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Electronic cigarettes for smoking cessation (Review)

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Electronic cigarettes for smoking cessation (Review)

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[Intervention Review]

Electronic cigarettes for smoking cessation

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ABSTRACT

Background

Electronic cigarettes (ECs) are handheld electronic vaping devices which produce an aerosol formed by heating an e-liquid. People who smoke report using ECs to stop or reduce smoking, but some organisations, advocacy groups and policymakers have discouraged this, citing lack of evidence of efficacy and safety. People who smoke, healthcare providers and regulators want to know if ECs can help people quit and if they are safe to use for this purpose. This review is an update of a review first published in 2014.

Objectives

To evaluate the effect and safety of using electronic cigarettes (ECs) to help people who smoke achieve long-term smoking abstinence.

Search methods

We searched the Cochrane Tobacco Addiction Group's Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and PsycINFO for relevant records to January 2020, together with reference-checking and contact with study authors.

Selection criteria

We included randomized controlled trials (RCTs) and randomized cross-over trials in which people who smoke were randomized to an EC or control condition. We also included uncontrolled intervention studies in which all participants received an EC intervention. To be included, studies had to report abstinence from cigarettes at six months or longer and/or data on adverse events (AEs) or other markers of safety at one week or longer.

Data collection and analysis

We followed standard Cochrane methods for screening and data extraction. Our primary outcome measures were abstinence from smoking after at least six months follow-up, AEs, and serious adverse events (SAEs). Secondary outcomes included changes in carbon monoxide, blood pressure, heart rate, blood oxygen saturation, lung function, and levels of known carcinogens/toxicants. We used a fixed-effect Mantel-Haenszel model to calculate the risk ratio (RR) with a 95% confidence interval (CI) for dichotomous outcomes. For continuous outcomes, we calculated mean differences. Where appropriate, we pooled data from these studies in meta-analyses.

Main results

We include 50 completed studies, representing 12,430 participants, of which 26 are RCTs. Thirty-five of the 50 included studies are new to this review update. Of the included studies, we rated four (all which contribute to our main comparisons) at low risk of bias overall, 37 at high risk overall (including the 24 non-randomized studies), and the remainder at unclear risk.

There was moderate-certainty evidence, limited by imprecision, that quit rates were higher in people randomized to nicotine EC than in those randomized to nicotine replacement therapy (NRT) (risk ratio (RR) 1.69, 95% confidence interval (CI) 1.25 to 2.27; $I^2 = 0\%$; 3 studies, 1498 participants). In absolute terms, this might translate to an additional four successful quitters per 100 (95% CI 2 to 8). There was low-certainty evidence (limited by very serious imprecision) of no difference in the rate of adverse events (AEs) (RR 0.98, 95% CI 0.80 to 1.19; $I^2 = 0\%$; 2 studies, 485 participants). SAEs occurred rarely, with no evidence that their frequency differed between nicotine EC and NRT, but very serious imprecision led to low certainty in this finding (RR 1.37, 95% CI 0.77 to 2.41; $I^2 = n/a$; 2 studies, 727 participants).

There was moderate-certainty evidence, again limited by imprecision, that quit rates were higher in people randomized to nicotine EC than to non-nicotine EC (RR 1.71, 95% CI 1.00 to 2.92; $I^2 = 0\%$; 3 studies, 802 participants). In absolute terms, this might again lead to an additional four successful quitters per 100 (95% CI 0 to 12). These trials used EC with relatively low nicotine delivery. There was low-certainty evidence, limited by very serious imprecision, that there was no difference in the rate of AEs between these groups (RR 1.00, 95% CI 0.73 to 1.36; $I^2 = 0\%$; 2 studies, 346 participants). There was insufficient evidence to determine whether rates of SAEs differed between groups, due to very serious imprecision (RR 0.25, 95% CI 0.03 to 2.19; $I^2 = n/a$; 4 studies, 494 participants).

Compared to behavioural support only/no support, quit rates were higher for participants randomized to nicotine EC (RR 2.50, 95% CI 1.24 to 5.04; $I^2 = 0\%$; 4 studies, 2312 participants). In absolute terms this represents an increase of six per 100 (95% CI 1 to 14). However, this finding was very low-certainty, due to issues with imprecision and risk of bias. There was no evidence that the rate of SAEs varied, but some evidence that non-serious AEs were more common in people randomized to nicotine EC (AEs: RR 1.17, 95% CI 1.04 to 1.31; $I^2 = 28\%$; 3 studies, 516 participants; SAEs: RR 1.33, 95% CI 0.25 to 6.96; $I^2 = 17\%$; 5 studies, 842 participants).

Data from non-randomized studies were consistent with RCT data. The most commonly reported AEs were throat/mouth irritation, headache, cough, and nausea, which tended to dissipate over time with continued use. Very few studies reported data on other outcomes or comparisons and hence evidence for these is limited, with confidence intervals often encompassing clinically significant harm and benefit.

Authors' conclusions

There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain. More studies are needed to confirm the degree of effect, particularly when using modern EC products. Confidence intervals were wide for data on AEs, SAEs and other safety markers. Overall incidence of SAEs was low across all study arms. We did not detect any clear evidence of harm from nicotine EC, but longest follow-up was two years and the overall number of studies was small.

The main limitation of the evidence base remains imprecision due to the small number of RCTs, often with low event rates. Further RCTs are underway. To ensure the review continues to provide up-to-date information for decision-makers, this review is now a living systematic review. We will run searches monthly from December 2020, with the review updated as relevant new evidence becomes available. Please refer to the *Cochrane Database of Systematic Reviews* for the review's current status.

PLAIN LANGUAGE SUMMARY

Can electronic cigarettes help people stop smoking, and do they have any unwanted effects when used for this purpose?

What are electronic cigarettes?

Electronic cigarettes (e-cigarettes) are handheld devices that work by heating a liquid that usually contains nicotine and flavourings. E-cigarettes allow you to inhale nicotine in a vapour rather than smoke. Because they do not burn tobacco, ECs do not expose users to the same levels of toxins that we know can cause smoking-related diseases in people who use conventional cigarettes.

Using an e-cigarette is known as 'vaping'. Many people use e-cigarettes to help them to stop smoking tobacco.

Why we did this Cochrane Review

Stopping smoking lowers your risk of getting lung cancer and other diseases. But many people find it difficult to quit. We wanted to find out if using e-cigarettes could help people to stop smoking, and if people using them for this purpose experienced any unwanted effects.

What did we do?

We searched for studies that looked at the use of e-cigarettes to help people stop smoking.

We looked for randomized controlled trials, in which the treatments people received were decided at random. This type of study usually gives the most reliable evidence about the effects of a treatment. We also looked for studies in which everyone received an e-cigarette treatment.

We were interested in finding out:

- how many people stopped smoking for at least six months; and
- how many people had any unwanted effects.

We included studies that reported on smoking habits for at least six months, or reported on unwanted effects for at least one week.

Search date: We included evidence published up to January 2020.

What we found

We found 50 studies in 12,430 adults who smoked. The studies compared e-cigarettes with:

- nicotine replacement therapy, such as patches or gum;
- varenicline;
- nicotine-free e-cigarettes;
- behavioural support, such as advice or counselling; or
- no support, for stopping smoking.

Some studies also tested using NRT and e-cigarettes together.

The studies took place in the USA (21 studies), the UK (9), Italy (7), Australia (2), New Zealand (2), Greece (2), and one study each in Belgium, Canada, Poland, South Korea, South Africa, Switzerland and Turkey.

What are the results of our review?

More people probably stop smoking for at least six months using nicotine e-cigarettes than using nicotine replacement therapy (3 studies; 1498 people), or nicotine-free e-cigarettes (3 studies; 802 people).

Nicotine e-cigarettes may help more people to stop smoking than no support or behavioural support only (4 studies; 2312 people).

For every 100 people using nicotine e-cigarettes to stop smoking, 10 might successfully stop, compared with only six of 100 people using nicotine-replacement therapy or nicotine-free e-cigarettes, or four of 100 people having no support or behavioural support only.

We are uncertain if there is a difference between how many unwanted effects occur using nicotine e-cigarettes compared with using nicotine-free e-cigarettes, nicotine replacement therapy, no support or behavioural support only. Similar low numbers of unwanted effects, including serious unwanted effects, were reported for all groups.

The unwanted effects reported most often with nicotine e-cigarettes were throat or mouth irritation, headache, cough and feeling sick. These effects reduced over time as people continued using nicotine e-cigarettes.

How reliable are these results?

Our results are based on a small number of studies, and in some the measured data varied widely.

We are moderately confident that nicotine e-cigarettes help more people to stop smoking than nicotine replacement therapy or nicotine-free e-cigarettes. However, these results might change if further evidence becomes available.

We are less confident about how nicotine e-cigarettes compare with no support, or behavioural support, to stop smoking.

Our results for the unwanted effects are likely to change when more evidence becomes available.

Key messages

Nicotine e-cigarettes probably do help people to stop smoking for at least six months. They probably work better than nicotine replacement therapy and nicotine-free e-cigarettes.

They may work better than no support, or behavioural support alone, and they may not be associated with serious unwanted effects.

However, we need more, reliable evidence to be confident about the effects of e-cigarettes, particularly the effects of newer types of e-cigarettes that have better nicotine delivery.

SUMMARY OF FINDINGS

Summary of findings 1. Nicotine EC compared to NRT for smoking cessation

Nicotine EC compared to NRT for smoking cessation

Patient or population: People who smoke
Setting: New Zealand, UK, USA
Intervention: Nicotine EC
Comparison: NRT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NRT	Risk with Nicotine EC				
Smoking cessation at 6 months to 1 year	Study population		RR 1.69 (1.25 to 2.27)	1498 (3 RCTs)	⊕⊕⊕○ MODERATE ^a	-
Assessed with biochemical validation	6 per 100	10 per 100 (8 to 14)				
Adverse events at 4 weeks to 6 months	Study population		RR 0.98 (0.80 to 1.19)	485 (2 RCTs)	⊕⊕○○ LOW ^b	-
Assessed by self-report	45 per 100	44 per 100 (36 to 53)				
Serious adverse events at 4 weeks to 1 year	Study population		RR 1.37 (0.77 to 2.41)	727 (2 RCTs)	⊕⊕○○ LOW ^b	-
Assessed via self-report and medical records	5 per 100	7 per 100 (4 to 13)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). For cessation, the assumed risk in the control group is based on assumed quit rates for NRT assuming receipt of limited behavioural stop-smoking support (as per [Hartmann-Boyce 2018a](#)). The assumed risk for adverse events and serious adverse events is a weighted mean average of quit rates across control groups in contributing studies.

CI: Confidence interval; **RCT:** randomised controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aDowngraded one level due to imprecision; small number of events (< 300 overall).

^bDowngraded two levels due to imprecision; confidence intervals encompass clinically-important harm as well as clinically important benefit.

Summary of findings 2. Nicotine EC compared to non-nicotine EC for smoking cessation

Nicotine EC compared to non-nicotine EC for smoking cessation

Patient or population: People who smoke cigarettes

Setting: Canada, Italy, New Zealand, UK, USA

Intervention: Nicotine EC

Comparison: Non-nicotine EC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-nicotine EC	Risk with Nicotine EC				
Smoking cessation at 6-12 months	Study population		RR 1.71 (1.00 to 2.92)	802 (3 RCTs)	⊕⊕⊕⊖ MODERATE ^{a,b}	-
Assessed with biochemical validation	6 per 100	10 per 100 (6 to 18)				
Adverse events at 1 week to 6 months	Study population		RR 1.00 (0.73 to 1.36)	346 (2 RCTs)	⊕⊕⊕⊖ LOW ^c	-
Assessed via self-report	35 per 100	35 per 100 (25 to 47)				
Serious adverse events at 1 week to 1 year	Study population		RR 0.25 (0.03 to 2.19)	494 (4 RCTs)	⊕⊕⊕⊖ LOW ^c	-
Assessed via self-report and medical records	2 per 100	0 per 100 (0 to 4)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). For cessation, the assumed risk in the control group is based on receipt of moderate-intensity behavioural stop-smoking support. The assumed risk for adverse events and serious adverse events is a weighted mean average of quit rates across control groups in contributing studies.

CI: Confidence interval; **RCT:** randomised controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aNot downgraded for risk of bias. One of three studies considered high risk of bias; removing this study increased the direction of the effect in favour of the intervention.

^bDowngraded one level due to imprecision; confidence intervals incorporate no clinically-significant difference as well as clinically-significant benefit.

^cDowngraded two levels due to imprecision: confidence intervals encompass clinically-significant harm as well as clinically-significant benefit.

Summary of findings 3. Nicotine EC compared to behavioural support only/no support for smoking cessation

Nicotine EC compared to behavioural support only/no support for smoking cessation

Patient or population: People who smoke

Setting: Canada, Italy, UK, USA

Intervention: Nicotine EC

Comparison: Behavioural support only/no support

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with behavioural support only/no support	Risk with Nicotine EC				
Smoking cessation at 6 to 12 months	Study population		RR 2.50 (1.24 to 5.04)	2312 (4 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,b}	-
Assessed using biochemical validation	4 per 100	10 per 100 (5 to 20)				
Adverse events at 12 weeks to 6 months	Study population		RR 1.17 (1.04 to 1.31)	516 (3 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,c}	-
Assessed via self-report	60 per 100	70 per 100 (62 to 78)				
Serious adverse events at 4 weeks to 6 months	Study population		RR 1.33 (0.25 to 6.96)	842 (5 RCTs)	⊕⊕⊕⊕ VERY LOW ^{d,e}	-
Assessed via self-report and medical records	1 per 100	1 per 100 (0 to 5)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). For cessation, the assumed risk in the control group is based on receipt of limited stop-smoking support. The assumed risk for adverse events and serious adverse events is a weighted mean average of quit rates across control groups in contributing studies.

CI: Confidence interval; **RCT:** randomised controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aDowngraded two levels due to risk of bias. All included studies judged to be at high risk of bias.

^bDowngraded one level due to imprecision; although confidence intervals are consistent with clinically- important difference, event count is very low (< 100).

^cDowngraded one level due to imprecision; confidence intervals incorporate no clinically-significant difference.

^dDowngraded two levels due to risk of bias; 4 out of 5 studies considered at high risk.

^eDowngraded two levels due to imprecision; confidence intervals incorporate clinically-significant benefit and clinically-significant harm.

BACKGROUND

Throughout this review, we discuss (1) conventional cigarettes and; (2) electronic cigarettes, defined as handheld electronic vaping devices that produce aerosol for inhalation formed by heating an e-liquid. In this review, all mention of smoking, smoking cessation, cigarette use, smoke intake, etc. concern combustible tobacco cigarettes. When the text concerns electronic cigarettes we use the abbreviation 'ECs'. EC users are sometimes described as vapers, and EC use as vaping. We refer to ECs that do not contain nicotine as non-nicotine ECs; these can also be conceptualized as placebo ECs, but we are using the term non-nicotine EC, as they can be conceptualized as an intervention in themselves. This review does not address the use of vaping devices to inhale substances other than nicotine, such as cannabis.

Description of the condition

Stopping smoking is associated with large health benefits. Despite most people who smoke wanting to quit, many find it difficult to succeed in the long term. Almost half who try to quit without support will not manage to stop for even a week, and fewer than five per cent remain abstinent at one year after quitting (Hughes 2004).

Behavioural support and medications such as nicotine patches or gum increase the chances of quitting through providing nicotine to help alleviate withdrawal symptoms, but even with this additional support long-term quit rates remain low (Cahill 2016; Hartmann-Boyce 2018b; Hartmann-Boyce 2019). One of the limitations of current treatments is that, despite substituting nicotine delivery, none adequately addresses the sensory, behavioural and social aspects of smoking that ex-smokers miss when they stop smoking (e.g. holding a cigarette in their hands, taking a puff, enjoyment of smoking, feeling part of a group). ECs may offer a way to overcome this limitation (Notley 2018b).

There is no doubt that people become dependent on tobacco, and find it difficult to stop smoking, primarily because of nicotine and its actions on the brain's reward system (Balfour 2004). However, other factors also contribute to tobacco dependence (Benowitz 2010; Rose 2006). Sensory and behavioural cues provide additional reinforcement of smoking behaviour (Rose 1993; Rose 2000) and over time become almost as rewarding as nicotine. There are several lines of evidence to support this. Firstly, people who smoke appear to have a preference for cigarette smoke compared to other forms of nicotine delivery. This is partly related to the speed of nicotine delivery through smoke inhalation. However, even when nicotine is administered intravenously it does not provide the same level of satisfaction or reward as smoking (Rose 2000; Westman 1996). Secondly, the local sensory effects of smoking (e.g. the 'scratch' in the back of the throat) may be important for enjoyment and reward. Numbing the sensations of cigarette smoke by anesthetizing the upper and lower respiratory tract leads to less enjoyment of smoking (Rose 1985). Conversely, products that mimic the sensory effects of smoking on the mouth and throat (such as citric acid, black pepper, and ascorbic acid) reduce craving and some withdrawal symptoms, at least in the short term (Levin 1993; Rose 1994; Westman 1995). Thirdly, very low nicotine content cigarettes (VLNCs) which have a very low content of nicotine (e.g. 0.08 mg instead of the normal 1 mg) and so have negligible or no central effects, have also been investigated for their role in aiding smoking cessation (Przulj 2013). Despite delivering low levels of nicotine, VLNCs are satisfying over the initial few days of abstinence

from nicotine (Donny 2007; Donny 2015; Pickworth 1999; Rose 2000). They also reduce tobacco withdrawal symptoms, including urges to smoke and low mood (Barrett 2010; Donny 2009; McRobbie 2016; Perkins 2010; Rose 2000), and have been shown to improve long-term continuous abstinence rates in one study (Walker 2012). Social aspects of smoking, such as feeling part of a like-minded group, or including smoking behaviour as part of one's social identity are also key elements of cigarette smoking that people who smoke report to be key aspects of cigarette dependence (Notley 2018a).

Considering the other factors that contribute to tobacco dependence, there is interest in developing smoking-cessation products that would not only help relieve the unpleasant effects of nicotine withdrawal but would also act as an effective substitute for smoking behaviour and the rituals and sensations that accompany smoking, without the health risks associated with the inhalation of tobacco smoke. Until recently the only pharmaceutical treatments available that had some of these characteristics were the nicotine inhalator and nicotine oral spray. However, these do not have greater cessation efficacy than the other nicotine replacement therapy (NRT) products (Hajek 1999; Hartmann-Boyce 2018a). This may in part be due to the considerable effort (e.g. 20 minutes of continuous puffing) needed to provide nicotine blood concentrations consistent with other NRTs (Schneider 2001). Adherence to correct use of the inhalator is low compared to other NRTs (Hajek 1999). It is therefore possible that any advantage of sensorimotor replacement is diminished by low nicotine delivery and limited similarities between inhalator use and sensations of smoking (Bullen 2010). A nicotine inhaler using pressurized air has recently been approved as a smoking cessation aid in the UK. The nicotine delivery is substantially lower than from cigarettes, and also lower than from the nicotine inhalator (Romeu 2020).

Description of the intervention

ECs are electronic vaping devices that are handheld and produce an aerosol formed by heating an e-liquid, designed for inhalation by the user. The e-liquid, usually comprising propylene glycol and glycerol, with or without nicotine and flavours, is stored in disposable or refillable cartridges or a reservoir or 'pod'. The commonly-used term for this aerosol is vapour, which we use throughout the review. In many countries, ECs are marketed as consumer products. Although routes are in place for licensing them as a medicine in some areas, no country yet has a licensed, medicinal EC.

ECs provide sensations similar to smoking a cigarette. They provide taste and throat sensations that are closer to smoking than those provided by the nicotine inhalator (Barbeau 2013). The vapour that looks like tobacco smoke is only visible when the user exhales after drawing on the mouthpiece, not when the device is being held. In qualitative studies users report a sense of shared identity with other users, similar to tobacco smoking identity, and also report pleasure and enjoyment of use, suggesting that ECs may be viewed less as a medical cessation aid but rather as an acceptable alternative to tobacco smoking (Cox 2017; Notley 2018a).

