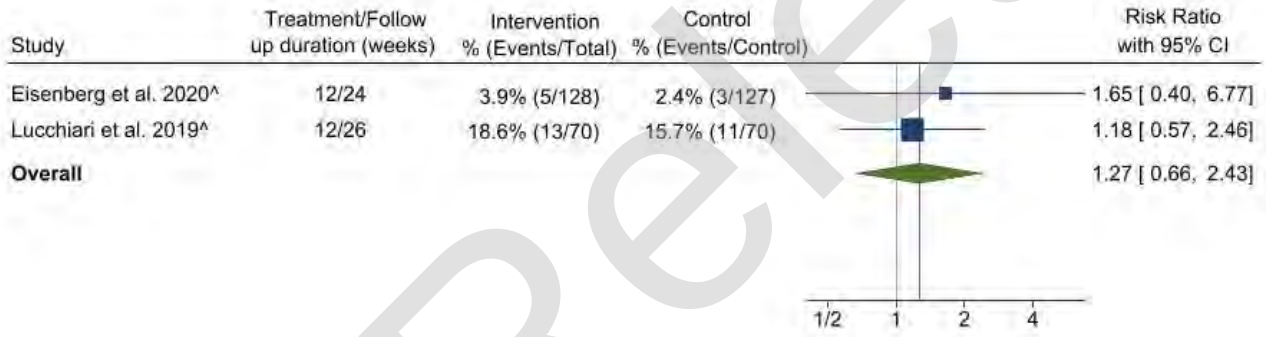
* Potential competing interest noted for study author(s)

Figure 8: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine e-cigarettes versus no intervention or usual care in studies with no reported potential competing interests.



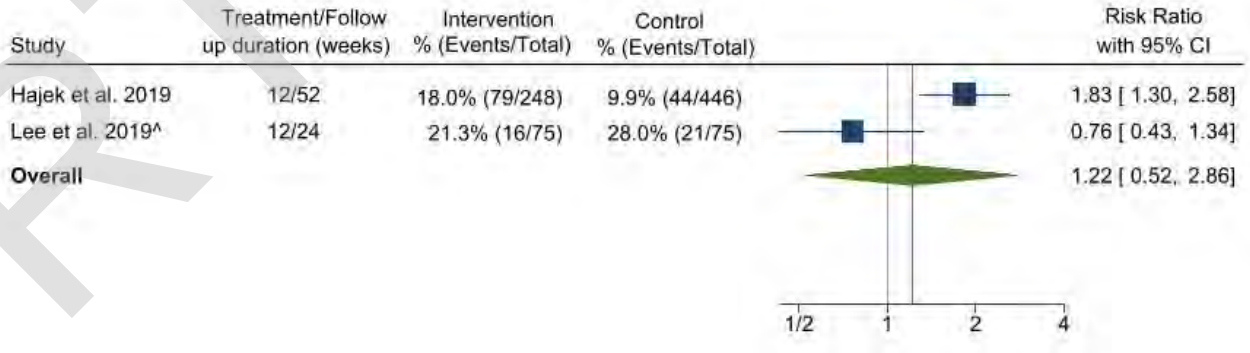
^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 27/284 in intervention group, 11/253 in control group
Heterogeneity: Tau2=0.00; Chi2= 0.94, df=3, p = 0.81; I2 =0.0%; Test for overall effect: Z=2.27, p=0.02

Figure 9: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine e-cigarettes versus non-nicotine contain-e-cigarettes in studies with no reported potential competing interests.



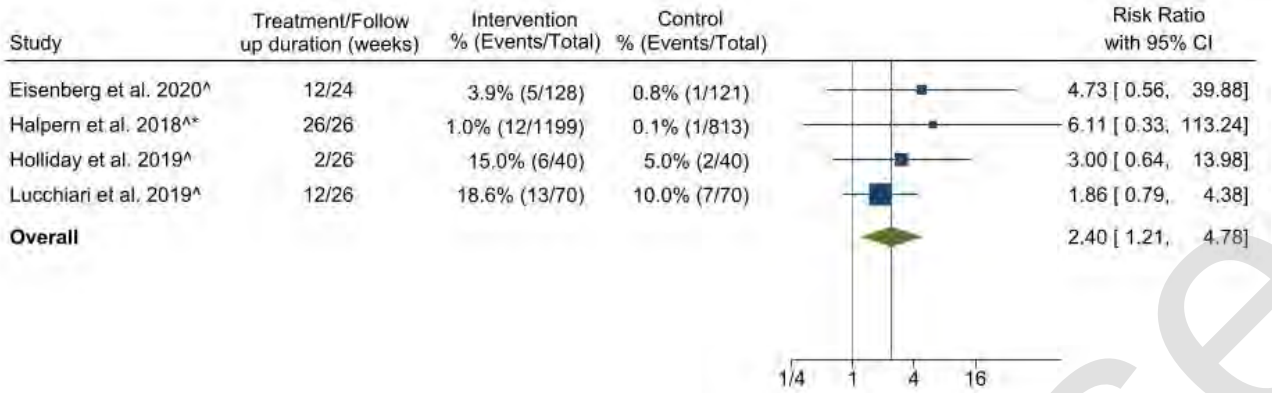
^ RRs are calculated from number of events or percentages reported in the published study
Total events: 18/198 in intervention group, 14/197 in control group
Heterogeneity: Tau2=0.00; Chi2= 0.17, df=1, p = 0.68; I2 =0.00%; Test for overall effect: Z=0.72, p=0.47

Figure 10: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine e-cigarettes versus other nicotine-replacement therapy in studies with no reported potential competing interests.



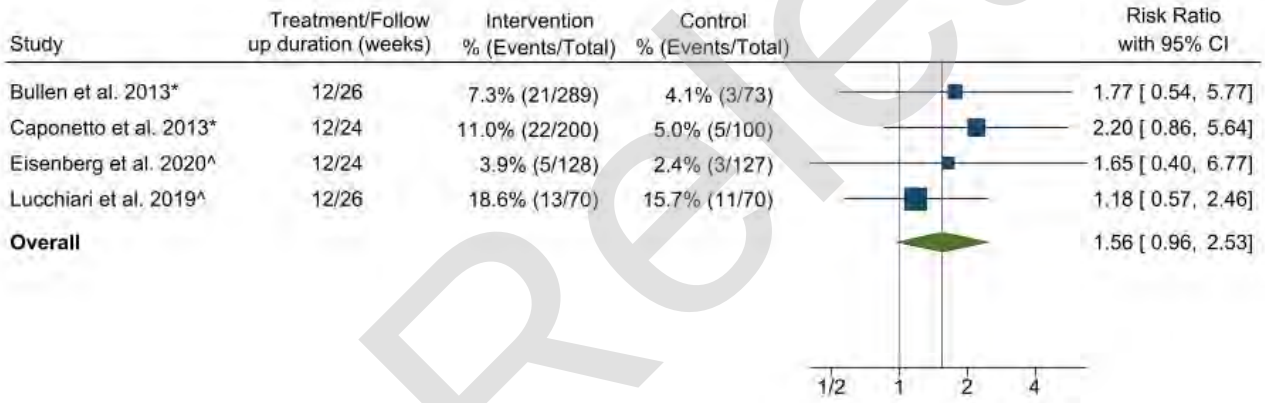
^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 95/513 in intervention group, 65/521 in control group
Heterogeneity: Tau2=0.00; Chi2= 6.70, df=1, p = 0.01; I2 =85.1%; Test for overall effect: Z=0.45, p=0.65

Figure 11: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine e-cigarettes versus no intervention or usual care at 6-month follow-up



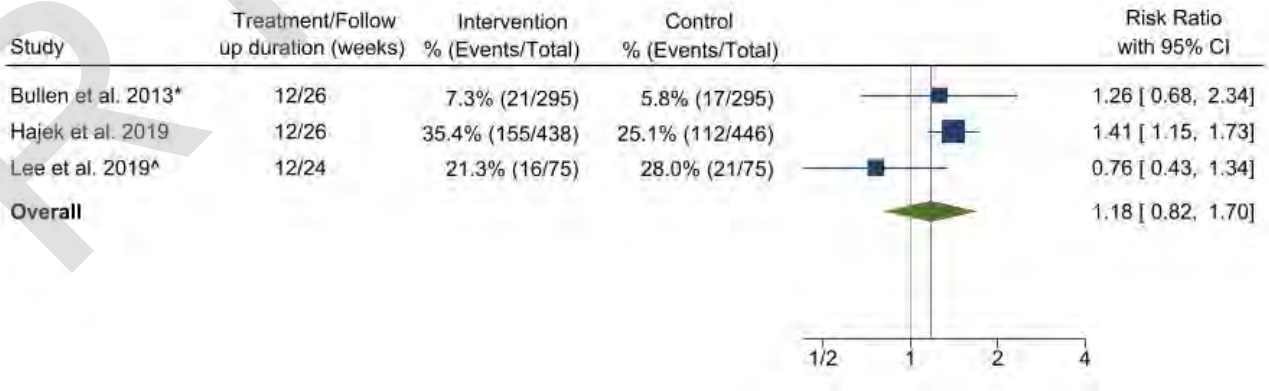
* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 61/687 in intervention group, 22/370 in control group
Heterogeneity: Tau2=0.00; Chi2= 1.12, df=3, p = 0.77; I2 =0.00%; Test for overall effect: Z=1.78, p=0.08

Figure 12: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine e-cigarettes versus non-nicotine e-cigarettes at 6-month follow-up.



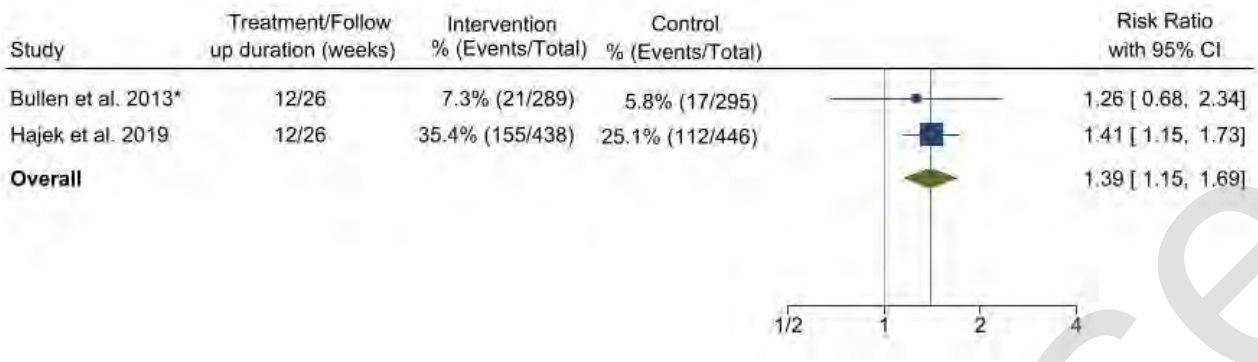
* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 20/1315 in intervention group, 8/905 in control group
Heterogeneity: Tau2=0.00; Chi2= 1.11, df=2, p = 0.57; I2 =0.0%; Test for overall effect: Z=1.64, p=0.10

Figure 13: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine e-cigarettes versus nicotine replacement therapy at 6-month follow-up.



* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 20/1315 in intervention group, 8/905 in control group
Heterogeneity: Tau2=0.00; Chi2= 4.02, df=2, p = 0.13; I2 =50.5%; Test for overall effect: Z=0.89, p=0.37

Figure 14: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine e-cigarettes (nicotine concentration >0.01 mg/mL) versus nicotine replacement therapy at 6-month follow-up.



* Potential competing interests have been noted
Total cessation events: 176/727 in intervention group, 129/741 in control group
Heterogeneity: Tau2=0.00; Chi2= 0.11, df=1, p = 0.74; I2 =0.00%; Test for overall effect: Z=3.36, p=0.00

Appendix 1: Search strategy

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

PsycINFO search terms:

1. Smoker.mp

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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*"

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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:

1. 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: 2

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Appendix 2: Inclusion and exclusion criteria and Cochrane RCT definition

Inclusion criteria:

Study designs:	Published, peer-reviewed randomised control trials
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-containing or non-nicotine-containing 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 containing e-cigarettes. Abstinence must be biochemically verified at a minimum 4 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 trial, intervention trial with no comparator (e.g., before and after study), qualitative studies, prospective cohort studies / cross over trials, retrospective cohort studies, cross-sectional studies, case-control studies, case studies, 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.

Cochrane criteria for randomised control trials (RCTs)

The Cochrane Community Glossary[19] 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?

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Appendix 3: Evidence to recommendation framework

Assessing the evidence

Assess	Risk of bias
Tool	Revised Cochrane risk -of-bias tool for randomised trials (RoB 2)

Possible ratings	Definition
Low	Low risk of bias for all domains
Some concerns	Some concerns in at least one domain, but not at high risk of bias for any domain.
High	High risk of bias in at least one domain for this result *OR* some concerns for multiple domains in a way that substantially lowers confidence in the result.

Domains appraised include:

- Randomisation process
- Deviations from the intended intervention (effect of assignment to intervention)
- Missing outcome data
- Measurement of the outcome
- Selection of the reported result

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 control trial, crossover)
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 quality ratings, conflict of interest Small studies
Inconsistency	Effect across studies	Variable findings
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

Formulate	Conclusions based on the evidence
Tool	Modified NASEM evidence to conclusion statements

Possible ratings	Definition
Conclusive evidence	High confidence, no limitations
Strong 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 relevant evidence

Rating	Supportive findings	Opposing findings	Type of studies
Conclusive	Many	None	Good-quality controlled
Strong	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

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Appendix 4: Additional details from randomised controlled trials of e-cigarettes and smoking cessation

Authors, year and setting	Blinding type	Population	Experimental intervention and number of participants randomised to each arm	Control intervention and number of participants randomised to control	Plan to quit	Sample size (enrolled/completed)	Statements regarding funding	Potential competing interests
Bullen et al., 2013[49] New Zealand Adults from the general community intending to quit, responding to media invitation	Single blinding	Adult smokers in New Zealand	Intervention 1 (n=289) Electronic nicotine delivery system (ENDS), 16 mg nicotine from 1 week before until 12 weeks after quit day Intervention 2 (n=73) Electronic non-nicotine delivery system (ENNDS) from 1 week before until 12 weeks after quit day	Nicotine patches (n=295) 21 mg nicotine patch, one daily accessed via exchanging a voucher received in mail for patches at a community pharmacy	Yes	Intervention 1 289/241 Intervention 2 73/57 Control 295/215 Total 657/513	Health Research Council of New Zealand. The e-cigarettes and cartridges were Elusion brand products provided by PGM International, New Zealand.	Yes
Caponnetto et al., 2013[52]* Italy Smokers not intending to quit were invited to try the 'Categoria' e-cigarette to reduce the risk of tobacco smoking	Double blinding	Adult smokers from Catania, Italy	Group A (n=100) E-cigarette loaded with 7.2 mg for 12 weeks Group B (n=100) E-cigarette with 7.2 mg nicotine cartridge for 6 weeks and 5.4 mg nicotine cartridges for 6 weeks	Group C (n=100) E-cigarettes with 12-week supply of non-nicotine cartridges	No	Intervention Group A: 100/65 Group B: 100/63 Control Group C=100/55 Total 300/183	This research was supported by a grant-in-aid from Lega Italiana AntiFumo. The study sponsor had no involvement in the study design, collection, analysis, and interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication. RP and PC are currently funded by the University of Catania, Italy. The e- cigarette supplier had no involvement in the study design, collection, analysis, and interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication. The ''Categoria'' electronic cigarette kit and cartridges were provided free of charge by the local distributor, Arbi Group Srl, Italy.	Yes

Authors, year and setting	Blinding type	Population	Experimental intervention and number of participants randomised to each arm	Control intervention and number of participants randomised to control	Plan to quit	Sample size (enrolled/completed)	Statements regarding funding	Potential competing interests
Carpenter et al., 2017[53] United States Non-treatment seeking smokers from the community, recruited via media	Not stated	Adults smokers in the local community in a south eastern US urban area; approximately 30% non-white	Intervention 1 (n=25) E-cigarette with 16 mg/mL nicotine Intervention 2 (n=21) E-cigarette with 24 mg/mL nicotine	No intervention (n=22)	Mixed	Intervention 1 25/19 Intervention 2 21/15 Control 22/16 Total 68/50	Support was provided by NIH R21 DA037407 (to M.J. Carpenter), P01 CA200512 (to K.M. Cummings, M.J. Carpenter, and M.L. Goniewicz), UL1 TR001450, and P30 CA138313. M.L. Goniewicz's laboratory is supported via P30CA016056. B.W. Heckman is supported via K12 DA031794 and K23 DA041616.	No
Baldassarri et al. 2018[44] United States Hospital outpatient pulmonary and primary care clinics, Tobacco Treatment Service, and medical providers referrals	Double blinding	Treatment-seeking adult smokers from New Haven, Connecticut	Intervention (n=20) E-cigarettes with 8-week supply of 24 mg/mL nicotine containing e-liquid, nicotine patch and counselling	Control (n=20) E-cigarette with 8-week supply of 0 mg/mL nicotine containing e-liquid, nicotine patch and counselling	Yes	Intervention 20/unknown Control 20/unknown Total 40/unknown	Funding was provided by the Yale School of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine and the National Heart, Lung, and Blood Institute grant T32HL007778.	No
Halpern et al., 2018[51] United States Employees and their spouses at 54 companies that used Vitality wellness programs	Not stated	Adult smokers who were employees or their spouses at 54 companies that used Vitality wellness programs across the United States	Intervention (n=1199) NJOY e-cigarettes with up to 20 chambers of 1.0-1.5% nicotine content per week in participants' chosen flavours	Usual care (n=813) Invitation to register for web-based smoking cessation, including information regarding the health benefits of smoking cessation, strategies to promote cessation, and the opportunity to register for the SmokeFreeTXT program of the National Cancer Institute	Mixed	Intervention 1199/253 Control 813/129 Total 2012/382	Supported by a grant from the Vitality Institute to the University of Pennsylvania Center for Health Incentives and Behavioral Economics.	Yes

Authors, year and setting	Blinding type	Population	Experimental intervention and number of participants randomised to each arm	Control intervention and number of participants randomised to control	Plan to quit	Sample size (enrolled/completed)	Statements regarding funding	Potential competing interests
Hajek et al., 2019[23] United Kingdom Adults attending UK National Health Service stop-smoking services	Single blinding	Adult smokers from London	Intervention (n=438) One 30mL bottle containing 18 mg/mL nicotine. Behavioural support including weekly one-on-one sessions with local clinicians	Nicotine-replacement (n=446) Range of NRT products (patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs) and preferred product selected. Use of combinations was encouraged and participants were free to switch products. Behavioural support including weekly one-on-one sessions with local clinicians	Yes	Intervention 438/356 Control 446/342 Total 884/698	Supported by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project number, 12/167/135) and by a grant (A16893) from the Cancer Research UK Prevention Trials Unit.	No
Holliday et al. 2019[46] United Kingdom Adult smokers with periodontitis attending the Newcastle Dental Hospital or primary care practitioners in North England	None		Intervention (n=40) ENDS, choice of nicotine concentration (0 mg/mL, 6 mg/mL, 12 mg/mL and 18 mg/mL) and behavioural counselling. No participants selected a nicotine concentration of 0 mg/mL	Control (n=40) Counselling only	Not stated	Intervention 40/29 Control 40/29 Total 80/58	Richard Holliday is funded by a National Institute for Health Research Doctoral Research Fellowship (DRF-2015-08-077). This paper presents independent research funded by the National Institute for Health Research (NIHR).	No
Lee et al., 2019[50] Korea Korean males from a motor company intending to quit	Single blinding	Male adult smokers employed at a motor company in Korea	Intervention (n=75) E-cigarette containing 0.01 mg/mL_nicotine for 12 weeks	Nicotine gum (n=75) 12-week supply of nicotine gum	Yes	Intervention 75/71 at 24 weeks Control 75/61 at 24 weeks Total 150/132	None	No

Authors, year and setting	Blinding type	Population	Experimental intervention and number of participants randomised to each arm	Control intervention and number of participants randomised to control	Plan to quit	Sample size (enrolled/completed)	Statements regarding funding	Potential competing interests
Lucchiari et al. 2019[47] Italy COSMOS II lung cancer screening participants at the European Institute of Oncology (IEO) Hospital	Double blinding	Adult (≥55 years) chronic smokers participating in the COSMOS II program	Intervention 1 (n=70) e-cigarette with 12 10mL liquid cartridges (8 mg/mL nicotine), telephone counselling Intervention 2 (n=70) e-cigarette with 12 10mL nicotine-free liquid cartridges, telephone counselling	Usual care (n=70) Antismoking telephone counselling including phone interviews at weeks 1, 4, 8, and 12	Yes	Intervention 1 70/52 Intervention 2 70/51 Control 70/52 Total 210/155	Supported by Fondazione Umberto Veronesi (FUV).	No
Walker et al., 2019[48] New Zealand Smokers from the community who were motivated to quit, recruited through media	Double blinding	Adult smokers in New Zealand	Intervention 1 (n=500) ENDS (60:40 propylene glycol to vegetable glycerin ratio), a masked nicotine content of 0 mg/mL and a 21 mg, 24 h nicotine patch Intervention 2 (n=499) ENDS (60:40 propylene glycol to vegetable glycerin ratio), a masked nicotine content of 18 mg/mL and a 21 mg, 24 h nicotine patch	Nicotine patch only (n=125) 21 mg, 24 h nicotine patch	Yes	Intervention 1 499/337 Intervention 2 500/339 Control 125/63 Total 1124/739	Health Research Council of New Zealand.	Yes

