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

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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.

## 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,

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

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

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.

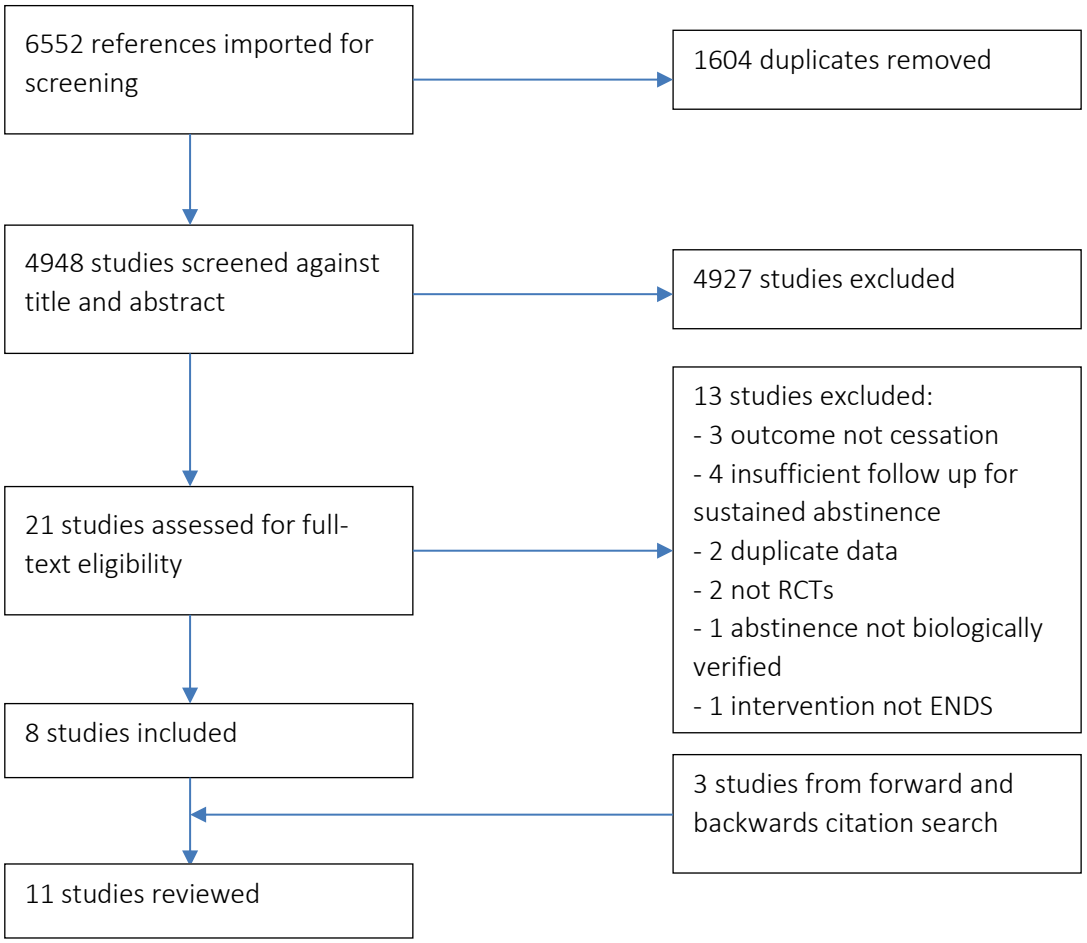
Furthermore, the Therapeutic Goods Administration of Australia can only provide approval for a product as a therapeutic tool if it has clear, unequivocal evidence that the product is beneficial, and that the balance of safety and efficacy is appropriate. It is upon the evidence of clinical trials that 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.



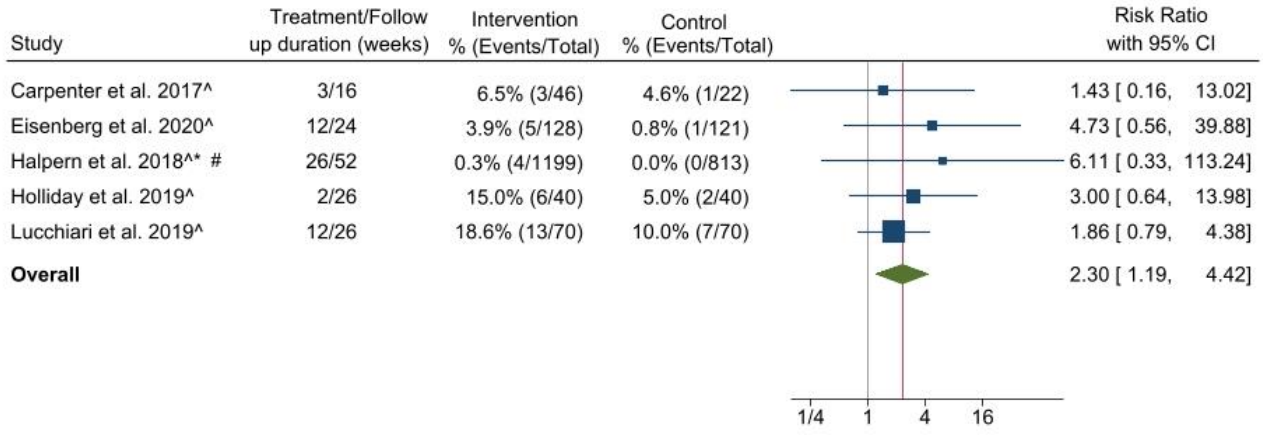
Experimental interventions included the use of ENDS and ENNDS. All ENDS were freebase products, according to the interventions listed in the study publications (Table 2) or according to the dates covered by the study intervention period, noting that nicotine salt products were introduced to European 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