There are many different brands and models of EC available. Variation exists both in the device ('product') and consumable (e-liquid used). There is a wide variation in the composition of e-liquids (nicotine content, flavours and other components) (Goniewicz 2012; Goniewicz 2014), with some users choosing to mix

their own e-liquids (Cox 2019b). Initial studies showed that early models of EC delivered very low amounts of nicotine to naïve users (Bullen 2010; Eissenberg 2010; Vansickel 2010). Later studies that have measured nicotine pharmacokinetics in both experienced and naïve EC users have found that some EC users can achieve blood nicotine levels similar to those achieved with smoking, albeit more slowly, and that their ability to do so often improves over time (Hajek 2015b; Vansickel 2012; Vansickel 2013; Yingst 2019a; Yingst 2019b).

Early on in their development, ECs looked like cigarettes and used disposable cartridges. These models were often called 'cig-a-likes'. The nicotine delivery from these products was low, and even the modern versions of EC devices that use pre-filled cartridges, mostly produced by the tobacco industry, for the most part have only low nicotine delivery (Hajek 2017). The later refillable, or 'tank', products have a larger battery and a transparent container that users fill with an e-liquid of their choice, and usually provide faster and more efficient nicotine delivery, allow a wider choice of flavours and nicotine concentrations, and are typically used by experienced vapers who manage to switch to vaping completely (ASH 2019; Dawkins 2013b; Farsalinos 2014; McNeill 2019). Observational evidence suggests people who smoke are more likely to successfully quit using tank models than with cig-a-likes (Chen 2016; Hitchman 2015). EC types are also often grouped by 'generation': first-generation devices are typically cig-a-likes; second-generation devices are usually tank models, sometimes referred to as 'vape pens'; and third-generation devices are tank models which, unlike second generation devices, allow users to adjust the power (wattage) level of the product (see NCSCT EC briefing for further information and images of different product types). More recently, smaller 'pod' devices, such as Juul, appeared that use nicotine salt. This nicotine formulation reduces irritant effects and allows the delivery of higher nicotine levels that closely mimic the pharmacokinetic profile of nicotine delivery from cigarettes, despite the low battery power of the device (Hajek 2020). Juul has now become the most popular EC in the USA (Huang 2019). The EU Tobacco Products Directive (European Parliament 2014) does not allow sales of e-liquids with nicotine content higher than 20 mg/ml, and so the US version of Juul (59 mg/nl nicotine) is not available within the EU (Huang 2019; Talih 2020).

The different device types (cig-a-like, refillable and pods using high nicotine content salts) may differ significantly in their efficacy in helping people who smoke to quit, as they differ in delivery of nicotine, the active ingredient. Nicotine itself, when delivered through mechanisms and doses similar to that delivered in traditional NRT, is not considered harmful (Hartmann-Boyce 2018a). The safety profile of the different types of EC may be similar as they use the same constituents, although within the generic range of EC types, there is some evidence to suggest EC providing less nicotine may pose higher risks. This is because low-nicotine delivery devices need to be puffed with higher intensity to provide users with the nicotine levels that they seek, and more intensive puffing is accompanied by increased inhalation of potential toxicants (Dawkins 2016; Dawkins 2018; Smets 2019). Throughout this review we refer to a nicotine-containing EC as 'nicotine EC' and to nicotine-free EC as 'non-nicotine EC', which can also be considered 'placebo EC'. The 'placebo' comparison is a test just of the nicotine effect and not of the potential sensorimotor or behavioural and social replacement that the EC may provide.

There is no one agreed classification system for EC devices, and product development has moved so quickly that the definitions used within trials of the devices tested may no longer be necessarily fit for purpose. In this review, the definitions used are based on those drawn from the included trials. We currently label three different types of EC as 'cartridges' for devices with disposable cartridges and - typically, but not always - low nicotine delivery (e.g. cig-a-likes); refillable ECs for devices that vapers fill with their own choice of e-liquids; and pods for the small devices that use nicotine salts. We may review this categorization system in future versions of the review as new trials and devices emerge.

Why it is important to do this review

Since ECs appeared on the market in 2006 there has been a steady increase in their use. In the UK the ASH 2019 survey found 19.4% of the adult population have ever tried vaping, but only 7.2% were current vapers. EC use remains slightly more common among men compared with women, although the difference is small. EC use is most prevalent in current (19.9%) and former (11.6%) smokers. Less than one per cent of never-smokers report regular EC use. Prevalence data from the USA in 2019 showed that 4.4% of adults were current EC users (Du 2020). Data from lower-income countries suggest similar levels of EC use and awareness (Besaratinia 2019; Jiang 2016; Palipudi 2016).

Particular concern has been raised about the increased use of EC in young people, especially among never-smokers. Data for 2019 from Canada, England, and the USA show regular use (≥ 20 days in the last 30 days) among 16- to 19-year-olds to be 5.7%, 2.7% and 6.7%, respectively. There appear to be some regional differences in the change in the prevalence of EC use. For example, in North America the rates of regular EC use among 16- to 19-year-old never-smokers has significantly increased between 2017 and 2019, compared to England where there has not been any significant change (0.2% to 0.3%) (Hammond 2020). However, as with adults, regular use is greatest among those who are also smoking and lowest among never-smokers (1.0%, 0.3%, and 1.8% for Canada, England and USA, respectively).

Regulatory approaches being used for ECs currently vary widely, from no regulation to partial and complete bans (McNeill 2019). Within the USA, for example, the Food and Drug Administration (FDA) has classified them as tobacco products and there are a range of laws that include prohibition of EC use indoors, require retailers to have a license to sell, and prohibit sales to minors. Laws prohibiting sales to minors apply nationwide, but other laws vary by state (Du 2020). The European Union includes ECs in their Tobacco Products Directive, except where therapeutic claims are made or in instances where they contain over 20 mg/nl of nicotine, when they will require medicines authorization (European Parliament 2014).

Categorical statements about the toxicity of ECs are not possible because of the large number of devices and liquids available and the frequent addition of new products to the market. In 2019, cases of severe lung injury associated with EC use were reported in the USA, and by February 2020 there were around 2800 hospitalized cases or deaths (CDC 2020). This illness was termed E-cigarette or Vaping-Associated Lung Injury (EVALI) and caused concern throughout the world (Hall 2020) and a negative change in people's perception of the risks of EC use compared to smoking (Tattan-Birch 2020). These cases were somewhat at odds with data from trials

and cohort studies, and it was later found that these injuries were related to use of tetrahydrocannabinol (THC)-containing EC, and in particular THC products adulterated with vitamin E acetate (Blount 2020; Hartnett 2020). Among those brands of nicotine EC that have been tested, levels of toxins have been found to be substantially lower than in cigarettes (Hajek 2014; McNeill 2019). Long-term effects beyond 12 months are unknown, although based on what is known about liquid and vapour constituents and patterns of use, a report from the UK's Royal College of Physicians has concluded that using an EC is likely to be considerably safer than smoking (RCP 2016). The US National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that ECs are likely to be far less harmful than continuing to smoke cigarettes, with the caveat that the long-term health effects of e-cigarette use are not yet known (NASEM 2018).

Despite general acknowledgement that EC use exposes the user to fewer toxicants and at lower levels than smoking cigarettes (McNeill 2019; NASEM 2018; RCP 2016), there remains some hesitancy in making these products available to people who smoke as a harm reduction tool or smoking cessation aid (e.g. McDonald 2020). Lack of quality control measures, possible harms of second-hand EC vapour inhalation, concerns that the products may be a gateway to smoking initiation or may prolong continued dual-use of tobacco, concerns that ECs may undermine smoke-free legislation if used in smoke-free spaces, concerns about the involvement of the tobacco industry, and concerns that the long-term effects of EC use on health are not yet known are often cited. However, there are limited data with which to support or refute these concerns, and others suggest that potential benefits outweigh potential disadvantages (Farsalinos 2014; Hajek 2014; McNeill 2019; NASEM 2018; RCP 2016).

People who smoke, healthcare providers and regulators are interested to know if ECs can help smokers quit and if it is safe to use them to do so. In particular, healthcare providers have an urgent need to know what they should recommend for people who want to stop smoking. The largest health gains are achieved from stopping smoking completely, as opposed to reducing cigarette consumption, and as such this review focuses on the effectiveness of ECs in aiding smoking cessation.

This is an update of a review first published in 2014 and last updated in 2016.

Following the publication of the 2020 update of this review, we will maintain it as a living systematic review (Brooker 2019). This means we will be continually running searches and incorporating new evidence into the review. For more information about the living systematic review methods being used, see Appendix 1. A living systematic review approach is appropriate for this review, for three reasons. First, the review addresses an important public health issue; the role of ECs in enabling people who smoke to stop smoking, with potential for substantial ongoing individual and societal benefits if effective. Secondly, there remains uncertainty in the existing evidence; despite searches including the current update (to January 2020) identifying 50 trials for inclusion in the review, more studies are needed to confirm the degree of benefit for different comparisons and product types, and there is considerable uncertainty about adverse events and other markers of safety. Thirdly, we are aware of multiple ongoing trials on this topic that are likely to have an important impact on the conclusions of the review.

OBJECTIVES

To evaluate the safety and effect of using electronic cigarettes (ECs) to help people who smoke achieve long-term smoking abstinence.

METHODS

Criteria for considering studies for this review

Types of studies

We include randomized controlled trials (RCTs) and randomized cross-over trials in which people who smoke are randomized to ECs or to a control condition. RCTs are the best available primary evidence, but the continued paucity of RCTs in this area requires that we also include uncontrolled intervention studies in which all participants are given an EC intervention.

We include studies regardless of their publication status or language of publication.

Types of participants

People defined as currently smoking cigarettes at enrolment into the studies. Participants could be motivated or unmotivated to quit.

Types of interventions

Any type of EC or intervention intended to promote EC use for smoking cessation, including studies which did not measure smoking cessation but provided ECs with the instruction they be used as a complete substitute for cigarette use. ECs may or may not contain nicotine.

Types of comparators

We compare nicotine ECs with non-nicotine ECs, ECs versus alternative smoking cessation aids, including NRT or no intervention, and ECs added to standard smoking cessation treatment (behavioural or pharmacological or both) with standard treatment alone.

Types of outcome measures

Primary outcomes

- Cessation at the longest follow-up point, at least six months from the start of the intervention, measured on an intention-to-treat basis using the strictest definition of abstinence, preferring biochemically-validated results where reported
- Number of participants reporting adverse events or serious adverse events at one week or longer (as defined by study authors)

Secondary outcomes

Changes in the following measures at one week or longer:

- Carbon monoxide, as measured through breath or blood
- Blood pressure
- Heart rate
- Blood oxygen saturation
- Lung function measures
- Known toxins/carcinogens, as measured through blood or urine (toxicant names and abbreviations are listed in Appendix 2)

Studies had to report one of the primary or secondary outcomes above to be eligible for inclusion.

Search methods for identification of studies

Electronic searches

For this update we searched the following databases on 20th January 2020:

- Cochrane Tobacco Addiction Group Specialized Register
- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE (OVID SP)
- Embase (OVID SP)
- PsycINFO (OVID SP)

We also searched the clinical trials registries ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP: www.who.int/ictrp/en/). At the time of the search, the Register included the results of searches of the Cochrane Central Register of Controlled trials (CENTRAL), issue 12, 2019; MEDLINE (via OVID) to update 20191127; Embase (via OVID) to week 202005; PsycINFO (via OVID) to update 20200127. See the [Tobacco Addiction Group website](#) for full search strategies and a list of other resources searched.

For the first version of the review we also searched CINAHL (EBSCO Host) (2004 to July 2014). We did not search this database from 2016 onwards as it did not contribute additional search results to the first version of the review. The search terms were broad and included e-cig\$ OR elect\$ cigar\$ OR electronic nicotine. The search for the 2016 update added the terms vape or vaper or vapers or vaping. The 2020 searches added further terms, including the MESH heading 'Electronic Nicotine Delivery Systems' and terms to limit by study design. Our search strategy for MEDLINE (Ovid SP) is listed in [Appendix 3](#). The previously-used search strategy is shown in [Appendix 4](#). The search date parameters of the original searches were limited to 2004 to the present, due to the fact that ECs were not available before 2004.

Searching other resources

We searched the reference lists of eligible studies found in the literature search and contacted authors of known trials and other published EC studies.

Data collection and analysis

Selection of studies

Two review authors (for this update from: JHB, CN, NL, AT, RB) independently prescreened all titles and abstracts obtained from the search, using a screening checklist, and then independently screened full-text versions of the potentially relevant papers for inclusion. We resolved any disagreements by discussion or with a third review author.

Data extraction and management

Two review authors (for this update from: JHB, CN, NL, AT, RB, and with support from freelance reviewer KR) extracted data from the included studies using a pre-piloted data extraction form, and checked them against each other. We resolved any disagreements by discussion or with a third review author. We extracted data on:

- Author
- Date and place of publication
- Study dates
- Study design
- Inclusion and exclusion criteria
- Setting
- Summary of study participant characteristics
- Summary of intervention and control conditions
- Number of participants in each arm
- Smoking cessation outcomes
- Type of biochemical validation (if any)
- Adverse events (AEs), serious adverse events (SAEs), and relevant biomarkers
- Assessment time points
- Study funding source
- Author declarations of interest
- Risk of bias in the domains specified below
- Additional comments

We adopted a broad focus to detect a variety of adverse events.

One review author then entered the data into [Review Manager 2020](#) software for analyses (JHB), and another checked them (NL).

Assessment of risk of bias in included studies

Two review authors (for this update from: JHB, CN, NL, AT, RB, and with support from freelancer KR) independently assessed the risks of bias for each included study, using the Cochrane 'Risk of bias' Tool v1 ([Higgins 2011](#)). This approach uses a domain-based evaluation that addresses seven different areas: random sequence generation; allocation concealment; blinding of participants and providers; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other potential sources of bias. We assigned a grade (low, high, or unclear) for risk of bias for each domain. We resolved disagreements by discussion or by consulting a third review author.

Specific considerations about judgements for individual domains in this review are outlined below:

- Random sequence generation/allocation concealment: We rated all non-randomized studies at high risk in these domains.
- Blinding of participants and personnel: We did not evaluate this domain for non-randomized studies, as we considered it not to be applicable. For randomized studies which did not use blinding, we considered studies to be at low risk in this domain if the intervention was compared to an active control of similar intensity, as we judged performance bias to be unlikely in this circumstance. If studies were unblinded and the comparator group was a minimal-intervention control or of lower intensity than the intervention group, we considered the study to be at high risk of bias in this domain.
- Following standard methods of the Cochrane Tobacco Addiction Review Group, we considered studies to be at low risk of detection bias (blinding of outcome assessment) if our primary outcome was objectively measured or if the intensity of intervention was similar between groups, or both. For studies where cessation was measured, our judgement was based on whether cessation was biochemically verified. For other studies,

we judged this domain based on adverse or serious adverse events.

- Again following standard methods of the Cochrane Tobacco Addiction Group, we rated studies at high risk of attrition bias if loss to follow-up was greater than 50% overall or if there was a difference in follow-up rates of more than 20% between study arms.

We judged studies to be at high risk of bias overall if they were rated at high risk in at least one domain, and at low risk of bias overall if they were judged to be at low risk across all domains evaluated. We judged the remaining studies to be at unclear risk of bias overall.

Measures of treatment effect

We analyzed dichotomous data by calculating the risk ratio (RR). For cessation, we calculated the RR as ((number of events in intervention condition/intervention denominator) / (number of events in control condition/control denominator)) with a 95% confidence interval (CI), using data at the longest follow-up period reported.

We analyzed continuous data (other measures of tobacco exposure) by comparing the difference between the mean change from baseline to follow-up in the intervention and comparator groups. For outcomes other than cessation where data were reported at multiple time points, we used data at the longest follow-up point at which ECs were still being provided.

Unit of analysis issues

In the case of trials with multiple arms, we do not combine data between arms unless this is the way it has been presented by study authors. We note in our analyses where this is the case.

For all but one study, the unit of assignment was the individual. [ISRCTN14140672](#) assigned condition based on homeless shelter; this was a small pilot study with very few events and hence we judged clustering to have very little impact on our overall result. If larger cluster-randomized trials are eligible in the future, we will assess whether study authors have adjusted for this clustering, and whether this had an impact on the overall result. When clustering appears to have had little impact on the results, we will use unadjusted quit-rate data; however when clustering does appear to have an impact on results, we will adjust for this using the intraclass correlation (ICC).

For randomized cross-over trials, we report results at the end of the first assignment period where available and where sufficiently long to meet our inclusion criteria for outcomes. All other outcomes from randomized cross-over trials are reported narratively. We offer a narrative synthesis of data from non-randomized studies, and where possible use effect direction plots as described in the *Cochrane Handbook* (Higgins 2020).

Dealing with missing data

For smoking cessation, we used a conservative approach, as is standard for the Cochrane Tobacco Addiction Group, treating participants with missing data as still smoking. We based the proportion of people affected by adverse events on the number of people available for follow-up, and not the number randomized. For other outcomes, we use complete-case data and do not attempt to impute missing values.

Assessment of heterogeneity

We assessed the clinical and methodological diversity between studies to guide our decision as to whether data should be pooled. We were also guided by the degree of statistical heterogeneity, assessed by calculating the I^2 statistic (Higgins 2003), and considering a value greater than 50% as evidence of substantial heterogeneity. We did not present pooled results where I^2 values exceeded 75%.

Assessment of reporting biases

Reporting bias is best assessed using funnel plots, where 10 or more RCTs contribute to an outcome. However, there are currently insufficient studies to support this approach.

Data synthesis

We provide a narrative summary of the included studies. Where appropriate, we have pooled data from these studies in meta-analyses. For dichotomous data, we used a fixed-effect Mantel-Haenszel model to calculate the RR with a 95% confidence interval, in accord with the standard methods of the Cochrane Tobacco Addiction Group for cessation studies.

For continuous outcomes, we pooled mean differences (or standardised mean differences for studies using different measures for the same construct), using the inverse variance approach (also with a 95% CI).

Subgroup analysis and investigation of heterogeneity

We had planned to undertake subgroup analyses to investigate differences between studies, such as:

- Intensity of behavioural support used;
- Type of EC (cartridge; refillable; pod);
- Instructions for EC use (e.g. study provision, length of provision, whether participants had a role in product choice);
- Type of participants (e.g. experience of EC use).

However, there were too few studies to conduct such analyses. Should further studies become available in future, we will follow this approach. For safety outcomes, we present subgroups by length of follow-up for descriptive purposes.

In the absence of sufficient data for subgroup analyses on EC type, in the text we specify the type of nicotine EC when reporting pooled results for cessation.

Sensitivity analysis

We conducted sensitivity analyses to detect whether pooled results were sensitive to the removal of studies judged to be at high risk of bias.

Summary of findings and assessment of the certainty of the evidence

Following standard Cochrane methodology, we created 'Summary of findings' tables for our three main comparisons using [GRADEpro GDT](#): nicotine EC versus non-nicotine EC; nicotine EC versus NRT; and nicotine EC versus behavioural support only/no support. We selected these comparisons a priori as being the most clinically relevant. In the 'Summary of findings' tables, we present data on our primary outcomes (cessation, adverse events, serious adverse

events) for these main comparisons. Also following standard Cochrane methodology, we used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome, and to draw conclusions about the certainty of evidence within the text of the review.

RESULTS

Description of studies

Results of the search

For this update, our bibliographic database searches identified 951 non-duplicate records (Figure 1). We found a further three records

through screening references in the papers identified through electronic searches. We screened all records and retrieved the full-text papers of 122 potentially relevant articles. After screening and checking the full-text of 122 papers, we included 79 records, representing 35 studies new for this update and 20 new ongoing studies (Characteristics of ongoing studies). Secondary study reports, commentaries, and correspondence relating to included studies are linked to studies in the reference section. Figure 2 and Figure 3 present PRISMA flow charts for previous versions of this review.