Authors, year and setting	Blinding type	Population	Experimental intervention and number of participants randomised to each arm	Control intervention and number of participants randomised to control	Plan to quit	Sample size (enrolled/completed)	Statements regarding funding	Potential competing interests
Eisenberg et al. 2020[45] Canada Smokers motivated to quit from outpatient, smoking cessation, and/or walk in clinics, and/or through advertising in city/community hardcopy and online newspapers	Double blinding	Smokers with a moderate or strong intention to quit	Intervention 1 (n= 128) ENDS, 15 mg/mL nicotine, and behavioural counselling Intervention 2 (n= 127) ENNDS, 0 mg/mL nicotine, and behavioural counselling	Control (n=121) Counselling only	Yes	Intervention 1 128/112 Intervention 2 127/109 Control 121/85 Total 376/306	This trial was funded by the Canadian Institutes of Health Research (CIHR; funding reference No. 133727 and 155969). Both nicotine e-cigarettes and non nicotine e-cigarettes were purchased from NJOY Inc (Scottsdale, Arizona).	No

* Potential competing interest noted for study author(s)

Appendix 5: Sensitivity analysis: meta-analysis of randomised controlled trials of e-cigarettes for smoking cessation including random- and fixed-effects models

Study	Treatment / Follow-up duration (weeks)	Outcome		Risk ratio (95% CI)	Random-effects		Fixed-effects	
		Intervention % (Events/Total)	Control % (Events/Total)		% weight	Risk ratio (95% CI)	% weight	Risk ratio (95% CI)
A. Nicotine e-cigarettes versus no intervention or usual care								
Carpenter et al. 2017^	3 / 16	6.5% (3/46)	4.5% (1/22)	1.43 (0.16-13.02)	8.84	2.30 (1.19-4.42)	11.30	2.46 (1.28-4.71)
Eisenberg et al. 2020^	12/24	3.9% (5/128)	0.8% (1/121)	4.73 (0.56-39.88)	9.45		8.58	
Halpern et al. 2018^#	26 / 52	0.3% (4/1199)	0.0% (1/813)	6.11 (0.33-113.24)	5.04		4.97	
Holliday et al. 2019	2/26	15.0% (6/40)	5.0% (2/40)	3.00 (0.64-13.98)	18.15		16.70	
Lucchiari et al. 2019^	12 / 26	18.6% (13/70)	10.0% (7/70)	1.86 (0.78-4.38)	58.52		58.45	
B. Nicotine e-cigarettes versus non-nicotine-e-cigarettes								
Bullen 2013*	12 / 26	7.3% (21/289)	4.1% (3/73)	1.77 (0.54-5.77)	17.82	1.61 (0.98-2.65)	19.85	1.70 (1.03-2.81)
Caponetto 2013*	12 / 52	11.0% (22/200)	4.0% (4/100)	2.75 (0.97-7.76)	23.11		22.10	
Eisenberg et al. 2020^	12/24	3.9% (5/128)	2.4% (3/127)	1.65 (0.40-6.77)	12.52		12.48	
Lucchiari et al. 2019^	12 / 26	18.6% (13/70)	15.7% (11/70)	1.18 (0.57-2.46)	46.55		45.58	
C. Nicotine e-cigarettes versus other nicotine-replacement therapy								
Bullen et al. 2013*	12 / 26	7.3% (21/289)	5.8% (17/295)	1.26 (0.68-2.34)	28.90	1.25 (0.74-2.11)	20.66	1.44 (1.10-1.87)
Hajek et al. 2019	12 / 52	18.0% (79/438)	9.9% (44/446)	1.83 (1.30-2.58)	40.16		53.55	
Lee et al. 2019^	12 / 24	21.3% (16/75)	28.0% (21/75)	0.76 (0.43-1.34)	30.94		25.79	
D. Nicotine e-cigarettes (nicotine concentration >0.01mg/mL) versus other nicotine-replacement therapy								
Bullen et al. 2013*	12 / 26	7.3% (21/289)	5.8% (17/295)	1.26 (0.68-2.34)	25.10	1.67 (1.21-2.28)	27.84	1.67 (1.24-2.25)
Hajek et al. 2019	12 / 52	18.0% (79/438)	9.9% (44/446)	1.83 (1.30-2.58)	74.90		72.16	
E. Non-nicotine e-cigarettes plus counselling versus counselling								
Eisenberg et al. 2020^	12/ 24	2.4% (3/127)	0.8% (1/121)	2.86 (0.30-27.10)	13.48	1.70 (0.75-3.89)	12.76	1.74 (0.76-3.96)
Lucchiari et al. 2019^	12 / 26	15.7% (11/70)	10.0% (7/70)	1.57 (0.65-3.82)	86.52		87.24	

* 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)

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Appendix 6: Risk of bias assessment of randomised controlled trials of e-cigarettes for smoking cessation

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Risk of bias in selection of the reported result	Risk of bias: overall judgment
Bullen et al. 2013[49]*	Low	Some concerns	Low	Low	Low	Some concerns
Caponnetto et al. 2013[52]*	Low	Some concerns	High	Low	Some concerns	High
Carpenter et al. 2017[53]	Some concerns	Some concerns	Low	High	Some concerns	High
Baldassarri et al. 2018[44]	Low	Low	High	Low	Some concerns	High
Eisenberg et al., 2020[45]	Low	Some concerns	High	Low	Low	High
Halpern et al., 2018[51]*	Some concerns	Some concerns	High	Low	Low	High
Hajek et al., 2019[23]	Low	Low	Low	Low	Low	Low
Holliday et al., 2019[46]	Low	Some concerns	High	Low	Low	High
Lee et al., 2019[50]	Low	Some concerns	High	Low	Some concerns	High
Lucchiari et al. 2019[47]	Low	Some concerns	Some concerns	Low	Low	Some concerns
Walker et al., 2019[48]*	Low	Low	High	Low	Low	High

* Potential competing interests have been noted

Appendix 7: GRADE assessment of randomised controlled trials of e-cigarettes for smoking cessation

Outcome	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the evidence
ENDS versus no intervention/usual care (5 studies)	Very serious concerns[1]	No concerns	No concerns	Serious concerns[2]	Undetected	Very low
ENDS versus ENNDS (4 studies)	Very serious concerns[1]	No concerns	No concerns	Serious concerns[2]	Undetected	Very low
ENDS versus approved NRT (3 studies)	Very serious concerns[1]	Serious concerns[3]	Serious concerns[4]	Very serious concerns[5]	Undetected	Very low
ENDS (nicotine >0.01mg/mL) versus approved NRT (2 studies)	Serious concerns[1]	No concerns	No concerns	Serious concerns[2]	Undetected	Low
ENDS plus NRT versus other comparators (2 studies)	Very serious concerns[1]	Serious concerns[3]	No concerns	Very serious concerns[5]	Undetected	Very low
ENNDS plus counselling versus counselling alone (2 studies)	Serious concerns[1]	No concerns	No concerns	Very serious concerns[5]	Undetected	Very low
ENNDS versus other NRT (1 study)	Serious councens[1]	No concerns	Not applicable, only one study	Very serious concerns[5]	Undetected	Very low
Overall: e-cigarettes versus all comparators (11 studies)	Very serious concerns[1]	No concerns	No concerns	Very serious concerns[5]	Undetected	Very low

[1]Downgraded based on the overall risk of bias assessment from the ROB2 tool and consideration of potential competing interests.
[2]Downgraded due to small number of events for each comparator (GRADE recommends minimum 300 events).
[3]Downgraded due to variability comparators
[4]Downgraded due to difference in direction of point estimates and due to considerable heterogeneity
[5]Downgraded due to small number of events for each comparator (GRADE recommends minimum 300 events) and presence of wide confidence intervals including both appreciable benefit and harm

Australian National University

Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation

Final report prepared for the National Health and Medical Research Council

June 2021

Emily Banks, Katie Beckwith, Amelia Yazidjoglou, Sinan Brown, Melonie Martin

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The authors would like to acknowledge the contribution of the authors of the main report - *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*.

DECLARATIONS OF INTEREST

The authors of this report have no affiliations with or involvement in any organisations or entities with any financial or non-financial interest in 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; all authors have authored papers based on the e-cigarettes program of work.

Banks E, Beckwith K, Yazidjoglou A, Brown S, Martin M. Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation. *Final report to the National Health and Medical Research Council.* June 2021.

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Executive Summary

Supplementary Report One

June 2021

Emily Banks, Katie Beckwith, Amelia Yazidjoglou, Sinan Brown, Melonie Martin

Background

E-cigarettes are a diverse group of battery-powered devices that create an aerosol from a liquid (e-liquid). Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol – mainly used in e-cigarettes as a solvent to produce visible aerosol – glycerine and flavouring agents, and commonly contains nicotine. E-liquids containing nicotine salt compounds are increasingly common.

This document provides supplementary material to the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* from February 2021. The *Review* presented the findings of three separate reviews; *Review one: Patterns of e-cigarette use* (*Patterns Review*), *Review two: E-cigarette use and smoking uptake* (*Uptake Review*) and *Review three: E-cigarette use and smoking cessation* (*Cessation Review*).

Aim and Methods

This report responds to a request for additional evidence and analyses from the AustralianNational Health and Medical Research Council's Electronic Cigarette Working Committee by supplementing the material presented in the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* on patterns of e-cigarette use and smoking uptake and cessation associated with e-cigarette use, using the studies identified in the *Review* as well as additional evidence as applicable. The specific areas addressed are to:

- Include the latest Australian evidence in the *Patterns Review*;
- Conduct additional analyses relating to conflict of interest for the *Cessation Review* and the *Uptake Review*;
- Consider risk of bias in non-randomised studies using the ROBINS-I tool, a breakdown of available demographic information from included studies, the likelihood that e-cigarettes will increase the number of young people using nicotine and smoking, and high concentration nicotine salt products for the *Uptake Review*.

For detailed methods, see individual reviews in the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*. Where applicable, methods were an extension of those from the main reviews. Where additional methods were adopted, they are outlined in the relevant section.

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Key Summary Points

Patterns Review – findings update

- The percentage of people in Australia aged 14 years and over who had ever used e-cigarettes increased significantly between 2013 (4.5%) and 2016 (8.8%), and 2016 and 2019 (11.3%). Among adults, ever-use increases with decreasing age, such that 26.1% of people aged 18-24 reported ever-use of e-cigarettes in 2019.
- The percentage of people in Australia aged 14 years and over reporting current use increased significantly between 2016 (1.2%) and 2019 (2.5%). Current use is greatest in younger adults aged less than 30 years and decreases with increasing age.
- The percentage of smokers in Australia aged 14 years and over who had ever used an e-cigarette increased significantly from 18.8% in 2013 to 31.0% in 2016, and increased further to 38.7% in 2019. Among non-smokers, 1.8% reported ever-use of e-cigarettes in 2013; this proportion increased significantly to 4.9% in 2016 and 6.8% in 2019.
- The percentage of smokers in Australia aged 14 years and over who were current 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%).
- In 2019, current daily use of e-cigarettes was reported by 3.2% of current smokers, 2.2% of ex-smokers and 0.2% of never smokers, a significant increase for current and ex-smokers compared to 2016 (1.5% and 0.8% respectively).
- Analyses using 2019 data from the National Drug Strategy Household Survey show that among people aged 14 years and over reporting current use of e-cigarettes (i.e., those reporting daily, weekly or at least monthly use of e-cigarettes):
    - 54.1% ± 95% Margin of Error 5.6% report being current smokers (daily, weekly or less than weekly);
    - 32.2% ± 5.5% report being ex-smokers;
    - 15.8% ± 4.4% report being never smokers.

Uptake and *Cessation Reviews* – sensitivity analysis

- There were no potentially competing interests identified among studies included in the *Uptake Review*. Hence, the main results are not changed when competing interests are considered: that non-smokers who use e-cigarettes are on average three times as likely to become smokers of combustible cigarettes as non-smokers who do not use e-cigarettes.
- The results of the *Cessation Review* did not differ materially when potential conflicts of interest were considered, although the available evidence base was reduced. These results were that the evidence is currently insufficient to conclude that e-cigarettes are efficacious as an aid to smoking cessation

compared to no intervention/usual care, non-nicotine e-cigarettes and standard nicotine replacement therapy, although early signs are that they may be useful in highly controlled clinical settings.

Uptake Review – quality assessment

- Of the 12 newly identified studies included in the *Uptake Review*, three were considered to be at a serious risk of bias and nine at a moderate risk of bias, using the ROBINS-I tool.

Uptake Review – discussion update

Distribution of demographic factors

- Demographic factors reported in the studies in the *Uptake Review* included age, sex, ethnicity, education, affluence, urbanisation, SES, and family structure.
- Participants with a range of demographic characteristics were included although most studies were of people aged between 11 and 18 years.
- Analysis according to demographic subgroups was scant. There was no specific evidence available of any variation in the relationship of e-cigarette use to smoking uptake according to demographic factors. Where assessed, no statistically significant difference in the likelihood of smoking relapse was identified for sex, age, income or non-Hispanic white compared to Hispanic white ethnic/cultural groups.

Uptake of nicotine and combustible cigarette smoking among young people

- Based on the current evidence, young people, whether school-aged or aged up to 30 years, who used e-cigarettes had a risk of initiating smoking of combustible cigarettes that was approximately three-fold that of those who did not use e-cigarettes. There was substantial variation in the results between studies.
- Based on the current evidence, young people, whether school-aged or aged up to 30 years, who use e-cigarettes had an approximate three-fold risk of transitioning from being a non-smoker to a current smoker compared to those who did not use e-cigarettes. There was substantial variation in the results between studies.
- Based on evidence from three studies, the risk of transitioning from being a non-smoker to a current regular smoker is elevated for young people aged ≤18 years who had used e-cigarettes compared to those who had not, and this risk may be impacted by nicotine content, however evidence is limited.
- E-cigarettes commonly deliver nicotine, so use of e-cigarettes will generally result in increased use of nicotine by young people.

High concentration nicotine salt products

- Information on the nicotine content and delivery devices used by participants in the studies including in the *Uptake Review* was extremely limited.

- No research specifically investigating the relationship of the use of nicotine salt products to combustible cigarette uptake was located.
- From a safety perspective, at this stage, the findings regarding e-cigarettes and smoking uptake should be considered to apply to the range of devices in use by participants in the studies that have been summarised. Furthermore, nicotine e-cigarettes which have not been the subject of studies regarding their impact on smoking – such as nicotine salt products – should be assumed to increase the uptake of combustible smoking, unless specific evidence to the contrary is available.
- Since high concentration nicotine salt products have been identified as key drivers of increased youth e-cigarette use in North America, they may be particularly hazardous for increasing youth smoking uptake, through increasing prevalence of e-cigarette use.

Purpose and scope

This document provides supplementary material to the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*, as was commissioned by the Australian Government Department of Health. The document includes:

- Updated results of the *Patterns Review* with inclusion of data from the 2019 National Drug Strategy Household Survey (NDSHS);
- Results of a sensitivity analysis assessing differences between industry and non-industry funded studies included in the *Uptake Review* and *Cessation Review*;
- Results of an assessment of risk of bias using the ROBINS-I tool on newly identified primary research articles in the *Uptake Review*; and
- Additional discussion on the outcomes from the *Uptake Review*, including a breakdown of demographic factors from included studies, the likelihood that e-cigarettes will increase the number of young people using nicotine and smoking combustible cigarettes, and high concentration nicotine salt products.

This report was commissioned by the National Health and Medical Research Council of Australia (NHMRC) to supplement evidence reported as part of a program of work on e-cigarettes for the Australian Government Department of Health, to inform the update of the NHMRC CEO Statement on electronic cigarettes. The work was undertaken independently by researchers from the National Centre for Epidemiology and Population Health, Research School of Population Health, the Australian National University.

Background

E-cigarettes are a diverse group of battery-powered devices that create an aerosol from a liquid (e-liquid).[1, 2] Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol – mainly used in e-cigarettes as a solvent to produce visible aerosol – glycerine and flavouring agents, and commonly contains nicotine.[1]

The *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* considered the current evidence regarding the effects of e-cigarettes on smoking behaviour. This included a summary of evidence from peer-reviewed and grey literature on the prevalence and patterns of e-cigarette use, as well as peer-reviewed published evidence on the relationship of e-cigarettes use to combustible smoking uptake and cessation. The report presented the findings of three separate reviews; *Review one: Patterns of e-cigarette use* (*Patterns Review*), *Review two: e-cigarette use and smoking uptake* (*Uptake Review*) and *Review three: e-cigarette use and smoking cessation* (*Cessation Review*). See the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* for more detail on the background.

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Aims

This report aims to supplement the material presented in the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* on patterns of e-cigarette use and smoking uptake associated with e-cigarette use. It usesstudies identified in the *Review* as well as additional evidence as applicable, to support the development of the NHMRC CEO Statement on electronic cigarettes.

This report is comprised of four main parts:

1. Incorporation of data from the NDSHS 2019 into an update of the *Patterns Review*;
2. Sensitivity analysis of studies included in the *Uptake Review* and the *Cessation Review*;
3. Quality assessment of newly identified primary research studies from the *Uptake Review*; and
4. Additional discussion points on the findings of the *Uptake Review*.

Methods

For detailed methods, see individual reviews in the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*. Where applicable, methods were an extension of those from the main reviews. Where additional methods were adopted, they are outlined in the relevant section.

Patterns Review – Findings update

Background

The narrative *Patterns Review* from the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* included results specific to the Australian context using data from the Australian Institute of Health and Welfare's (AIHW) NDSHS, published in 2013[3] and 2016.[4]

The main findings from the *Patterns Review* included that:

- In 2016, current use of e-cigarettes was relatively uncommon in Australia, as was dual use of e-cigarettes and combustible cigarettes.
    - Around 9% of people aged 14 years and over in Australia ever used e-cigarettes;
    - 0.5% of people aged 14 years and over reported daily e-cigarette use, and 1.2% reported current use;
    - 0.2% of people aged 14 years and over were estimated to be dual daily e-cigarette and combustible cigarette users, and 0.5% were estimated to be dual users.[4]
- In the general Australian population, the majority of people using e-cigarettes were either current or former users of combustible tobacco.[4]

Aims and Methods

This section provides an updated narrative review of NDSHS findings. Data from the newly published 2019 NDSHS were incorporated into the synthesis of findings from the 2013 and 2016 NDSHS surveys. The population sample sizes for the surveys were 22,274 (2019), 23,722 (2016) and 23,855 (2013).

Findings

Prevalence of lifetime e-cigarette use in Australia

National data on ever-use of e-cigarettes in Australia were first collected in the 2013 NDSHS,[3] with data on frequency of use collected in the 2016[4] and 2019[5] NDSHS surveys. Data are not available on whether or not these e-cigarettes delivered nicotine. In 2013, 4.5% of people in Australia aged 14 years and over were estimated to have ever used e-cigarettes,[3] increasing significantly to 8.8% in 2016[4] and increasing significantly again to 11.3% in 2019 (Table 1).[5] The prevalence of ever-use increased between 2016 and 2019 for all age groups other than for individuals aged 70 years and older, among whom use was low and did not change materially (1.0% in 2016 and 0.9% in 2019).[4, 5] The greatest absolute increases in the prevalence of ever-use between 2016 and 2019 were for 18–24-year-olds (19.2% to 26.1%; 6.9% absolute increase, 35.9% relative increase) and for 25–29-year-olds (14.8% to 20.4%; 5.6% absolute increase, 37.8% relative increase).[4, 5]

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Prevalence of current e-cigarette use in Australia

In 2016, current use of e-cigarettes (defined as daily, weekly, monthly or less than monthly use) was reported by 1.2% of people in Australia aged 14 years and over (Table 2).[4] This figure rose significantly to 2.5% in 2019.[5] Across all age groups, current use increased between 2016 and 2019.[4, 5] The increase was greatest in younger age groups, with the exception of ages 14–17 years, where both 2016 and 2019 estimates should be treated with caution (relative standard error (RSE) of 25% to 50%). Among 18–24-year-olds it increased from 2.8% in 2016 to 5.3% in 2019 (89.3% relative increase).[4, 5] The 25–29 year age group showed a statistically significant four-fold increase from 1.2% to 4.8%, although the former estimate should be used with caution (RSE 25% to 50%).[4, 5] Similar to ever-use statistics, current use of e-cigarettes, according to the 2019 NDSHS, was greatest in younger age groups (18–24 years; 5.3%, 25–29 years; 4.8%, 30–39 years; 2.8%).[5] Across older age groups, there was an increase between 2016 and 2019 estimates in current usage for all age groups, with significant increases among 40–49-year-olds (1.5% to 2.6%) and 50–59-year-olds (0.8% to 2.0%).[5]

Patterns of dual use in Australia

Dual users comprise individuals with varying frequencies and intensities of e-cigarette and combustible cigarette use concurrently. In 2013, 18.8% of current smokers and 1.8% of non-smokers (never or no current use) aged 14 years and over had ever used e-cigarettes in the NDSHS;[3] these figures increased significantly to 31.0% of smokers and 4.9% of non-smokers in 2016 (Table 1).[4] In the 2019 NDSHS, 38.7% of smokers and 6.9% of non-smokers aged 14 years and over had ever used an e-cigarette, a further significant increase for both groups compared to the 2016 survey results.[4, 5] There were no clear trends in relative changes of ever-use of e-cigarettes for smokers and non-smokers across different age groups between 2016 and 2019, although a result of note was the stagnation of prevalence amongst smokers aged 30–39 years (0.5% relative increase), and the significant increase for non-smokers of the same age (42.9% relative increase).[4, 5]

The proportion of male and female smokers aged 14 years and over ever using e-cigarettes was similar in 2016 (31.5% and 30.3% respectively) (Table 3).[4] The corresponding figures in 2019 highlighted a significant increase for both sexes (39.7% for male smokers and 37.5% for female smokers).[4, 5] Among current smokers in 2019, ever-use of e-cigarettes decreased consistently across older age groups, from 63.9% for 18–24-year-olds to 10.7% for individuals aged 70 years or over.[5] When stratifying by sex, the same relationship was seen among current male smokers. Among female smokers, this pattern was disrupted among older age groups from 40–49 years.[5]

Current (daily, weekly, monthly or less than monthly) use of e-cigarettes increased significantly for both current smokers (daily, weekly or less than weekly smoking) (4.4% to 9.7%; 5.3% absolute increase, 120.5% relative increase) and non-smokers (never or no current use) (0.6% to 1.4%; 0.8% absolute increase, 133.3% relative increase) between 2016 and 2019 among NDSHS participants aged 14 years and over (Table 2).[4, 5]

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Between 2016 and 2019, current use of e-cigarettes among current smokers increased across all age categories. The absolute increase was largest for age groups 14–17-year-olds (4.3% to 17.5%; 13.2% absolute increase, 307.0% relative increase) (RSE 51% to 90% for both estimates), followed by 18–24 years (6.8% to 18.7%; 11.9% absolute increase, 175.0% relative increase) and 25–29 years (3.6% to 13.7%; 10.1% absolute increase, 280.6% relative increase).[4, 5] For non-smokers, there was a significant 2.7% absolute and 540.0% relative increase among 25–29-year-olds, from 0.5% in 2016 (RSE 25% to 50%) to 3.2% in 2019.[4, 5] A significant increase was also evident between 2016 and 2019 among 30–39-year-olds (0.5% to 1.7%; 1.2% absolute increase, 240.0% relative increase).