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]

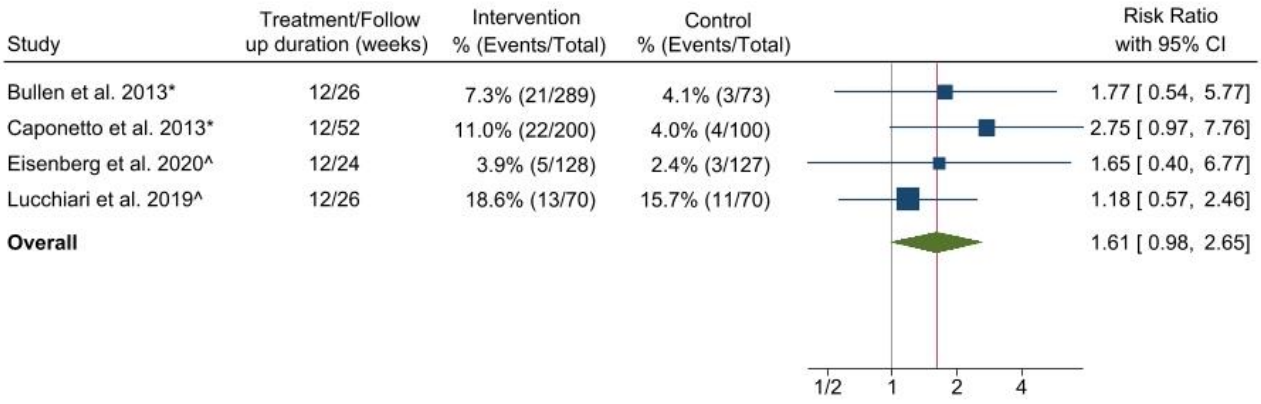
No individual study reported a significant difference in cessation outcomes between randomised groups. Results from the random-effects meta-analysis found a significant difference at four-to-12-month follow-up (RR 2.30; 95%CI 1.19-4.42; $I^2$ = 0.0%) (Figure 2) and at six-month follow-up (RR 2.40; 95% CI 1.21-4.78) (Figure

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).

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

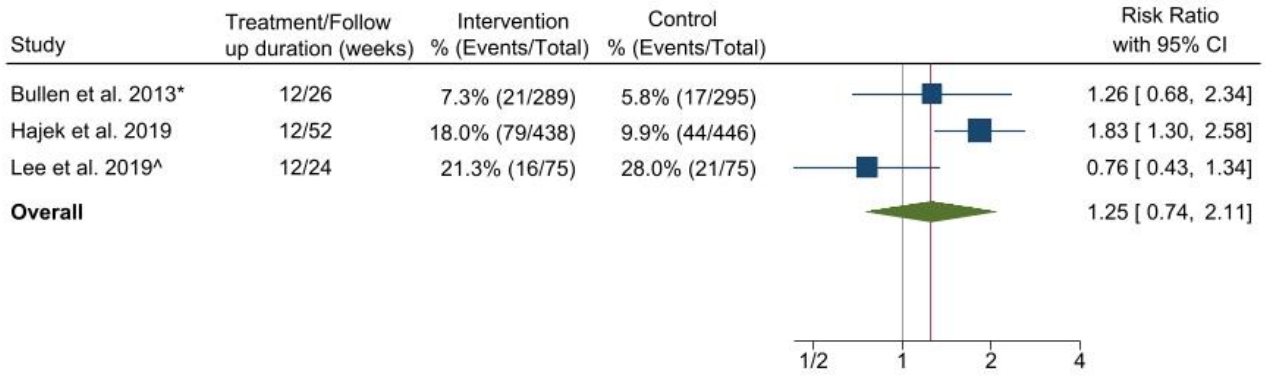
Three RCTs were identified that compared ENDS to approved NRT (Table 2 and Appendix 4).[23 49 50] The studies were conducted between 2013 and 2019. They included a total of 1,618 participants, all of whom were smokers motivated to quit and were randomised to 12-week treatment programs; 198 achieved smoking 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.