Figure 1. 2020 Flow diagram

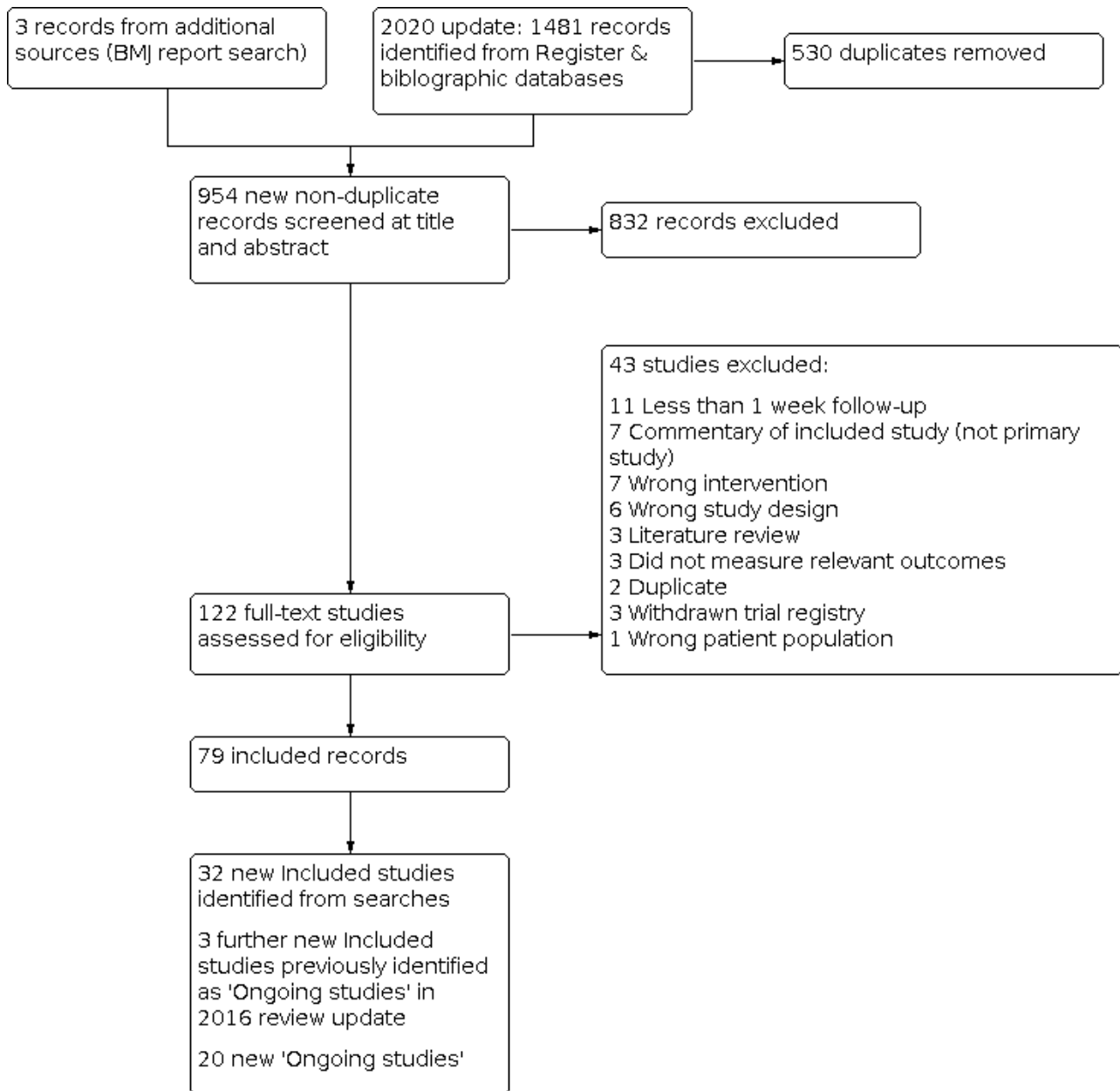


Figure 2. Study flow diagram for review update 2016

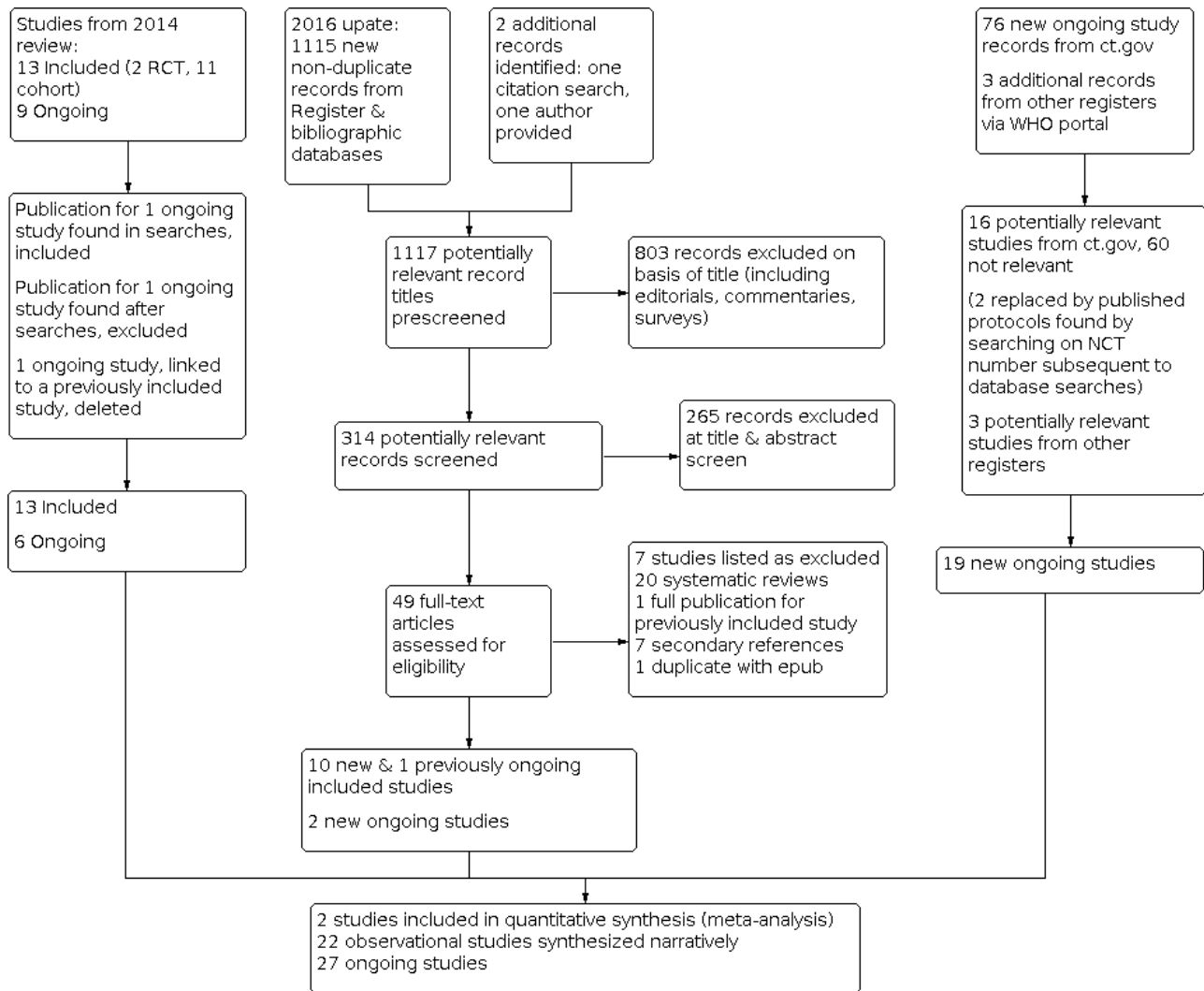
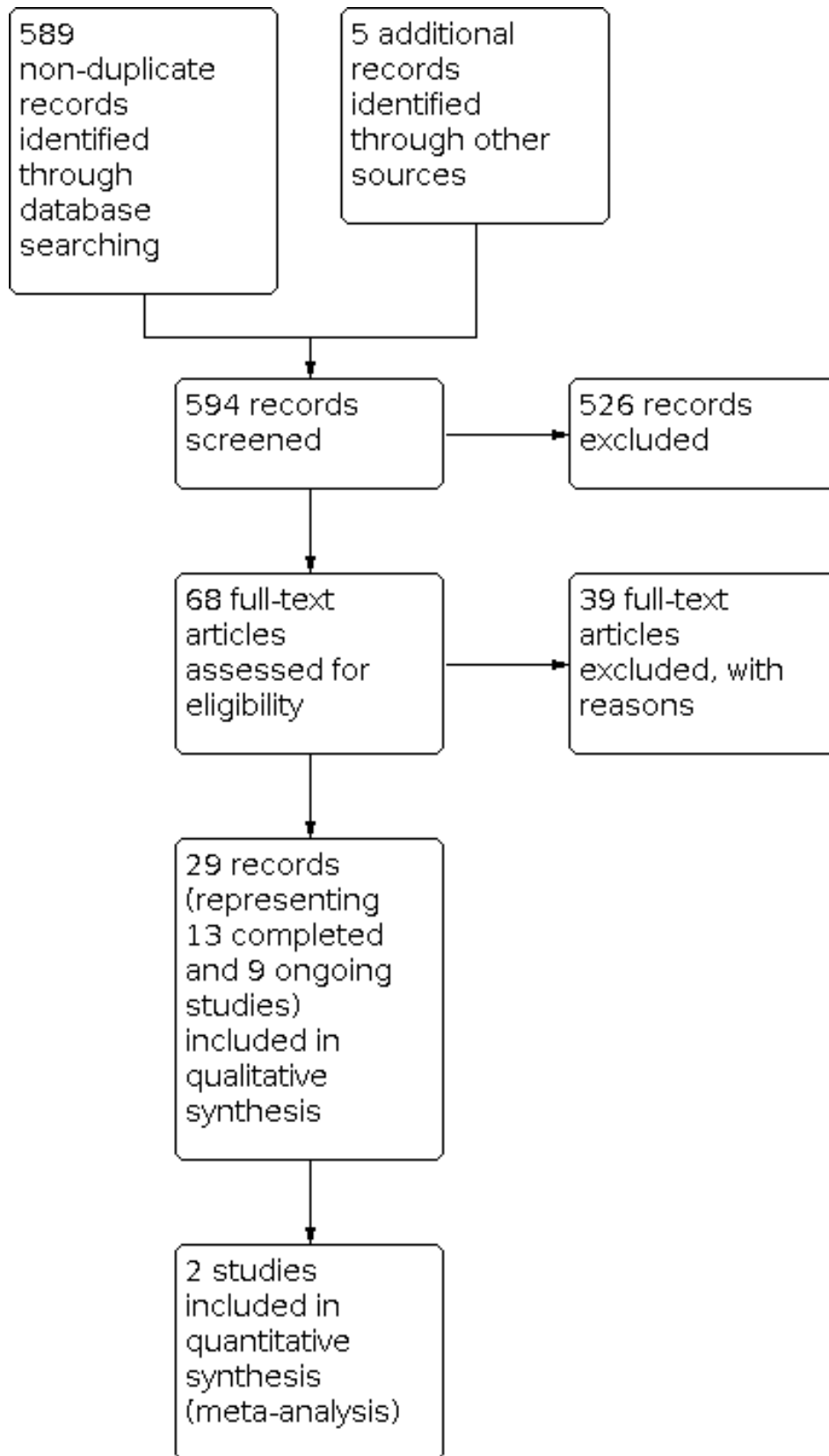


Figure 3. Study flow diagram for original review, 2014



Included studies

In total, we include 50 studies, 35 new included studies and 15 eligible included studies identified in previous versions of the review. Key features of the included studies are summarized below. Further details on each included study can be found in the [Characteristics of included studies](#) tables.

Participants

The 50 included studies represented 12,430 participants. Twenty-one studies were conducted in the USA, nine were conducted in the UK, seven in Italy, two each in Australia, New Zealand, and Greece, and one each in Belgium, Canada, Poland, the Republic of Korea, South Africa, Switzerland, and Turkey. All studies were conducted in adults who smoke. Fifteen studies exclusively recruited participants who were not motivated to quit smoking, and 27 studies exclusively recruited participants motivated to quit; motivation was not specified for the other studies. Fifteen studies recruited from specific population groups; this included five studies which recruited participants based on physical health condition (heart attack, cancer, HIV, periodontitis, awaiting surgery), three studies which recruited participants with serious mental illness, and three studies which recruited participants in treatment or having recently completed treatment for alcohol or other drug use. One study each recruited: people aged 55 or older, young adults, and people accessing homeless centres.

Interventions and comparators

All studies provided nicotine EC, either alone (45 studies) or in conjunction with NRT or varenicline (5 studies). In two studies where nicotine EC was provided on its own, nicotine levels were judged to be so low as to be clinically comparable to non-nicotine EC ([Lee 2019](#); [Van Staden 2013](#)); we include these studies in non-nicotine EC comparisons. Eight studies compared nicotine EC with non-nicotine EC, 12 studies compared nicotine EC to behavioural support only or no support, and eight studies compared nicotine EC to NRT. Results from these studies are reported by comparison in [Effects of interventions](#). Further details on the intervention and comparator groups (where applicable) for each study can be found in the [Characteristics of included studies](#) tables.

Where reported in the original publications, details on the devices tested can also be found in the [Characteristics of included studies](#) tables. Of the studies with sufficient data with which to judge, 25 used cartridge devices (only one of which had high nicotine

delivery), 18 used refillable devices, two used both types, and the remainder did not report device type. No studies reported testing used pod systems.

Outcomes

Of the 50 included studies:

- 20 reported data on abstinence
- 34 reported data on adverse events
- 23 reported data on serious adverse events
- 30 reported data on carbon monoxide
- 9 reported data on heart rate
- 10 reported data on blood pressure
- 2 reported data on blood oxygen saturation
- 7 reported data on at least one known toxin/carcinogen
- 4 reported data on at least one measure of lung function

Study types and funding

Twenty-six studies were RCTs, twelve of which contributed to cessation analyses. Three studies used randomized cross-over designs, and the remainder were uncontrolled cohort studies. Of the 40 studies which reported funding information, 32 had no EC industry funding or support.

Excluded studies

We list 90 studies excluded at full-text stage, along with reasons for exclusion, in the [Characteristics of excluded studies](#) table. The most common reason for exclusion during this update was follow-up of less than a week. We excluded nine studies from this update that had been previously included; this is because they did not include any EC intervention (see [Differences between protocol and review](#)).

Risk of bias in included studies

Overall, we judged four studies ([Bullen 2013](#); [Hajek 2019](#); [Lee 2018](#); [Lee 2019](#)) to be at low risk of bias, nine to be at unclear risk, and the remaining 37 at high risk of bias (note, this includes the 24 non-randomized studies, which we deemed to be at high risk due to this lack of randomization).

Details of 'Risk of bias' judgements for each domain of each included study can be found in the [Characteristics of included studies](#) table. [Figure 4](#) illustrates judgements for each included study.

Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Adriaens 2014	+	?	+	+	+	?	
Baldassarri 2018	+	?	+	+	-	+	
Bell 2017	-	-			+	+	
Bullen 2013	+	+	+	+	+	+	
Caponnetto 2013a	+	+	+	+	+	?	
Caponnetto 2013b	-	-			+	?	
Carpenter 2017	?	?	-	-	+	?	+
Ely 2013	-	-			+	?	?
Felicione 2019	?	?	?	?	+	?	
George 2019	+	+	?	-	?	+	
Goniewicz 2017	-	-			+	+	
Guillaumier 2018	+	+	-	-	+	+	
Hajek 2015a	-	-			?	?	
Hajek 2019	+	+	+	+	+	+	
Halpern 2018	?	?	-	+	-	+	
Hatsukami 2020	?	?	?	+	+	+	
Hickling 2019	-	-			+	+	
Holliday 2019	+	+	-	+	+	+	
Humair 2014	-	-			?	?	
Ikonomidis 2018	?	?	-	?	+	?	?
Ioakeimidis 2018	?	?	+	+	?	?	-
ISRCTN14140672	-	?	-	+	-	+	
Kumral 2016	?	?	-	-	?	+	

Figure 4. (Continued)

ISRCTN14140672	-	?	-	+	-	+	
Kumral 2016	?	?	-	-	?	+	
Lee 2018	+	+	+	+	+	+	
Lee 2019	+	+	+	+	+	+	
Lucchiari 2020	+	+	+	+	+	-	
Martner 2019	-	-			?	?	
McRobbie 2015	-	-			+	+	
Meier 2017	?	?	+	+	?	+	
NCT02417467	?	?	+	+	+	?	?
NCT02648178	-	-			+	?	
NCT02918630	?	?	?	?	?	-	?
Nides 2014	-	-			+	+	
Oncken 2015	?	?	+	+	+	?	
Pacifici 2015	-	-			+	-	
Polosa 2011	-	-			+	?	
Polosa 2014b	-	-			+	?	
Polosa 2015	-	-			+	?	
Pratt 2016	-	-			+	+	
Pulvers 2018	-	-			+	+	
Smith 2020	?	?	+	+	+	?	
Stein 2016	-	-			+	+	
Strasser 2016	?	?	?	+	-	+	
Tseng 2016	+	?	+	+	+	+	
Valentine 2018	-	-			?	?	
Van Staden 2013	-	-			+	?	
Veldheer 2019	+	+	+	+	?	-	
Wadia 2016	-	-			+	+	
Walele 2018	+	+	-	-	+	+	
Walker 2020	+	+	-	+	+	?	

Allocation

We judged 22 studies to be at high risk of selection bias; for 21, this is because the studies were not randomized. We also rated a pilot cluster-randomized trial at high risk as randomization was not carried out as intended for pragmatic reasons (ISRCTN14140672). We judged 12 studies to be at low risk of selection bias, and the remainder to be at unclear risk as there was insufficient information with which to judge.

Blinding

Of the 29 studies assessed for these domains, we judged 15 to be at low risk for both performance and detection bias. We rated ten at high risk for performance or detection bias, or both. In these studies, blinding was not used and different levels of support were provided; this alone or in conjunction with the outcome measures being used (subjective rather than objective measures) meant we thought there was a high risk of bias being introduced. We judged the rest to be at unclear risk.

Incomplete outcome data

We judged most studies (36 out of 50) to be at low risk of attrition bias. We rated four studies with substantial loss to follow-up at high risk of attrition bias, and a further 10 did not provide sufficient data on which to judge, and hence we judged them to be at unclear risk.

Selective reporting

Of the 50 studies, we considered that half were at low risk of reporting bias, as all prespecified/expected outcomes were reported. We rated four at high risk, as data were not presented as specified in the original protocols. We judged the rest to be at unclear risk, due to insufficient information with which to make a judgement.

Other potential sources of bias

We considered loakeimidis 2018 to be at high risk of other bias; data were from a conference poster and the associated abstract, and quit rates in the intervention arm differed between the two sources.

Effects of interventions

See: [Summary of findings 1](#) Nicotine EC compared to NRT for smoking cessation; [Summary of findings 2](#) Nicotine EC compared to non-nicotine EC for smoking cessation; [Summary of findings 3](#) Nicotine EC compared to behavioural support only/no support for smoking cessation

Data on our outcomes of interest are summarized below. Due to the volume of data available, some relevant information is hosted on a companion repository; these data are open-access and can be found at <https://doi.org/10.5287/bodleian:JbEwdM7d>. They are referred to below as supplemental tables. Forest plots are available through 'analysis' links; for some outcomes, benefit is plotted on the right, for others on the left. This is due to direction of effect, e.g. an increase in cessation is a benefit, whereas an increase in a carcinogen is not.

Direct comparisons between nicotine EC and other pharmacotherapies

Comparisons reported here include cartridge and refillable nicotine ECs versus NRT, and cartridge nicotine ECs versus varenicline. Only randomized controlled trials contribute data.

Cessation

Pooled data from three studies (2 cartridge, 1 refillable), all of which we rated at low risk of bias, showed higher quit rates in people randomized to nicotine EC than to NRT (RR 1.69, 95% CI 1.25 to 2.27; $I^2 = 0\%$; 1498 participants; [Analysis 1.1](#)). One study ([loakeimidis 2018](#)), available as a conference presentation only and considered at high risk of bias due to inconsistencies in the data reported and an unclear definition of abstinence, found lower quit rates in people allocated to nicotine EC (cartridge) compared to those allocated to varenicline (RR 0.31, 95% CI 0.11 to 0.82; 54 participants; [Analysis 2.1](#)).