Stratifying by sex, the greatest absolute and relative increases in current e-cigarette use among male smokers was for 18–24-year-olds, from 7.4% (RSE 25% to 50%) in 2016 to 20.9% in 2019 (13.5% absolute increase, 182.4% relative increase) and 25–29-year-olds, with a 12.5% absolute increase and more than three-fold relative increase from 3.5% (RSE 25% to 50%) in 2016 to 16.0% (RSE 25% to 50%) in 2019 (Table 4). Among female smokers, the greatest absolute increases between 2016 and 2019 were also seen among the youngest age groups; for 18–24-year-olds (5.9% (RSE 25% to 50%) to 15.4% (RSE 25% to 50%); 9.5% absolute increase, 161.0% relative increase) and 25–29-year-olds (3.9% (RSE 51% to 90%) to 11.1% (RSE 25% to 50%); 7.2% absolute increase, 184.6% relative increase). Statistically significant increases were seen among 40–49-year-olds, with a 5.9% absolute increase and close to four-fold relative increase from 2.2% (RSE 25% to 50%) in 2016 to 8.1% in 2019, and 50–59-year-olds, from 3.0% (RSE 25% to 50%) in 2016 to 8.3% in 2019 (5.3% absolute increase, 176.7% relative increase).[4, 5]

Frequency of e-cigarette use in Australia according to smoking status

In 2016, current daily use of e-cigarettes was reported by 1.5% of current (daily, weekly or less than weekly) smokers, 0.8% of ex-smokers and 0.2% (RSE 51% to 90%) of never smokers (Table 5).[4] In 2019, current daily use of e-cigarettes was reported by 3.2% of current smokers, 2.2% of ex-smokers and 0.2% (RSE 25% to 50%) of never smokers, a significant increase for current and ex-smokers compared to 2016.[4, 5] In 2016, 6.8% of current smokers, 1.7% of ex-smokers and 0.3% of never smokers reported previous use of e-cigarettes.[4] In 2019, 10.2% of current smokers, 1.9% of ex-smokers and 0.3% of never smokers reported previous use of e-cigarettes.[5] The proportion of current smokers reporting trying e-cigarettes 'only once or twice' decreased from 19.9% to 18.8%, whilst never-use significantly decreased from 69.0% to 61.3%.[4, 5] There was little change across each frequency category for never smokers between 2016 and 2019.[4, 5]

Stratifying by sex, between 2016 and 2019, there was a greater absolute increase in daily use for males (7.4% to 11.3%; 3.9% absolute increase) compared to females (3.6% to 7.0%; 3.4% absolute increase), and in at least weekly (but not daily) use for females (2.2% to 5.0%; 2.8% absolute increase) compared to males (3.2% to 5.3%; 2.1% absolute increase) (Table 6).[4, 5] These increases were statistically significant.

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Proportion of e-cigarette users who are current smokers, ex-smokers and never smokers

The prevalence ± margin of error (MOE) of at least monthly e-cigarette use in the 2019 NDSHS was 2% ± 0.24% (Table 5). Applying these to the Australian Bureau of Statistics (ABS) population estimates according to smoking status (total = 20.9M; Table 7), the number of current daily, weekly or at least monthly e-cigarette users aged 14 years and over were estimated to be 418,000 ± 50,671 overall. From NDSHS 2019 data on estimated numbers of smokers (Table 7) and data on e-cigarette use according to smoking status (Table 5), among people aged 14 years and over reporting current use of e-cigarettes (classified as those using e-cigarettes, daily, weekly or at least monthly) it is estimated that:

- 54.1% ± 95% MOE 5.6% report being current smokers (daily, weekly or less than weekly);
- 32.2% ± 5.5% report being ex-smokers;
- 15.8% ± 4.4% report being never smokers.

The number of current e-cigarette users who report being never smokers would be 66,000 ± 20,228 noting the following assumptions/limitations:

1. MOEs for smoking prevalence estimates have been incorporated into the MOE for proportions of e-cigarette use;
2. Rounding of numbers in ABS estimates;
3. Approximations used in the equations.

Summary

- The percentage of people in Australia aged 14 years and over who had ever used e-cigarettes increased significantly between 2013 (4.5%) and 2016 (8.8%), and 2016 and 2019 (11.3%). Among adults, ever-use increases with decreasing age, such that 26.1% of people aged 18-24 reported ever-use of e-cigarettes in 2019.
- The percentage of people in Australia aged 14 years and over reporting current use increased significantly between 2016 (1.2%) and 2019 (2.5%). Current use is greatest in younger adults aged less than 30 years and decreases with increasing age.
- The percentage of smokers in Australia aged 14 years and over who had ever used an e-cigarette increased significantly from 18.8% in 2013 to 31.0% in 2016, and increased further to 38.7% in 2019. Among non-smokers, 1.8% reported ever-use of e-cigarettes in 2013; this proportion increased significantly to 4.9% in 2016 and 6.9% in 2019.
- The percentage of smokers in Australia aged 14 years and over who were current 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%).
- In 2019, current daily use of e-cigarettes was reported by 3.2% of current smokers, 2.2% of ex-smokers

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and 0.2% of never smokers, a significant increase for current and ex-smokers compared to 2016 (1.5% and 0.8% respectively).

- Analyses using 2019 data from the NDSHS show that among people aged 14 years and over reporting current use of e-cigarettes (i.e., those reporting daily, weekly or at least monthly use of e-cigarettes):
    - 54.1% ± 95% Margin of Error 5.6% report being current smokers (daily, weekly or less than weekly);
    - 32.2% ± 5.5% report being ex-smokers;
    - 15.8% ± 4.4% report being never smokers.

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Table 1: Ever-use of electronic cigarettes (e-cigarettes), by age and smoking status, 2013 to 2019 (per cent)

Age group (years)	Proportion								
	Smokers[a]			Non-smokers[b]			Persons		
	2013	2016	2019	2013	2016	2019	2013	2016	2019
14-17[c]	‡	50.8	63.6	‡	8.0	7.8	‡	9.2	9.6
18-24	30.8	49.1#	63.9†	4.9	13.6#	19.6†	9.5	19.2#	26.1†
25-29	26.0	37.6#	53.5†	3.0	9.0#	14.2†	7.9	14.8#	20.4†
30-39	19.3	39.0#	39.2	1.9	6.3#	9.0†	5.1	12.2#	13.9
40-49	13.8	26.2#	35.6†	0.9	3.3#	4.2	3.3	7.8#	10.3†
50-59	11.4	20.9#	30.6†	1.2	2.1#	3.3†	2.9	5.2#	8.3†
60-69	8.6	18.7#	25.8†	1.0	1.0	1.4	1.9	3.0#	4.3†
70+	9.5	11.6	10.7	*0.3	*0.3	*0.3	0.9	1.0	0.9
14+	18.8	31.0#	38.7†	1.8	4.9#	6.9†	4.5	8.8#	11.3†
18+	17.9	30.8#	38.4†	1.8	4.7#	6.8†	4.4	8.8#	11.4†

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

Statistically significant change between 2013 and 2016.

† Statistically significant change between 2016 and 2019.

‡ NDSHS 2013 included individuals 12-17 years of age, and not 14-17 years of age.

(a) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

(b) Includes those who have never smoked more than 100 combustible cigarettes (manufactured and/or roll-your-own), and those who have smoked this amount of combustible tobacco and report no longer smoking.

(c) Due to the small sample size, estimates should be interpreted with caution.

Note: A number of changes were made to the questionnaire to better capture the use of electronic cigarettes in 2016, including modifying the question about lifetime use and current use of electronic cigarettes (see questionnaire changes for more information). These changes mean that 2016 and 2013 data are not fully comparable. However, data may still be used to give an indication of the change in use of electronic cigarettes between 2013 and 2016.

Source: NDSHS 2019 (Table 2.19), NDSHS 2016 (Table 3.16)

Table 2: Current use(a) of electronic cigarettes (e-cigarettes), by age and smoking status, 2016 and 2019 (per cent)

	Proportion					
	Smokers[b]		Non-smokers[c]		Persons	
Age group (years)	2016	2019	2016	2019	2016	2019
14-17[d]	**4.3	**17.5	*0.8	*1.3	*0.9	*1.8
18-24	6.8	18.7†	*2.0	2.9	2.8	5.3†
25-29	*3.6	13.7†	*0.5	3.2†	*1.2	4.8†
30-39	5.9	8.6	0.5	1.7†	1.5	2.8†
40-49	4.3	9.4†	0.8	1.0	1.5	2.6†
50-59	3.3	6.4†	*0.3	1.0†	0.8	2.0†
60-69	*2.9	7.0†	*0.4	*0.4	0.7	1.2
70+	**0.8	*2.5	**<0.1	*0.1	*0.1	*0.2
14+	4.4	9.7†	0.6	1.4†	1.2	2.5†
18+	4.4	9.6†	0.6	1.4†	1.2	2.6†

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

** Estimate has a high level of sampling error (relative standard error 51% to 90%), meaning that it is unsuitable for most uses.

† Statistically significant change between 2016 and 2019.

(a) Includes people who reported smoking electronic cigarettes daily, weekly, monthly, or less than monthly.

(b) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

(c) Includes those who have never smoked more than 100 combustible cigarettes (manufactured and/or roll-your-own), and those who have smoked this amount of combustible tobacco and report no longer smoking.

(d) Due to the small sample size, estimates should be interpreted with caution.

Source: NDSHS 2019 (Table 2.24)

Table 3: Ever-use of electronic cigarettes (e-cigarettes), current smokers(a) by age and sex, 2013 to 2019 (per cent)

Age group (years)	Proportion								
	Males			Females			Persons		
	2013	2016	2019	2013	2016	2019	2013	2016	2019
12-17	53.7	*46.0	‡	43.4	*52.1	‡	50.1	50.8	‡
18-24	36.2	47.9	63.4†	24.1	50.4#	64.2	30.8	49.1#	63.9†
25-29	26.6	41.8#	52.5	25.4	32.5	54.9†	26.0	37.6#	53.5†
30-39	21.1	39.0#	42.9	16.3	39.1#	34.8	19.3	39.0#	39.2
40-49	13.4	29.3#	35.8	14.2	22.2#	35.2†	13.8	26.2#	35.6†
50-59	8.4	19.4#	32.2†	15.1	22.5#	28.9	11.4	20.9#	30.6†
60-69	*7.4	15.6#	22.7	10.1	22.6#	29.8	8.6	18.7#	25.8†
70+	*7.4	*8.8	*10.5	*11.8	15.3	*11.2	9.5	11.6	10.7
14+	19.7	31.5#	39.7†	17.6	30.3#	37.5†	18.8	31.0#	38.7†
18+	18.5	31.4#	39.5†	17.1	30.0#	37.1†	17.9	30.8#	38.4†

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

Statistically significant change between 2013 and 2016.

† Statistically significant change between 2016 and 2019.

‡ NDSHS 2019 did not include data on individuals 12-17 years of age.

(a) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

Note: A number of changes were made to the questionnaire to better capture the use of electronic cigarettes in 2016, including modifying the question about lifetime use and current use of electronic cigarettes (see questionnaire changes for more information). These changes mean that 2016 and 2013 data are not fully comparable. However, data may still be used to give an indication of the change in use of electronic cigarettes between 2013 and 2016.

Source: NDSHS 2019 (Table 2.20), NDSHS 2016 (Table 3.17)

Table 4: Current use(a) of electronic cigarettes (e-cigarettes), smokers(b), by age and sex, 2016 and 2019 (per cent)

	Proportion					
	Males		Females		Persons	
Age group (years)	2016	2019	2016	2019	2016	2019
18-24	*7.4	20.9†	*5.9	*15.4	6.8	18.7†
25-29	*3.5	*16.0†	**3.9	*11.1	*3.6	13.7†
30-39	7.1	9.7	*3.9	7.5	5.9	8.6
40-49	*6.0	10.4	*2.2	8.1†	4.3	9.4†
50-59	*3.7	*4.4	*3.0	8.3†	3.3	6.4†
60-69	*1.9	*7.1#	*4.3	*7.0	*2.9	7.0†
70+	n.p.	**2.6	**1.8	**2.4	**0.8	*2.5
14+	5.0	10.6†	3.5	8.7†	4.4	9.7†
18+	5.0	10.4†	3.5	8.7†	4.4	9.6†

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

** Estimate has a high level of sampling error (relative standard error 51% to 90%), meaning that it is unsuitable for most uses.

† Statistically significant change between 2016 and 2019.

n.p. not published because of small numbers, confidentiality, or other concerns about the quality of the data.

(a) Includes people who reported smoking electronic cigarettes daily, weekly, monthly, or less than monthly.

(b) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

Source: NDSHS 2019 (Table 2.25)

Table 5: Frequency of electronic cigarette (e-cigarette) use by smoking status, people aged 14 and over, 2016 and 2019 (col per cent)

Frequency of e-cigarette use	Proportion							
	Smokers[a]		Ex-smokers[b]		Never smoked[c]		Total	
	2016	2019	2016	2019	2016	2019	2016	2019
Daily	1.5	3.2†	0.8	2.2†	**0.2	*0.2	0.5	1.1†
At least weekly (but not daily)	1.2	3.0†	*0.1	*0.5†	*<0.1	*<0.1	0.3	0.6†
At least monthly (but not weekly)	0.7	1.6†	**<0.1	**<0.1	*<0.1	*0.2†	0.1	0.4†
At least monthly	*3.4*	*7.8†*	*1.0*	*2.8†*	**0.3*	*0.5*	*0.9*	*2.0†*
Less than monthly	1.0	1.9†	*0.2	*0.4	*0.2	0.2	0.3	0.5†
I used to use them, but no longer use	6.8	10.2†	1.7	1.9	0.3	0.3	1.6	2.0†
I only tried them once or twice	19.9	18.8	4.7	6.4†	3.2	4.2†	6.0	6.7†
Never used	69.0	61.3†	92.5	88.6†	96.1	94.8†	91.2	88.7†

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

** Estimate has a high level of sampling error (relative standard error 51% to 90%), meaning that it is unsuitable for most uses.

† Statistically significant change between 2016 and 2019.

(a) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

(b) Smoked at least 100 combustible cigarettes (manufactured and/or roll-your-own) or the equivalent amount of tobacco in their life, and reported no longer smoking.

(c) Never smoked 100 combustible cigarettes (manufactured and/or roll-your-own) or the equivalent amount of combustible tobacco products.

Source: NDSHS 2019 (Table 2.22)

Table 6: Frequency of electronic cigarette (e-cigarette) use by sex, people aged 14 and over who have used an e-cigarette in their lifetime, 2016 and 2019 (per cent)

Frequency of e-cigarette use	Proportion					
	Males		Females		Persons	
	2016	2019	2016	2019	2016	2019
Daily	7.4	11.3†	3.6	7.0†	5.8	9.4†
At least weekly (but not daily)	3.2	5.3	2.2	5.0†	2.9	5.1†
At least monthly (but not weekly)	*1.4	3.4†	*2.0	3.3	1.6	3.4†
At least monthly	*12.0*	*19.9†*	*7.8*	*15.3†*	*10.3*	*17.9†*
Less than monthly	4.0	4.4	2.7	4.1	3.4	4.4
I used to use them, but no longer use	19.1	19.2	16.5	16.9	18.0	18.1
I only tried them once or twice	64.9	56.5†	73.0	63.7†	68.3	59.6†

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

† Statistically significant change between 2016 and 2019.

Note: Base is people who had used electronic cigarettes in their lifetime.

Source: NDSHS 2019 (Table 2.21)

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Table 7: Tobacco smoking status, people aged 14 and over, by sex, 2019 (persons)

Smoking status	n	RSE	MOE
Daily smoker	2,300,000	2.7	100,000
Current occasional - weekly	300,000	7.6	40,000
Current occasional - less than weekly	300,000	6.9	50,000
Current smokers[(a)]	*2,900,000*	*2.3*	*100,000*
Ex-smoker[(b)]	4,800,000	1.6	100,000
Smoker in their lifetime[(c)]	*7,700,000*	*1.3*	*200,000*
Never smoked[(d)]	13,200,000	0.7	200,000

(a) Includes people who reported smoking daily, weekly, or less than weekly.

(b) Smoked at least 100 cigarettes (manufactured and/or roll-your-own) or the equivalent amount of tobacco in their life, and reported no longer smoking.

(c) Includes people who reported smoking daily, weekly or less than weekly and ex-smokers.

(d) Never smoked 100 cigarettes (manufactured and/or roll-your-own) or the equivalent amount of tobacco.

Source: NDSHS 2019 (Table 2.2)

Uptake and Cessation reviews – Sensitivity Analyses

Background

The *Uptake Review* assessed the relationship of e-cigarette use to smoking uptake. The *Cessation Review* assessed current published peer-reviewed Randomised Control Trial (RCT) evidence on the efficacy of e-cigarettes – with or without nicotine – for the sustained cessation of combustible tobacco cigarette smoking and for the cessation of ongoing exposure to nicotine.

For the *Uptake Review* and the *Cessation Review*, it was important to consider whether authors of the studies under review held 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 part of the methods, research funding and author conflict of interest information was extracted from each study.

Aims and Methods

This section presents findings from the *Uptake Review* and the *Cessation Review* separately according to whether or not the research was funded by the tobacco or e-cigarette industry, to consider whether findings differ materially according to funding source and to consider evidence independent of industry, if differences are observed.

The methods used for this analysis are those detailed in the *Uptake Review* and *Cessation Review*. In short, details of research funding sources and author conflict of interest for each study were extracted. Studies were considered to have a conflict of interest 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. No data requests were made of the authors of any papers to seek additional information. In RCTs that did not report risk ratios regarding cessation, risk ratios were calculated from number of events or percentages reported. Where applicable, sensitivity analyses were conducted using fixed-effects modelling restricted to studies without noted potential competing interests. All analyses were conducted using STATA version 16.1.

Findings

See the *Uptake Review* and *Cessation Review* for detailed reporting on the findings of the main reviews, including PRISMA flowchart, study characteristics, narrative summary of included studies, effect measures and missing data.

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Uptake Review

There were 25 primary research studies in total included in the Uptake Review. There were 13 eligible primary research studies included from three systematic review papers identified in the umbrella review on the uptake of combustible cigarette smoking, involving sample sizes ranging from 298 to 17,318. Twelve studies were newly identified for the top-up systematic review, involving sample sizes ranging from 374 to 14,623.

Table 8 contains the conflict of interest and funding information extracted for each study included in the *Uptake Review*. No potentially competing interests were identified from the studies themselves, or the authors, among the systematic reviews in the umbrella review or the primary research studies in the top-up systematic review, based on the disclosure statements from the publications. One primary research study identified during screening in the top-up systematic review, Lee et al.,[6] was funded by the tobacco industry. This study was excluded from the review because there was a large overlap with data presented in a more recent paper by Berry et al.[7]

Cessation Review

Nine RCTs of ENDS were identified that examined smoking cessation as an outcome, involving the randomisation of a total of 5,445 smokers; 2,836 randomised to ENDS and 2,609 to comparison groups.

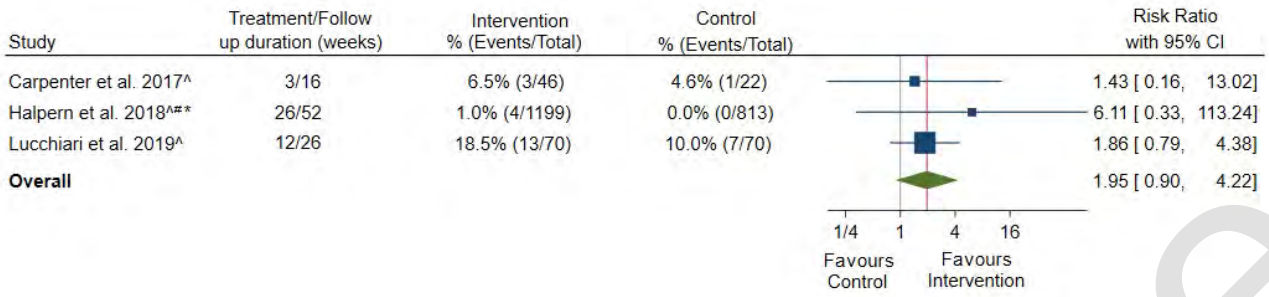
Four of the RCTs consisted of three arms. The study by Lucchiari et al. contained an ENDS, an ENNDS and a usual care arm[8] and Bullen et al. contained an ENDS, an ENNDS and a NRT arm[9]. As such, both were included in two separate meta-analyses according to the relevant comparator. There were two ENDS arms with differing nicotine concentrations in two RCTs.[10, 11] These arms were combined for the meta-analysis.