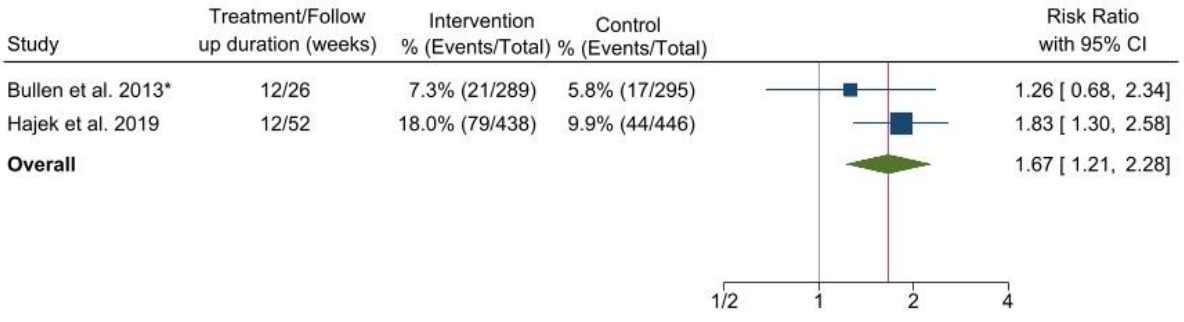

* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total events: 116/802 (14.5%) in intervention group, 82/816 (10.0%) in control group; absolute difference 44.1 more per 1,000 (25.1 less to 110.5 more)
Heterogeneity: 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

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



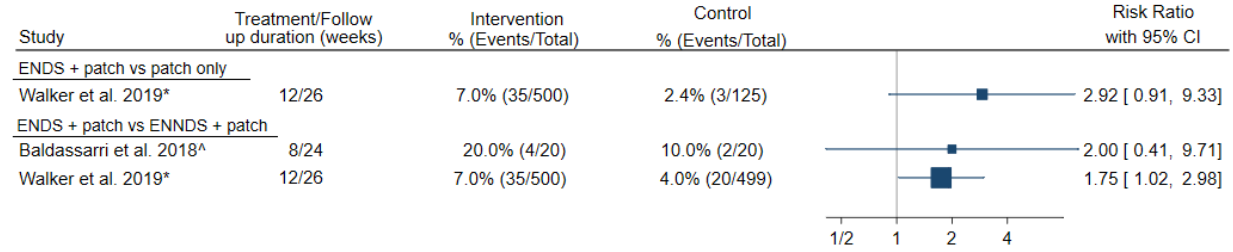

* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total events: 100/727 (13.8%) in intervention group, 61/741 (8.2%) in control group; absolute difference 55.2 more per 1,000 (17.3 more to 105.4 more)
Heterogeneity: Tau2=0.00; Chi2= 1.06, df=1, p = 0.30; I2 =5.48%; Test for overall effect: Z=3.17, p=0.00

### 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

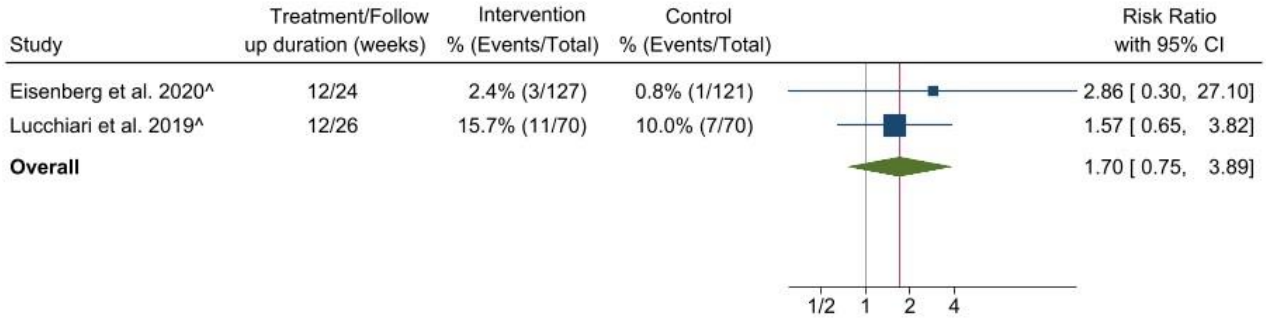
Two RCTs were identified that compared ENNDS plus counselling to counselling alone (Table 2 and Appendix 4).[45 47] The studies were conducted between 2019-2020 in Italy and in Canada. There was a total of 388 participants, all of whom received a 12-week treatment program and were followed for six months; 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]

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.

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.

### 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. |

| | |
|---|---|
| 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.<br><br>There is **moderate evidence** from randomised controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation.<br><br>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]

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.

- 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.

- 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

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

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]

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.