Adverse events

Pooled data from two studies (both considered at low risk of bias) showed no evidence of a difference in the number of participants reporting adverse events (AEs) between nicotine EC and NRT arms (RR 0.98, 95% CI 0.80 to 1.19; $I^2 = 0\%$, 485 participants; [Analysis 1.2](#)). [Hajek 2019](#) did not contribute data to this analysis due to the way in which events were recorded; of their prespecified adverse reactions of interest, nausea was more frequent in the NRT group, throat/mouth irritation was more frequent in the nicotine EC group, and there was little difference in other reactions (see [Supplemental Table 1](#) for more detail).

In [loakeimidis 2018](#), reports of sleep disorders were evenly distributed between groups, and nausea was more common in the varenicline arm than in the nicotine EC arm (see [Supplemental Table 1](#) for more detail).

Serious adverse events

Two studies comparing nicotine ECs with NRT provided data on SAEs; in one ([Lee 2018](#)) none occurred in either arm. In [Hajek 2019](#) ($n = 698$), more events occurred in the nicotine EC arm than in the NRT arm, but the confidence interval was wide and included no difference as well as the possibility of more events in the NRT arm (RR 1.37, 95% CI 0.77 to 2.41; [Analysis 1.3](#)). As noted above, [Bullen 2013](#), which compared nicotine EC, non-nicotine EC, and NRT,

only reported that no serious adverse events (SAEs) occurred that were considered related to study treatment. No events occurred in [loakeimidis 2018](#) ([Analysis 2.2](#)).

Carbon monoxide (CO)

Pooled data from two studies ([Hatsukami 2020](#); [Lee 2018](#); neither considered at high risk of bias) comparing nicotine EC with NRT found that CO levels decreased more in those randomized to nicotine EC, but the point estimate was small, confidence intervals were wide, and statistical heterogeneity was substantial (MD -0.66 ppm, 95% CI -1.94 to 0.62 ; $I^2 = 69\%$, 136 participants; [Analysis 1.4](#)).

Heart rate, blood pressure, and oxygen saturation

Only [Hatsukami 2020](#) contributed data for these outcomes. A small benefit in favour of EC was found for change in heart rate ([Analysis 1.5](#)). No difference was found for blood pressure or blood oxygen saturation, although confidence intervals were wide ([Analysis 1.6](#); [Analysis 1.7](#)).

Toxicants

Again, only [Hatsukami 2020](#) contributed data for these outcomes. For 3-HPMA, 2-HPMA, HMPMA, PheT, and CEMA, point estimates favoured EC but confidence intervals included no difference ([Analysis 1.8](#); [Analysis 1.10](#); [Analysis 1.11](#); [Analysis 1.12](#); [Analysis 1.13](#)). Both AAMA and NNAL decreased more in NRT than in EC groups, with confidence intervals excluding no difference ([Analysis 1.9](#); [Analysis 1.14](#)).

Lung function

[Lee 2018](#) measured change in FEV1 and FEV1/FVC; for both outcomes, point estimates favoured EC over NRT; confidence intervals excluded no difference for FEV1 ([Analysis 1.15](#); [Analysis 1.16](#)).

Nicotine EC alone or versus control

Comparisons reported here include nicotine EC versus non-nicotine EC, and nicotine EC compared to behavioural support only or to no support. In this section, we also report results from studies in which all participants received nicotine EC (cohort studies and randomized studies which did not differ across arms in EC provision, device generation, or nicotine content).

Cessation

Randomized controlled trials

Quit rates were higher in nicotine EC groups than in comparator groups. Compared to EC without nicotine (placebo EC), pooled results showed nicotine EC produced higher quit rates (RR 1.71, 95% CI 1.00 to 2.92; 3 studies of cartridge devices, 802 participants; $I^2 = 0\%$; [Analysis 3.1](#)). Confidence intervals indicated that potential effects could extend to include no benefit over non-nicotine EC, but the effect size increased and the confidence interval no longer included one when we removed the one study at high risk of bias ([Lucchiari 2020](#)). The effect was more pronounced when comparing nicotine EC to behavioural support only or to no support (RR 2.50, 95% CI 1.24 to 5.04; 4 studies (2 refillable, 2 cartridge), 2312 participants; $I^2 = 0\%$; [Analysis 4.1](#)). All studies in this comparison were at high risk of bias in at least one domain.

Data from other studies

Eight studies provided all participants with nicotine EC and assessed abstinence at six months or longer (Table 1; 1 refillable, 6 cartridge, 1 not specified). The highest proportion of quitters was observed in Ely 2013 (cartridge), in which all participants (n = 48) used EC and 18 used additional pharmacotherapy: 44% of participants were abstinent at six months. The lowest quit rates were seen in two studies where participants were not motivated to quit at baseline: in Caponnetto 2013b, 14% of participants were abstinent at 12 months, and in Polosa 2011 23% of participants were abstinent at six months, but this fell to 13% at 24 months (both studies used cartridge devices).

Adverse events

Randomized controlled trials

Pooled data from two studies (neither at high risk of bias) showed no evidence of a difference in the number of participants experiencing adverse events when comparing nicotine EC to non-nicotine EC (RR 1.00, 95% CI 0.73 to 1.36; $I^2 = 0\%$; 346 participants; Analysis 3.2). When comparing nicotine EC to behavioural support only or to no support, more people in the groups randomized to nicotine EC reported experiencing adverse events (RR 1.17, 95% CI 1.04 to 1.31; $I^2 = 28\%$; 3 studies, 516 participants; Analysis 4.2). All three studies in this analysis were rated at high risk of bias.

A further five randomized controlled trials provided adverse event or related data for this comparison, but could not be included in the meta-analysis due to the way in which data were presented (see Supplemental Table 1). In the studies comparing nicotine EC to non-nicotine EC, one found similar event rates across arms (Caponnetto 2013a), and two reported more events in the nicotine EC arms (Felicione 2019; Tseng 2016). In a further study comparing nicotine to non-nicotine EC, events were reported by type, with an increase in some seen in the nicotine group and an increase in others seen in the non-nicotine group (Lucchiari 2020). In the one study comparing nicotine EC to behavioural support only, there was an increase in sinonasal symptoms in the group receiving nicotine EC (Kumral 2016).

Data from other studies

Fifteen studies provided all participants with nicotine EC and assessed adverse events at one week or longer (see Supplemental Table 1). In the seven studies which tracked event rates over time, six showed adverse events reducing over time (Bell 2017; Caponnetto 2013b; Goniewicz 2017; Polosa 2011; Polosa 2014b; Pratt 2016). Hickling 2019 showed no change. The most commonly-reported adverse events were throat/mouth irritation, headache, cough, and nausea.

Serious adverse events

Randomized controlled trials

Four studies compared nicotine EC with non-nicotine EC and reported data on SAEs; in three of these, no events occurred, so results could not statistically contribute to the meta-analysis, although they are included in the forest plots for descriptive purposes. In the one study (n = 255) where events occurred, more were reported in the non-nicotine arm (RR 0.25, 95% CI 0.03 to 2.19; Analysis 3.3). The data from this study (NCT02417467) came from a clinical trial record and hence details were limited; we considered the study to be at unclear risk of bias.

Bullen 2013, which compared nicotine EC, non-nicotine EC, and NRT, only reported that no SAEs occurred that were considered related to study treatment. In a study in people experiencing homelessness (ISRCTN14140672), SAEs were not reported, but authors report that four to seven participants in the usual-care arm and five to seven participants in the nicotine EC arm visited Accident & Emergency services at a hospital. Further detail can be seen in Supplemental Table 2.

Data from other studies

Seven studies provided all participants with nicotine EC and reported SAEs at a week or longer (Supplemental Table 2). In five of these (Bell 2017; Caponnetto 2013b; Humair 2014; Polosa 2011; Valentine 2018), authors report that no SAEs occurred. In NCT02648178 (19 participants), one death occurred (no further detail provided). Hickling 2019 (50 participants) recruited participants from mental health settings; five SAEs were recorded during the study, all of which were psychiatric hospitalizations. None were considered related to study treatment.

Carbon monoxide

Randomized controlled trials

Pooled data from two trials (neither considered at high risk of bias) comparing nicotine EC with non-nicotine EC found lower exhaled CO levels in people randomized to nicotine EC (MD -2.44 ppm, 95% CI -3.91 to -0.97; 171 participants; Analysis 3.4). Although statistical heterogeneity was substantial ($I^2 = 71\%$), point estimates in both studies favoured nicotine EC. Three further randomized studies measured CO levels in those assigned to nicotine EC and those assigned to non-nicotine EC, but did not present data in a way that could be pooled: George 2019 did not compare data by group; Tseng 2016 reports no between-group differences; and Meier 2017 found a slightly higher CO reading in those using nicotine EC, but the clinical and statistical significance of this difference was not clear (see Supplemental Table 3 for more detail). These data are from all study participants based on group randomized, not on subsequent EC or cigarette use.

Pooled data from five studies comparing nicotine EC to behavioural support alone or no support resulted in a high I^2 value (93%); pooled results are not presented here (see Analysis 4.4 for individual study data). Heterogeneity was primarily driven by magnitude rather than direction of effect, with results generally favouring nicotine EC. Two further trials reported data which could not be included in a meta-analysis. Walele 2018 compared nicotine EC to cigarettes and found CO levels declined in the EC group and remained similar to baseline in the cigarette group. Veldheer 2019 compared nicotine EC with a cigarette substitute (non-pharmacological); change in CO was similar between groups. Further detail can be seen in Supplemental Table 3.

Data from other studies

Sixteen studies provided all participants with nicotine EC and reported data on CO at one week or longer. In the 15 studies that presented change over time, CO declined from baseline, although in Ikonomidis 2018 CO levels were equivalent to baseline again at 24 weeks, and in Polosa 2014b a decline was observed in people who quit smoking or reduced cigarette consumption by at least half, but not in those who continued smoking at least half as many cigarettes as they had from baseline. Further detail can be found in Supplemental Table 3.

Electronic cigarettes for smoking cessation (Review)

Heart rate

Randomized controlled trials

One RCT ([Caponnetto 2013a](#)) provided data on heart rate and compared nicotine EC with non-nicotine EC; there was a greater decrease in heart rate in the nicotine EC arm (MD -2.80, 95% CI -3.85 to -1.74; 141 participants; [Analysis 3.5](#)). This was comparable with findings from the one RCT ([Hatsukami 2020](#)) comparing nicotine EC with no pharmacotherapy, which also found a greater reduction in the EC arm (MD -2.70, 95% CI -4.25 to -1.15; 90 participants; [Analysis 4.5](#)).

A further three RCTs provided data on heart rate which could not be included in a meta-analysis. [George 2019](#) compared nicotine to non-nicotine EC and found no difference in heart rate between arms; [Walele 2018](#) compared a nicotine EC with a traditional cigarette and reported "no clinically significant changes", and [Veldheer 2019](#) found decreases in both the nicotine EC and QuitSmart cigarette substitute groups, with the decrease being slightly greater in the latter group. See [Supplemental Table 4](#) for further information.

Data from other studies

Five studies in which all participants received a nicotine EC also reported data on heart rate; changes were minimal and directions of effect were mixed (see [Supplemental Table 4](#)).

Blood pressure

[Caponnetto 2013a](#) found no difference in the change in systolic blood pressure (BP) between nicotine EC and non-nicotine EC arms (MD 0.60, 95% CI -0.99 to 2.19; 141 participants; [Analysis 3.6](#)). Similarly, [Hatsukami 2020](#) found no difference in the change in blood pressure when comparing nicotine EC to cigarettes (MD 1.35, 95% CI -0.29 to 2.99; 90 participants; [Analysis 4.6](#)). Three further RCTs measured change in blood pressure but presented results in such a way that they could not be pooled. [George 2019](#) compared nicotine EC and non-nicotine EC and combined data from both groups; BP declined over time. Compared to a QuitSmart cigarette substitute, [Veldheer 2019](#) found EC led to a greater reduction in BP. [Walele 2018](#) found "no clinically significant changes" when comparing nicotine EC to a conventional cigarette at two weeks. Further data can be found in [Supplemental Table 5](#).

Five studies which provided nicotine EC to all participants reported change in blood pressure; results were mixed and small ([Hickling 2019](#); [Ikonomidis 2018](#); [Oncken 2015](#); [Van Staden 2013](#); [Walele 2018](#); see [Supplemental Table 5](#)).

Oxygen saturation

[Hatsukami 2020](#) found a small increase in blood oxygen saturation when comparing nicotine EC to cigarettes (MD 0.50%, 95% CI 0.31 to 0.69; 89 participants; [Analysis 4.7](#)). [Van Staden 2013](#), a short-term pre-post study which measured outcomes after two weeks of EC use, found that people who smoked who switched to ECs had significant improvement in blood oxygen saturation (96.2% (SD 1.8) to 97.5% (SD 1.3); 1.3% increase, 95% CI 0.6 to 2.1; $P = 0.002$).

Toxicants

All randomized controlled trials measuring these outcomes compared nicotine EC with no pharmacotherapy.

Two trials measured change in **3-HPMA** (one at high risk of bias). In both, the point estimate favoured the EC arm, but statistical heterogeneity was substantial ($I^2 = 97%$), reflecting differences in magnitude of effect. We therefore do not present a pooled result, but data from the studies can be seen in [Analysis 4.8](#). Four further studies in which all participants were given nicotine EC measured 3-HPMA; all found reductions over time ([Supplemental Table 6](#)).

Three trials measured change in **NNAL** (two at high risk of bias; [Analysis 4.9](#)). Two of the three studies found results favouring nicotine EC, but for the third the point estimate went in the opposite direction; statistical heterogeneity was again high ($I^2 = 81%$), so pooled results are not presented. [Pulvers 2018](#), which provided all participants with nicotine EC, found a reduction in NNAL over time ([Supplemental Table 6](#)).

One trial found reductions in **2-HPMA** and **AAMA** compared to control ([Analysis 4.10](#); [Analysis 4.14](#)), and a further two studies in which all participants received nicotine EC found reductions in both of these measures over time ([Supplemental Table 6](#)).

One trial found reductions in **S-PMA** compared to control ([Analysis 4.15](#)); this was consistent with the one study ([Goniewicz 2017](#)) in which all participants received nicotine EC that measured S-PMA, where levels declined over time ([Supplemental Table 6](#)).

In single trials, changes favoured EC for reductions in HMPMA ([Analysis 4.11](#)), PheT ([Analysis 4.12](#)), and CEMA ([Analysis 4.13](#)). Of the 18 remaining measurements in studies where all participants received an EC, 13 reduced over time and five increased ([Supplemental Table 6](#)).

Lung function

[Caponnetto 2013a](#) measured a number of lung function parameters. FeNO increased more in the nicotine EC than the non-nicotine EC group (MD 2.35, 95% CI 1.78 to 2.92; 90 participants; [Analysis 3.7](#)). No difference was found between nicotine and non-nicotine EC for FEV1, FVC, or FEV1/FVC ([Analysis 3.8](#); [Analysis 3.9](#); [Analysis 3.10](#)). [Veldheer 2019](#), which randomized participants to nicotine EC or the QuitSmart cigarette substitute, measured change in a number of lung function parameters: direction of effect was mixed across these, with no statistically or clinically significant between-group differences at 12 weeks ([Supplemental Table 7](#)).

Two studies which provided all participants with nicotine EC measured change in lung function over time: [Hickling 2019](#) found an increase in peak flow, and [Oncken 2015](#) reported "no significant differences" in airway function ([Supplemental Table 7](#)).

Combination therapy: nicotine EC and NRT

This section covers two comparisons: studies in which all arms received NRT and participants were randomized to nicotine EC or non-nicotine EC, and studies in which all participants received NRT and one arm was randomized to nicotine EC in addition. All studies contributing data are randomized controlled trials. No studies in this group reported data on heart rate, blood pressure, oxygen, or toxicants.

Cessation

Two trials (both at high risk of bias, both testing refillable devices) in which all participants received NRT compared nicotine EC to non-nicotine EC; pooled results favoured nicotine EC (RR 1.77, 95% CI

1.07 to 2.94; $I^2 = 0\%$; 1039 participants; [Analysis 5.1](#)). [Walker 2020](#) also compared nicotine EC + NRT to NRT alone; the point estimate favoured nicotine EC but the confidence interval was wide and included no difference ([Analysis 6.1](#)).

Adverse events

The two trials (both at high risk of bias) in which nicotine ECs were compared to non-nicotine ECs in participants receiving NRT found no evidence of a difference in the number of people experiencing AEs between arms; data from [Walker 2020](#) can be seen in [Analysis 5.2](#); [Baldassarri 2018](#) reported results combined across groups but noted "no significant differences by treatment group" ([Supplemental Table 1](#)).

The two trials comparing nicotine EC + NRT to NRT alone that contributed data to this outcome were both at high risk of bias. Statistical heterogeneity was high when combining data ($I^2 = 79\%$) and hence we do not present pooled results. In one study ([Walker 2020](#)), AEs were lower in the EC group and the confidence interval excluded no difference, while in the other study ([Guillaumier 2018](#)) AEs were higher in the EC group but the confidence interval was wide ([Analysis 6.2](#)).

Serious adverse events

[Walker 2020](#), comparing nicotine EC with non-nicotine EC as adjuncts to NRT, had fewer SAEs in the nicotine EC group than in the non-nicotine EC group, but the confidence interval includes no difference ([Analysis 5.3](#)).

Four studies provided data on SAEs and compared nicotine EC + NRT to NRT alone. The pooled estimate favoured the NRT-alone group, but again the confidence interval was wide and included no difference (RR 1.41, 95% CI 0.60 to 3.31; $I^2 = 0$; 930 participants; [Analysis 6.3](#)).

Carbon monoxide

[Walker 2020](#) (which compared nicotine EC + NRT, non-nicotine EC + NRT, and NRT alone) measured change in CO levels but did not report data in a way that could be pooled. CO declined over time, with the greatest reduction seen in the nicotine EC group (see [Supplemental Table 3](#)). [Baldassarri 2018](#), comparing nicotine and non-nicotine EC as adjuncts to NRT, found a slightly greater reduction in CO in the nicotine EC group, but the confidence interval included no clear evidence of a difference ([Analysis 5.4](#)) between groups.

Lung function

[Baldassarri 2018](#), which compares nicotine EC to non-nicotine EC and in which both groups receive NRT, found no between-group differences in FeNO, FEV1, or FVC ([Analysis 5.5](#); [Analysis 5.6](#); [Analysis 5.7](#)); confidence intervals were wide for all outcomes.

Comparisons based on nicotine dose

One randomized trial provided data comparing different doses of nicotine in EC ([Caponnetto 2013a](#)) (although other studies provided a range of doses, these were not randomly assigned). Cessation and adverse event data were not available. No serious adverse events were reported in either arm ([Analysis 7.1](#)). There were no clinical or statistically significant differences between arms for carbon

monoxide, heart rate, blood pressure, or lung function measures ([Analysis 7.2](#) to [Analysis 7.8](#)).

Non-nicotine EC

Although non-nicotine ECs serve as a 'control group' in our primary analysis, due to their behavioural properties they can also be considered an intervention in and of themselves. Comparisons included here are: non-nicotine EC versus NRT; non-nicotine EC versus usual care; and non-nicotine EC as an adjunct to NRT. All contributing data are from randomized controlled trials. None of these studies reported data on change in CO, heart rate, blood pressure, oxygen saturation, toxicants, or lung function.

Cessation

When comparing non-nicotine EC to behavioural support only, [Lucchiari 2020](#) found higher quit rates in participants randomized to non-nicotine EC, but the confidence interval included the possibility of no difference ([Analysis 8.1](#)). When evaluating non-nicotine EC as an adjunct to NRT, [Walker 2020](#) also found higher quit rates in participants randomized to non-nicotine EC, although again the confidence interval included no difference ([Analysis 9.1](#)).

[Lee 2019](#) compared non-nicotine EC with NRT; the point estimate favoured NRT but the confidence interval included no difference ([Analysis 10.1](#)).