Nicotine-delivering e-cigarettes versus no intervention or usual care

Three of the RCTs included in the review compared ENDS to no intervention or usual care.[8, 11, 12] 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. However, Halpern et al.[12] reported receiving e-cigarettes donated by an e-cigarette company. Sensitivity analysis was conducted excluding Halpern et al.[12]

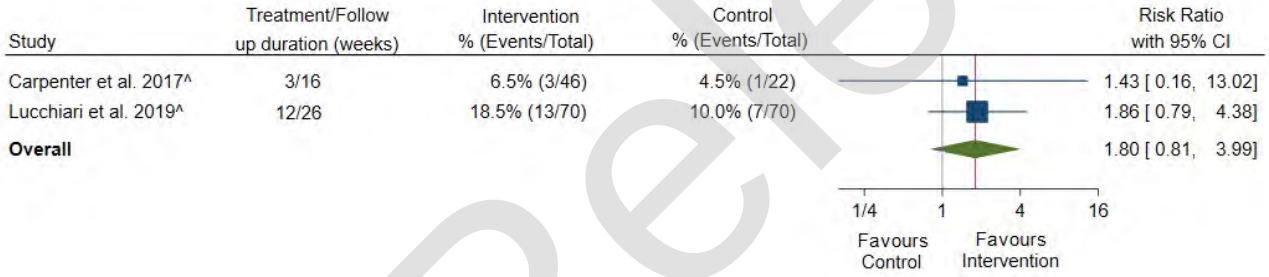
Findings showed that no individual study reported a significant difference in cessation outcomes between randomised groups (Figure 1). Halpern et al.[12] reported an RR of 6.11 (95% CI 0.33-113.24). Results from the random-effects meta-analysis found no significant difference between randomised groups when the random-effects meta-analysis was restricted to studies with no noted potential competing interests (RR 1.80; 95% CI 0.81-3.99; I^2 = 0.0%) (Figure 2).

Figure 1: Biochemically verified sustained smoking cessation in smokers randomised to nicotine-delivering e-cigarettes versus no intervention or usual care: random-effects meta-analysis.



^ 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: 20/1315 in intervention group, 8/905 in control group
Heterogeneity: Tau^2=0.00; Chi^2= 0.67, df=2, p = 0.71; I^2 =0.0%; Test for overall effect: Z=1.71, p=0.09

Figure 2: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine-delivering e-cigarettes versus no intervention or usual care in studies with no reported potential competing interests: random-effects meta-analysis.



^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 16/116 in intervention group, 8/92 in control group
Heterogeneity: Tau^2=0.00; Chi^2= 0.05, df=1, p = 0.83; I^2 =0.0%; Test for overall effect: Z=1.44, p=0.15

Nicotine-delivering e-cigarettes versus e-cigarettes which do not deliver nicotine

Three RCTs compared smoking cessation outcomes in participants randomised to ENDS and ENNDS (considered a placebo).[8-10] No studies were directly funded by the tobacco or e-cigarette industry. Bullen et al.[9] had a study author who reported previously receiving research funding from an e-cigarette manufacturer and Caponnetto et al.[10] had a study author who had received funding from the tobacco industry. Both studies reported using e-cigarettes donated by an e-cigarette company.[9, 10] As only one paper did not have noted competing interests, sensitivity analysis was not conducted.

Findings were that no statistically significant difference between ENDS and ENNDS was found in any study (Figure 3). Restricting the evidence to that without known potential competing interests, one study remained with a RR of 1.18 (95% CI 0.57-2.46) for cessation in smokers randomised to ENDS versus ENNDS.[8]

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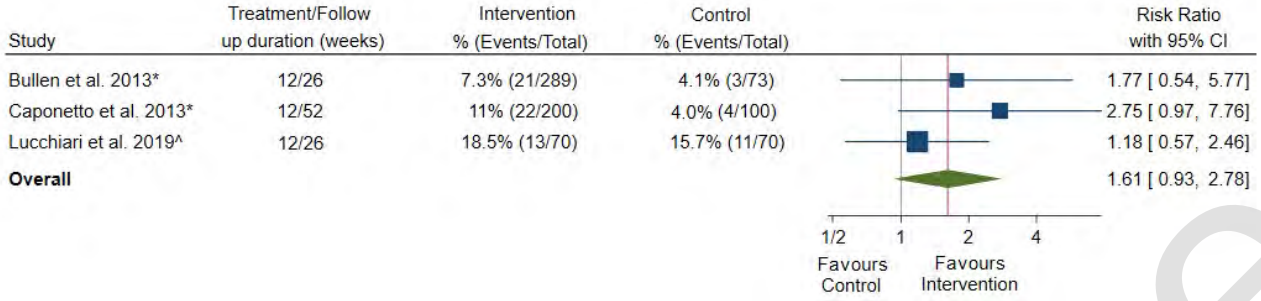
Figure 3: Biochemically verified sustained smoking cessation in smokers randomised to nicotine-delivering e-cigarettes versus non-nicotine-e-cigarettes: random-effects meta-analysis.



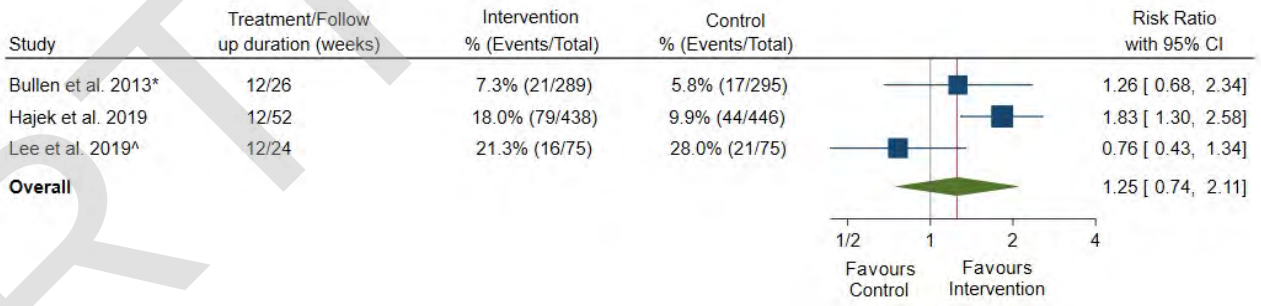
* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total events: 56/559 in intervention group, 18/243 in control group
Heterogeneity: Tau^2=0.01; Chi^2= 1.73, df=2, p = 0.42; I^2 =3.4%; Test for overall effect: Z=1.71, p=0.09

Nicotine-delivering e-cigarettes versus other nicotine replacement therapy

Three RCTs were identified that compared ENDS to approved NRT.[9, 13, 14] Bullen et al.[9] had the potential competing interests noted above; no other studies had reported competing interests. Sensitivity analysis was conducted.

Findings showed that, of the three relevant studies, two reported no statistically significant difference between ENDS and approved NRT,[9, 15] and the other found significantly greater cessation in those randomised to ENDS (Figure 4).[13] Results from the random-effects meta-analysis found that 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%) (Figure 5).

Figure 4: Biochemically verified sustained smoking cessation in smokers randomised to nicotine-delivering 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=0.40

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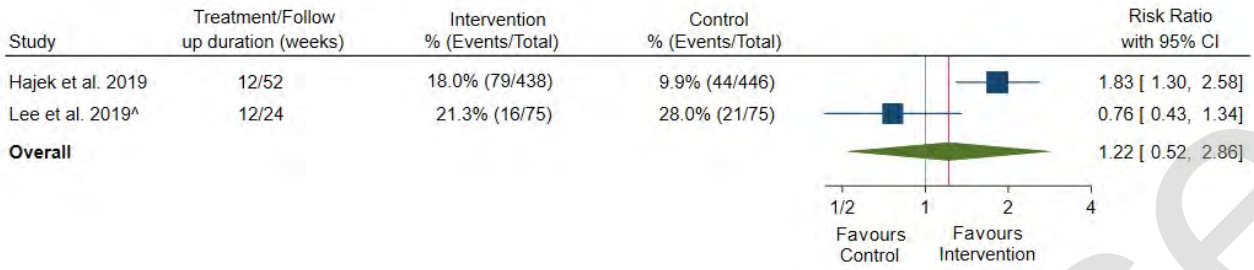
Figure 5: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine-delivering e-cigarettes versus other nicotine-replacement therapy in studies with no reported potential competing interests: random-effects meta-analysis.



^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 95/513 in intervention group, 65/521 in control group
Heterogeneity: Tau^2=0.00; Chi^2= 6.70, df=1, p = 0.01; I^2 =85.1%; Test for overall effect: Z=0.45, p=0.65

Summary

- There were no potential competing interests identified among studies included in the *Uptake Review*. Hence, the main results are not changed when competing interests are considered: that non-smokers who use e-cigarettes are on average three times as likely to become smokers of combustible cigarettes as non-smokers who do not use e-cigarettes.
- The results of the *Cessation Review* did not differ materially when potential conflicts of interest were considered, although the available evidence base was reduced. These results were that the evidence is currently insufficient to conclude that e-cigarettes are efficacious as an aid to smoking cessation compared to no intervention/usual care, non-nicotine e-cigarettes and standard nicotine replacement therapy, although early signs are that they may be useful in highly controlled clinical settings.

Table 8: Competing interest information extracted from papers identified in the Uptake Review and conflict of interest assessment

Reference	Funding/ conflict of interest statement	Assessment
Newly identified studies		
Aleyan et al. 2019[16]	Funding: The COMPASS study has been supported by a bridge grant from the CIHR Institute of Nutrition, Metabolism and Diabetes (INMD) through the "Obesity – Interventions to Prevent or Treat" priority funding awards (OOP-110788; awarded to SL), an operating grant from the CIHR Institute of Population and Public Health (IPPH) (MOP-114875; awarded to SL), a CIHR project grant (PJT-148562; awarded to SL), a CIHR bridge grant (PJT-149092; awarded to KP/SL), a CIHR project grant (PJT-159693; awarded to KP), and by a research funding arrangement with Health Canada (#1617-HQ-000012; contract awarded to SL). Adam Cole was funded by the Canadian Institute of Health Research (CIHR) during the time of the study. The funding sources noted above had no involvement in the study design, collection, analysis, interpretation of data and writing of the report. Conflicts of Interest: The authors declare no conflict of interest.	None
Barrington-Trimis et al. 2019[17]	Funding sources: Research reported in this publication was supported by grant number P50CA180905 (J.B.T., A.M.L., F.L., T.B.C., R.M.) from the National Cancer Institute at the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) Center for Tobacco Products (CTP), and grant numbers R01DA033296 (A.M.L.), P50DA036151 (G.K., M.M., S.K.S.), K01DA042950 (J.B.T.) from the National Institute on Drug Abuse at NIH, and DGE- 1418060 (M.B.) from the National Science Foundation Graduate Research Fellowship Program. The funder had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the article. Conflicts of interest: The authors have no conflicts of interest to disclose.	None
Berry et al. 2019[7]	Conflict of interest disclosures/funding: Drs Fetterman, Benjamin, Bhatnagar, and Stokes and Ms Berry were supported by grants P50HL120163 and 2U54HL120163-06 from the National Heart, Lung, and Blood Institute of the National Institutes of Health and Center for Tobacco Products. Drs Barrington-Trimis and Leventhal were supported by grants P50CA180905 and U54CA180905 from the National Cancer Institute of the National Institutes of Health. Dr Stokes reported receiving research funding from Johnson & Johnson outside of the submitted work. No other disclosures were reported.	None
Bold et al. 2018[18]	Financial disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose. Funding: Supported in part by grants from the National Institute on Drug Abuse and the Food and Drug Administration Center for Tobacco Products (P50DA036151, P50DA009241, T32DA019426, and l40DA042454). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration. Funded by the National Institutes of Health (NIH). Potential conflict of interest: The authors have indicated they have no potential conflicts of interest to disclose.	None

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Brose et al. 2019[19]	Competing interests: The authors declare that they have no competing interests. Funding: This work was supported by Cancer Research UK (C52999/A21496; C57277/A23884).	None
Chien et al. 2019[20]	Funding: The work was supported by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan (Grant Number: MOHW105-HPA-H-114-133708), from the Health and Welfare Surcharge on Tobacco Products—Grant Number: 03724606—Project Code: 1051218-107), and grants R01DA043950 from the US National Institute of Drug Abuse and P50CA180890 from the National Cancer Institute, the Food and Drug Administration (FDA) Center for Tobacco Products. The content is solely the responsibility of the authors and does not necessarily represent the official views of Health Promotion Administration, NIH or the Food and Drug Administration. The funding agencies had no role in study design, data collection, analysis, and interpretation, or writing of this study. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication. Conflicts of interest: The authors declare no conflict of interest.	None
Conner et al. 2019[21]	Funding: The research was supported by a grant from the UK Medical Research Council/National Preventive Research Initiative. CA is additionally supported by the National Institute for Health Research Manchester Biomedical Research Centre and the National Institute of Health Research Greater Manchester Patient Safety Translational Research Centre. All authors report receiving grants from the National Prevention Research Initiative during the study. Competing interests: None declared.	None
Dai et al. 2019[22]	Role of funding source: Research reported in this publication was supported by the National Cancer Institute and the FDA Center for Tobacco Products (CTP) under Award Number R03CA228909 (Dai) and Award Number U54CA180905 (Leventhal). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration. Conflict of interests: No conflict declared.	None
Kinnunen et al. 2019[23]	Role of funding source: Nothing declared. Conflict of interest: Not reported.	Unclear
McMillen et al. 2019[24]	Declaration of conflicting interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Funding: The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This article was made possible by the Flight Attendant Medical Research Institute under award No. 052302_CoE to the American Academy of Pediatrics. The information, views, and opinions contained herein are those of the authors and do not necessarily reflect the views and opinions of the funding organizations.	None

Osibogun et al. 2020[25]	Funding: OO is supported by the NIDA T32DA043449 grant. ZB is sup- ported by the FIU-Research Center in Minority Institution (grant U54MD012393-01). WM is supported by NIH (grants R01- DA035160, R01-TW010654, R01-DA042477) and the NIDA T32DA043449 grant. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH. Conflict of interest: Not reported. No other financial disclosures were reported by the authors of this paper.	Unclear
Penzes et al. 2018[26]	Role of funding sources: This work was supported by the Fogarty International Center and National Cancer Institute of the National Institutes of Health under Grant Number 1R01TW009280. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Fogarty International Center and National Cancer Institute of the National Institutes of Health had no involvement in study design, collection, analysis, or interpretation of data, writing the manuscript, and the decision to submit the manuscript for publication. Conflict of interest: None.	None
Studies in previous meta-analyses		
Barrington-Trimis et al. 2018[27]	Financial disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose Funding: Supported by grant P50CA180905 (Drs Barrington-Trimis, Leventhal, Cruz, and McConnell and Ms Liu) from the National Cancer Institute at the National Institutes of Health and the Food and Drug Administration Center for Tobacco Products and grants R01DA033296 (Dr Leventhal), P50DA036151 (Drs Kong and Krishnan-Sarin and Ms Mayer), and K01DA042950 (Dr Barrington-Trimis) from the National Institute on Drug Abuse at the National Institutes of Health. The funders had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the article. Funded by the National Institutes of Health (NIH). Potential conflict of interest: The authors have indicated they have no potential conflicts of interest to disclose.	None
Best et al. 2017[28]	Funding: This project was funded by the UK National Institute for Health Research (NIHR) PHR project 10/3000/07. The study sponsor had no influence on study design and the collection, analysis, and interpretation of data and the writing of the article and the decision to submit it for publication. Competing interests: None declared.	None

East et al. 2017[29]	Conflicts of interest: Katherine East, Sara Hitchman, and Ann McNeill are members of the UK Centre for Tobacco and Alcohol Studies. Ioannis Bakolis is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and by the NIHR Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. Sarah Williams is an employee at Public Health England and was previously an employee at Action on Smoking and Health at the time this study was conducted. Hazel Cheeseman and Deborah Arnott are employees of Action on Smoking and Health, which receives funding from the British Heart Foundation, Cancer Research UK (CRUK), and the Department of Health. This study was funded by CRUK grant code A21559. CRUK was not involved in the study design, data collection, analysis or interpretation of the data, the write up of the manuscript, or decision to submit the article for publication. The views expressed are those of the author(s) and not necessarily those of Public Health England, CRUK, Action on Smoking and Health, the NHS, the NIHR or the Department of Health. Funding sources: This work was funded by Cancer Research UK grant code A21559. Thanks are also given to the UK Public Health Research Consortium (grant number PHPEHF50/13) for funding the development of some of the covariates included in this study.	None
Leventhal et al. 2015[30]	Conflict of interest disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported. Funding/support: This research was supported by grants R01-DA033296 and P50-CA180905 from the National Institutes of Health. Role of funder/sponsor: The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.	None
Loukas et al. 2018[31]	Role of funding source: Research reported in this publication was supported by grant number [1 P50 CA180906] from the National Cancer Institute and the Food and Drug Administration (FDA) Center for Tobacco Products. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the FDA. Conflict of interest: All authors declare that they have no conflicts of interest.	None
Lozano et al. 2017[32]	Conflict of interest: No conflict declared. Source of funding: This research was supported by a grant from the Fogarty International Center and the National Cancer Institute of the United States' National Institute of Health (R01 TW009274). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.	None
Meich et al. 2017[33]	Funding: This study was supported by the National Institute on Drug Abuse, part of the National Institutes of Health, by grants numbers R01DA001411 and R01DA016575. Competing interests: None declared.	None

Primack et al. 2015[34]	Conflict of interest disclosures: None reported. Funding/Support: This study was supported by grant R01-CA077026 for the survey from the National Cancer Institute (Dr Sargent), grants R01-CA140150 and R21-CA185767 from the National Cancer Institute (Dr Primack), and grant KL2-TR001088 from the National Center for Advancing Translational Sciences (Dr Soneji). Role of the funder/sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.	None
Primack et al. 2018[35]	Funding source: National Cancer Institute (R01-CA140150). Dr. Primack is supported by a two grants from the National Cancer Institute (R01-CA140150 and R21-CA185767). Dr. Sargent is supported by the National Cancer Institute (R01-CA077026). Dr. Soneji is supported by the National Cancer Institute (R21-CA197912). The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. Conflict of interest: The authors have no conflicts of interest to report.	None
Spindle et al. 2017[36]	Conflict of interest: The authors have no conflicts of interest to declare. Funding: Spit for Science: The VCU Student Survey has been supported by Virginia Commonwealth University, P20AA107828, R37AA011408, K02AA018755, and P50 AA022537 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and UL1RR031990 from the National Center for Research Resources (NCRR) and National Institutes of Health Roadmap for Medical Research. Research reported in this publication was also supported by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health under Award Numbers P50DA036105 and F31DA040319 and the Center for Tobacco Products of the U.S. Food and Drug Administration (FDA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration. NIAAA, NCRR, NIDA, NIH, and FDA had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.	None
Treur et al. 2018[37]	Funding: This work was supported by the European Research Council (ERC; 284167), Netherlands Organization for Health Research and Development (ZonMw; 200100003) and the National Institute for Public Health and the Environment (RIVM). Conflict of interest: Not reported.	Unclear
Unger et al. 2016[38]	Role of funding source: This research was supported by the National Institutes of Health (grant 5R01DA016310). Conflict of interest: The authors report no conflicts of interest.	None
Wills et al. 2017[39]	Funding: This research was supported by grants R01 CA153154 and P30 071789-16S2 from the National Cancer Institute. Competing interests: None declared.	None

Uptake Review – Quality Assessment

Background

The *Uptake Review* assessed the relationship of e-cigarette use to smoking uptake. In the *Uptake Review*, a quality assessment was performed on non-randomised studies using the Newcastle Ottawa Scale (NOS).[40] The NOS totals (out of 10 stars) ranged from 5 to 8, with ascertainment of exposure, assessment of outcome and adequacy of follow-up of cohorts as the main areas impacting the NOS scores.

Aims and Methods

This section presents the results of an updated risk of bias assessment of the articles included in the *Uptake Review*.

The Risk Of Bias In Non-randomized Studies of Interventions[41] (ROBINS-I) was used to assess the risk of bias in the primary research studies included in the systematic review. Two authors (AY and SB) independently assessed each article as per the ROBINS-I guidelines[42] and discussed any conflicts to reach a consensus. If no consensus was found, a third author (KB) was consulted. No data requests were made of the authors of any papers to seek additional information.

Findings

See the *Uptake Review* for details of identified studies. Of the 12 newly identified studies in the *Uptake Review*, three were considered to be at a serious risk of bias and nine at a moderate risk of bias using the ROBINS-I tool (Table 9). No study was deemed a low risk. All studies, with the exception of Brose et al., 2019[19], had a low risk of bias for classification of the intervention, deviation from intended intervention and measurement of outcomes. Confounding and participant selection were the main domains that introduced bias. In all studies, no information regarding the selection of the reported risk was found (study protocols and details suggesting *a priori* analyses were absent).

Summary

- Of the 12 newly identified studies included in the *Uptake Review*, three were considered to be at a serious risk of bias and nine at a moderate risk of bias, using the ROBINS-I tool.

Table 9:ROBINS-I risk assessment for the primary research studies included in the smoking uptake systematic review

Reference	Bias domain							Final Judgement
	Confounding	Participant selection	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported risk	
Aleyan et al. 2019[16]	Moderate	Moderate	Low	Low	Low	Low	No information	Moderate
Barrington-Trimis et al. 2019[17]	Moderate	Moderate	Low	Low	Low	Low	No information	Moderate
Berry et al. 2019[7]	Moderate	Low	Low	Low	Low	Low	No information	Moderate
Bold et al. 2018[18]	Serious	Moderate	Low	Low	Low	Low	No information	Serious
Brose et al. 2019[19]	Serious	Moderate	Serious	Low	No information	Low	No information	Serious
Chien et al. 2019[20]	Moderate	Moderate	Low	Low	Low	Low	No information	Moderate
Conner et al. 2019[21]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
Dai et al. 2019[22]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
Kinnunen et al. 2019[23]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
McMillen et al. 2019[24]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
Osibogun et al. 2020[25]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
Penzes et al. 2018[26]	Serious	Moderate	Low	Low	No information	Low	No information	Serious

Uptake Review – Discussion update

Background

The *Uptake Review* assessed the relationship of e-cigarette use to smoking uptake. The main findings from the *Uptake Review* included that:

- 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.
- The current evidence indicates that, on average, 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.
- There is uncertainty regarding the constituents of the e-liquids in the studies reviewed. Where evidence on nicotine content was available, it indicated that a substantial majority of e-cigarettes in those studies delivered nicotine.