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

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

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

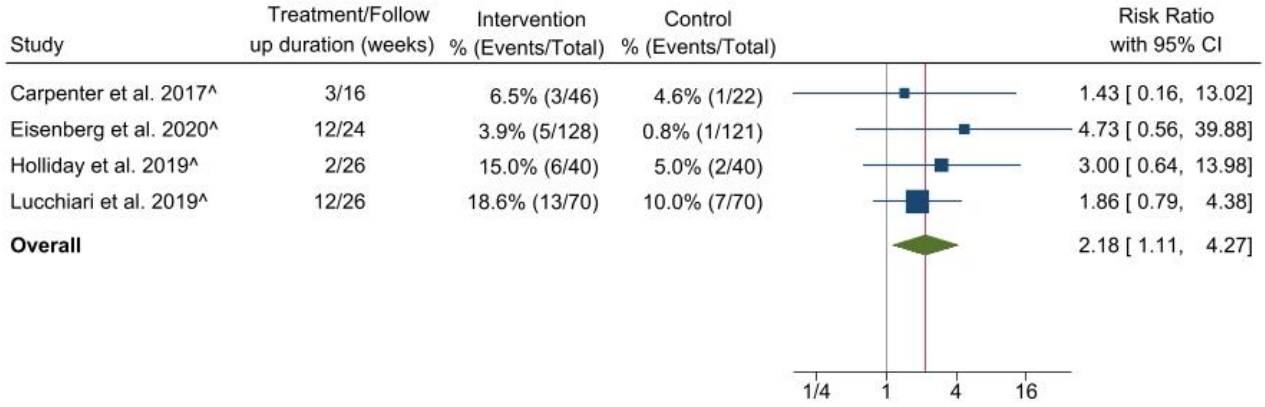
| Authors, year, country and participants | Duration (treatment and follow-up) | Experimental intervention (n= randomised participants) | Control intervention (n= randomised participants) | Participants not using any nicotine at follow-up: ENDS, NRT or conventional cigarettes | Participants using NRT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

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | to study clinic | | | | | | |
| Carpenter et al., 2017[53]<br><br>United States<br><br>Non-treatment seeking smokers from the community, recruited via media | Treatment<br>3 weeks, laboratory visits at 2, 3 and 4 weeks<br><br>Follow-up<br>Laboratory visits at 8, 12, and 16 weeks | Intervention 1 (n=25)<br>E-cigarette with 16 mg/mL nicotine<br><br>Intervention 2 (n=21)<br>E-cigarette with 24 mg/mL nicotine | No intervention (n=22) | Not stated | **ENDS use at week 16**<br>Intervention 1<br>32% (8/25)<br>Intervention 2<br>60% (13/21)<br>Control<br>13% (3/22) | Not stated | Not stated |
| Baldassarri et al. 2018[44]<br><br>United States<br><br>Motivated smoking patients from hospital outpatient pulmonary and primary care clinics, tobacco treatment service, and medical provider referrals | Treatment<br>8 weeks, laboratory visits at 2, 4, 6, and 8 weeks<br><br>Follow-up<br>Laboratory visit at 24 weeks | Intervention (n=20)<br>E-cigarettes with 8-week supply of 24 mg/mL nicotine containing e-liquid, nicotine patch and counselling | Control (n=20)<br>E-cigarette with 8-week supply of 0 mg/ml nicotine containing e-liquid, nicotine patch and counselling | ENNDS + patch: 5% (1/20)<br>ENDS + patch: 10% (2/20)<br><br>**Relative Risk (95% CI)****<br>ENDS + patch vs ENNDS + patch<br>2.00 (0.20-20.33) | Not stated | ENNDS + patch: 50% (1/2)<br>ENDS + patch: 50% (2/4)<br><br>**Relative Risk (95% CI)****<br>ENDS + patch vs ENNDS + patch<br>1.00 (0.18-5.46) | Not stated |
| Hajek et al., 2019[23]<br><br>United Kingdom<br><br>Adults attending UK National Health Service stop-smoking services | Treatment<br>12 weeks, trial visit at enrolment and week 4<br><br>Follow-up<br>52 weeks, phone call at 26 and | Intervention (n=438)<br>One 30mL bottle containing 18 mg/mL nicotine. Behavioural support including weekly one-on-one sessions with local clinicians | Nicotine-replacement (n=446)<br>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)<br>NRT: 8.97% (40/446)<br><br>**Relative Risk (95% CI)****<br>ENDS vs approved NRT<br>0.41 (0.23-0.72) | **Adherence at 52 weeks**<br>ENDS: 39.5% (173/438)<br>NRT: 4.3% (19/446)<br><br>**Relative Risk (95% CI)****<br>ENDS vs approved NRT<br>9.27 (5.88-14.61) | ENDS: 80% (63/79)<br>NRT: 9% (4/44)<br><br>**Relative Risk (95% CI)****<br>ENDS vs approved NRT<br>8.77 (3.42-22.48) | ENDS: 30.6% (110/359)<br>NRT: 3.7% (15/402)<br><br>**Relative Risk (95% CI)****<br>ENDS vs approved NRT<br>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]*<br><br>New Zealand<br><br>Smokers from the community who were motivated to quit, recruited through media | Treatment<br>12 weeks, 14-week supply delivered by courier<br><br>Follow-up<br>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)<br>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<br><br>Intervention 2 (n=499)<br>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)<br>21 mg, 24 h nicotine patch | Not stated | **Adherence at 6 months**<br>Control:<br>21/52 (40%)<br>Intervention 1<br>Both: 41/308 (13%)<br>ENNDS only: 111/308 (36%)<br>Patch only 88/308 (29%)<br>Intervention 2<br>Both: 36/317 (11%)<br>ENDS only: 143/317 (45%)<br>Patch only: 70/317 (22%)<br><br>**Relative Risk (95% CI)****<br>Patch + ENDS vs Patch only<br>1.53 (1.05-2.22)<br>Patch + ENNDS vs Patch only<br>1.52 (1.05-2.21)<br>Patch + ENDS vs Patch + ENNDS<br>1.00 (0.88-1.15) | Not stated | Not stated |