Adverse events

[Walker 2020](#) found fewer adverse events in participants receiving non-nicotine EC + NRT compared to NRT alone, with the confidence interval excluding no difference ([Analysis 9.2](#)). [Lee 2019](#) also found that fewer participants receiving non-nicotine EC reported adverse events than those receiving NRT, with the confidence interval excluding no difference ([Analysis 10.2](#)).

Serious adverse events

In [Walker 2020](#), more SAEs occurred in the group randomized to non-nicotine EC + NRT than in the NRT-alone group, but the confidence interval included no difference as well as the potential for a clinically significant difference in favour of the intervention ([Analysis 9.3](#)). No SAEs were reported in either arm of [Lee 2019](#) (non-nicotine EC versus NRT).

DISCUSSION

Summary of main results

This update includes a further 35 studies compared with the previously published version, with substantive changes to conclusions. Our previous two main comparisons, nicotine EC compared to NRT, and nicotine EC compared to non-nicotine EC, now show moderate-certainty evidence of increased quit rates in people assigned to nicotine EC arms ([Summary of findings 1](#); [Summary of findings 2](#)). In absolute terms, pooled data suggest an additional four people for every 100 would quit smoking with nicotine EC compared to non-nicotine EC or to NRT. Most data come from studies of cartridge devices which deliver relatively little nicotine in comparison to newer device models. For the first time, we have studies contributing to a third main comparison: nicotine EC compared to behavioural support only, or to no support; here we also found higher quit rates in people assigned to nicotine EC arms (very low certainty, [Summary of findings 3](#)). In absolute terms,

our calculations suggest a further six people per 100 people would quit if offered a nicotine EC compared to being offered behavioural support alone or no support.

Evidence on adverse events (AEs) and serious adverse events (SAEs) was of low to very low certainty across all comparisons, due to a paucity of data. SAEs were rare, in both intervention and comparator arms, with many of the studies which measured SAEs reporting no such events in either study arm. For nicotine EC compared to non-nicotine EC, pooled data suggest no difference in the number of people experiencing AEs and two fewer people per 100 experiencing SAEs with nicotine EC compared to non-nicotine EC arms, but confidence intervals include no difference. Conversely, data from comparisons between nicotine EC and behavioural support alone or no support suggest an additional 10 people per 100 assigned to nicotine EC may experience AEs, with no difference in the number experiencing SAEs. Compared to NRT, one fewer person per 100 might be expected to experience an AE if assigned to nicotine EC, and two additional people per 100 might be expected to experience an SAE. These figures should be treated with caution, due to large confidence intervals encompassing no clinically significant difference. The small amount of contributing data, and the variation in 'control group' risk across comparisons, reflect different methods of collecting data and different lengths of follow-up. No studies in any of the different comparison conditions detected serious harms considered to be related to EC use.

In this update, we also include studies evaluating nicotine EC as an adjunctive treatment to NRT, and comparisons where non-nicotine EC is considered the intervention treatment. Beyond AEs and SAEs, we consider data on a range of safety- and health-related outcomes, including carbon monoxide and other toxins, lung function, blood pressure, pulse, and oxygen levels. Data on all of these outcome measures are limited; for most outcomes within most comparisons, only one study currently contributes data. Pooled data from two studies in which all participants received nicotine replacement therapy showed that nicotine EC led to higher quit rates than non-nicotine EC, but we judged both studies to be at high risk of bias, meaning the effect remains uncertain.

Overall completeness and applicability of evidence

This field of research and EC devices themselves continue to evolve rapidly. The evidence published since the previous update has important implications for decision-makers; moving forward, we plan to conduct this review as a living systematic review for the next 18 months, meaning we can rapidly incorporate new evidence (see [Appendix 1](#)). This is important, as all of our analyses currently suffer from imprecision.

This update captures data from the past four years, up to January 2020. Subsequent monthly updates will keep this review current. Although studies predominantly came from the USA and UK, overall this review covers data from 13 countries; geographical range in studies may be particularly important in this area, due to the marked differences in EC regulation between countries; for example, studies conducted in countries that limit nicotine dose in EC or allow only certain EC devices to be tested may observe less pronounced effects on quitting. This review includes studies in some 'harder to reach' populations, including people not motivated to quit smoking, people with substance misuse disorders, and people experiencing homelessness. Quit rates in these groups are traditionally lower, which may make it more

difficult to detect effects of interventions. However, it could be that these groups may particularly stand to benefit from EC if they are effective, because in absolute terms conventional cessation methods are often not as effective for them.

As well as the rapid pace of research in this field, EC technology itself continues to evolve, which poses a challenge when considering the applicability of our evidence to the present. We had marked down the certainty of our data in the 2016 update, as the devices tested in the trials were first-generation 'cig-a-like' devices which did not deliver nicotine well, meaning the studies may have yielded more conservative estimates than would be seen with newer models, as newer devices and models have tended towards improved nicotine delivery. In this update, we have more data from newer devices, although there will always be a time lag between current devices and the research evidence available. None of the analyses of our primary outcomes signified substantial levels of statistical heterogeneity, despite the fact that different devices were used in the included studies. However, this could be because confidence intervals were wide for individual studies, and does not rule out clinically significant differences in effects between EC types. As further data emerge, we hope to be able to formally test for differences in subgroup analyses, and ideally over time in head-to-head comparisons of different device types. Our review now includes data on both (disposable) 'cartridge' (26 studies report using) and 'refillable' (19 studies report using) device types, but studies of pod devices are still notably absent.

The adverse effects described in both the RCT and cohort studies continue to look similar, regardless of the brand of EC used or nicotine content, with placebo and nicotine-containing ECs showing similar numbers and types of adverse events in direct comparisons. They also reflect what is reported in survey data ([Dawkins 2013b](#); [Etter 2011](#)), so we believe that they are broadly applicable to most EC brands.

There has been concern raised that the dual use of cigarettes and EC may expose people to greater health risks, including higher nicotine levels. However, given that people who smoke like to maintain relatively stable blood nicotine levels ([Russell 1990](#)), receiving nicotine from an alternative source (i.e. EC) is likely to reduce nicotine intake from cigarettes, which should be accompanied by a reduction in smoke and toxin intake ([Fagerström 2004](#)). In a study assessing biochemical changes exclusively in dual-users, there was a significant decrease in cotinine, exhaled carbon monoxide levels, and urinary 3-HMPA ([McRobbie 2015](#)). These results are supported by longer-term studies in people who smoke and were provided with ECs, which found decreases in exhaled carbon monoxide among dual-users, and no significant increases in cotinine levels across the study populations ([Adriaens 2014](#); [Pacifci 2015](#); [Polosa 2011](#); [Polosa 2014b](#)).

The structure of our analyses follows standard practice of the Cochrane Tobacco Addiction Group, i.e. evaluating outcomes on an intention-to-treat basis, meaning our pooled results represent the effect of *offering an EC intervention*. This is different from evaluating the per protocol effect, or the effect only in those who use the EC to quit smoking entirely, or continue to smoke whilst also using EC. Some of our included studies have also assessed data using these groupings and we have attempted to note this in the supplemental tables. Although pragmatic and hopefully of use to those designing and delivering interventions, we acknowledge that our intention-to-treat approach limits the ability to use the data presented here

to draw conclusions about biomarkers in subgroups of participants based on subsequent EC use/smoking profiles.

Certainty of the evidence

We consider the certainty of the evidence below as it relates to primary outcomes for our three main comparisons: nicotine EC versus NRT; nicotine EC versus non-nicotine EC; nicotine EC versus behavioural support only/no support ([Summary of findings 1](#); [Summary of findings 2](#); [Summary of findings 3](#)). The certainty of evidence for all other comparisons and outcomes should be considered very low due to a paucity of data.

Our 'Summary of findings' tables and assessments of certainty are based on the evidence from randomized controlled trials (RCTs). The cohort studies that we include were all deemed to have high risks of bias, which is inherent in the study design. Data presented from these studies need to be interpreted with caution. However, data from cohort studies was reassuringly consistent with data from RCTs.

Although we rated most of our included studies at high risk of bias, this did not impact on the certainty of evidence for comparisons between nicotine and non-nicotine EC, or between nicotine EC and NRT. For the latter, we judged all three studies to be at low risk of bias overall. For the former, removing the one study at high risk of bias increased the effect estimate for our efficacy outcome. Risk of bias decreased our certainty in the effect estimates for our nicotine EC versus behavioural support only/no support comparison, as all included studies were rated at high risk of bias. All of our main comparisons were downgraded for imprecision, due to wide confidence intervals and few events. Other than risk of bias and imprecision, we identified no other issues which decreased the certainty of the primary outcomes for our main comparisons. In the previous version of this review we had downgraded cessation outcomes for indirectness, due to the included studies testing devices that were no longer available due to poor nicotine delivery (we therefore judged it plausible our analyses could be underestimating the effect of devices available at the time the review was published). In this version, we no longer downgrade on this basis, as this update includes a wider range of EC models, including more recent devices, and heterogeneity in outcomes remains low.

Cessation

All three comparisons found effect estimates favouring nicotine EC for smoking cessation. For nicotine EC versus non-nicotine EC and for nicotine EC versus NRT, we judged the evidence to be of moderate certainty, meaning we think the true effect is likely to be close to the estimate of effect. For nicotine EC versus behavioural support only/no support, we judged the evidence to be of low certainty, meaning our confidence in the estimate is limited. Another way to look at this, however, is to consider that nicotine EC versus non-nicotine EC comparisons isolate the effect of nicotine as provided by an EC, and nicotine EC versus NRT comparisons isolate the effect of the sensorimotor elements provided by an EC. Given that both of these comparisons find a benefit of nicotine EC for smoking cessation, it might logically follow that the comparison between nicotine EC and behavioural support only/no support would find a benefit in favour of nicotine EC, since this comparison would capture both pharmacological and sensorimotor mechanisms of effect. This increases our confidence

in the effect of nicotine EC when compared to behavioural support alone or to no support.

Adverse and serious adverse events

For all three comparisons, effect estimates of adverse events and serious adverse events were judged to be of low or very low certainty, with the main problem being imprecision. This means the true effect may be substantially different from the estimate of the effect. None of the analyses signalled serious harm, nor did complementary data from cohort studies, but unlike our cessation analyses, many of the confidence intervals encompassed the possibility of both clinically significant harm and clinically significant benefit. This uncertainty should reduce as more studies become available.

Potential biases in the review process

We consider the review process used to be robust. For outcome assessment, we followed the standard methods used for Cochrane Tobacco Addiction Review Group cessation reviews. Our search strategy included the Cochrane Tobacco Addiction Group Specialized Register and we were able to capture a number of ongoing studies. However, there may be unpublished data that our searches did not uncover. We also considered participants lost to follow-up as continuing to smoke, which is standard practice in this field.

Three of our authors are authors of included studies. These authors were not involved in the decisions about inclusion of their studies, or in data extraction or 'Risk of bias' assessment for these studies.

Agreements and disagreements with other studies or reviews

This Cochrane Review aligns with but updates the conclusions of the 2018 U.S. National Academies of Science, Engineering, and Medicine's Consensus Study Report, *Public Health Consequences of E-cigarettes* ([NASEM 2018](#)), which reviewed literature published through August 2017 to address the question, "Do e-cigarettes help smokers quit smoking combustible tobacco cigarettes?". Focusing on RCTs and existing systematic reviews, it used a prespecified Level of Evidence framework to develop conclusions. The report's overall conclusion was that there was "limited evidence that e-cigarettes may be effective aids to promote smoking cessation." Based on the RCTs available, it concluded that there was "moderate evidence" that e-cigarettes containing nicotine were more effective for cessation than e-cigarettes without nicotine, but "insufficient evidence" about the effectiveness of e-cigarettes compared to no treatment or to FDA-approved smoking cessation treatments. Our review contradicts this latter point, as we now find moderate-certainty evidence of benefit when comparing nicotine EC with NRT; this is primarily due to a large RCT published after [NASEM 2018](#).

Findings are also broadly consistent with those from other reviews published in the past two years. A 2018 review by Liu et al (searches to 2017) concluded that e-cigarettes are "moderately effective" for smoking cessation, and found adverse events frequently occurred, with mouth and throat irritation, anxiety, depressed mood, nausea, and insomnia most commonly reported ([Liu 2018](#)). A 2019 review restricted to studies in vulnerable groups found limited evidence assessing effectiveness and did not identify any serious adverse events ([Gentry 2019](#)). A 2020 review which did not evaluate effectiveness and focused only on safety found very

low- to moderate-certainty evidence on a range of possible adverse effects, with the most frequently reported being cough, dry mouth, shortness of breath, irritation of the mouth and throat, and headache (Amato 2020).

Reviews of ECs for policymaking are often broader in scope than our review, which focuses exclusively on their role in supporting smoking cessation in people who smoke. There remain unanswered questions about the impact of EC availability and use on young people; we hope to evaluate this in a separate review.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence suggesting nicotine EC can aid in smoking cessation is consistent across several comparisons. There was moderate-certainty evidence, limited by imprecision, that EC with nicotine increased quit rates at six months or longer compared to non-nicotine EC and compared to NRT. There was very low-certainty evidence (limited by risk of bias as well as imprecision) that EC with nicotine increased quit rates compared to behavioural support alone or to no support.

The effect of nicotine EC when added to NRT was unclear.

None of the included studies (short- to mid-term, up to two years) detected serious adverse events considered possibly related to EC use. The most commonly-reported adverse effects were throat/mouth irritation, headache, cough, and nausea, which tended to dissipate over time. In some studies, reductions in biomarkers were observed in people who smoked who switched to vaping, consistent with reductions seen in smoking cessation.

Implications for research

Further randomized controlled trials of nicotine EC are needed, following up participants at six months or longer. Studies with active comparators (i.e. comparing nicotine EC to frontline smoking cessation pharmacotherapies) are likely to be of particular use to decision-makers. All studies (including uncontrolled intervention cohort studies) should aim to assess the safety profile of electronic cigarettes for as long as possible (the current review only includes data up to two years), and ideally be powered to detect differences in safety outcomes, including adverse events and serious adverse events. Evidence from one well-conducted RCT suggests that people who quit smoking using EC may continue to use EC longer than they might use other stop-smoking pharmacotherapies, making assessments of their long-term safety profile particularly

important. Safety results should be presented in both absolute and relative risk terms (in comparison to the risks of continuing to smoke tobacco).

Studies should offer recent devices to participants, to be most representative of what will be on the market at the time results are released. Data on pod-type EC are particularly lacking. Protocols and statistical analysis plans should be registered in advance and openly available.

Further RCTs need to be adequately powered. Trials of pod devices would be of particular value, as would RCTs providing EC in a way that would be used in real-world settings (e.g. taking into account individual preferences for strengths and flavours of e-liquids and even EC devices, and also allowing for changes in preferences over time).

Further reviews, using best available methods, need to be conducted to evaluate the possible relationships between EC use and availability and youth uptake of EC and conventional cigarettes.

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McRobbie 2014

McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No: CD010216. [DOI: [10.1002/14651858.CD010216.pub2](https://doi.org/10.1002/14651858.CD010216.pub2)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Adriaens 2014
Study characteristics

Methods	Design: 3-armed RCT; with all participants then assigned to nicotine EC (treated as cohort in this review)
	Recruitment: Advertisement on university website, flyers on university campuses, emails to personnel and advertisement in local newspaper
	Setting: Community and laboratory, Belgium

Electronic cigarettes for smoking cessation (Review)

Adriaens 2014 (Continued)

Study start date/end date: Not stated

Participants	<p>Total N: 48 provided data</p> <p>Randomized to: EC1 16; EC2 17; control 17</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Smoker for at least 3 years, • Smoking at least 10 cpd, not intending to quit in the near future but willing to try a less unhealthy alternative <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Diabetes; • Severe allergies; • Asthma or other respiratory diseases; psychiatric problems; • Dependence on chemicals other than nicotine; • Pregnancy; • Breastfeeding; • Hypertension; • CV disease; • Currently using any kind of smoking cessation therapy; prior use of EC <p>56% women, mean age 44, mean cpd 19, mean FTCD 5.79, all unwilling to quit with no baseline EC use</p>
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Interventions	<p>EC: Refillable</p> <p>Intervention: 2 intervention groups (EC1 and EC2) provided with EC and instructed to use EC or smoke ad libitum (EC1 group provided with Joyetech eGO-C, EC2 group provided with Kanger T2-CC) and provided guidance on EC use. For both types, provided 30 mL bottles of tobacco-flavoured e-liquid (Dekang "Turkish Blend"), containing 18 mg/mL of nicotine. 4 bottles at baseline replenished at 4 weeks, keep any remaining after 8 weeks</p> <p>Control: 6 bottles for 2 months at week 8 (half offered EC1, half offered EC2); no guidance on use</p>
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Outcomes	<p>3 lab sessions over 2 months (weeks 1, 4 and 8), plus online questionnaires, further follow-up at 3 and 6 m after last lab session</p> <p>Cessation: measured but definition not provided, validated with eCO 5 ppm or less</p> <p>Adverse events and biomarkers: eCO, salivary cotinine measured during lab sessions. Also collected craving and withdrawal symptoms via lab sessions, "benefits and complaints", mood, EC usage</p>
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Study funding	<p>"No external funding for this study was obtained. Electronic cigarettes and e-liquids were purchased at E-cig4U (' t Rond 10, 4285 DE Woudrichem, The Netherlands; http://www.e-cig4u.nl/) with balances of previous research funds obtained by Frank Baeyens."</p>
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Author declarations	<p>The authors declare no conflict of interest</p>
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Notes	<p>Randomization was for short-term outcomes only</p> <p>Additional data provided from authors</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization was performed by using a randomization tool available on the website www.randomizer.org

Adriaens 2014 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unblinded but as this review only includes data on objective measurements and not cessation judged unlikely to affect outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unblinded but as this review only includes data on objective measurements and not cessation judged unlikely to affect outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	36 out of 48 completed follow-up (11/16 in EC1 group, 12/17 in EC2 group, 13/17 in control group)
Selective reporting (reporting bias)	Unclear risk	Outcome reporting somewhat non-traditional; for example, collecting complaints but not explicitly adverse events, and incidence of AEs not reported. Unable to find prospectively-registered protocol

Baldassarri 2018
Study characteristics

Methods	<p>Design: Randomized parallel-assignment double-blind trial</p> <p>Recruitment: outpatient pulmonary and primary care clinics, Tobacco Treatment Service, referrals from medical providers</p> <p>Setting: Hospital outpatient and primary care clinics, USA</p> <p>Study start date: October 2014; Study end date: June 2014</p>
Participants	<p>Total N: 40</p> <p>N per arm: Non-Nicotine: 20; Nicotine EC: 20</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Age 18 years or older • Smoking 1 or more cpd • Willing to quit smoking <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Unstable psychiatric or medical conditions requiring hospitalisation within the past 4 months; • Acute coronary syndromes or stroke within the past 30 days; • History of allergic reactions to adhesives; • Women who were pregnant, nursing, or not practicing effective contraception; • Current use of an EC for the purpose of stopping tobacco cigarette smoking <p>Women: 52.5%; Mean age: 53 Mean cpd: 17 Mean FTND: 5.9; motivated to quit</p> <p>E cigarette use at baseline: Not reported</p>
Interventions	EC: Refillable

Baldassarri 2018 (Continued)

Both groups received standard care (8 weeks nicotine patch and counselling) and were randomized to **nicotine EC** or **non-nicotine EC**.