Aims and Methods

The aim of this section is to consider the evidence from the *Uptake Review* in relation to the following points:

- Demographic characteristics of participants in studies included in the *Uptake Review*;
- Likelihood that e-cigarettes will increase the number of young people using nicotine and smoking combustible cigarettes; and
- High concentration nicotine salt products.

No data requests were made of the authors of any papers to seek additional information.

Demographic data from the primary research articles – including articles that had been included in previous systematic reviews and newly identified studies – were extracted into Microsoft Excel by one report author (MM) using the data extraction template of the *Uptake Review*. The data extraction was checked by a second author (AY or SB). Discrepancies were resolved through consensus or by a third review author (KB).

Information extracted in the process described above was used to document the age distribution of the study populations and to allow specific consideration of studies of young people. Where only school grade was reported, age was estimated based on the usual age group of students of that grade in the relevant country.

Studies included in the *Uptake Review* were searched for consideration of high nicotine salt devices or JUUL.

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To supplement the discussion based on articles included in the *Uptake Review*, a brief informal, non-systematic literature search was conducted to identify relevant additional discussion points in articles and grey literature.

Resultant findings from the above three processes are then considered and discussed.

Discussion

Distribution of demographic factors

Primary research papers

Out of the 12 studies, three[19, 22, 24] were of an adult population aged 18 years and over (Table 10). All other studies were with school-aged children ranging from 12–17 years. Four studies[16, 17, 20, 23] did not specify age but listed the school grade. Sex was reported in all studies, except for Penzes et al.,[26] with females accounting for 44.8%–56.3%. Ten studies[7, 16-22, 24, 25] reported data on ethnicity. The most common ethnic subgroup was white/Caucasian, present in nine studies and omitted only from Chien et al.,[20] a Taiwanese based study. Of these studies, all but Connor et al.[21] reported a white majority, with 94.1% (British and other white combined) reported in Brose et al.[19]

Education level, either participant education for the adult samples or parent's education in the youth samples, was reported in five studies.[7, 20, 22, 24, 25] Dai and Leventhal,[22] McMillen et al.[24] and Osibogun et al.[25] reported college or above in 60–70% of the sample while Berry et al.[7] and Chien et al.[20] reported a lower proportion with college education or greater (35%).

Affluence was reported in five studies.[16, 18, 19, 21, 22] Bold et al.[18] found a mean family affluence score of 5.92 in participants (standard deviation (SD) 1.38; score of 8 indicates most affluent) and Connor et al.,[21] using the same measure, reported a mean score of 2.72 (SD 0.49). Brose et al.[19] measured annual income with 41.3% of respondents reporting a high annual income greater than £30,000. Dai and Leventhal[22] measured household income relative to the federal poverty line with 54.2% more than 200% above the poverty line. Aleyan et al.[16] measured the amount of money available to the child to be spent or saved with the majority (44.1%) receiving between $1-20 and 7.1% receiving greater than $100.

One study[7] (Berry et al.) measured urbanisation status with 80.4% of participants living in urban areas and 19.6% in rural areas. Chien et al.[20] was the only study to measure parent's employment status and family living arrangements.

One study examined the association of e-cigarettes on combustible cigarette initiation and another on relapse.

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Barrington-Trimis et al.[17] found the adjusted odds of dual use at follow-up was considerably higher in non-Hispanic whites (aOR 7.44; 95% CI 3.63–15.3) compared to Hispanic whites (aOR 3.64; 95% CI 1.62–8.18), however, confidence intervals overlapped. Among ex-smoking e-cigarette users, Brose et al.[19] found that there was no statistically significant difference in the likelihood of relapse for sex, age and income.

Papers from systematic reviews

Thirteen studies were extracted from systematic reviews (Table 11), with nine being conducted in the United States,[27, 30, 31, 33-36, 38, 39] two in the United Kingdom,[28, 29] one in Mexico[32] and one in The Netherlands.[37] Eight studies[27-30, 32, 33, 37, 39] used youth populations (11–18 years) and five[31, 34-36, 38] used adult populations (greater than 18 years). Age was reported in all but two studies,[27, 33] in which instance school grade was reported (ranging from ninth to twelfth grade). In studies reporting the mean age of participants, the range was 13.8 years in Treur et al.[37] to 22.7 years in Unger et al.[38] The mean age across studies providing an average was 17.5 years.[28, 30, 31, 34, 36-39] In studies which categorised age, the lowest limit was 11 years[29, 32, 37] and the upper limit was 30 years.[35]

Sex was reported in all but one study, Best et al.[28] The proportion of females ranged from 48.2%[37] to 67.7%.[31]

Ethnicity was reported in eleven of the publications.[27, 30-39] Non-Hispanic white was the most prevalent ethnic subgroup (ranging from 31.8% to 76.5%) in five[31, 33-36] studies and Hispanic/Latino white (ranging from 37.9% to 100.0%) in four[27, 30, 32, 38], two[32, 38] of which included Hispanic ethnicity only. Filipino-Americans (27.0%) accounted for the largest proportion of participants in Wills et al.[39] In Treur et al.,[37] Dutch individuals accounted for the largest proportion of participants in both cohorts (78.1% and 81.4% respectively).

Several studies also reported on educational attainment, both of the participants' parents[30, 32, 34, 39], and the participants[35, 37] themselves. In Leventhal et al.,[30] the most common highest parental education level achieved was 'College graduate' (33.7%), whilst '≤8th grade' was the least common (3.3%). Lozano et al.[32] found 'Secondary education' (38.0%) to be the most prevalent parental education level, with 'Primary education' being the least prevalent (16.0%). ENDS use at baseline was associated with more advanced maternal education compared to no ENDS use at baseline (mean scores 7.5 and 6.9 respectively) in Primack et al.[34] In a weighted sample of predominately white, non-Hispanic participants, a 'High school or less' education was the most common educational level (45.8%) among ENDS users, whilst 'Bachelors or higher' was the least common (19.3%), in Primack et al.[35] Educational level differed across each cohort in Treur et al.,[37] with the most common educational level in Cohort 1 (mean age 13.8 years, 48.2% female) being 'Low' level (students with learning difficulties and lowest levels of pre-vocational secondary education; 33.4%), in contrast to Cohort 2 (mean age 17.3 years, 61.3% female) where the most common educational level was 'High' (pre-university

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or university education; 36.7%).

Best et al.,[28] conducted in Scotland, presented the distribution of study participants according to the socioeconomic status and urban-rural profile of their school's location. The greatest proportion was from accessible small town/medium-low deprivation areas. In the Primack et al.[35] weighted sample, ENDS users were most commonly in the 'High' (>$75,000) yearly household income category (47.6%) and least common in the 'Low' (<$30,000) yearly household income category (16.3%). Wills et al.[39] presented data on family structure demographics with 'Two biological parents' being the most common category (60.0%) and 'Extended family structure' (two parents plus two or more relatives in the household) being the least common (11.0%).

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Table 10: Demographic data - primary research articles

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Aleyan et al. 2019 Canada	Age not reported Grade 9th: 56.1% 10th: 43.9%	Female: 52.2% Male: 47.8%	White: 76.1% Black: 3.1% Latin-American: 1.9% Asian: 5.4% Aboriginal: 2.2% Other: 11.3%	Weekly spending money $0: 26.0% $1-20: 44.1% $20-100: 22.8% Over $100: 7.1%	No analysis
Barrington-Trimis et al. 2019 US	Age not reported Grade 9th: 58.7% 10th: 6.2% 11th: 19.6% 12th: 15.4%	Female: 46.5% Male: 53.5%	Non-Hispanic white (NHW): 37.4% Hispanic white (HW): 37.9% Other: 24.7%		Current (past 30 day) smoking at follow-up, baseline never smokers aOR (95% CI)^ Non-Hispanic White Nonusers: Reference Dual use: 7.44 (3.63–15.3) Hispanic White Nonusers: Reference Dual use: 3.64 (1.62–8.18) ^Adjusted for sex; random effect for school or community
Berry et al. 2019 US	12 years: 27.3% 13 years: 26.5% 14 years: 25.0% 15 years: 21.3% Mean (SD): 13.4 (1.2) years	Female: 49.5% Male: 50.5%	Non-Hispanic, white: 54.1% Non-Hispanic, black: 13.9% Hispanic: 22.8% Non-Hispanic, other: 9.2%	Parental Education Lower than a college degree: 64.1% College or higher: 35.9% Residence Urban: 80.4% Rural: 19.6%	No analysis
Bold et al. 2018 US	Age 13–17 years Mean (SD): 15.04 (0.90) years	Female: 53% Male: 47%	White: 87.6% Asian: 5.7% Hispanic and/or Latino: 5.1% Black or African American: 2.6% American Indian or Alaskan Native: 1.0% Native Hawaiian or Pacific Islander: 0.7% Middle Eastern: 0.9% Other: 0.4%	Socioeconomic status Mean (SD): 5.92 (1.38) (Family Affluence Scale: scored out of 8, higher score equals greater affluence)	No analysis

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Brose et al. 2019 UK	Age-Mean (SD) Ex-smokers: 48.1 (15.3) Vaping ex-smokers: 49.2 (14.1)	Female: 45.2% Male: 54.8%	White English/Welsh/Scottish /Northern Irish/British: 90.9% Any other white: 3.2% Mixed/multiple ethnic groups: 1.1% Asian/Asian British: 2.9% Black/African/Caribbean/Black British: 1.3% Other ethnic group: 0% Prefer not to say: 0.5%	Annual Income Low (< £15,000): 16.7% Moderate (£15,001-£30,000): 28.7% High(> £30,000): 41.3% Not disclosed: 13.3%	Relapse to smoking during follow-up, baseline ex-smokers to vaping ex-smokers at follow-up (n = 159) OR (95% CI); p value Sex Female: Reference Male: 0.99 (0.52-1.87); p=0.96 Age Per year increase: 0.98 (0.96-1.00); p=0.068 Income High: Reference Other: 0.70 (0.36-1.34); p=0.28
Chien et al. 2019 Taiwan	Age not reported Grade 7th (Junior High): 42.3% 10th (Senior High): 57.7%	Female: 56.3 Male: 43.7%	Mother's ethnicity* Native: 87.9% Indigenous: 3.0% Foreigner: 7.7%	Father's education* Below junior high: 17.6% Senior/vocational high: 37.4% Above college: 35.5% Parent's employment status* Full-time job: 93.5% Part-time job: 1.9% Unemployed: 3.6% Family living arrangement Parents/extended family: 78.9% Single parents: 16.4% Grandparents: 2.1% Other relatives: 2.5%	No analysis
Conner et al. 2019 UK	Age 13-14 years	Female: 52.3% Male: 47.7%	White: 17.2% Non-white: 82.8%	Family affluence Low: 2.72 (0.49) (Family Affluence Scale) Children per school eligible for free school meals (no. of schools): Low: 48.9% High: 44.4%	No analysis

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Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Dai & Leventhal 2019 US	18-24: 10.0% 25-34: 18.6% 35-44: 16.3% 45-54: 16.5% 55-64: 18.4% 65+: 20.2%	Female: 54.8% Male: 45.2%	Non-Hispanic White: 74.9% Non-Hispanic Black: 7.6% Hispanic: 10.5% Other: 7.0%	Education Less than high school: 8.1% High school graduate: 23.3% Some College: 38.5% Bachelor's degree or above: 29.8% Household income Below poverty line: 16.4% 100%-200% poverty line: 21.0% >200% poverty line: 54.2% Unknown: 8.5%	No analysis
Kinnunen et al. 2019 Finland	Age not reported Grade 9 (age 15-16 years)	Female: 51.8% Male: 48.2%	Not reported	Not reported	No analysis
McMillen et al. 2019 US	18-34: 46.1% ≥35: 53.6% (Unweighted)	Female: 44.8% Male: 55.0% (Unweighted)	Non-Hispanic white: 69.9% Non-Hispanic black: 17.0% Other: 10.3% (Unweighted)	Education <High school: 10.6% High school/GED: 26.1% Some college: 34.5% ≥ College degree: 28.0% (Unweighted)	No analysis
Osibogun et al. 2020 US	12-14 years: 76.4% 15-17 years: 23.6%	Female: 48.0% Male: 52.0%	White: 47.1% African American: 14.0% Hispanic: 29.6% Other: 9.3%	Parent's education level* High school or less: 38.1% Some college: 31.1% Bachelor's degree or higher: 30.3%	No analysis
Penzes et al. 2018 Romania	Mean (SD): 14.88 (0.48) years Grade 9	Not reported	Not reported	Not reported	No analysis

*Numbers may not sum to the total because of missing data

Table 11: Demographic data - articles from systematic reviews

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Barrington-Trimis et al. 2018 US	Age not reported Grade 9th: 58.7% 10th: 6.2% 11th: 19.6% 12th: 15.4%	Female: 53.5% Male: 46.5%	Non-Hispanic white: 37.4% Hispanic white: 37.9% Other: 24.7%	Not reported	No analysis
Best et al. 2017 UK	Mean (SD): 14.4 (1.58) years	Not reported	Not reported	Number of pupils from each school by SES/urban profile School 1 - Accessible small town/medium–low deprivation: 858 School 2 - Urban/medium–low deprivation: 738 School 3 - Other urban/high deprivation: 672 School 4 - Urban/high deprivation: 733 Total: 3001	No analysis
East et al. 2017 UK	11-13 years: 38.02% 14-15 years: 29.34% 16-18 years: 32.64%	Female: 53.8% Male: 46.2%	Not reported	Not reported	No analysis
Leventhal et al. 2015 US	Mean (95% CI): 14.06 (14.04-14.07) years	Female: 53.2% Male: 46.8%	American Indian/Alaska Native: 0.8% Asian: 19.0% Black: 4.8% Hispanic: 44.2% Native Hawaiian/Pacific Islander: 3.6% White: 16.2% Other: 5.7% Multi-ethnic or multi-racial: 5.7%	Highest parental education level ≤8th grade: 3.3% Some high school: 7.8% High school graduate: 15.2% Some college: 19.5% College graduate: 33.7% Graduate degree: 20.6%	No analysis
Loukas et al. 2018 US	Mean (SD): 19.71 (1.61) years	Female 67.7% Male: 32.3%	Non-Hispanic white: 31.8% Hispanic/Latino: 27.4% Asian: 23.4% African-American/Black: 9.8% Other or reported two or more race/ethnicities: 7.5%	Not reported	No analysis

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Lozano et al. 2018 Mexico	11-12 years: 33.0% 13+ years: 67.0%	Female: 52.0% Male: 48.0%	Hispanic/Latino-Mexican: 100.0%	Parental education Primary: 16.0% Secondary: 38.0% High school: 19.0% University: 19.0% Unknown: 8.0%	No analysis
Miech et al. 2017 US	Age not reported Grade 12th grade	Female: 56.3% Male: 43.7%	White: 60.1% Non-white: 39.9%	Not reported	No analysis
Primack et al. 2015 US	Age - mean (SD) ENDS use at baseline, n=16: 19.5 (2.0) years No ENDS use at baseline, n=678: 20.0 (2.4) years	Female: 53.9% Male: 46.1%	Non-Hispanic white: 76.5% Non-Hispanic black: 6.8% Hispanic: 7.6% Other: 9.1%	Maternal Education* - Mean (SD) ENDS use at baseline, n = 16: 7.5 (1.8) No ENDS use at baseline, n = 678: 6.9 (2.5) (*Higher scores equates to higher education)	No analysis
Primack et al. 2018 US	Unweighted data 18-20 years: 21.8% 21-23 years: 32.7% 24-26 years: 24.2% 27-30 years: 21.4% Weighted data 18-20 years: 31.6% 21-23 years: 23.9% 24-26 years: 18.7% 27-30 years: 25.7%	Unweighted Female: 61.6% Male: 38.4% Weighted Female: 50.3% Male: 49.7%	Unweighted White, non-Hispanic: 64.8% Black, non-Hispanic: 10.9% Hispanic: 14.2% Other: 10.1% Weighted White, non-Hispanic: 55.2% Black, non-Hispanic: 14.6% Hispanic: 19.7% Other: 10.4%	Yearly Household Income Unweighted Low (<$30,000): 25.0% Medium ($30,000-$74,999): 38.1% High (>$75,000): 36.8% Weighted Low (<$30,000): 16.3% Medium ($30,000-$74,999): 36.0% High (>$75,000): 47.6% Education Unweighted High school or less: 28.0% Some college: 39.6% Bachelors or higher: 32.5% Weighted High school or less: 45.8% Some college: 34.9% Bachelors or higher: 19.3%	No analysis

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Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Spindle et al. 2017 US	Mean (SD): 18.5 (0.43) years	Female: 62.0% Male: 48.0%	White: 47.0% Black: 19.0% Asian: 17.0% Hispanic/Latino: 6.0% Mixed race/ethnicity: 7.0% American Indian/Alaskan Native, Native Hawaiian/Other Pacific Islander, unknown race or ethnicity, or chose not to answer: 4.0%	Not reported	No analysis
Treur et al. 2018 Netherlands	Cohort 1 Age - Mean (SD): 13.8 (1.1) years 11-13 years: 39.7% 14-15 years: 54.3% 16-17 years: 6.0% Cohort 2 Age - Mean (SD): 17.3 (1.8) years 14-15 years: 17.4% 16-17 years: 39.9% 18-21 years: 42.7%	Cohort 1 Female: 48.2% Male: 51.8% Cohort 2 Female: 61.3% Male: 38.7%	Cohort 1 - Ethnicity Netherlands: 78.1% Surinam/Aruba/Netherlands Antilles: 1.8% Morocco: 2.9% Turkey: 2.0% Other: 10.1% Missing data: 5.1% Cohort 2 - Ethnicity Netherlands: 81.4% Surinam/Aruba/Netherlands Antilles: 1.9% Morocco: 2.0% Turkey: 2.1% Other: 4.1% Missing data: 8.5%	Cohort 1 - Educational level Low: 33.4% Average: 31.3% Middle: 17.2% High: 16.2% Missing data: 1.9% Cohort 2 - Educational level Low/Average: 34.2% Middle: 27.3% High: 36.7% Missing data: 1.8%	No analysis
Unger et al. 2016 US	Mean (SD): 22.7 (0.39) years	Female: 59.0% Male: 41.0%	Hispanic: 100.0%	Not reported	No analysis
Wills et al. 2017 US	Mean (SD): 14.7 (0.7) years Grade 9th: 49.0% 10th: 42.0% 11th: 9.0%	Female: 53.0% Male: 47.0%	Asian-American: 24.0% Caucasian: 19.0% Filipino-American: 27.0% Native Hawaiian or other Pacific Islander: 20.0% Other: 10.0%	Father's education (1-6 scale) Mean (SD): 4.2 (1.2) Family structure Single parent: 17.0% Step-parent family: 12.0% Two biological parents: 60.0% Extended family structure: 11.0%	No analysis

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Uptake of nicotine and combustible cigarette smoking among young people

The two uptake outcomes reviewed in the *Uptake Review* were:

Outcome 1. Cigarette smoking initiation among never smokers at baseline, in relation to e-cigarette use; and

Outcome 2. 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.

Additional analyses were reported in the *Uptake Review*, that assessed the odds of taking up regular combustible cigarette smoking, as associated with e-cigarette use:

Outcome 3. Current (past 30-day) regular cigarette smoking among non-smokers (never smokers or no past 30-day-use) at baseline, in relation to e-cigarette use.

The risk of uptake of other nicotine products was not assessed in any of the included studies as an outcome. However, as e-cigarettes commonly deliver nicotine, use of e-cigarettes will generally result in increased use of nicotine by young people.

The populations of the included papers in the *Uptake Review* could be divided into school-aged young people (ages ≤18 years), and young people (ages ≤30 years) (Table 12), which incorporated 17 and 22 papers respectively out of the original included 25. Two studies[19, 22] were excluded from the following discussion altogether as the only outcome investigated was smoking relapse, and the study populations included ages over 30 years. One paper remained that had been included in the meta-analyses for Outcomes 1 and 2 with a population of 18 years and over and no upper age limit, making it out-of-scope for both young people populations. This allowed for consideration of how the exclusion of this study's data might impact on the calculated pooled adjusted odds ratios (aOR) and gave an indication of the likely risk applicable to the young populations of interest.

Outcome 1: Cigarette smoking initiation among never smokers at baseline, in relation to e-cigarette use

Overall, 17 studies investigated cigarette smoking initiation among never smokers at baseline, in relation to e-cigarette use, including both newly identified studies and studies drawn from previous meta-analyses. Eleven studies[7, 20, 21, 26-30, 32, 33, 39] assessed populations of school-aged young people (ages ≤18 years). These 11 studies and an additional five studies[31, 34-37] assessed populations of young people aged up to 30 years (ages ≤30 years). One study[24] included all ages over 18 years, and was thus out of scope (Figure 6).

Among studies of school-aged young people (ages ≤18 years), all of the studies found that those who used e-cigarettes were significantly more likely than non-users to initiate smoking of combustible cigarettes, with odds ratios varying substantially from 1.60 to 10.57, and two studies with a comparatively high degree of intra-

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study variance[29, 33] and associated lower weight of contribution to the overall aOR for all included studies (Figure 6). The studies with the least amount of intra-study variance tended to have a lower aOR (1.60 to 4.09);[7, 20, 21, 32, 39] likewise, the two studies with the highest degree of within-study variance had the highest aOR.[29, 33]

Among studies of young people to the age of 30 years (ages ≤30 years), the odds ratios ranged from 1.36 to 11.90, and five studies had a high degree of intra-study variance (Figure 6).[34, 35, 37]

The single study with a sample population including people aged older than 30 years (aged 18 years and older, no upper age limit), McMillen et al.,[24] had a comparatively higher aOR (aOR 6.60 (95% CI 3.70 – 11.79)) and moderate intra-study variance. While the removal of this study from analysis may result in a slight decrease in the overall aOR reported in the review, the effect is liable to be minor, indicating an overall aOR for studies assessing populations aged up to 30 years would remain relatively unchanged from the overall aOR reported in the review (pooled aOR 3.19 (95% CI 2.44 – 4.16)) (Figure 6). In support of this inference, the 'studies in previous meta-analyses', as shown in Figure 6, assessed populations aged ≤30 years and had similar pooled aOR (pooled aOR 3.17 (95% CI 2.44 – 4.61)) to the overall aOR.