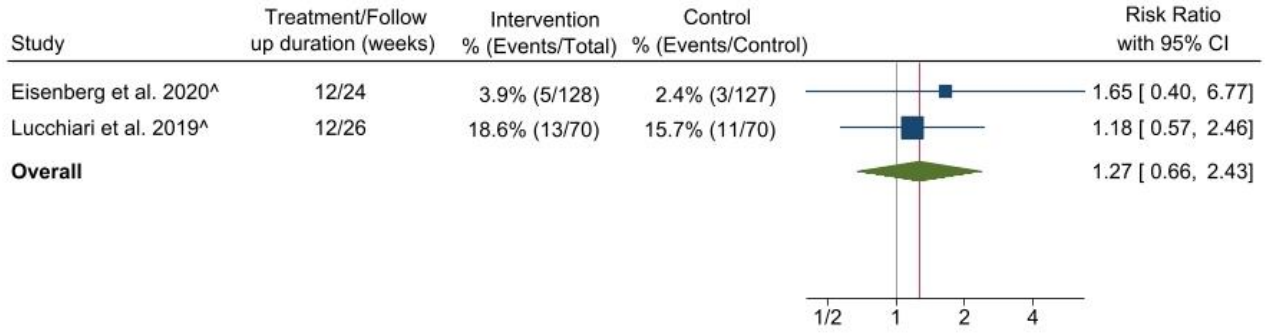
* Potential competing interest noted for study author(s)

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.



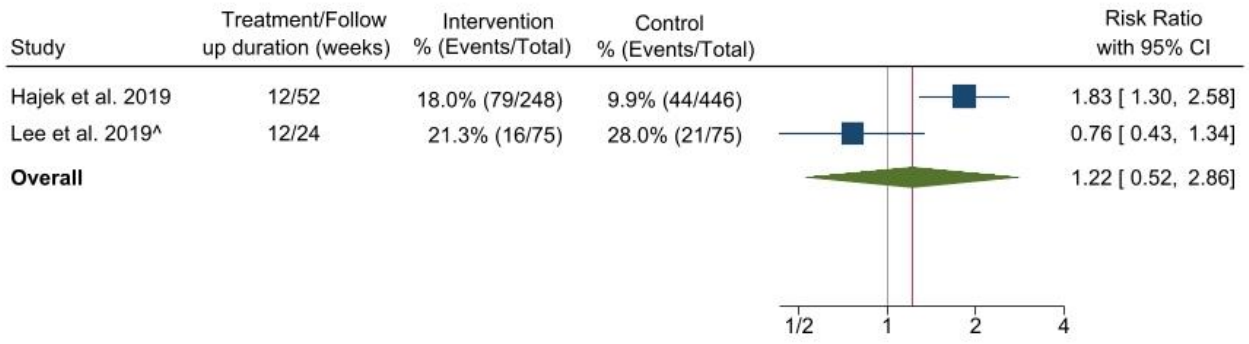

^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 27/284 in intervention group, 11/253 in control group
Heterogeneity: Tau2=0.00; Chi2= 0.94, df=3, p = 0.81; I2 =0.0%; Test for overall effect: Z=2.27, p=0.02

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.