EC: eGO style EC (650 mAh battery, EVOD clearomizer, 3.7 V, 1.8 Ω single bottom coil), provided with e-liquid purchased from an online vape shop (0 mg/ml or 24 mg/ml nicotine strength, 70/30 propylene glycol/vegetable glycerin, tobacco flavour); Instructed to use it as needed as a substitute for tobacco to try to satisfy cravings to smoke. If the patch alone proved adequate to prevent withdrawal and smoking cravings, the participant was advised not to use the EC. Additional EC devices, replacement coils, and liquid were provided as needed for the first 8 weeks of the study

Outcomes	<p>Questionnaires and CO measurements taken at baseline, treatment visits at week 2, 4, 6, 8 and follow-up at week 24</p> <p>Cessation: 7-day point prevalence abstinence, eCO ≤ 6 ppm</p> <p>Adverse events and biomarkers: Side effects were measured although it is unclear whether a questionnaire with prespecified symptoms was used</p> <p>Spirometry and FeNO at baseline and 6-month follow-up</p> <p>Other outcomes: Change in reported number of cpd at weeks 8 and 24; Change in per cent predicted FEV1 and FVC from baseline to week 24, and EC use patterns</p>
Study funding	"Funding for this study 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. NHLBI had no role in the study design, collection, analysis, or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication."
Author declarations	"Dr. Toll received a grant from Pfizer for medicine only for a research study, and he receives funding as an expert witness in litigation filed against the tobacco industry. Dr. Chupp received grants from NIH, Genetech, Glaxo Smith Kline, Astra Zeneca/Medimmune and Boston Scientific. He received consulting/speaking fees from Genetech, Astra Zeneca/Medimmune, Mannkind, and Boston Scientific. There are no other conflicts of interest for the remaining authors."
Notes	<p>New for 2020 update. Study listed as ongoing study NCT02498145 in 2016 review update</p> <p>Additional data provided from authors</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomized using a random number generator with 1:1 blocked randomization (block size n= 8)."
Allocation concealment (selection bias)	Unclear risk	Both groups received standard care (nicotine patch and counselling) and were randomized to: nicotine EC or non-nicotine EC (no further detail given)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment assignment was blinded to both the investigators and participants"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	CO biochemically validated
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Quote: "The study had a modest loss to follow-up (20%) at week 24."</p> <p>Number lost to follow-up in each group is not reported in the paper</p>

Baldassarri 2018 (Continued)

Week 24 retention rate: Nicotine EC group: 19/20 (95%); Non-nicotine EC group: 13/20 (65%); > 20% difference between groups

Selective reporting (reporting bias)	Low risk	Outcomes reported align with those listed in the clinicaltrials.gov record. (registered 2015; prior to study completion in 2016)
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Bell 2017
Study characteristics

Methods	Design: Pragmatic, uncontrolled, mixed-methods trial Recruitment: Targeted settings for people with HIV Setting: Community, Brisbane, Australia Study start date: 21 February 2017; Study end date: 26 October 2017
Participants	Total N: 30 Inclusion criteria: <ul style="list-style-type: none"> • Diagnosis of HIV • Aged 18 years, or over • Smoke \geq 5 cpd at the time of enrolment into the trial • Have been smoking for at least 12 months • Willing to attempt to quit tobacco smoking after study enrolment Exclusion criteria: <ul style="list-style-type: none"> • Participating in a smoking-cessation programme • Pregnant or breastfeeding or planning to be during trial period • Experienced chest pain, or another cardiovascular event or procedure in the last month • Being treated with oxygen therapy Inclusion based on specific population characteristic: People living with HIV 29 participants identified as male, and 1 participant did not identify as male or female; Mean age: 42; Mean cpd: 18 EC use at baseline: 46.7% (n = 14) Never tried; 50% (n = 15) Tried, never used for an extended period; 3.3% (n = 1) Used on a regularly (weekly) basis Willing to attempt to quit
Interventions	EC: Refillable Single-arm study. Print materials to help quit smoking. Provided booklet with instructions on how to use, store and handle EC; copies of device user manuals. Given Innokin Endura T18 [®] vaporiser kit, Innokin Endura T22 [®] vaporiser kit, 4 spare coils, 1 wall charger, 10 x 10-mL bottles of Nicophar [®] 12 mg nicotine e-liquid. Supplies to last 12 weeks
Outcomes	Weeks 1, 4, 8, 12, 24; Self-report and semistructured interviews Cessation: 7 days point prevalence at weeks 4, 8, 12 and 24. Continuous abstinence at weeks 12 and 24. No biochemical validation Adverse events

Bell 2017 (Continued)

Other outcomes: Acceptability and use of trial products; Number of quit attempts

Study funding	"This work was supported by the HIV Foundation Queensland. The funder will play no role in the analysis and interpretation of results. All trial products were purchased and the suppliers have no involvement in the conduct of the trial or the interpretation or reporting of the results."
Author declarations	"No other authors declare conflicts of interest. Mark Boyd has received research grant funding (paid to the institution) from AbbVie, Gilead and Merck and received honoraria for participation in HIV Advisory Boards and for the preparation and delivery of educational materials from AbbVie, Boehringer-Ingelheim, Bristol Myers Squibb, Gilead, Janssen-Cilag, Merck and ViiV Healthcare."
Notes	Additional data provided from authors. New for 2020 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled study
Allocation concealment (selection bias)	High risk	Uncontrolled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "At Week 24, 26 of the 30 participants who enrolled in the study were followed up." (confirmed by authors)
Selective reporting (reporting bias)	Low risk	Study not published at time of data extraction, but study protocol published

Bullen 2013
Study characteristics

Methods	<p>Design: 3 parallel groups RCT</p> <p>Recruitment: People who smoke recruited from the community, via newspaper advertisements</p> <p>Setting: Research Unit, New Zealand</p> <p>Study start date: 6 September 2011; Study end date: 5 July 2013</p>
Participants	<p>Total N: 657. 289 nicotine EC (NEC), 295 patch, 73 non-nicotine EC (PEC)</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • 18 years of age or older; • Smoked 10 or more cpd over past year; • Wanted to stop smoking <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Pregnant and breastfeeding • Using cessation medicines or using other support to quit • Heart attack, • Stroke, • Severe angina in the last 2 weeks,

Bullen 2013 (Continued)

- Poorly-controlled medical disorder,
- Allergies,
- Other chemical dependence

62% women, mean age 42, 1/3 NZ Maori, smoking 18 cpd, mean FTND score 5.5

Motivated to quit

E cigarette use at baseline: Not specified

Interventions	<p>EC: Cig-a-like</p> <p>Randomized to NEC, PATCH or PEC use for 13 weeks (from 1 week prior to TQD)</p> <ul style="list-style-type: none"> • NEC: Elusion brand 16 mg cartridges; sent product via courier • PATCH: 21 mg/24-hour patch; sent voucher to exchange for NRT at pharmacy (dispensing costs covered) • PEC: As per EC, but 0 mg cartridges <p>All participants referred to Quitline and received an invitation to access phone- or text-based support. This was accessed by < 10%</p>
Outcomes	<p>Sustained (≤ 5 cigarettes allowed) validated (exhaled breath CO < 10 ppm) abstinence at 6 months</p> <p>$\geq 50\%$ self-reported reduction in baseline cigarettes at 6 months</p> <p>Participants reporting any adverse events</p> <p>Proportion of AEs that were serious</p> <p>Proportion of unrelated AEs</p>
Study funding	Health Research Council of New Zealand
Author declarations	<p>"We declare that we have received no support from any companies for the submitted work and have no non-financial interests that might be relevant to the submitted work. ML, via his company Health New Zealand, previously did research funded by Ruyan (an e-cigarette manufacturer). CB and HM have done research on Ruyan e-cigarettes funded by Health New Zealand, independently of Ruyan. HM has received honoraria for speaking at research symposia, has received benefits in kind and travel support from, and has provided consultancy to, the manufacturers of smoking cessation drugs. NW has provided consultancy to the manufacturers of smoking cessation drugs, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation drugs. JW has provided consultancy to the manufacturers of smoking cessation medications."</p>
Notes	Accessed support: NEC: 115/289; PATCH: 106/295; PEC: 26/73

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized block randomization
Allocation concealment (selection bias)	Low risk	Computerized via study statistician
Blinding of participants and personnel (performance bias) All outcomes	Low risk	NEC and PEC were blind to treatment condition in relation to one another. No blinding for NEC/PEC vs PATCH conditions, but as NEC and PATCH were both active treatments performance bias judged unlikely

Bullen 2013 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU 22% (all considered to be smoking). Patch group had a higher LTFU and withdrawal than EC (loss to follow-up 17% NEC, 27% patches, 22% PEC). However, minimal difference in per-protocol and ITT analyses
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Caponnetto 2013a
Study characteristics

Methods	<p>Design: 3-arm double-blind randomized controlled trial: EC with 7.2 mg nicotine for 12 weeks; same for 6 weeks followed by 5.2 mg for 6 weeks: EC with no nicotine for 12 weeks</p> <p>Recruitment: Newspaper advertisements</p> <p>Setting: Outpatient clinic, Italy</p> <p>Study start date: April 2010; Study end date: April 2012</p>
Participants	<p>Total N: 300</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Smoked at least 10 cpd for past 5 years; Age 18 - 70 In good health Not currently or intending to quit smoking in the next 30 days <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Symptomatic cardiovascular or respiratory disease Regular psychotropic medicine use Current or past history of alcohol abuse Use of smokeless tobacco or NRT Pregnant or breastfeeding <p>36% women, mean age 44 (SD 12.5), mean cpd 20 (IQR: 15 - 25)</p> <p>Not currently or intending to quit smoking in the next 30 days</p> <p>E cigarette use at baseline: Not specified</p>
Interventions	<p>EC: Cig-a-like</p> <p>EC presented as a healthier alternative to tobacco smoke and could be freely used, ad libitum (up to 4 cartridges a day) for 12 weeks, as a tobacco substitute</p> <p>EC used: 'Categoria' (model 401) with disposable cartridges</p> <ul style="list-style-type: none"> Grp A: 12 weeks of 7.2 mg capsules ('Original') Grp B: 6 weeks 7.2 mg ('Original'), then 6 weeks 5.4 mg ('Categoria') Grp C: 12 weeks of 0 mg ('Original')

Caponnetto 2013a (Continued)

Baseline visit and up to 7 follow-up visits to receive more cartridges, hand-in diaries, measure CO and vital signs

Outcomes	<p>Abstinence at 12 months (complete self-reported abstinence from tobacco smoking since previous visit at 6 months, confirmed with CO < 7 ppm at 12 months)</p> <p>≥ 50% reduction in baseline cigarettes at 12 months</p> <p>Recorded AEs thought to be related to tobacco smoking and EC at baseline and at each study visit (7 follow-up visits over 12 weeks, plus at 24 and 52 weeks)</p>
Study funding	<p>"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."</p>
Author declarations	<p>"RP has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has served as a consultant for Pfizer and Arbi Group Srl, the distributor of the Categoria™ e-Cigarette. The other authors have no relevant conflict of interest to declare in relation to this work."</p>
Notes	<p>Additional data provided from authors</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, block size 15 (5:5:5 ratio)
Allocation concealment (selection bias)	Low risk	Randomization carried out by pharmacy, who did not have direct contact with the participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Double-blind.</p> <p>Quote: "Blinding was ensured by the identical external appearance of the cartridges. The hospital pharmacy was in charge of randomization and packaging of the cigarettes"</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	211 (70.3%) and 183 (61%) attended 6- and 12-month follow-up (at 12 m, 35% lost in 7.2 group; 37% lost in 5.4 group; 45% lost in no-nicotine group)
Selective reporting (reporting bias)	Unclear risk	Unclear if original intention was to combine groups A+B or not. In sample size calculation they compared A+B with C, but results are not always reported in this way

Caponnetto 2013b

Study characteristics

Caponnetto 2013b (Continued)

Methods	<p>Design: Prospective cohort</p> <p>Recruitment and setting: Inpatients at a psychiatric institution in Italy</p> <p>Study start date/end date: Not specified</p>
Participants	<p>Total N: 14</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Smoked ≥ 20 cpd for at least the past 10 years • Diagnosis of schizophrenia <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Alcohol and illicit drug use • Recent myocardial infarction • Angina pectoris • High blood pressure (BP > 140 mmHg systolic or 90 mmHg diastolic, or both) • Diabetes mellitus • Severe allergies • Poorly-controlled asthma or other airway diseases • Inclusion based on specific population characteristic: Diagnosis of schizophrenia <p>57% women, mean age 44.6 (SD 12.5), mean pack years smoked 28.8 (SD 12.9)</p> <p>Motivated to quit: Not specified</p> <p>E cigarette use at baseline: Not specified</p>
Interventions	<p>EC: Cig-a-like</p> <p>Seen at baseline, given EC ('Categoria' brand) with an initial 4-week supply of 7.4 mg nicotine cartridges. Instructed to use ad libitum up to 4 cartridges a day. EC cartridges supplied at months 1, 2, and 3</p> <p>No instruction on cessation or reduction was provided.</p>
Outcomes	<p>Follow-up at 1, 2, 3, 6 and 12 months where cigarette consumption, CO, AEs and positive and negative symptoms of schizophrenia were measured</p> <p>Sustained reduction of $\geq 50\%$ for at least 30 days at 12 months</p> <p>30-day point prevalence CO-validated abstinence at 12 months</p> <p>Adverse events</p>
Study funding	<p>"We wish to thank Arbi Group Srl (Milano, Italy) for the free supplies of "Categoria" e-cigarette kits and nicotine cartridges as well as their support. We would also like to thank LIAF (Lega Italiana AntiFumo) for the collaboration."</p>
Author declarations	<p>"Pasquale Caponnetto, Roberta Auditore, Cristina Russo and Giorgio Carlo Cappello declare no conflict of interest. Riccardo Polosa has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has served as a consultant for Pfizer and Arbi Group Srl (Milano, Italy), the distributor of the CategoriaTM e-cigarette."</p>
Notes	
Risk of bias	

Caponnetto 2013b (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort; no randomization
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/14 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Carpenter 2017
Study characteristics

Methods	<p>Design: Randomized parallel-assignment open-label trial</p> <p>Recruitment: Recruitment from local urban community in southeastern USA, using various media outlets</p> <p>Setting: Community, southeastern USA</p> <p>Study start date: November 2014; Study end date: May 2016</p>
Participants	<p>Total N: 68</p> <p>N per arm: Control group: 22; ENDS group: 46 (split into 2 non-randomized groups: BluCig 16 mg: 25; BluCig 24 mg: 21)</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Age 18+ • Current smoker of ≥ 5 cpd for ≥ 1 year • No recent history of cardiovascular distress, COPD, cancer (any non-dermatologic), or uncontrolled diabetes mellitus • Neither pregnant nor breastfeeding (verified) • Absence of any major current psychiatric impairment, including current alcohol/drug abuse/dependence • Current, active use of email • At least some concern for health effects of smoking (> none at all on a Likert scale) • Not used any ENDS product in the past 6 months • Never purchased an ENDS product <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Use of non-cigarette tobacco products (e.g. cigarillos) in the last 30 days • Current use of any smoking cessation medications • Current enrolment in a smoking cessation treatment study <p>Women: 59.7%; Mean age: 42.2; Mean cpd: 15.3; Heaviness of smoking (0 - 6): 2.9</p> <p>EC use: Control: 9%; ENDS 16 mg group: 4%; ENDS 24mg group: 33%</p>

Carpenter 2017 (Continued)

Motivation to quit smoking in next month (0 – 10): Control: 4.0; ENDS 16 mg: 5.0; ENDS 24 mg: 4.4

Interventions	EC: Cig-a-like Intervention: At study start, choice of tobacco or menthol flavour Blu Starter Pack EC, with 16 mg/mL nicotine. Midway through study, the manufacturer of Blu altered the product and discontinued availability of the device, replaced with BluPlusb, with 24 mg/mL nicotine. 3-week sampling period, given up to 7 cartridges at each of 3 weekly visits. Instructions on usage "kept minimal to preserve naturalistic intent." The study team suggested that ENDS could be used "as you wish, to cut down or quit smoking, help manage smoking restrictions, or both." Control: own brand of cigarettes	
Outcomes	Weeks 2, 3, 4, 8, 12 and 16 Carbon monoxide, NNAL Other outcomes: cessation (< 6 months), product evaluation, EMA	
Study funding	"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 P30 CA016056. B.W. Heckman is supported via K12 DA031794 and K23 DA041616. T.L. Wagener's effort is partially supported by the Oklahoma Tobacco Research Center, which is funded by the Oklahoma Tobacco Settlement Endowment Trust."	
Author declarations	"M.L. Goniewicz is a consultant/advisory board member for Johnson & Johnson. K.M. Cummings reports receiving a commercial research grant from and is a consultant/advisory board member for Pfizer Inc., and has provided expert witness testimony for various plaintiffs in lawsuits involving cigarette manufacturers. No potential conflicts of interest were disclosed by the other authors."	
Notes	New for 2020 update. Listed as ongoing study NCT02357173 in 2016 review update. Additional data provided from authors In all, 25 participants (54%) received the Blu Starter Pack (16 mg), and 21 participants (46%) received BluPlusb (24 mg); no switches were made within participants. Note: this is not included in our analysis of higher v lower as assignment to nicotine dose was not done at random; 24 mg and 16 mg merged in our main analysis	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization to group was stratified by motivation to quit in the next 30 days (0–6 vs. 7–10 on a VAS scale) but proportioned 2:1 (ENDS:control) to increase precision estimates for e-cigarette uptake and usage."
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and includes non-active control
Blinding of outcome assessment (detection bias) All outcomes	High risk	CO biochemically verified but abstinence not used as outcome in this review, so rated based on adverse event reporting. Self-report, no blinding of participants.
Incomplete outcome data (attrition bias)	Low risk	Retention rate:

Carpenter 2017 (Continued)

All outcomes

Week 4: Control:19/22 (86%); ENDS 16 mg: 23/25 (92%); ENDS 24 mg: 20/21 (95%)

Week 16: Control: 16/22 (73%); ENDS 16 mg: 19/25 (76%); ENDS 24 mg: 15/21 (71%)

Selective reporting (reporting bias)	Unclear risk	Not specified
Other bias	Low risk	Midway through the study, the manufacturer of Blu altered the product and discontinued availability of the device, replaced with BluPlus [®] , with 24 mg/mL nicotine, again offered in both tobacco and menthol flavourings, and with improved battery duration (4-watt battery for both devices). In all, 25 participants (54%) received the Blu Starter Pack (16 mg), and 21 participants (46%) received BluPlus [®] (24 mg); no switches were made within participants. The change in product (IRB approved) allowed us the unexpected opportunity to assess what impact, if any, the change in product design had on study outcomes. Note that the manufacturer, style of device, and packaging did not change, nor did our messaging to participants. The only difference was the strength of product. Thus, trial outcomes are reported across 3 groups: control versus 16 mg versus 24 mg ENDS. We have not rated this as high risk of bias as our analyses do not compare on nicotine strength and both nicotine arms are combined in our main analysis

Ely 2013
Study characteristics

Methods	Design: Prospective cohort Recruitment: Letter sent to family practice patients who currently smoked Setting: Single family practice, Colorado USA Study start date: 14 April 2013; Study end date: Not specified
Participants	Letters sent to 640 patients, 48 chose to participate and 44 completed the programme, 4 were lost to follow-up Inclusion criteria: <ul style="list-style-type: none"> Want to quit or switch from tobacco cigarettes to ECs Exclusion criteria: <ul style="list-style-type: none"> None reported Of the 44 participants, 66% women, all non-Hispanic/white, aged 20 - 75 (30% were age 51 - 60), 57% had a high school education or less Motivated to quit: Want to quit or switch from tobacco cigarettes to ECs E-cigarette use at baseline: Not specified
Interventions	EC: Cig-a-like The 6-month smoking cessation programme was based on The '5 A's' model and transtheoretical model. Options for treatment were discussed with each participant at the start of the programme. All used an EC, with 16 using bupropion and 2 using varenicline as well

Ely 2013 (Continued)

Participants were provided with written information on “blu cig” and “smoke tip” ECs, about cost, availability, nicotine dosage options

Outcomes	Phone follow-ups at 2 weeks, 1 month, 3 months, and 6 months At completion of programme (using ITT) Abstinence from smoking and EC use Abstinence from smoking but not EC use ≥ 50% reduction of baseline cigarette consumption (still using ECs)
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Study funding	Not specified
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Author declarations	Not specified
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/48 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	No definition of abstinence provided Not clear if 'completed programme' was at 6 months.