Interestingly, the meta-analysis of 'newly identified studies' as shown in Figure 6, included four studies on people aged ≤18, and the out-of-scope McMillen et al. 2019 study[24] (Figure 6). The pooled aOR for these five studies does not differ materially from the overall aOR found in the review, and restriction of data to the four studies on school-aged young people (ages ≤18 years) only would yield a result consistent with the overall aOR figure.

In summary, based on the current evidence, young people, whether school-aged or aged up to 30 years, who used e-cigarettes had a risk of initiating smoking of combustible cigarettes that was approximately three-fold that of those who do not use e-cigarettes.

Outcome 2: 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

Eight studies investigated 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, including both newly identified studies and studies drawn from previous meta-analyses. Six studies[16-18, 21, 23, 25] assessed populations of school-aged young people (ages ≤18 years). These six studies and an additional one study[37] assessed populations of young people aged up to 30 years (ages ≤30 years). One study[24] included all ages over 18 years, and was thus out of scope (Figure 7).

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Among studies of school-aged young people (ages ≤18 years), all of the studies found the risk of transitioning from being a non-smoker to current smoker was higher in people who had used e-cigarettes than those that had not used e-cigarettes. Odds ratios varied substantially from 1.18 to 7.44, and two studies[23, 25] showed a comparatively high degree of intra-study variance and associated lower weight of contribution to the pooled aOR for all included studies (Figure 7). The studies with the least amount of intra-study variance were those with the lowest aOR (1.18 and 2.17).[16, 21]

With the additional one study by Unger et al.[38] that included young people to the age of 30 years (ages ≤30 years), the variation in aOR remained the same, with a comparative aOR of 3.32 (95% CI 1.55 – 7.11) and moderate intra-study variance for the additional study (Figure 7). This suggests that the overall findings from studies of school-aged young people and young people aged up to 30 years are likely to be similar.

There was a single study with a sample population including people aged older than 30 years,[24] which found that non-smokers who used e-cigarettes had an aOR of 8.00 (95% CI 2.81 – 22.78) of going on to be a current smoker (Figure 7). This study had a relatively high variance. Focusing results on the remaining seven studies would be likely to give a similar finding to the reported pooled aOR of 3.14 (95% CI 1.93 – 5.11).

In summary, based on the current evidence, young people, whether school-aged or aged up to 30 years, who use e-cigarettes had an approximate three-fold risk of transitioning from being a non-smoker to a current smoker compared to those who do not use e-cigarettes.

Outcome 3: Current (past 30-day) regular cigarette smoking among non-smokers (never smokers or no past 30-day-use) at baseline, in relation to e-cigarette use

Four studies were identified that assessed current regular use of combustible cigarettes (Table 13). Of these, three[21, 23, 25] were conducted among school-aged populations (≤18 years), and one was out-of-scope, having assessed a sample population including people aged older than 30 years.[24] The three in-scope studies used definitions of regular use (smoking at least 20 out of 30 days)[21, 25] or daily use[23] of combustible cigarettes as assessed outcomes.

Conner et al.[21] investigated the association of e-cigarette use at baseline and combustible tobacco smoking in adolescents (13 to 14 years old) between Waves 3 and 5 (2014 to 2016) of a cluster RCT in 20 schools in England. Participants were found to have significantly higher odds of taking up regular current combustible cigarette smoking by follow-up, based on ever-use of e-cigarettes at baseline (aOR 1.27; 95% CI 1.17 – 1.39).

Kinnunen et al.[23] used MEtLoFIN, a school-based longitudinal cohort dataset in 3,474 Finnish adolescents

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between 2014 and 2016. Kinnunen et al., separated the use of e-cigarettes using nicotine contents and found among baseline never smokers, ever-use of nicotine-containing e-cigarettes predicted uptake of daily smoking (aOR 2.92; 95% CI 1.09 – 7.85) but non-nicotine containing e-cigarettes did not (aOR 0.94; 95% CI 0.22 – 4.08).

Osibogun et al.[25] used data on youth (12-17 years old) non-smokers from Waves 1 to 3 of the Population Assessment of Tobacco and Health (PATH) study, a US nationally representative longitudinal study. At one-year follow-up, current e-cigarettes users at baseline had significantly higher odds of having become regular current combustible cigarette users (aOR 5.0; 95% CI 1.9 – 12.8), an affect which had attenuated at two-year follow-up (aOR 3.4; 95% CI 1.0 – 11.5).

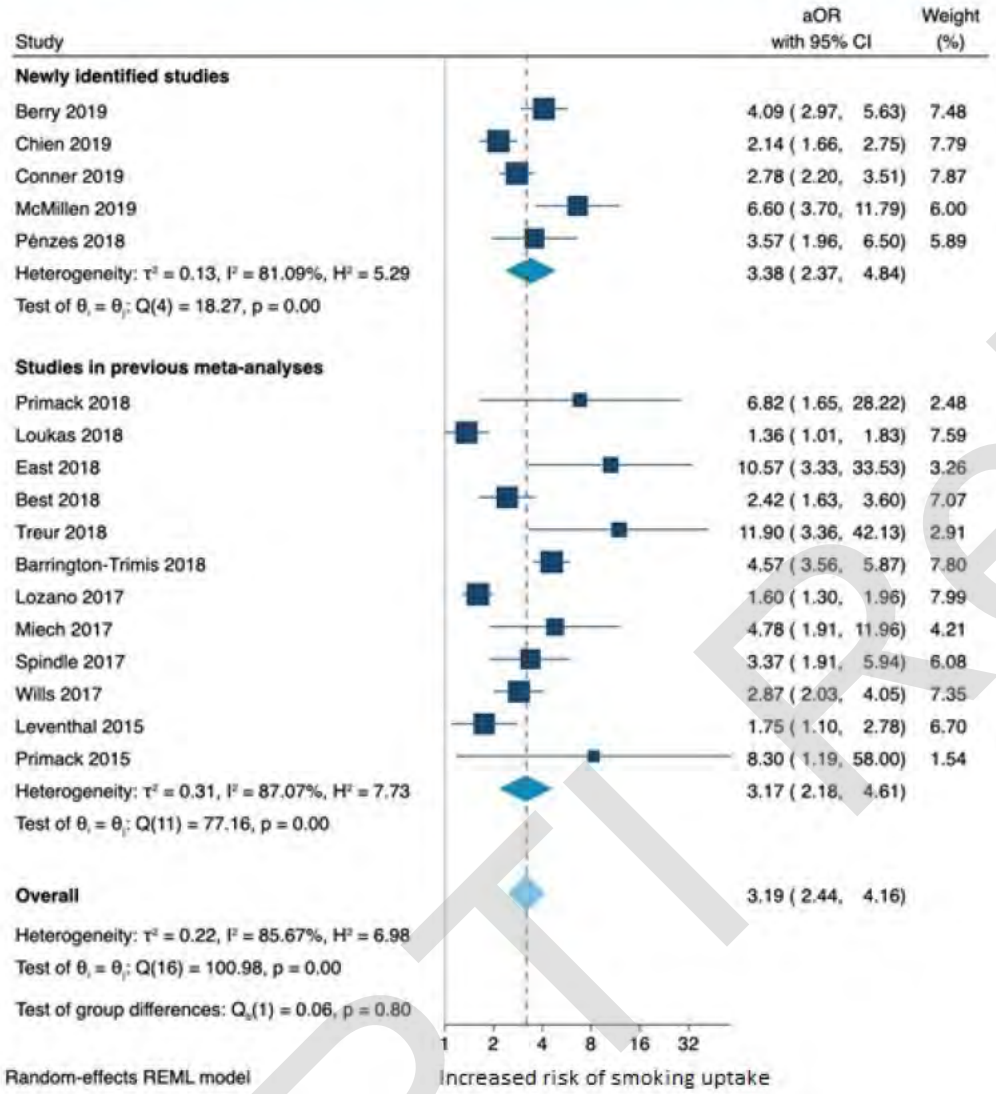
The available evidence from three studies indicates that, among young people, there is an elevated risk for those who had used e-cigarettes of transitioning from being a non-smoker to a current regular smoker compared to those that had not used e-cigarettes. Nicotine content of e-cigarettes may influence the degree of risk. At this time, however, there is insufficient available evidence to draw firm conclusions.

Table 12: Studies included in the *Uptake Review* by young person age group, ordered by age group of sample

Reference	Age (yrs)	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	>30
Lozano et al. 2017[32]	12 - 13		■	■																		
Conner et al. 2019[21]	13 - 14			■	■																	
Berry et al. 2019[7]	12 - 15		■	■	■	■																
Penzes et al. 2018[26]	14 - 15				■	■																
Leventhal et al. 2015[30]	14 - 15				■	■																
Chien et al. 2019[20]	13, 16			■			■															
Wills et al. 2017[39]	14 - 16				■	■	■															
Aleyan et al. 2019[16]	14 - 16				■	■	■															
Kinnunen et al. 2019[23]	15 - 16					■	■															
Osibogun et al. 2020[25]	12 - 17		■	■	■	■	■	■														
Bold et al. 2018[18]	13 - 17			■	■	■	■	■														
Best et al. 2017[28]	11 - 18	■	■	■	■	■	■	■	■													
East 2017[29]	11 - 18	■	■	■	■	■	■	■	■													
Barrington-Trimis et al. 2019[17]	14 - 18				■	■	■	■	■													
Barrington-Trimis et al. 2018[27]	14 - 18				■	■	■	■	■													
Miech et al. 2017[33]	17 - 18							■	■													
Spindle et al. 2017[36]	18 - 19								■	■												
Treur et al. 2018[37]	14 - 21				■	■	■	■	■	■	■	■										
Unger et al. 2016[38]	22 - 23												■	■								
Loukas et al. 2018[31]	18 - 25								■	■	■	■	■	■	■	■						
Primack et al. 2015[34]	16 - 26						■	■	■	■	■	■	■	■	■	■	■					
Primack et al. 2018[35]	18 - 30								■	■	■	■	■	■	■	■	■	■	■	■	■	
McMillen et al. 2019[24]	18+								■	■	■	■	■	■	■	■	■	■	■	■	■	■

Green outline denotes studies included in discussion for school-aged young people (ages ≤18 years)
Yellow outline denotes studies included in discussion for young people aged ≤30 years

Figure 6: Adjusted odds ratios and meta-analysis of smoking initiation at follow-up among baseline never smokers in relation to current versus never e-cigarette use at baseline, with age group and rating of comparative odds ratio, variance and weight



Comparative rating	
Variance	Weight
L	H
L	H
L	H
M	M
M	M

H	L
L	H
H	L
M	M
H	L
M	H
L	H
H	L
M	M
L	H
M	M
H	L

L = Low; M = Medium; H = High.

Aged <=18 years (and <=30 years)
Aged <=30 years
Out-of-scope (aged 18+ years)

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Figure 7: Adjusted odds and meta-analysis of current smoking at follow-up among baseline non-smokers in relation to current versus not current e-cigarette use at baseline, with age group and rating of comparative odds ratio, variance and weight

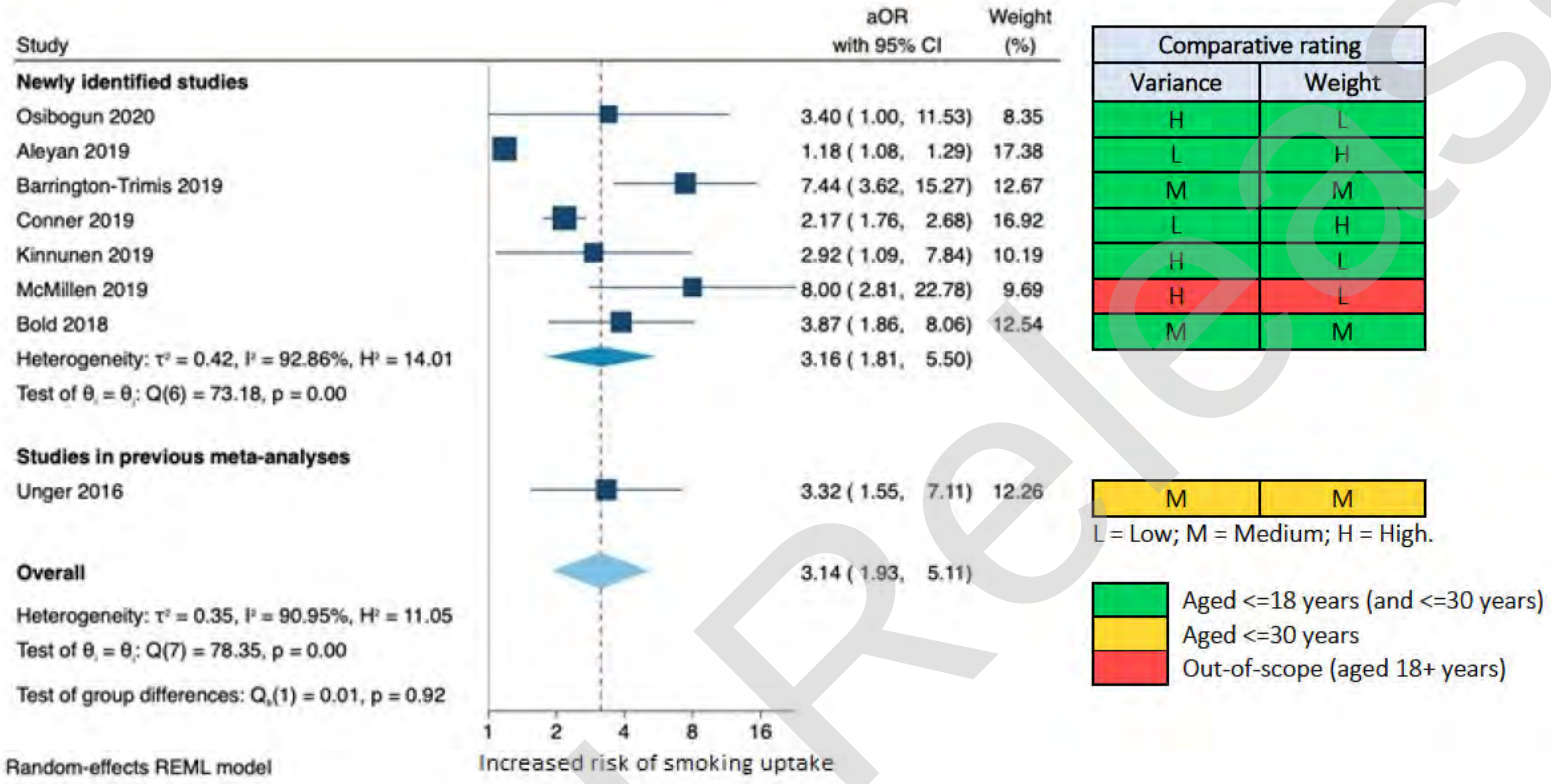

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Table 13: Odds ratios and adjusted odds ratios of the association between e-cigarette use and current[a] (past 30-day) combustible tobacco smoking initiation among non-smokers (never or no past 30-day use) at baseline.

Study	Ages	Country	Baseline cigarette use	E-cigarette use at baseline	Cigarette use at follow-up	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Conner et al., 2019[21]	≤18 years	UK (England)	Never smokers	Ever	Current	3.38 (2.72–4.21)	2.17 (1.76–2.69)
				Ever	Regular[a]	3.60 (2.35–5.51)	1.27 (1.17–1.39)
Kinnunen et al., 2019[23]	≤18 years	Finland	Never smokers	Ever	Daily use	Nicotine containing 11.52 (4.91–27.01) Firth: 11.70 (4.91–26.56) Non-nicotine containing 1.88 (0.25–14.45) Firth: 2.71 (0.29–11.14)	Nicotine-containing 8.50 (2.14–29.19) With school clustering: 2.92 (1.09–7.85) Non-nicotine containing 2.50 (0.25–12.05) With school clustering: 0.94 (0.22–4.08)
Osibogun et al., 2020[25]	≤18 years	US	Non-smokers (never or no current use)	Current	Regular use[a]	Year 1: 16.4 (7.8–34.5) Year 2: 11.1 (3.5–35.2)	Year 1: 5.0 (1.9 – 12.8) Year 2: 3.4 (1.0 – 11.5)
McMillen et al., 2019[24]	18+ years	US	Never smoker	Ever (not current)	Established[b]	5.9 (1.7–20.7)	2.5 (0.6–10.9)
				Current	Established[b]	25.5 (10.6–61.4)	8.0 (2.8–22.7)

[a] Regular defined as ≥20 days/30 days; [b] Established defined as ≥100 combustible cigarettes in the past 12 months and currently smokes every day or some days

Aged ≤18 years (and ≤30 years)
Out-of-scope (aged 18+ years)

High concentration nicotine salt products

Nicotine salts are an alternative to free-base e-liquid in e-cigarette devices. Unlike free-base e-liquids, they do not contain glycerol or propylene glycol, instead consisting of a nicotine base and a weak organic acid that forms a nicotine salt upon activation of the device, which is then released as an aerosol for inhalation.[43]

Nicotine salts are used in 'pod vaporizers' or 'vape pods', the leading product in the US market being JUUL developed by JUUL Labs.[44, 45] There is evidence of considerable concern among researchers, health bodies and policy makers about pod devices, centred around JUUL, with JUUL Labs facing investigation in the US for their role in what has been called the 'youth nicotine addiction epidemic'[46] in the US. The main points of concern are summarised below.

The substance is based on the nicotine salts found in leaf-based tobacco rather than free-base nicotine.[44] Nicotine salt products deliver comparatively high levels of nicotine,[44, 47, 48] with the standard US JUUL or Puffbar having a nicotine concentration of 5% or 59mg/mL and a single cartridge containing as much nicotine as 1-2 packets of cigarettes.[49] The nicotine is delivered more rapidly than when using standard e-liquids,[49] with a peak at about five minutes, creating an experience similar to combustible cigarette smoking.[44]

The design of nicotine pods is generally small, light, easy to conceal and easy to use inconspicuously[50] - with the design resembling a USB stick – these design features are appealing to young people.[44, 49] They are discrete enough to evade detection in class at school or from parents.[44, 45] The flavoured nicotine cartridges, with flavours such as Fruit Medley and Crème Brulee,[44] were also considered to appeal to youth.[49] Numerous easily concealable devices have come on to the market following widespread use of JUUL.[45]

This youth appeal has been compounded by marketing tactics which have been shown to deliberately target children and youth.[47] The JUUL device was prolifically advertised through social media campaigns including on Instagram and Twitter, employing memes, hashtags, tag lines, and promotional friend-tagging, and recruiting 'thousands of online 'influencers'' to market JUUL.[46] JUUL reportedly marketed directly to teenagers and children as young as 8 years old by gaining access to schools, summer camps, and public out-of-school programs.[47] A significant number of retailers in the US were warned by the FDA for reported illegal sales of JUUL products to youth.[47]

Further compounding of these issues is a lack of knowledge and awareness among young users of nicotine pods. Many young users are unaware or unsure that they are e-cigarettes.[48] Several studies have shown that most students do not know the nicotine content of nicotine pods or that they have a high content.[47, 48] In the US hearing into JUUL, The Respiratory Health Association reported that around 60% of young people using JUUL were not aware that the product contained nicotine.[49]

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In the Australian context, while limited evidence indicates that Australian youth have been subjected to e-cigarette marketing, particularly via social media, the extent to which this relates to nicotine salt products is not known.[46, 51]

As noted in the *Uptake Review*, there is uncertainty regarding the constituents of the e-liquids in the studies reviewed. Where evidence on nicotine content was available, it indicated that a substantial majority of e-cigarettes in those studies delivered nicotine. Detail on the specific devices used by participants was generally not reported. Three papers[19, 21, 22] contained some device information and none of these indicated use of nicotine salt vaping devices. A further three papers[31, 32, 36] noted the likely impact of device type and other characteristics on uptake of combustible cigarette smoking as an important area for future research.

One paper referenced nicotine salt products,[16] specifically the JUUL device, in the discussion section. This was in the context of the product's entry into the market as a driver of the need for revised policies to discourage e-cigarette use among young people, referencing the deleterious effect of nicotine on the developing adolescent brain.

After completion of study searches and following submission of the first verison of this report, in early July 2021 Health Canada reduced the cap on nicotine concentrations permitted in e-cigarettes to 20mg/mL. They noted in their justification that "Health Canada has identified the availability of high-nicotine-concentration vaping products in the Canadian market since 2018 as one of the key factors that have contributed to the rapid rise in youth vaping."[52] In particular, they noted a doubling in the prevalence of current/recent e-cigarette use (defined as use within the past 30 days) among school students from 2016-2017 to 2018-2019. They also state: "In 2018, a new generation of vaping products were introduced to the Canadian market, characterized by high concentrations of nicotine in salt form (called "nicotine salts") that made nicotine less aversive when inhaled. As a result, vaping products above 20 mg/mL nicotine (a majority of which contained nicotine salts) quickly took a dominant market position, capturing 62% of the domestic market by value of nicotine-containing vaping substances in 2019.[52]footnote 13 footnote 14[53, 54]

In summary, despite concerns about nicotine salt products, no research specifically examining their relationship to combustible cigarette uptake was able to be located during the specified search period. Thus, whether the higher nicotine content or the more rapid release of nicotine associated with nicotine salt products impacts the uptake of combustible cigarette smoking is not known. From a safety perspective, at this stage, the findings regarding e-cigarettes and smoking uptake should be considered to apply to the range of devices in use by participants in the studies that have been summarised. Nicotine e-cigarettes which have not been the subject of studies regarding their impact on smoking should be assumed to increase the uptake of combustible smoking, unless specific evidence to the contrary is available. Moreover, the emerging evidence

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that high-concentration nicotine salt products are likely to increase the prevalence of youth e-cigarette use means they may be particularly hazardous with respect to increasing combustible tobacco smoking, as they are associated with increasing prevalence of exposure.