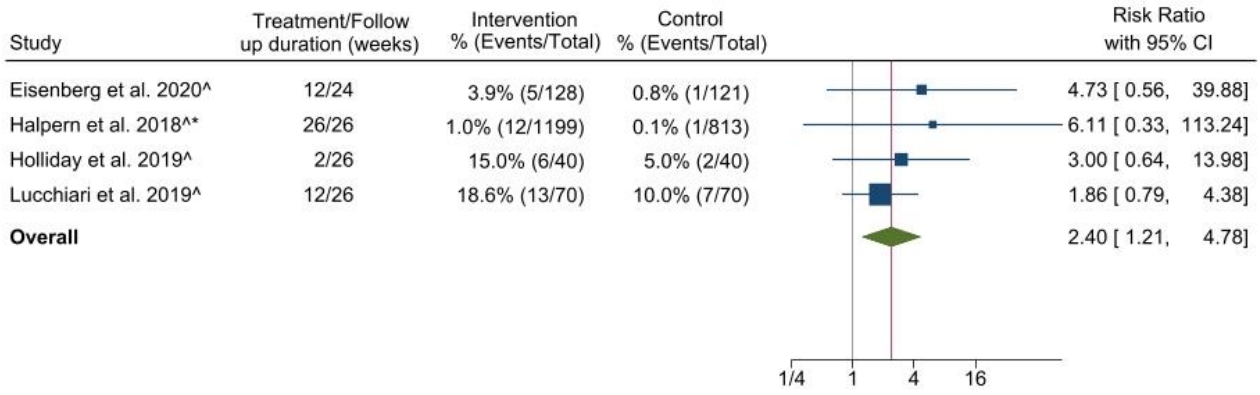

^ RRs are calculated from number of events or percentages reported in the published study
Total events: 18/198 in intervention group, 14/197 in control group
Heterogeneity: Tau2=0.00; Chi2= 0.17, df=1, p = 0.68; I2 =0.00%; Test for overall effect: Z=0.72, p=0.47

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.



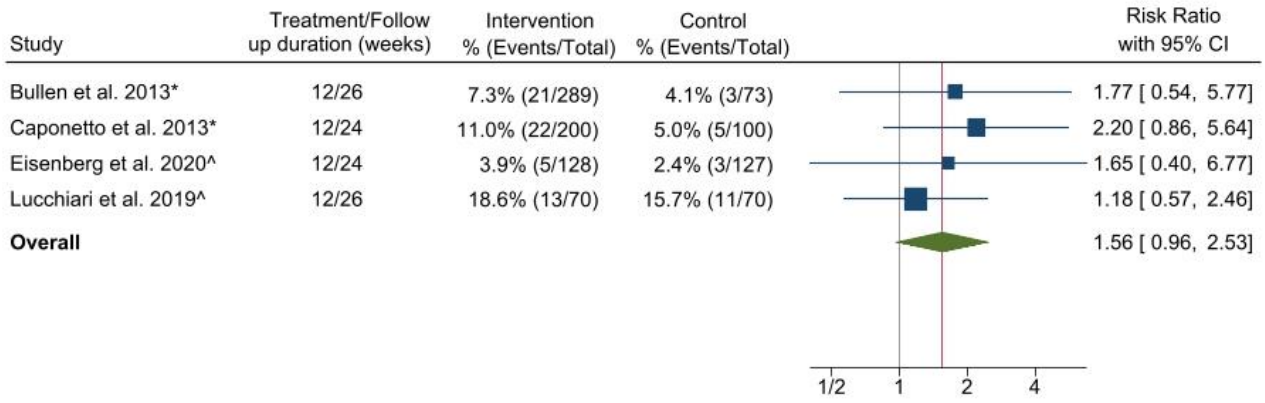

^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 95/513 in intervention group, 65/521 in control group
Heterogeneity: Tau2=0.00; Chi2= 6.70, df=1, p = 0.01; I2 =85.1%; Test for overall effect: Z=0.45, p=0.65

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



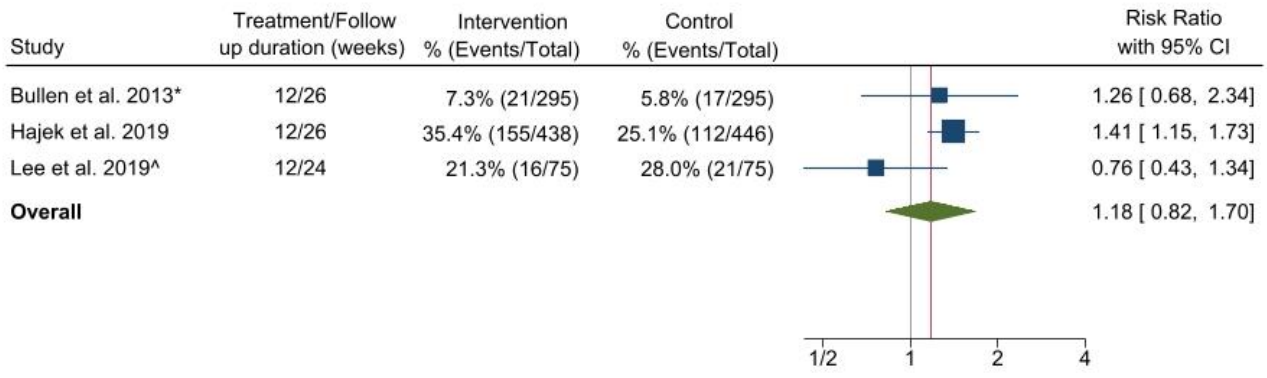

* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 61/687 in intervention group, 22/370 in control group
Heterogeneity: Tau2=0.00; Chi2= 1.12, df=3, p = 0.77; I2 =0.00%; Test for overall effect: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