Felicione 2019
Study characteristics

Methods	Design: Double-blind RCT Recruitment: People who smoke were recruited from an outpatient opioid-maintenance clinic in West Virginia, USA Setting: Outpatient opioid-maintenance clinic in West Virginia, USA Study start date/Study end date: Not reported
Participants	Total N: 25; N per arm: Placebo (non-nicotine): 11; Active (18 mg/ml nicotine): 14 Inclusion criteria: <ul style="list-style-type: none"> ≥18 years of age

Felicione 2019 (Continued)

- Report smoking ≥ 10 cpd for \geq one year
- Report a current interest in quitting smoking

Exclusion criteria:

- Reported regular use of any nicotine/tobacco product other than cigarettes, including EC, or were already engaged in attempts to quit smoking

Inclusion based on specific population characteristic: People who smoke who were currently receiving a buprenorphine/naloxone combination in sublingual form, and had maintained sobriety from opioids and all other illicit substances for at least 90 consecutive days as verified via urinalysis

73.0% women; mean age 32.5; mean cpd 22; mean FTND 5.8

Motivated to quit: Quit ladder Score (range 1 - 10): 5.6 average

Interventions	<p>EC: Refillable</p> <p>Compared nicotine (18 mg/ml) to non-nicotine EC.</p> <p>Second-generation EC consisted of the eGo-T battery (900mAh, 3.3 V constant output) (Joyetech; Irvine, CA) and the Kanger mini Protank-II, 1.5 ml Pyrex glass tank with a drip tip and atomizer head coils (KangerTech; China), choice between tobacco (n = 15) and menthol (n = 10) flavoured liquid (2-week supply). Participants were then trained in EC device operation, including assembly, liquid filling, manual battery operation, and cleaning/storage. Practised puffing on EC in the presence of a team member, and asked questions if needed. Participants instructed to use their ECIG ad libitum every day for 2 weeks</p>
Outcomes	<p>Baseline (day 1), 14 days, 28 days for clinic measures. Data also collected via text-messages over 2-week intervention period</p> <p>Withdrawal/side effects: Every evening during the 2-week intervention period, participants rated a variety of effects possibly experienced as a result of nicotine/tobacco withdrawal and/or use of the ECIG: nausea, dizziness, throat irritation/soreness, cough, dry mouth, headache, shortness of breath, irritability/frustration/anger, craving/urge to smoke, and other. Each item was rated on a continuous scale that ranged from 0 (not at all) to 100 (extremely)</p> <p>Expired air CO</p> <p>Other outcomes: Self-reported cigarette and EC use; readiness to quit at day 1, 14 and 28</p>
Study funding	Not reported
Author declarations	Not reported
Notes	New for 2020 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Using a mixed factorial, simple randomization, double-blind study design, participants were assigned to one of two ECIG conditions..." (No further details given)
Allocation concealment (selection bias)	Unclear risk	No details on allocation given.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "double-blind study design", no further detail given

Felicione 2019 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: “double-blind study design”, no further details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “...80.6% completed the two-week intervention (n=14 active; n=11 placebo), and 70.9% also completed the follow-up session (n=13 active; n=9 placebo).” Active follow-up completion rate: 13/14 = 93%; Placebo follow-up completion rate: 9/11= 82% N.B. 6 participants were disqualified post-randomization: Quote: “Of those individuals who were screened for the study, 93.9% were enrolled (n = 18 active; n = 13 placebo); two individuals who were ineligible provided an expired air CO level < 10 ppm. Six of the enrolled participants (n = 4 active and n = 2 placebo; n = 5 tobacco flavor and n = 1 menthol flavor) were disqualified for responding to 7 or fewer days of text messages.”
Selective reporting (reporting bias)	Unclear risk	All measures listed were reported: Self-reported cigarette use, text message-based cigarette use, e-cig use, expired air CO, readiness to quit ladder, withdrawal/side effect; No study protocol or clinical trial record available to confirm all intended outcome measures were reported

George 2019
Study characteristics

Methods	<p>Design: Prospective, randomized controlled trial with a parallel, nonrandomized preference cohort</p> <p>Recruitment: Participants were recruited from local advertisements, smoking cessation databases, and visits to local businesses, as well as via the Scottish Primary Care Research Network</p> <p>Setting: Single tertiary research centre, UK</p> <p>Study start date: August 2016; Study end date: July 2018</p>
Participants	<p>Total N: 114 in “final evaluable dataset” (145 recruited into the trial)</p> <p>N per arm: Tobacco cigarettes (TC): 40; EC nicotine (16 mg): 37; EC-Nicotine-free: 37</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • People who smoke ≥ 18 years of age who had smoked ≥ 15 cigarettes/day for at least 2 years • were free from established CV disease, diabetes, and chronic kidney disease; and were not on medication for those conditions • Willing to stop tobacco cigarettes for period of study if required • Willing not to use electronic cigarettes if required • Able to give informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Pregnant or lactating • Women of childbearing potential who do not abstain from sex or use effective contraception • On current prescribed medication for cardiovascular disease

George 2019 (Continued)

- History of cardiovascular disease (excluding hypertension), diabetes, active malignance or chronic renal disease
- Nut allergy
- Participation in another clinical trial (other than observational trials and registries) with an investigational product and/or intervention within 30 days before visit 1

65.4% women; mean age 46.9; mean cpd 18.7

Motivated to quit: TC group: No; EC nicotine (16 mg): Yes; EC-Nicotine-free: Yes.

Interventions	<p>EC: Cig-a-like</p> <p>EC nicotine (16 mg) arm: EC containing 16 mg nicotine (Vapourlites Starter Kit with XR5 16 mg nicotine cartomizer; Vapourlites, Peterlee, United Kingdom)</p> <p>EC-Nicotine-free arm: Nicotine-free EC plus nicotine flavouring (Vapourlites Starter Kit with 0 mg nicotine cartomizer)</p> <p>(non-randomized) TC arm: continued their usual daily smoking habits and did not use EC for the 4-week period of the trial</p>
Outcomes	<p>Week 4</p> <p>Adverse events and biomarkers: BP, heart rate, adverse events</p> <p>Other outcomes measured: Endothelial function, oxidized low-density lipoprotein, high-sensitivity C-reactive protein, tissue plasminogen activator, and platelet activation inhibitor-1</p>
Study funding	<p>"The VESUVIUS (Vascular Effects of Regular Cigarettes Versus Electronic Cigarette Use) trial was funded by the British Heart Foundation (grant PG/15/64/31681); and supported by Immunoassay Biomarker Core Laboratory, University of Dundee, the Tayside Medical Sciences Centre, and the NHS Tayside Smoking Cessation Service. The funder had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication."</p>
Author declarations	<p>"Dr. Donnan has received research grants from AbbVie, Shire, and Gilead Sciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose."</p>
Notes	<p>New for 2020 update</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Consented participants who were willing to quit smoking were randomized to one of the EC arms in a 1:1 fashion using a centrally controlled web-based good clinical practices-compliant randomization system to either: 1) EC containing 16 mg nicotine; or 2) nicotine-free EC plus nicotine flavouring because it was considered by the institutional ethics committee as ethically unacceptable to randomize those who were willing to quit smoking into a smoking arm. Those unwilling to consider quitting smoking continued in the parallel preference TC cohort
Allocation concealment (selection bias)	Low risk	Central randomization
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified

George 2019 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded and AE/SAE data are self-report only. For other outcomes, low risk as objectively measured: Quote: "Patients fasted overnight and measurements were conducted at baseline and 1 month according to the International Brachial Artery Reactivity Task Force guidelines (19) by a single operator (M.H.) blinded to study allocation at a single site." "Pulse wave velocity and augmentation index were measured at baseline and 1 month by a single operator (M.H.) blinded to study allocation."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number randomized not provided per group. Quote: "A total of 145 patients were recruited into the trial (Figure 1). A final number of 114 patients (40 TC, 37 EC-nicotine, 37 EC-nicotine-free) completed both visits."
Selective reporting (reporting bias)	Low risk	Clinical trial record lists: Change in FMD; Change in oxidised LDL; Change in PAI-1; Change in hs-CRP; Change in Pulse Wave Velocity; Change in tPA; Change in Augmentation Index@75bpm All reported in the paper

Goniewicz 2017

Study characteristics

Methods	Design: Longitudinal within-subjects observational Recruitment: Advertisements in the media, the internet, posted advertisements in clinics and offices, and by word of mouth Setting: University, Poland Study start date: March 2011; Study end date: June 2011
Participants	Total N: 22 started out and 2 dropped out in the first week due to an adverse event (nausea) and inability to commit to clinic visits. This resulted in analytic sample of 20 Inclusion criteria: <ul style="list-style-type: none"> • 18 or older, current daily cigarette smokers (> 5 cpd within the last 12 months) • May have had interest in quitting smoking, in good health (at the clinic screening visit) • Able to communicate in Polish • Able to use an e-cigarette safely Exclusion criteria: <ul style="list-style-type: none"> • Diagnosed as having asthma, COPD, hypertension, inhaled allergies, chronic heart disease, or cancer • were taking a cardiac medication • were pregnant 60% women; mean age 31; mean cpd 16; mean FTND 3.9 Motivated to quit: At the time of screening, 95% of participants (n = 19) reported planning to quit smoking, with 80% (n = 16) reporting that they have made at least 1 quit attempt prior to involvement in the study E cigarette use at baseline: Not reported

Goniewicz 2017 (Continued)

Interventions	EC: Cig-a-like Pen-style M201 e-cigarettes for 2 weeks, with an automatically-operated battery with an output power of 4.6 Volts (280 mAh) and the heating element resistance of 3.6 – 3.8 Ohms. At baseline, provided with EC (M201 Mild, Poland) with 20 tobacco-flavoured cartridges a week containing 11.0 ± 1.5 mg of nicotine in a mixture of propylene glycol and vegetable glycerin (50:50). Encouraged to substitute their regular cigarettes with the e-cigarette for 2 weeks and refrain from smoking	
Outcomes	Day 7, Day 14 Adverse events and biomarkers: <ul style="list-style-type: none"> • Biomarkers were metabolites of 13 major carcinogens and toxicants in cigarette smoke: 1 tobacco-specific nitrosamine (NNK), eight volatile organic compounds (1,3-butadiene, crotonaldehyde, acrolein, benzene, acrylamide, acrylonitrile, ethylene oxide, and propylene oxide), and 4 polycyclic aromatic hydrocarbons (naphthalene, fluorene, phenanthrene, and pyrene) • Questionnaire on 'health': At each visit, participants were asked, "In the last week, have you experienced any of the following symptoms?", while providing a response of "never," "rarely," or "often" to the following list of health effects: daytime cough, difficulty concentrating, difficulty breathing during sleep, difficulty sleeping, dizziness, headache, irritability, nausea, nighttime cough, chest pain, phlegm, shortness of breath, tightness in chest, visual disturbances, and wheezing. Responses of "rarely" or "often" were combined to indicate presence of an adverse health effect • Expired CO Other outcomes measured: <ul style="list-style-type: none"> • 7 nicotine metabolites (3-Hydroxycotinine, Cotinine, Cotinine N-Oxide, Nicotine N-Oxide, Norcotinine, Nornicotine, Nicotine) • Revised Minnesota Nicotine Withdrawal Scale (MNWS-R) administered to measure 'withdrawal symptoms' (0 - 5 rating scale) 	
Study funding	"This work was supported by the Ministry of Science and Higher Education of Poland (grant number N N404 025638). Instrumentation and analytical chemistry at UCSF was supported by the National Institutes of Health, P30 DA012393 and S10 RR026437. 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."	
Author declarations	"MLG was a faculty member of the Medical University of Silesia, Poland during the study. He received a research grant from Pfizer, a pharmaceutical company that markets smoking cessation medications. MLG and NLB have been consultants to pharmaceutical companies that market smoking cessation medications. NLB has been an expert witness in litigation against tobacco companies. The other authors declare no potential conflicts of interest."	
Notes	New for 2020 update	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts – 1 for nausea, 1 could not complete clinic visits. Analysis based on 20 completers

Goniewicz 2017 (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes reported
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Guillaumier 2018
Study characteristics

Methods	<p>Design: Pragmatic, open-label, single-centre, 2-arm randomized controlled trial</p> <p>Recruitment: Withdrawal service in Melbourne, Australia</p> <p>Setting: Substance use disorder treatment setting, and following discharge, community setting, Melbourne, Australia</p> <p>Study start date: 1 August 2017; Study end date: April 2019.</p>
Participants	<p>Total N: 100</p> <p>N per arm: EC intervention = 50; NRT Control = 50</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Aged 18 years or over • Tobacco smoker on entering the residential service • Have the capacity to consent and able to understand the participant materials and follow the study instructions and procedures (e.g. sufficient English language ability) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Have used an END containing nicotine in the past month; • Currently pregnant or breast-feeding (measured by self-report); • Currently enrolled in another study; • Scheduled to be transferred to a long-term rehabilitation unit following discharge from the residential withdrawal unit. <p>Inclusion based on specific population characteristic: Participants were discharged from a smoke-free alcohol or other drugs (AOD) residential withdrawal service</p> <p>32% women; mean age 40.9; mean cpd 21</p> <p>Motivated to quit: Median (SD) = 7.3 (2.4) of 1 to 10 scale with 10 "highly motivated"</p>
Interventions	<p>EC: Refillable.</p> <p>Up to an hours training session, information pack. Innokin Endura T22 starter kit and refill liquid (Nicophar). 4-week supply of liquid nicotine, with further supplies of liquid nicotine mailed twice at 4-week intervals. Dosing schedule of e-liquid dependent nicotine dependence score: high-nicotine-dependence category assigned initial 4-week e-liquid supply (total 8 × 10 ml bottles) consisting of: 2 × 10 ml bottles of 18 mg e-liquid and 6 × 10 ml bottles of 12 mg e-liquid. The second and third batches = 8 × 10 ml bottles of 12 mg e-liquid only. Participants scoring in the moderate- and low-dependence categories: three 4-week supplies of 8 × 10 ml bottles of 12 mg e-liquid. Participants given 1-week supply of nicotine patches for use while getting used to the EC.</p> <p>NRT control: Information pack, 12 weeks NRT on the same schedule as for ENDS. 4-week supply of patches plus a nicotine spray and inhaler, followed by refills including patches plus inhaler, gum and lozenges.</p>

Guillaumier 2018 (Continued)

Both groups received proactive referral to quitline counselling (call-back service), which provides calls at pre-discharge and on days 1, 3, 7, 14 and 28 post-discharge, with an emphasis on relapse prevention. Counsellors trained on the use of ENDS.

Outcomes	Week 6, 12; self-report. Adverse events collected Other outcomes measured: <ul style="list-style-type: none"> • Acceptability and feasibility of interventions • Treatment adherence • Cigarettes smoked per day - Heaviness of Smoking Index • Frequency of cravings • Minnesota Nicotine Withdrawal Scale (MNWS) • 10-item Kessler Psychological Distress Scale (Kessler-10) • Quitting self-efficacy, motivation to quit and the Heaviness of Smoking Index were assessed at baseline 	
Study funding	<p>From published protocol: "The study is supported by a VicHealth Innovation Research Grant (2016–0096). AG is supported by a post-doctoral fellowship from the Heart Foundation. ALB is supported by an Australian National Health and Medical Research Council (NHMRC) senior research fellowship and a Faculty of Health and Medicine, University of Newcastle Gladys M Brawn senior research fellowship. BB is supported by an Australian NHMRC career development fellowship (GNT1063206) and a Faculty of Health and Medicine, University of Newcastle Gladys M Brawn career development fellowship."</p> <p>From unpublished manuscript: "This study was supported by a VicHealth Innovation Research Grant (2016-0096)."</p>	
Author declarations	<p>From published protocol: "The authors declare that they have no competing interests."</p> <p>From unpublished manuscript: "None to declare."</p>	
Notes	New for 2020 update Additional data provided from authors	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Upon completing the baseline survey, participants were randomised 1:1 to an intervention via a computer-sequenced 4–6 block randomisation embedded in the tablet device software."
Allocation concealment (selection bias)	Low risk	Quote: "At the end of the baseline survey, participants will be randomised 1:1 to an intervention via a computer-sequenced 4–6 block randomisation embedded in the iPad."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants were informed of their intervention group by the RA and provided with a training session of up to one hour." "Due to the nature of the intervention, neither participants nor staff can be blinded to allocation. However, the data safety monitoring committee and the statistician responsible for the data analysis will be blinded."
Blinding of outcome assessment (detection bias) All outcomes	High risk	No biochemical validation, self-report data

Guillaumier 2018 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "At 6 and 12-weeks, 63 participants (63%) and 50 participants (50%) were followed up, respectively. While slightly higher retention rates were evidence in the VNP group at 6-weeks (68% vs 58% in NRT group; p=0.300); there were no differences between groups at 12-weeks (25 recontacted in both arms; i.e., 50%)."
Selective reporting (reporting bias)	Low risk	Unpublished findings provided by authors report on all outcomes mentioned in the protocol

Hajek 2015a
Study characteristics

Methods	Design: Prospective cohort, intervention provided Recruitment: People who smoke attending stop-smoking service Study start date: March 2014; Study end date: March 2015 Setting: Stop-smoking service, London, UK
Participants	Total N: 100 (69 of whom accepted offer of EC) Inclusion criteria: <ul style="list-style-type: none"> All people who smoked joining stop-smoking service 38% women (those who accepted) 55% women (those who declined), mean age 41, mean cpd 14, all motivated to quit. EC use at baseline not specified but some who declined EC offer had used EC in the past Motivated to quit: Yes E-cigarette use at baseline: Not specified
Interventions	EC: Cig-a-like and refillable EC: offered to all people who smoke joining service; offered choice of 'cig-a-like' (Gamucci, 1.6% or 2.2% nicotine per ml) product or tank model (EVOD, 1.8%; later replaced with Aspire product due to leakage issues). 69% of those offered received an EC on TQD Medication: Offered stop-smoking medications including NRT and varenicline as in standard protocol. Of EC users 33% opted to also use NRT, 29% varenicline, 38% nothing Support: weekly, as in standard protocol
Outcomes	Adverse events collected throughout, method for collection unclear Also collected: 4-week biochemically-validated abstinence, participant feedback, cost
Study funding	"The pilot study was sponsored by City of London Corporation."
Author declarations	"Peter Hajek received research funds from and provided consultancy to manufacturers of smoking cessation medications. The remaining authors have no conflicts of interest to declare."
Notes	

Risk of bias
Electronic cigarettes for smoking cessation (Review)

Hajek 2015a (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	26% lost in EC group, dropout rate in EC decliners not reported. Reasons for dropout not stated
Selective reporting (reporting bias)	Unclear risk	Unclear which outcomes authors set out to collect, no protocol available

Hajek 2019
Study characteristics

Methods	<p>Design: Multicentre pragmatic randomized controlled trial to examine the efficacy of e-cigarettes compared with nicotine replacement therapy</p> <p>Recruitment: participants attending UK stop-smoking service and via social media</p> <p>Setting: U.K. National Health Service stop-smoking services</p> <p>Study start date: 1 April 2015; Study end date: 31 March 2018</p>
Participants	<p>Total N: 886</p> <p>N per arm: EC: 439; NRT: 447</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Adults who smoke (aged 18 or over) with no strong preference to use or not to use nicotine replacement or e-cigarettes, and were currently not using either type of product Able to read/write/understand English <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Pregnant or breastfeeding Strong preference to use or not use NRT or EC, currently not using either type of product <p>48% women; median age 41; median cpd 15 ; mean FTND 4.6; 41.5% reported past use of ECs</p> <p>Motivated to quit: Not reported</p>
Interventions	<p>EC: Refillable</p> <p>NRT: Informed of range of NRT products and selected preferred product, encouraged to use combination. Participants free to switch products. Supplies provided for up to 3 months</p> <p>EC: Starter pack (1 Kit, Aspire UK) provided along with 30 ml bottle of Tobacco Royale flavour e-liquid, concentration 18 mg/ml. Participants showed how to use and asked to purchase future e-liquid online or from local vape shops and to buy different EC device if the 1 provided did not meet their needs. Encouraged to experiment with e-liquids of different strengths and flavours. If unable to obtain own supply, provided with further 10-ml bottle (not proactively offered). Oral and written info on how to operate EC</p>

Hajek 2019 (Continued)