Summary

Distribution of demographic factors

- Demographic factors reported in the studies in the *Uptake Review* included age, sex, ethnicity, education, affluence, urbanisation, SES, and family structure.
- Participants with a range of demographic characteristics were included although most studies were of people aged between 11 and 18 years.
- Analysis according to demographic subgroups was scant. There was no specific evidence available of any variation in the relationship of e-cigarette use to smoking uptake according to demographic factors. Where assessed, no statistically significant difference in the likelihood of smoking relapse was identified for sex, age, income or non-Hispanic white compared to Hispanic white ethnic/cultural groups.

Uptake of nicotine and combustible cigarette smoking among young people

- Based on the current evidence, young people, whether school-aged or aged up to 30 years, who used e-cigarettes had a risk of initiating smoking of combustible cigarettes that was approximately three-fold that of those who did not use e-cigarettes. There was substantial variation in the results between studies.
- Based on the current evidence, young people, whether school-aged or aged up to 30 years, who use e-cigarettes had an approximate three-fold risk of transitioning from being a non-smoker to a current smoker compared to those who did not use e-cigarettes. There was substantial variation in the results between studies.
- Based on evidence from three studies, the risk of transitioning from being a non-smoker to a current regular smoker is elevated for young people aged ≤18 years who had used e-cigarettes compared to those who had not, and this risk may be impacted by nicotine content, however evidence is limited.
- E-cigarettes commonly deliver nicotine, so use of e-cigarettes will generally result in increased use of nicotine by young people.

High concentration nicotine salt products

- Information on the nicotine content and delivery devices used by participants in the studies including in the uptake review was extremely limited.
- No research specifically examining the relationship of nicotine salt products to combustible cigarette uptake was located.

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- From a safety perspective, at this stage, the findings regarding e-cigarettes and smoking uptake should be considered to apply to the range of devices in use by participants in the studies that have been summarised. Furthermore, nicotine e-cigarettes which have not been the subject of studies regarding their impact on smoking should be assumed to increase the uptake of combustible smoking, unless specific evidence to the contrary is available.
- Since high concentration nicotine salt products have been identified as key drivers of increased youth e-cigarette use, they may be particularly hazardous for increasing youth smoking uptake, through higher prevalence of e-cigarette use.

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PROSPERO
International prospective register of systematic reviews

E-cigarette use and the risk of initiation of combustible tobacco cigarette smoking among non-smokers: An umbrella review and a systematic review

Olivia Baenziger, Laura Ford, Miranda Harris, Robyn Lucas, Emily Banks

Citation

Olivia Baenziger, Laura Ford, Miranda Harris, Robyn Lucas, Emily Banks. E-cigarette use and the risk of initiation of combustible tobacco cigarette smoking among non-smokers: An umbrella review and a systematic review. PROSPERO 2020 CRD42020168596 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020168596

Review question

Among current non-smokers, does e-cigarette use (nicotine-containing or non-nicotine-containing) affect the subsequent risk of ever smoking combustible tobacco cigarettes?

Searches

Sources: PubMed; Scopus; Web of Science; PsycINFO (Ovid); MEDLINE (Ovid); Cochrane

Search dates: no start date limit on the search

Language restriction: available in English

Types of study to be included

Inclusion:

- Published, peer-reviewed literature
- Randomised/ non-randomised controlled trials, clinical trials (although interventional studies are not expected)

- Prospective cohort studies

- Cross-sectional studies

Exclusion:

- Non-systematic reviews-literature reviews

- Intervention trial with no comparator (e.g. before and after study)

- Qualitative studies

- Retrospective cohort studies

- Case-control studies

- Case studies

- Grey literature, conference abstracts, letters, editorials, correspondence, opinion pieces, government reports, position statements

Condition or domain being studied
Tobacco smoking and e-cigarette use

Participants/population

Non-tobacco smokers – including never and former users. Any age (youth, young adults and adults)

Intervention(s), exposure(s)
Nicotine-containing or non-nicotine-containing e-cigarettes or e-liquid devices (also referred to as vaping products)

Comparator(s)/control
Non-users of e-cigarette products

Main outcome(s)
Primary outcome – ever smoking combustible tobacco cigarettes

* Measures of effect

Relative risks, odds ratios or risk difference

Additional outcome(s)
None

* Measures of effect

N/A

Data extraction (selection and coding)

For review management, EndNote and Covidence software will be used. Two review authors will independently screen titles, abstracts and then full text from the search results using a screening checklist. If a discrepancy arises, the full text will be reviewed and discussed with a third reviewer.

The data extraction template for the umbrella review includes: general characteristics (author, date of publication, type of review, number of studies and designs), search strategy, population, exposure (e-cigarette) measures, outcome (cigarette) measures, method of analysis, quality assessment, results, effect measure, limitations, conclusion, funding/ conflict of interest.

The data extraction template for the systematic review includes: general characteristics (author, date of publication, country), study design and objective, duration, population, selection method, inclusion/ exclusion criteria, exposure (e-cigarette) characterisation, outcome (cigarette) assessment, consideration of confounding, quality assessment, conclusion, funding/ conflict of interest.

Risk of bias (quality) assessment
Cochrane Collaboration's tool for assessing risk of bias in randomised trials will be used for any randomised studies included. The risk of bias in non-randomised studies – of interventions (ROBINS-I) tool will be used for non-randomised studies including cohort and crossover trials. AMSTAR (2) will be used for systematic reviews and meta-analyses

Strategy for data synthesis
A summary of findings (SoF) table will be created. The extent of clinical and methodological heterogeneity will be considered and if suitable, statistical heterogeneity across included studies will be assessed. If data are sufficient and consistent, a meta-analysis will be undertaken by extracting data from primary research identified in the umbrella review and systematic review.

Analysis of subgroups or subsets
If relevant, a subgroup analysis will be undertaken separating studies of the general population from those of specific subpopulations.

Contact details for further information

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Organisational affiliation of the review

Australian National University
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Professor Robyn Lucas. The Australian National University
Professor Emily Banks. The Australian National University

Type and method of review

Epidemiologic, Review of reviews, Systematic review

Anticipated or actual start date

01 March 2020

Anticipated completion date

31 December 2020

Funding sources/sponsors

The Australian Government Department of Health

Conflicts of interest

None known

Language

English

Country

Australia

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

05 July 2020

Date of first submission

30 March 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

05 July 2020
05 July 2020

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PROSPERO
International prospective register of systematic reviews

A systematic review of the efficacy of e-cigarettes as combustible tobacco smoking and nicotine cessation aids

Emily Banks, Robyn Lucas, Miranda Harris, Laura Ford, Amelia Yazidjoglou, Tehzeeb Zulfiqar, Melonie Martin

Citation

Emily Banks, Robyn Lucas, Miranda Harris, Laura Ford, Amelia Yazidjoglou, Tehzeeb Zulfiqar, Melonie Martin. A systematic review of the efficacy of e-cigarettes as combustible tobacco smoking and nicotine cessation aids. PROSPERO 2020 CRD42020170692 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020170692

Review question

The primary research question is: Are e-cigarettes (nicotine-containing or non-nicotine containing) effective combustible tobacco smoking cessation aids, in comparison with no e-cigarette use, smoking cessation interventions such as nicotine replacement therapy (NRT), or placebo (e.g. non-nicotine containing e-cigarette when the intervention is a nicotine-containing e-cigarette)?

The secondary research question is: What is the effect of use of e-cigarettes as a smoking cessation aid on the longer-term use of nicotine, compared with no e-cigarette use, other NRT, or placebo?

Searches

Databases: PubMed; Scopus; Web of Science; PsycINFO (Ovid); MEDLINE (Ovid); Cochrane.

There will be no date limit on the search. Only studies published in English will be included.

Types of study to be included

Randomised controlled trials

Condition or domain being studied

E-cigarettes are marketed as devices to help in smoking cessation, however there is limited evidence regarding the efficacy of e-cigarettes (nicotine containing or non-nicotine containing) as smoking and nicotine cessation aids.

Participants/population

Current tobacco smokers

Intervention(s), exposure(s)

E-cigarettes (nicotine or non-nicotine containing)

Comparator(s)/control

No e-cigarettes, smoking cessation treatment interventions (e.g. NRT, behavioural therapy), or placebo (e.g. non-nicotine containing e-cigarette when the intervention is nicotine-containing e-cigarette).

Main outcome(s)

Combustible tobacco smoking cessation – defined as stopping all combustible tobacco product use.

* Measures of effect

Relative risks, odds ratios or risk difference

Additional outcome(s)
(1) Cessation of nicotine in any form (e.g. combustible tobacco, e-cigarettes, other NRT) among all participants; (2) Use of NRT, including e-cigarettes, or non-nicotine e-cigarettes, among all participants; (3) Use of NRT, including e-cigarettes, or non-nicotine e-cigarettes, among tobacco smoking quitters; (4) Use of NRT, including e-cigarettes, or non-nicotine e-cigarettes, among those who do not quit tobacco smoking.

* Measures of effect

Relative risks

Data extraction (selection and coding)
EndNote and Covidence software will be used for review management. Two review authors will independently review and extract the data. Titles and abstracts will be screened for inclusion, followed by full text articles. Disagreement will be resolved by consensus, and if not reached, by third party adjunction. After consensus on which studies to include, data will be entered on the data extraction template.

The data extraction template includes: author and publication year, country, study objective, duration (treatment and follow up), blinding type, sampling method, study population (sample size, experimental, control), sample age/sex, inclusion/exclusion criteria, experimental intervention, control intervention, smoking outcome, nicotine exposure outcome, effect measures, non-nicotine containing e-cigarette use outcomes, conclusion, funding/conflict of interest statement.

Risk of bias (quality) assessment
Two review authors will independently assess the risk of bias for each included RCT. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials will be used.

Strategy for data synthesis
A table of findings and narrative summary will be provided. The extent of clinical and methodological heterogeneity will be considered and if suitable, statistical heterogeneity across included studies will be assessed. If appropriate, the results will be combined in a meta-analysis.

Analysis of subgroups or subsets
If relevant, a subgroup analysis will be undertaken separating studies of the general population from those of specific subpopulations (e.g. people with a mental health condition).

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Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

28 April 2020

National Centre for Epidemiology
and Population Health

Australian
National
University

Electronic cigarettes and health outcomes: systematic review of global evidence

Report for the Australian Department of Health

Emily Banks, Amelia Yazidjoglou, Sinan Brown, Mai Nguyen, Melonie Martin,
Katie Beckwith, Amanda Daluwatta, Sai Campbell, Grace Joshy

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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

Emily Banks, Amelia Yazidjoglou, Sinan Brown, Mai Nguyen, Melonie Martin, Katie Beckwith, Amanda Daluwatta, Sai Campbell, Grace Joshy

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.

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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.

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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).

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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]

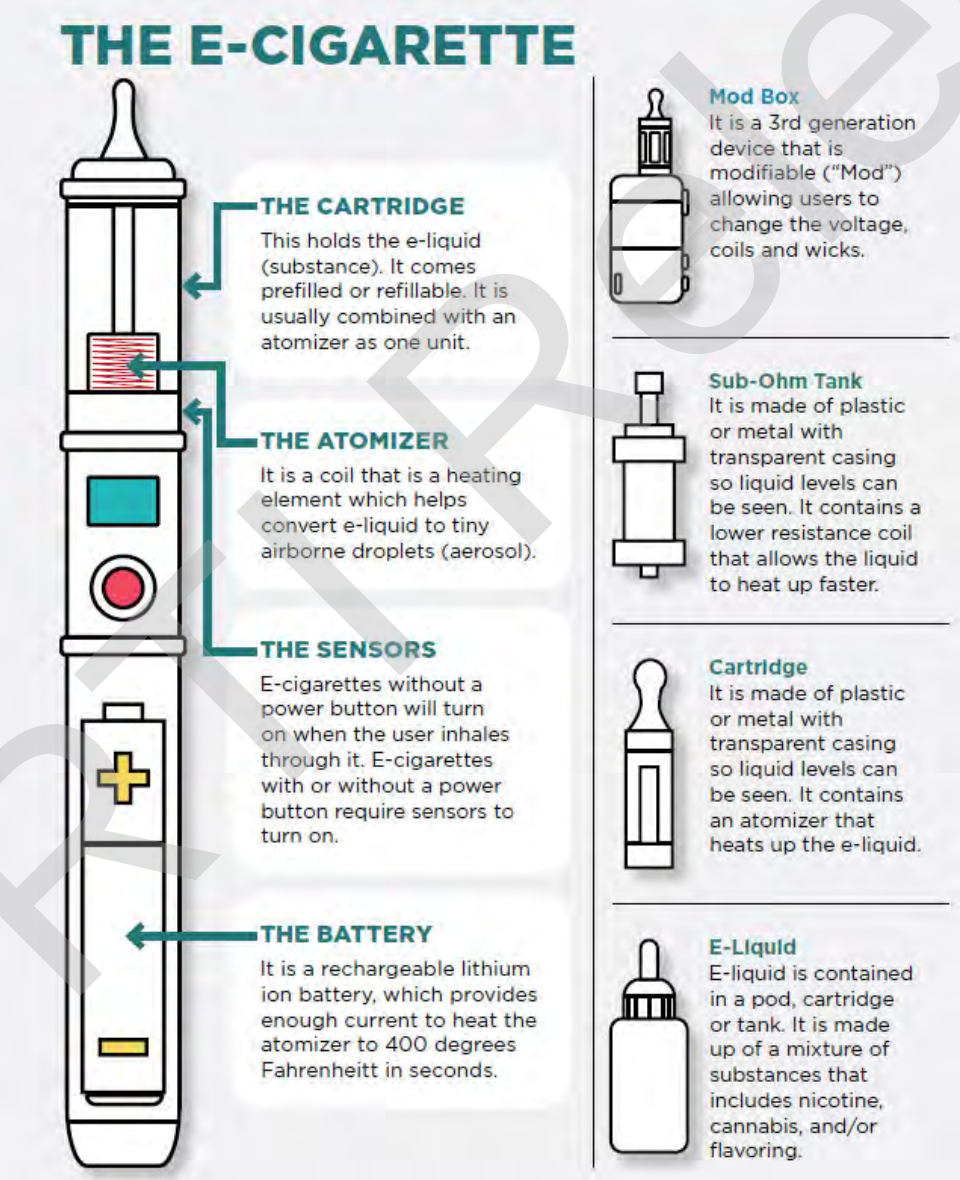
3.1.1 E-liquids

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:

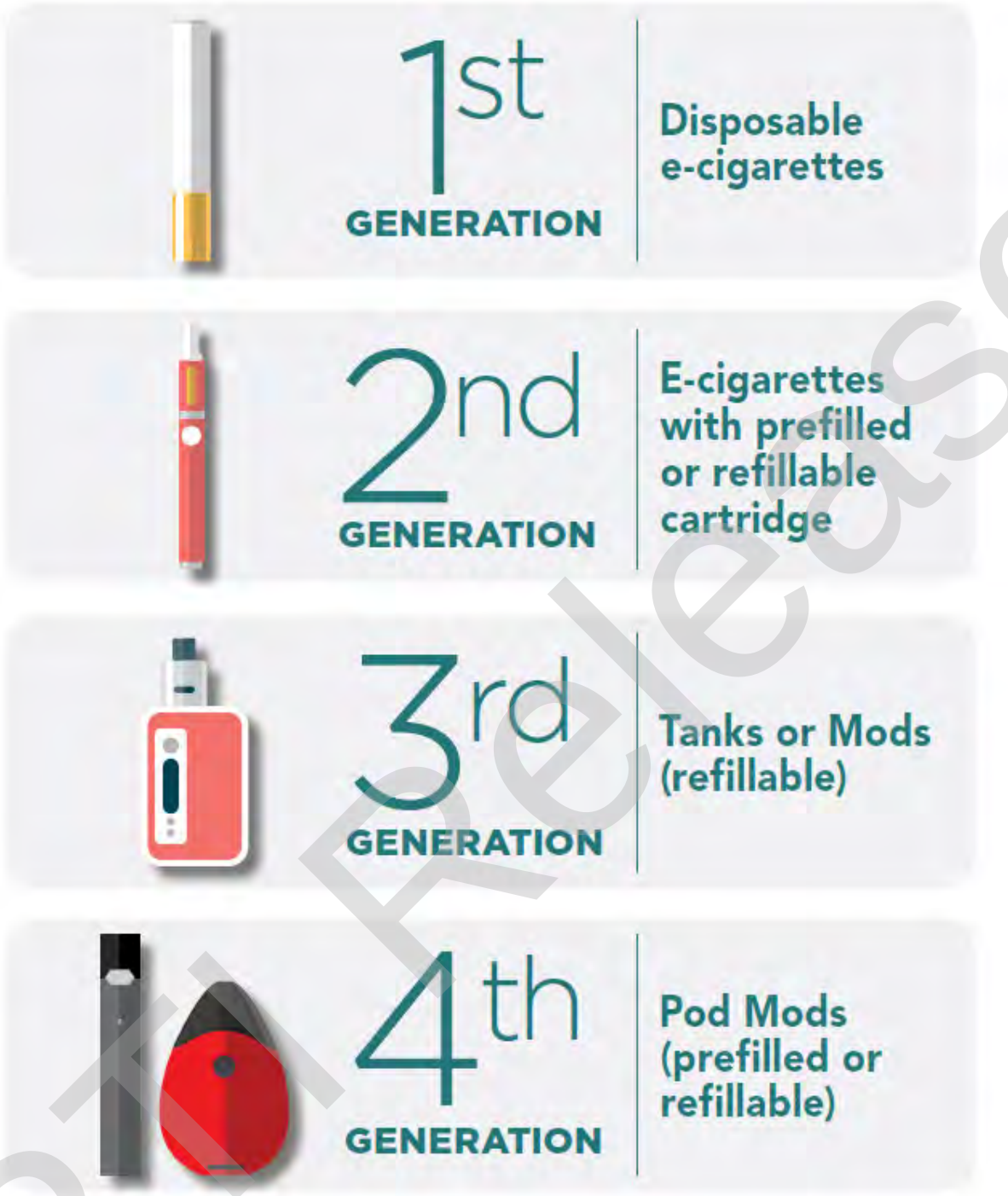
Cigalikes (first generation):
First generation e-cigarettes are designed to mimic the visual appearance and the smoking experience of combustible tobacco cigarettes. They are commonly referred to as "cigalikes" and come with fixed and low voltage batteries. They provide the least control over heating 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

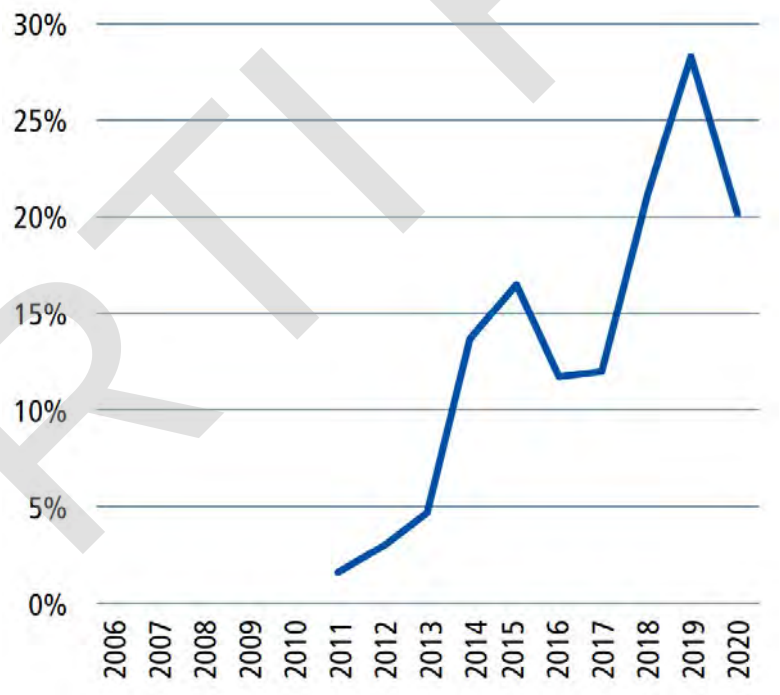
ever used e-cigarettes.[4,100] More than 20% of respondents reported ever having used e-cigarettes in Ireland (29%), Estonia (25%), France and the United Kingdom (both 22%), Luxembourg and Latvia (both 21%) and Belgium (20%); less than 10% reported such use in Poland (6%), Malta, Portugal and Romania (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]