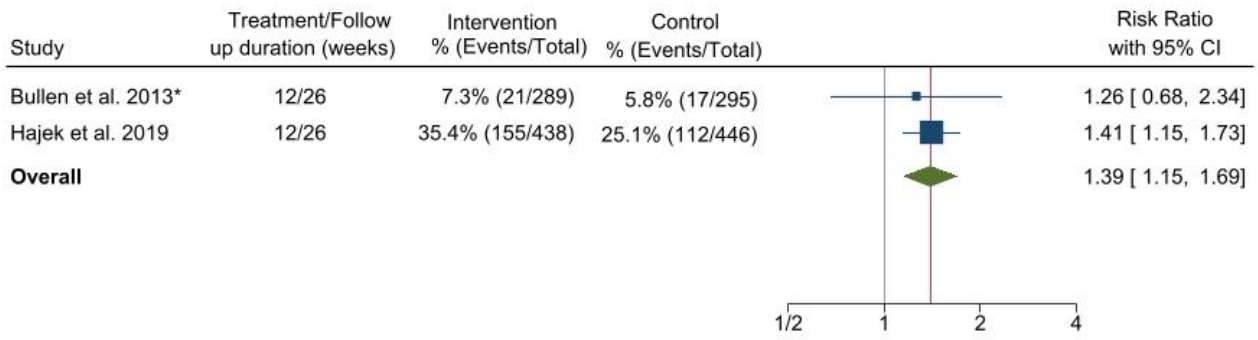

* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 20/1315 in intervention group, 8/905 in control group
Heterogeneity: Tau2=0.00; Chi2= 1.11, df=2, p = 0.57; I2 =0.0%; Test for overall effect: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

2. Smokers.mp
3. Ex-Smokers.mp
4. Ex-Smokers.mp
5. Smokers.mh
6. Ex-smokers.mh
7. 1 or 2 or 3 or 4 or 5 or 6
8. E-cigarette.mp
9. E-cigarettes.mp
10. “electronic cigarette”.mp
11. “electronic cigarettes”.mp
12. “electronic nicotine de*”.mp
13. “electronic nicotine delivery system”.mp
14. Vape.mp
15. Vaping.mp
16. Vapo*.mp
17. E-liquid.mp
18. E-hookah.mp
19. “Electronic inhalant device”.mp
20. “Electronic nicotine delivery systems”.mh
21. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. “Smoking cessation”.mp
23. Cessation.mp
24. Quit.mp
25. Abstinence.mp
26. “Smoking cessation”.mh
27. “Tobacco use cessation devices”.mh
28. “Smoking cessation agents”.mh
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 7 and 21 and 29
31. Limit 30 to “0300 clinical trial”

Results: 13

PubMed search terms:

1. ((("smoking cessation" OR Cessation OR quit OR Abstinence OR "smoking cessation" [MeSH Terms] OR "tobacco use cessation devices"[MeSH Terms] OR "smoking cessation agents"[MeSH Terms]) AND (E-cigarette OR E-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*"

OR "Electronic nicotine delivery system" OR Vape OR Vaping OR E-liquid OR Vapo* OR E-hookah OR "Electronic inhalant device" OR "Electronic nicotine delivery systems"[MeSH Terms]) AND (Smoker OR Smokers OR Ex-smoker OR Ex smokers OR Smokers[MeSH Terms] OR Exsmokers[MeSH Terms]))) AND Randomized Controlled Trial[ptyp]

Results: 87

Scopus search terms:

1. TITLE-ABS-KEY (("smoking cessation" OR Cessation OR quit OR Abstinence OR "tobacco use cessation devices" OR "smoking cessation agents") AND (E-cigarette OR E-cigarettes OR "Electronic cigarette" OR "Electronic cigarettes" OR "Electronic nicotine de*" OR "Electronic nicotine delivery system" OR Vape OR Vaping OR E-liquid OR Vapo* OR E-hookah OR "Electronic inhalant device") AND (Smoker OR Smokers OR Ex-smoker OR Ex-smokers) AND (LIMIT-TO (DOCTYPE, “ar”)))

Results: 3,759

Web of Science search terms:

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

## 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<br>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<br>Any other treatments or aids intended to assist with cessation. |
| Outcome: | Primary or secondary outcome variable is combustible tobacco smoking cessation.<br>RCT contains outcome data on cessation of nicotine exposure in any form and cessation of non-nicotine containing e-cigarettes.<br>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?

## 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<br>*OR*<br>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 |

## 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]<br><br>New Zealand<br><br>Adults from the general community intending to quit, responding to media invitation | Single blinding | Adult smokers in New Zealand | Intervention 1 (n=289)<br>Electronic nicotine delivery system (ENDS), 16 mg nicotine from 1 week before until 12 weeks after quit day<br><br>Intervention 2 (n=73)<br>Electronic non-nicotine delivery system (ENNDS) from 1 week before until 12 weeks after quit day | Nicotine patches (n=295)<br>21 mg nicotine patch, one daily accessed via exchanging a voucher received in mail for patches at a community pharmacy | Yes | Intervention 1<br>289/241<br><br>Intervention 2<br>73/57<br><br>Control<br>295/215<br><br>Total<br>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]*<br><br>Italy<br><br>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)<br>E-cigarette loaded with 7.2 mg for 12 weeks<br><br>Group B (n=100)<br>E-cigarette with 7.2 mg nicotine cartridge for 6 weeks and 5.4 mg nicotine cartridges for 6 weeks | Group C (n=100)<br>E-cigarettes with 12-week supply of non-nicotine cartridges | No | Intervention<br>Group A: 100/65<br>Group B: 100/63<br><br>Control<br>Group C=100/55<br><br>Total<br>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]<br><br>United States<br><br>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)<br>E-cigarette with 16 mg/mL nicotine<br><br>Intervention 2 (n=21)<br>E-cigarette with 24 mg/mL nicotine | No intervention (n=22) | Mixed | Intervention 1<br>25/19<br><br>Intervention 2<br>21/15<br><br>Control<br>22/16<br><br>Total<br>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]<br><br>United States<br><br>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)<br>E-cigarettes with 8-week supply of 24 mg/mL nicotine containing e-liquid, nicotine patch and counselling | Control (n=20)<br>E-cigarette with 8-week supply of 0 mg/mL nicotine containing e-liquid, nicotine patch and counselling | Yes | Intervention<br>20/unknown<br><br>Control<br>20/unknown<br><br>Total<br>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]<br><br>United States<br><br>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)<br>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)<br>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<br>1199/253<br><br>Control<br>813/129<br><br>Total<br>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]<br><br>United Kingdom<br><br>Adults attending UK National Health Service stop-smoking services | Single blinding | Adult smokers from London | Intervention (n=438)<br>One 30mL bottle containing 18 mg/mL nicotine. Behavioural support including weekly one-on-one sessions with local clinicians | Nicotine-replacement (n=446)<br>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<br>438/356<br><br>Control<br>446/342<br><br>Total<br>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]<br><br>United Kingdom<br><br>Adult smokers with periodontitis attending the Newcastle Dental Hospital or primary care practitioners in North England | None | | Intervention (n=40)<br>ENDS, choice of nicotine concentration (0 mg/mL, 6 mg/mL, 12 mg/mL and 18 mg/mL) and behavioural counselling.<br><br>No participants selected a nicotine concentration of 0 mg/mL | Control (n=40)<br>Counselling only | Not stated | Intervention<br>40/29<br><br>Control<br>40/29<br><br>Total<br>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]<br><br>Korea<br><br>Korean males from a motor company intending to quit | Single blinding | Male adult smokers employed at a motor company in Korea | Intervention (n=75)<br>E-cigarette containing 0.01 mg/mL nicotine for 12 weeks | Nicotine gum (n=75)<br>12-week supply of nicotine gum | Yes | Intervention<br>75/71 at 24 weeks<br><br>Control<br>75/61 at 24 weeks<br><br>Total<br>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]<br><br>Italy<br><br>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)<br>e-cigarette with 12 10mL liquid cartridges (8 mg/mL nicotine), telephone counselling<br><br>Intervention 2 (n=70)<br>e-cigarette with 12 10mL nicotine-free liquid cartridges, telephone counselling | Usual care (n=70)<br>Antismoking telephone counselling including phone interviews at weeks 1, 4, 8, and 12 | Yes | Intervention 1<br>70/52<br><br>Intervention 2<br>70/51<br><br>Control<br>70/52<br><br>Total<br>210/155 | Supported by Fondazione Umberto Veronesi (FUV). | No |
| Walker et al., 2019[48]<br><br>New Zealand<br><br>Smokers from the community who were motivated to quit, recruited through media | Double blinding | Adult smokers in New Zealand | Intervention 1 (n=500)<br>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<br><br>Intervention 2 (n=499)<br>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)<br>21 mg, 24 h nicotine patch | Yes | Intervention 1<br>499/337<br><br>Intervention 2<br>500/339<br><br>Control<br>125/63<br><br>Total<br>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]<br><br>Canada<br><br>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)<br>ENDS, 15 mg/mL nicotine, and behavioural counselling<br><br>Intervention 2 (n= 127)<br>ENNDS, 0 mg/mL nicotine, and behavioural counselling | Control (n=121)<br>Counselling only | Yes | Intervention 1<br>128/112<br><br>Intervention 2<br>127/109<br><br>Control<br>121/85<br><br>Total<br>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)

## 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