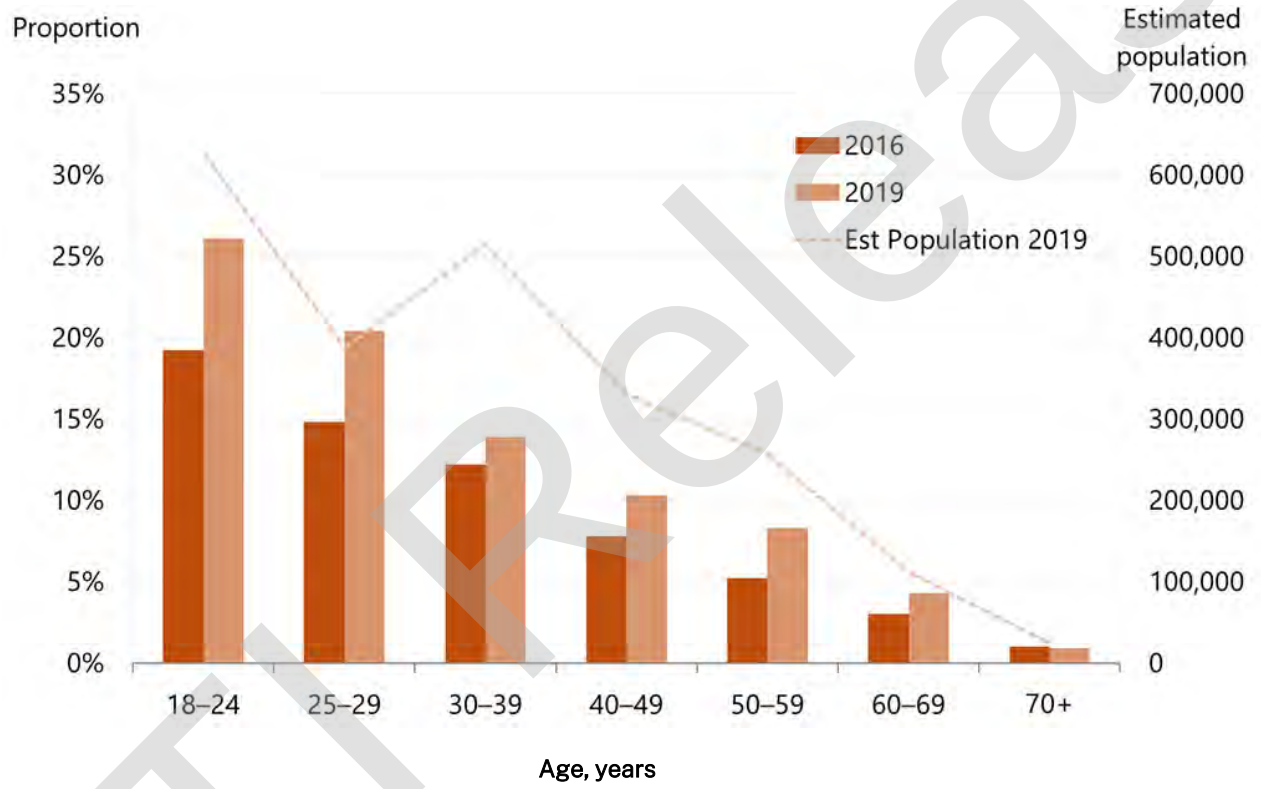
3.5.2 Prevalence and trends in use in Australia

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

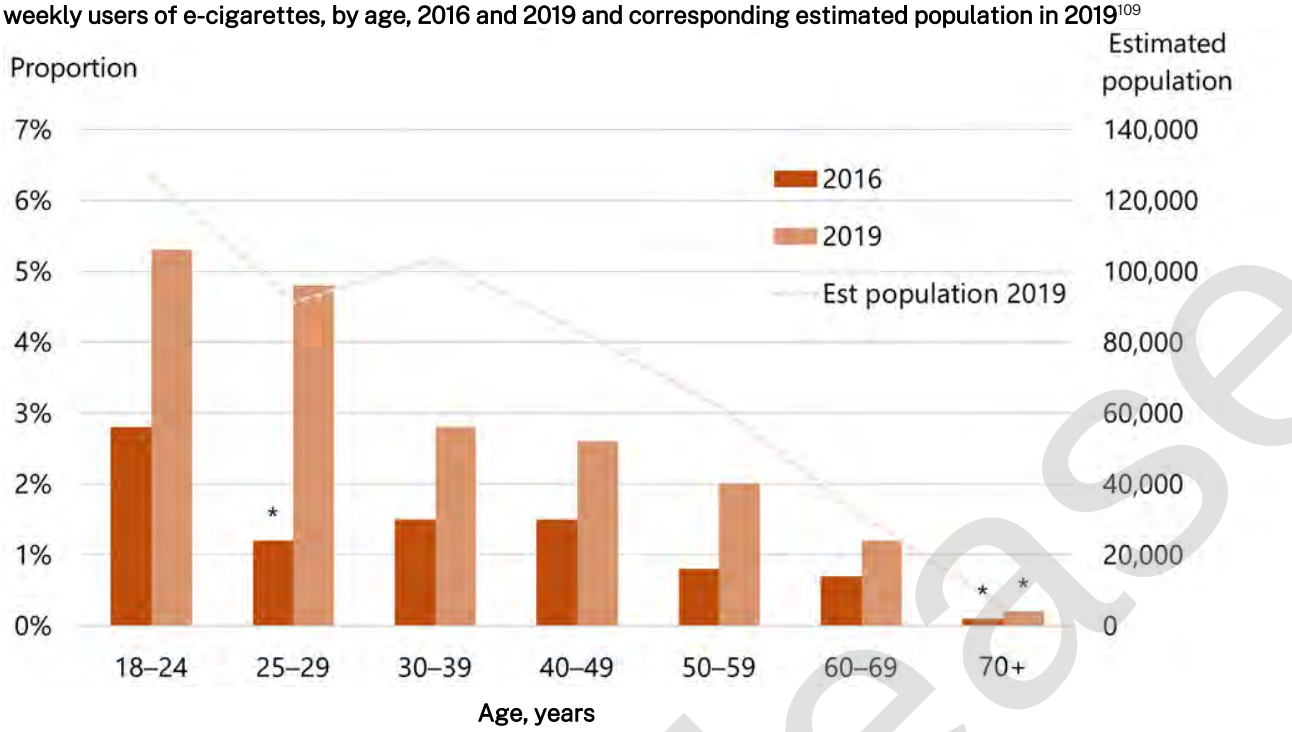
Data from the 2019 National Drug Strategy Household Survey (NDSHS) indicate that an estimated 11.3% of people aged 14 and over in Australia (approximately 2.4 million people) reported ever having used e-cigarettes, up from 8.8% in 2016 and 4.5% in 2013.[108] In 2019, around 60% of ever-users reported 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

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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) Conventional cigarette: Mean (SD) 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

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<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

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<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 rowspan="2"></th><th colspan="2">Drug Content Nicotine</th><th colspan="2">Instructional Set Told Nicotine</th><th rowspan="2">F (N)</th><th rowspan="2">F (I)</th><th rowspan="2">F (N X I)</th></tr>
<tr><th>Yes</th><th>No</th><th>Yes</th><th>No</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

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
Stiles et al., 2018[194] US Randomised, open-label, crossover trial Study date not reported	Study size 71 participants Sample 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) Gender (%) Male: 62 Female: 38 Age – mean (SD) years 34.3 (10.2)	Intervention 1 ENDS: 14mg, 29mg or 36mg, menthol flavour Intervention 2 Cigarettes (high-abuse liability) Comparator Nicotine gum (low abuse liability) Materials ENDS: Vuse Solo Cigarettes: own Nicorette White Ice Mint 4mg nicotine polacrilex gum Patter of exposure 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	Subjective effects (overall and maximum effect (E_{max}) – mean (95% CI)) Product liking Intent to use again Liking of positive effects Disliking of negative effects	Subjective effects - mean (95% CI) ENDS 14mg / 29mg / 36mg / Cigarette / Gum Product liking: 1521.63†§ (1314.14, 1729.12) / 1426.20†§ (1204.32, 1648.08) / 1256.89†§ (1035.52, 1478.27) / 3148.10 (2933.18, 3363.02) / 907.29 (692.69, 1121.89) E_{max}: 5.08†§ (4.46, 5.70) / 4.51† (3.86, 5.16) / 4.53† (3.86, 5.19) / 9.29 (8.65, 9.93) / 3.25 (2.61, 3.89) Intent to use again: 1489.01†§ (1346.90, 1631.12) / 1534.54†§ (1383.20, 1685.87) / 1412.88†§ (1261.88, 1563.89) / 2403.50 (2256.57, 2550.43) / 1143.37 (996.69 1290.05 E_{max}: 4.40†§ (3.99, 4.80) / 4.49†§ (4.06, 4.91) / 4.25† (3.82, 4.68) / 6.93 (6.52, 7.35) / 3.32 (3.82, 4.68) Liking of positive effects: 766.72† (475.9, 1057.54) / 1003.47† (709.08, 1297.87) / 704.70† (400.05, 1009.36) / 1388.31 (1102.92, 1673.70) / 842.96 (542.72, 1143.21) E_{max}: 6.45† (5.79, 7.11) / 6.44† (5.76, 7.12) / 6.74† (6.01, 7.47) / 8.63 (8.00, 9.27) / 6.02 (5.32, 6.72) Disliking of negative effects: 596.25 (297.04, 895.46) / 822.23 (512.69, 1131.77) / 491.65 (207.8, 775.51) / 787.93 (462.74, 1113.12) / 771.89 (498.84 1044.94 E_{max}: 5.16 (4.15, 6.17) / 6.16 (5.10, 7.21) / 5.17 (4.23, 6.11) / 6.06 (4.94, 7.17) / 6.24 (5.34, 7.13) † Significantly different from cigarettes; p<0.05 § Significantly different from gum; p<0.05	Moderate methodological quality Very small study size Conflicts of interest Authors full time employees of tobacco company subsidiary. Consultant services for pharmaceutical and tobacco companies Funding RJ Reynolds Vapor Company through its affiliate RJ Reynolds Tobacco Company

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

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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

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
Cohort studies					
Du et al., 2019[142] US Longitudinal cohort study Online e-cigarette survey 2012-2017	Study size 494 participants Exclusive EC: 412 Poly users: 59 Sample Exclusive EC: past 7-day use Poly users: EC and any other tobacco product Gender (%) EC Male: 67.5 Female: 32.5 Poly Male: 64.4 Female: 35.6 Mean age (SD) years EC: 41.2 (11.9) Poly: 36.5 (11.9)	Exposure EC: any nicotine concentration Comparator Within participants, baseline and follow-up Materials Own brand EC Follow-up 6 years Baseline: 2012-2014 Follow-up: 2017-2018	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	EC users Outcomes / Baseline / Follow-up / p PSECDI-mean (SD) 8.5 (3.4) 8.4 (3.8) 0.33 Times per day-mean (SD) 23.9 (24.7) 21.8 (23.9) 0.14 Time to first EC, mins-mean (SD) 44.5 (77.5) 41.7 (73.3) 0.54 Awaken to use EC – n (%) 29 (7.1) 39 (9.5) 0.10 Nights per week awaken to use E-mean (SD) 0.3 (1.2) 0.4 (1.3) 0.22 Hard quit EC – n (%) 133 (32.4) 83 (20.2) <0.0001 Craving to use EC – n (%) 176 (42.8) 182 (44.3) 0.60 Urge to use EC – n (%) 59 (14.3) 59 (14.3) 1.00 Hard to keep from using EC – n (%) 44 (10.7) 61 (14.8) 0.04 Irritable if can't use EC – n (%) 131 (31.8) 120 (29.1) 0.34 Anxious if can't use EC – n (%) 137 (33.3) 130 (31.6) 0.53 Poly users: EC and any tobacco product Outcomes / Baseline / Follow-up / p / P (EC vs. poly) PSECDI-mean (SD) 7.5 (3.8) 8.0 (3.9) 0.46 0.46 Times per day-mean (SD) 16.2 (14.6) 15.9 (22.9) 0.95 0.08 Time to first EC, mins-mean (SD) 64.9 (105.4) 59.0 (109.3) 0.75 0.12 Awaken to use EC – n (%) 6 (10.2) 9 (15.3) 0.32 0.17 Nights per week awaken to use EC- mean (SD) 0.5 (1.5) 0.5 (1.5) 0.84 0.43 Hard quit EC – n (%) 20 (33.9) 13 (22.0) 0.14 0.74	Low methodological quality Moderate study size Conflicts of interest Consultant fees and grants from pharmaceutical companies Funding Supported by the National Institute on Drug Abuse of NIH 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
			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

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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

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Hughes et al., 2020[190]

US

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

Study date not reported

Study size
30 participants enrolled, 18 used in analysis (compliant)

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

Gender – compliant (%)
Male: 61
Female: 39

Age (compliant)- mean (SD) years
22 (4)

Intervention
ENDS: nicotine concentration unknown

Comparator
Pre- and post

Materials
Own ENDS

Pattern of use
7 days continuous EC 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	p
Withdrawal - mean					
Overall	0.10	0.33	0.23 (0.28)	3.4	0.003
Angry	0.06	0.44	0.39 (0.53)	3.1	0.006
Anxious	0.14	0.42	0.28 (0.65)	1.8	0.09
Increased appetite	0.06	0.33	0.28 (0.71)	1.7	0.12
Difficulty concentrating	0.06	0.33	0.28 (0.52)	2.3	0.04
Depressed	0.14	0.25	0.11 (0.63)	0.7	0.47
Insomnia	0.14	0.25	0.11 (0.27)	1.7	0.10
Restlessness	0.14	0.31	0.17 (0.34)	2.1	0.05
EC craving - mean					
How much of time felt urge	1.44	2.08	0.64 (0.97)	2.8	0.01
How strong urge	1.47	2.19	0.72 (1.00)	3.1	0.007
Potential withdrawal - mean					
Impatient, impulsive	0.08	0.33	0.25 (0.39)	2.7	0.02
Enjoy pleasant events less	0.03	0.06	0.03 (0.27)	0.4	0.67
Less positive outlook	0.06	0.06	0.00 (0.17)	0.0	1.00
Mood swings	0.00	0.14	0.14 (0.29)	2.1	0.06
Control - mean					
Diarrhea	0.08	0.19	0.11 (0.61)	0.8	0.45
Headache	0.11	0.42	0.31 (0.82)	1.6	0.13
Tremors	0.00	0.03	0.03 (0.12)	1.0	0.33

*Based on paired t-test (17 df)

Symptoms interfered with functioning

Vaping	Abstinent
11%	33%

Moderate methodological quality

Very small study size

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

Funding
National Cancer Institute

Cobb et al., 2019[155]

US

Study size
20 participants

Sample

Intervention 1
ENDS: eGo device 36mg/mL nicotine

Drug Effects Scale (visual analogue scale)
"Do you feel a rush?"

Drug Effects Scale

	Condition (C) F	Condition (C) p	Bout (B) F	Bout (B) p	Time (T) F	Time (T) p
Rush	11.3	<.0001	0.5	0.464	36.1	<.0001

Moderate methodological quality

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>Non-randomised intervention study (7 Latin-square ordered conditions)

Study date not reported</td>
<td>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)

<u>Gender (%)</u>
Male: 50
Female: 50

<u>Age – mean (SD) years</u>
19.9 (1.1)</td>
<td>concentration, in one of three flavours

<u>Intervention 2</u>
ENNDS: eGo device 0mg/mL nicotine concentration, in one of three flavours

<u>Comparator</u>
Own brand (OB) cigarette

<u>Materials</u>
ENDS, ENNDS and own brand cigarette

<u>Pattern of use</u>
10-puff (30s interpuff interval) product administration at baseline (bout 1) and 60 minutes (bout 2)</td>
<td>“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?”

<u>Direct Effects of Nicotine Scale (DENS) (visual analogue scale)</u></td>
<td>
<table>
<tr><td>Like effects</td><td>5.8</td><td><.0001</td><td>0.0</td><td>0.885</td><td>16.3</td><td><.0001</td></tr>
<tr><td>Dislike effects</td><td>1.5</td><td>0.182</td><td>0.4</td><td>0.519</td><td>3.4</td><td>0.009</td></tr>
<tr><td>Feel good</td><td>9.5</td><td><.0001</td><td>0.1</td><td>0.809</td><td>20.2</td><td><.0001</td></tr>
<tr><td>Feel bad</td><td>3.5</td><td>0.002</td><td>0.2</td><td>0.621</td><td>3.6</td><td>0.006</td></tr>
</table>
<u>Drug Effects Scale (e-cigarette conditions only and bout 1)</u>
<table>
<tr><td></td><td colspan="2">Flavour (F)</td><td colspan="2">Nicotine (N)</td></tr>
<tr><td></td><td>F</td><td>p</td><td>F</td><td>p</td></tr>
<tr><td>Rush</td><td>4.66</td><td>0.010</td><td>35.21</td><td><.001</td></tr>
<tr><td>Like effects</td><td>2.34</td><td>0.097</td><td>16.07</td><td><.001</td></tr>
<tr><td>Dislike effects</td><td>2.06</td><td>0.128</td><td>2.46</td><td>0.117</td></tr>
<tr><td>Feel good</td><td>0.73</td><td>0.484</td><td>24.76</td><td><.001</td></tr>
<tr><td>Feel bad</td><td>3.86</td><td>0.022</td><td>8.15</td><td>0.004</td></tr>
</table>
<u>Direct Effects of Tobacco Scale</u>
<table>
<tr><td></td><td colspan="2">Condition (C)</td><td colspan="2">Bout (B)</td><td colspan="2">Time (T)</td></tr>
<tr><td></td><td>F</td><td>p</td><td>F</td><td>p</td><td>F</td><td>p</td></tr>
<tr><td>Satisfy</td><td>42.6</td><td><.0001</td><td>17.7</td><td><.0001</td><td>26.8</td><td><.0001</td></tr>
<tr><td>Pleasant</td><td>50.0</td><td><.0001</td><td>29.8</td><td><.0001</td><td>36.6</td><td><.0001</td></tr>
<tr><td>Taste good</td><td>27.2</td><td><.0001</td><td>24.1</td><td><.0001</td><td>36.6</td><td><.0001</td></tr>
<tr><td>Calm</td><td>12.0</td><td><.0001</td><td>1.3</td><td>0.261</td><td>22.0</td><td><.0001</td></tr>
<tr><td>Like to use another</td><td>5.3</td><td><.0001</td><td>0.1</td><td>0.742</td><td>5.0</td><td>0.001</td></tr>
</table>
<u>Direct Effects of Tobacco Scale (e-cigarette conditions only and bout 1)</u>
<table>
<tr><td></td><td colspan="2">Flavour (F)</td><td colspan="2">Nicotine (N)</td></tr>
<tr><td></td><td>F</td><td>p</td><td>F</td><td>p</td></tr>
<tr><td>Satisfy</td><td>4.46</td><td>0.012</td><td>0.08</td><td>0.773</td></tr>
<tr><td>Pleasant</td><td>2.69</td><td>0.069</td><td>49.72</td><td><.001</td></tr>
<tr><td>Taste good</td><td>16.32</td><td><.001</td><td>29.30</td><td><.001</td></tr>
<tr><td>Calm</td><td>0.23</td><td>0.796</td><td>18.82</td><td><.001</td></tr>
<tr><td>Like to use another</td><td>5.75</td><td>0.003</td><td>10.84</td><td>0.001</td></tr>
</table>
</td>
<td>Very small study size

<u>Conflicts of interest</u>
Paid consultant in litigation against the tobacco industry

<u>Funding</u>
Virginia Foundation for Healthy Youth, National Cancer Institute, National Institute on Drug Abuse, Center for Tobacco Products of the US FDA</td>
</tr>
</table>

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

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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

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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 / p / n^2_p; Time F / p / n^2_p MCP: 9.75 / <.001 / .30; 1.96 / *ns* / .08 Direct Effects of Product Use Calm: 14.86 / <.001 / .41; 11.43 / <.001 / .35 Pleasant: 34.26 / <.001 / .62; 4.59 / <.05 / .18 Satisfy: 44.20 / <.001 / .68; 2.54 / *ns* / .11 Taste good: 40.48 / <.001 / .66; 3.87 / <.05 / .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: Enjoyment of sensation 4.1 (1.5); Craving reduction 4.2 (1.7); Satisfaction 14.3 (4.3); Psychological reward 19.7 (7.6); Aversion 5.1 (3.3) Tobacco cigarette: Enjoyment of sensation 4.6 (1.6); Craving reduction 5.6 (1.7); Satisfaction 16.6 (3.3); Psychological reward 23.2 (6.7); Aversion 5.5 (2.9) p: Enjoyment of sensation 0.05; Craving reduction <0.001; Satisfaction 0.001; Psychological reward 0.006; Aversion 0.44 Subjective effects QSU – ENDS types (ENDS arm) QSU Factor 1 (p): Urge to smoke 0.035; Urge to vape Not reported QSU Factor 2 (p): Urge to smoke 0.009; Urge to vape 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 Condition: F / P; Time: F / P; Condition x Time: 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	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

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

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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

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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

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<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

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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

Jankowski et al., 2019[164]

Poland

YoUng People E-Smoking Study (YUPESS)

January-March 2019

Sample size
90 participants

Sample
Exclusive ENDS users, smokers and dual users

Gender - % female
39.8

Age – mean (SD) years
22.4 (2.2)

Exposure (n=30)
Exclusive e-cigarette users, duration of e-cigarette use was 29.0 ± 24.1 months

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

Comparator 2 (n=30)
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

Materials
Own brand EC

Fagerström Test for Nicotine Dependence (FTND)
Scored out of 10
1-2: low dependence
3-4: low/moderate dependence
5-7: moderate dependence
8+: high dependence

Aspects of cigarette and e-cigarette dependence based on FTND

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

Moderate methodological quality

Small sample size

Conflict of interest
None declared

Funding
Medical University Silesia

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

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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

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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) Want to quit / Quit attempt Dual user: 24.2 (10.0, 48.0) / 22.9 (9.1, 46.9) EC: 53.3 (37.6, 68.4) / 45.7 (30.2, 62.1) Symptoms of e-cigarette dependence - % (95% CI) Really need / ≤30 mins / Strong urge Dual user: 32.7 (16.9, 53.9) / 16.4 (7.3, 32.7) / 35.7 (18.3, 57.8) EC: 5.0 (2.2, 10.9) / 5.7 (2.5, 11.9) / 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) Find it difficult to concentrate / Feel irritable / Feel anxious Dual user: 19.2 (9.1, 36.0) / 29.0 (12.8, 53.1) / 15.4 (6.9, 30.9) EC: 1.6 (0.4, 5.7) / 4.7 (2.1, 10.3) / 2.8 (1.1, 7.4) E-cigarette-specific symptoms of nicotine dependence AOR (95% CI) EC: 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 — Mean (SD): 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

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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

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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

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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.