Both arms received multi-session behavioural support as per UK stop-smoking service practice (one-to-one sessions weekly with local clinicians, exhaled CO monitored for at least 4 wks post-TQD); signed behavioural contract not to use other therapy for at least 4 weeks

Outcomes	<p>Weeks 4, 26 and 52</p> <p>Cessation: Sustained and biochemically-validated CO < 8 ppm</p> <p>Adverse events and biomarkers: “adverse reactions”: presence or absence of nausea, sleep disturbance and throat and mouth irritation, and respiratory symptoms (presence or absence of shortness of breath, wheezing, coughing and phlegm), death</p> <p>Other outcomes measured:</p> <ul style="list-style-type: none"> • Use and ratings of trial products • Rating of withdrawal symptoms (weeks 1 - 6) • Reduction of cigarette consumption • Cost effectiveness
Study funding	<p>“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.”</p>
Author declarations	<p>From ICJME disclosure forms: “Miss Natalie Bisal has nothing to disclose. Dr. Dawkins reports personal fees from Johnson & Johnson, outside the submitted work; Dr. Goniewicz reports personal fees from Johnson and Johnson, outside the submitted work; Dr. Hajek reports grants and personal fees from Pfizer, outside the submitted work; Ms. Li reports grants from NCCHTA, during the conduct of the study; Dr. McRobbie reports grants from NIHR HTA programme, during the conduct of the study; personal fees from Pfizer, personal fees from Johnson & Johnson, outside the submitted work; Dr. Myers Smith has nothing to disclose. Dr. Parrott has nothing to disclose. Dr. Pesola has nothing to disclose. Mrs Anna Phillips-Waller has nothing to disclose. Dr. Przulj reports grants from Pfizer, outside the submitted work; Dr. Ross has nothing to disclose. Dr. Sasiemi has nothing to disclose. Ms. Wu has nothing to disclose.”</p>
Notes	<p>New for 2020 update, listed as ongoing study ISRCTN60477608 in 2016 review update</p> <p>Note higher use of allocated product at 12 m in intervention group compared to control group: “Among participants with 1-year abstinence, 80% (63 of 79) were using e-cigarettes at 52 weeks in the e-cigarette group and 9% (4 of 44) were using nicotine replacement in the nicotine-replacement group.”</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomization took place on the quit date to limit differential dropout. Randomization sequences (1:1 ratio in permuted blocks of 20, stratified according to trial site) were generated with the use of a pseudorandom number generator in Stata software and were embedded into an application that only revealed the next treatment assignment once a participant had been entered into the database.”
Allocation concealment (selection bias)	Low risk	Refer to 'Random sequence generation'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded, but as both arms contained active interventions performance bias judged unlikely

Hajek 2019 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 12 months: EC Arm: 356/439 NRT Arm: 342/447
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Halpern 2018
Study characteristics

Methods	<p>Design: Randomized clinical trial</p> <p>Recruitment: Eligible participants were employees and their spouses at 54 companies that used Vitality wellness programmes</p> <p>Setting: Online resources via workplace setting (54 companies), USA</p> <p>Study start date: First phase of recruitment October 2014, second phase November 2015 (to meet recruitment target); Study end date: 20 April 2017</p>
Participants	<p>Total N: 6006</p> <p>N per arm: Usual care: 813; Free e-cigarettes: 1199; Free cessation aids: 1588; Reward incentives plus free cessation aids: 1198; Redeemable deposit plus free cessation aids: 1208.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • At least 18 years old • Reported current smoking on a health risk assessment within the previous year • Employees and their spouses that used Vitality wellness programmes <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Participants who express wanting to opt out of this programme will be un-enrolled and excluded <p>51.1% women; median age 44; median cpd 10</p> <p>Ecig use at baseline: 10.7% current use; 23.1% past but not current use; 39.7% never used ECs</p> <p>Motivated to quit: Unselected sample (total sample): 9.2% no plan to quit; 61.6% want to quit later; 27.7% want to quit/need help</p>
Interventions	<p>EC: Cig-a-like</p> <p>a) Usual care:</p> <p>Standardized Vitality programme aimed at promoting tobacco cessation. This programme includes existing employee benefits for quitting and the use of text/email messages to encourage tobacco cessation</p> <p>b) as (a), plus free EC:</p>

Halpern 2018 (Continued)

Free NJOY e-cigarettes (including battery sticks, a USB charger, and up to 20 chambers with 1.0 to 1.5% nicotine per week in participants' chosen flavours). Use of all products was free until 6 months after the quit date

c) as (b) plus access to free NRT, bupropion or varenicline

d) as (c) plus incentives across 6 m for testing negative for tobacco use

e) as (c) plus provide money at start and lose money from this fund if they do not test negative across 6 m

Outcomes	Months 1, 3, 6 and 12 Cessation: Sustained smoking abstinence for 6 months, biochemical validation (urine cotinine, anabasin and blood carboxyhaemoglobin) Other outcomes measured: Costs
Study funding	"Supported by a grant from the Vitality Institute to the University of Pennsylvania Center for Health Incentives and Behavioral Economics."
Author declarations	"Disclosure forms provided by the authors are available with the full text of this article at NEJM.org. Check these and: Dr. Troxel reports other from VAL Health, outside the submitted work. Dr. Volpp reports grants and personal fees from CVS Health, personal fees from VAL Health, grants from Humana, grants from Merck, grants from Weight Watchers, grants from Hawaii Medical Services Association, grants from Oscar Health Insurance, outside the submitted work. All of the other authors state that they have nothing to disclose."
Notes	New for 2020 update. Study listed as ongoing study NCT02328794 in 2016 review update Only arms (a) and (b) included in our analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and different amounts of support given to each group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	High risk	At 12 months very low numbers completed biochemical validation. Submitted a sample n = CG:1, free e-cigs:4, free cessation:5, rewards: 14, deposits:16
Selective reporting (reporting bias)	Low risk	Expected outcomes reported and checked with trial registration

Hatsukami 2020
Study characteristics

Methods	Design: randomized trial Recruitment: Media advertisements Setting: Clinic visits in community, USA Study start date: 25 November 2014; Study end date: 2 December 2018
Participants	Total N: 264 N per arm: Usual brand: 36; AD-E: 76; CS-E: 76; CS-NRT: 76. Inclusion criteria: <ul style="list-style-type: none"> • At least 18 years of age • Smoking at least 5 cpd for the past year with a breath CO at least 10 ppm or NicAlert test = level 6 if CO less than 10 ppm • In stable physical and mental health Exclusion criteria: <ul style="list-style-type: none"> • A serious quit attempt in the past 3 months • Recent (< 3 months) alcohol or drug abuse problems • Regular use of other nicotine or tobacco products (e.g. > 9 days per month to minimize confounding effects of these products on biomarker outcomes) • Planning to quit smoking in the next 3 months • Chronic conditions affecting results of biomarker analyses (e.g., liver disease) • Currently using NRT or other cessation medications • Pregnant, planning to become pregnant, or breastfeeding 49% women; mean age 45.2; mean cpd 15.2; mean FTND 3.4 E cigarette use at baseline: Not reported Motivated to quit: Initially uninterested
Interventions	<p>EC: Cig-a-like, but the only cig-a-like product with high nicotine content</p> <p>Usual brand arm: Purchased their own usual brand of cigarettes; at end of clinical trial phase (week 8), offered ECs or NRT for up to 8 weeks, with a choice of product and no specific instructions for use</p> <p>EC AD-E arm: Use EC whenever you like instead of a cigarette; can smoke as many or as few cigarettes as you want</p> <p>EC CS-E arm: Complete substitution with e-cigarettes (i.e. “you will stop smoking cigarettes and use only e-cigarettes”)</p> <p>The primary e-cigarette product was Vuse Solo (4.8% nicotine, manufactured by RJ Reynolds, Inc). Initially a choice of Blu cigarettes (cartridge-based system, marketed previously by Lorillard) and Fin (pre-filled tanks system, manufactured by Fin Branding Group) was offered; but because Vuse attained the highest market share during the early phase of the study, switched exclusively to Vuse. Participants could choose 1 of 4 flavours: tobacco, mint, menthol, and berry. Participants were provided 7 cartridges a week with the option of returning to the clinic before their next visit to obtain additional cartridges if needed. All products provided free to the participants. All unused products and used EC cartridges were collected at each visit</p> <p>CS-NRT arm: Complete substitution with 4 mg nicotine gum or lozenge, with the participant choosing what product they would like to use (i.e. “you will stop smoking cigarettes and use only nicotine gum or lozenge”). The 4 mg was down-titrated to 2 mg if adverse side effects were experienced. Nicotine gum</p>

Hatsukami 2020 (Continued)

came in mint, cinnamon, and fruit flavours, while the nicotine lozenge was mint or cherry flavours. All these products were provided free to the participants and unused products were collected at each visit

Behavioural support: **CS-E arm** and **CS-NRT arm**: received brief counselling on how to avoid smoking cigarettes

Outcomes	2-week baseline period (weeks -1 and 0); Week 1, 2, 3, 4, 6 and 8 Adverse events and biomarkers: <ul style="list-style-type: none"> • Urinary total nicotine equivalents (total nicotine + total cotinine + total 3'-hydroxycotinine; TNE) • Exhaled CO • Urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL, biomarker for NNK) • Urinary phenanthrene tetraol (PheT, an indicator of carcinogenic polycyclic aromatic hydrocarbons) • Urinary metabolites of VOCs (mercapturic acids)—2-cyanoethylmercapturic acid (CEMA, biomarker for acrylonitrile), 3-hydroxypropylmercapturic acid (3-HPMA, biomarker for acrolein), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA, biomarker for crotonaldehyde/methylvinyl ketone), 2-hydroxypropylmercapturic acid (2-HPMA, biomarker for propylene oxide), and N-acetyl-S-(carbamoyl-ethyl)-L-cysteine(AAMA, biomarker for acrylamide) • A safety check for adverse events was conducted at a week-20 follow-up • Blood pressure, heart rate and oxygen saturation Other outcomes measured: <ul style="list-style-type: none"> • Cessation (< 6 months)
Study funding	"supported by grants U19CA157345 from the National Cancer Institute (DKH/PS), UL1 TR000062 and UL1 TR002494 from the National Center for Advancing Translational Science of the National Institutes of Health, and T32 DA007097 from the National Institute of Drug Abuse (EM). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies"
Author declarations	"RJC is a member of the FDA Tobacco Products Scientific Advisory Committee. PGS serves or has served as an expert witness in tobacco company litigation on behalf of plaintiffs"
Notes	New for 2020 update. AD-E arm not included in this review Additional data provided from authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded and some interventions contained different levels of support
Blinding of outcome assessment (detection bias)	Low risk	Not blinded but all relevant outcomes for our analyses were objective

Hatsukami 2020 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "There was a significant difference in dropout rates across groups following study entry ($p = .041$), with the highest dropout rates observed in the complete substitution groups, particularly in the NRT group..."</p> <p>AD-E: Week 1 = 73/76; Week 2 = 73/76; Week 4 = 69/76; Week 6 = 66/76; Week 8 = 65/76 = 85%</p> <p>CS-E: Week 1 = 69/76; Week 2 = 67/76; Week 4 = 66/76; Week 6 = 61/76; Week 8 = 58/76 = 69.7%</p> <p>CS-NRT: Week 1 = 72/76; Week 2 = 65/76; Week 4 = 60/76; Week 6 = 57/76; Week 8 = 53/76 = 69.7%</p> <p>UB: Week 1 = 35/36; Week 2 = 35/36; Week 4 = 33/36; Week 6 = 33/36; Week 8 = 32/36 = 88.8%</p>
Selective reporting (re- porting bias)	Low risk	Table in supplementary section describes that heart rate, blood pressure and oxygen levels were measured, but findings not reported in paper; however, provided by authors upon request

Hickling 2019
Study characteristics

Methods	<p>Design: Single-group assignment – pre-test post-test pilot study</p> <p>Recruitment: Participants were referred from community mental health teams within the South London and Maudsley NHS Foundation Trust.</p> <p>Setting: Healthcare setting, UK.</p> <p>Study start date: 24 September 2014; Study end date: 2 May 2017</p>
Participants	<p>Total N: 50</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Aged 18–70 years; • Daily smoker (unwilling to quit soon); • Exhaled CO level of more than five parts per million; • An established clinical diagnosis of schizophreniform, schizophrenia, schizoaffective disorder or bipolar disorder, or attending an early detection service in a high-risk state <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • The use of e-cigarettes on more than two occasions in the past 30 days; • Intention to quit smoking in the next 30 days; • Medication use that may reduce smoking (including, bupropion, nicotine replacement therapies, acamprosate, varenicline, baclofen, clonidine, naltrexone, buprenorphine, nortriptyline, disulfiram and anti-seizure medications) • Hospitalisation/change in dose of psychotropic medication(s) in the last 30 days; • Unstable physical health in the past 3 months; • A previous serious stomach ulcer and/or phaeochromocytoma • Severe heartburn, stroke, unstable kidney/liver disease, an uncontrolled overactive thyroid gland in the past 3 months;

Hickling 2019 (Continued)

- Individuals who meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for illicit/alcohol drug dependency;
- Medical contraindications to nicotine;
- Asthma
- Suicidal ideation/suicide attempt in the past month
- Pregnancy

Inclusion based on specific population characteristic: People who smoke tobacco with a psychotic disorder (established clinical diagnosis of schizophreniform, schizophrenia, schizoaffective disorder or bipolar disorder, or attending an early detection service in a high-risk state)

24% women; mean age 38.96; mean cpd 17.94; mean FTND not reported

Motivated to quit: "unwilling to quit soon"

E-cigarette use at baseline: Must not have used e-cigarettes on more than 2 occasions in the past 30 days

Interventions	<p>EC: Cig-a-like</p> <p>Participants provided with free tobacco-flavoured NJOY traditional bold disposable e-cigarette (4.5% nicotine) in an "amount equivalent to 150% of their daily tobacco use (as recommended by the manufacturer)" for 6 weeks. Participants were instructed in the use EC; not required to stop smoking tobacco, but were encouraged to replace it with EC as much as possible. Followed up at 4 weeks and encouraged to continue EC use, informed about EC types and where these could be purchased</p>
Outcomes	<p>Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 24</p> <p>Self-reported and biochemical validation</p> <p>Cessation: Tobacco use, as measured by the Time Line Follow Back. Tobacco cigarette use was also indexed weekly by measuring exhaled CO levels with a Smokerlyzer ED50 CO meter (Bedfont Instruments, UK)</p> <p>Adverse events and biomarkers:</p> <ul style="list-style-type: none"> • Side effects associated with e-cigarette use – reported weekly • Respiratory symptoms: lung capacity (measured by Wright's Mini Peak-flow Meter (Clement Clarke International Ltd., UK) at baseline, weeks 6, 10 and 24; Peak flow was obtained 3 times at each assessment • Heart rate and blood pressure • Occurrence of (serious) adverse events was assessed on a weekly basis <p>In a subsample of participants (N = 8), 3-hydroxypropylmercapturic acid (3-HPMA, a measure of the toxicant acrolein) and formic acid were measured at baseline and week 6. These participants were chosen as their tobacco intake had decreased by more than 50% in this period. The measurement of 3-HPMA and formic acid was also performed by validated LC-MS/MS assays</p> <p>Other outcomes measured:</p> <ul style="list-style-type: none"> • Urinary cotinine • Weight • Motivation to Stop Scale (MTSS) • Smoking Consequences Questionnaire-Adult (SCQ-A) • Positive and Negative Syndrome Scale (PANSS) • Calgary Depression Scale for Schizophrenia (CDSS)
Study funding	<p>"This work was funded by the Maudsley Charity (grant number 715); and supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London."</p>

Hickling 2019 (Continued)

Author declarations "R.P-I. has received honoraria and speaker support from Lundbeck. L.D. has provided consultancy for the pharmaceutical industry (Johnson & Johnson 2015, 2017) and acted as an expert witness for an e-cigarette patent infringement case (Porzio, Bromberg & Newman Attorneys at Law, 2015). Between 2011 and 2013, she conducted research for several independent electronic cigarette companies (Totally Wicked, SKYCIGS and E-Lites) for which the University of East London received funds. The e-cigarette companies involved had no input into the design, conduct or write up of these projects and she has not received any funds from e-cigarette companies in the last 4 years. She has no links with, and has not received any funds from, the tobacco industry, although two e-cigarette companies that she worked with in 2013 were subsequently acquired by the tobacco industry (SKYCIGS and E-Lites). L.H., T.R., K-V.S., J.M., A.M. and P.M. have no conflicts of interest."

Notes Study listed as ongoing study NCT02212041 in the 2016 review update

Additional data provided from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled study
Allocation concealment (selection bias)	High risk	Uncontrolled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: Week 6: 46/50; Week 10: 42/50; Week 24: 40/50
Selective reporting (reporting bias)	Low risk	Report all outcomes listed on http://clinicaltrials.gov except NNAL. Authors confirmed that they had intended to test for NNAL but had major issues with the assays

Holliday 2019
Study characteristics

Methods	Design: Pilot RCT Recruitment: Recruited via the Newcastle Dental Hospital and by primary care practitioners working in the north-east England region Setting: Dental clinical research facility (DCRF), located in the Newcastle Dental Hospital, Newcastle upon Tyne, UK. Study start date: 20 September 2016; Study end date: 31 July 2018
Participants	Total N: 80 N per arm: Intervention group: 40; Control group: 40 Inclusion criteria: <ul style="list-style-type: none"> • Aged over 18 years old; smoker (≥ 10 cigarettes/day) • Willing and able to come to the DCRF for the required study visits • Having a minimum of 16 natural teeth (excluding third molars) • Being diagnosed with periodontitis

Holliday 2019 (Continued)

Exclusion criteria:

- Having used an e-cigarette for more than 2 days in the last 30 days
- Infectious or systemic diseases that may be unduly affected by participation in this study
- Haemodynamically unstable
- Patients taking the medication adenosine (due to drug interaction risk)
- Lack of capacity to be able to consent to the research project or inability to follow study instructions, or both
- Participation in a dental research study within the previous 20 days
- Pregnant by medical history, or nursing
- Received any non-surgical periodontal therapy other than a routine scale and polish in the last 6 months
- Currently undergoing or requiring extensive dental, orthodontic or implant treatment, or treatment for peri-implantitis

Inclusion based on specific population characteristic: Periodontitis

52.5% women; mean age 44.36; mean cpd 17.4; mean FTND 5

Motivated to quit: Not selected on motivation and not reported

E-cigarette use at baseline: Not currently using an e-cigarette, or not having used 1 for more than 2 days in the last 30 days

Interventions	<p>EC: Refillable</p> <p>All participants given standard stop-smoking advice (10 - 15 minutes in duration) and offer of referral to stop-smoking services</p> <p>Intervention: given EC starter kit (Vype eTank clearomizer) and brief training on its use by a dentist. Provided with an approximately 2-week supply of e-liquid (20 ml) with a choice of flavour (Blended Tobacco, Crisp Mint, Dark Cherry and Vpure (flavourless)) and nicotine strength (0 mg/ml, 6 mg/ml, 12 mg/ml, 18 mg/ml) and information on where to buy more. EC intervention delivered directly following the standard stop-smoking advice and was expected to be 10 - 15 minutes in duration</p> <p>Control group: no further intervention</p>
Outcomes	<p>Months 1 and 6; Self-report and biochemical validation of smoking status</p> <p>Cessation: Rates of continuous eCO-verified smoking abstinence at 6 months were calculated following the Russell Standard (RS6)</p> <p>Adverse events and biomarkers: expired air CO, adverse events monitored at each study visit</p> <p>Other outcomes measured:</p> <ul style="list-style-type: none"> • Feasibility outcomes • Oral health outcomes • Smoking behaviour outcomes comprised: self-reported tobacco and e-cigarette use, eCO, e-salivary cotinine (SC), salivary anabasine (SA), FTND and Mood and Physical Symptoms Scale (MPS)
Study funding	<p>"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). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care."</p>
Author declarations	<p>"The authors declare that they have no competing interests."</p>
Notes	<p>New for 2020 update.</p>

Holliday 2019 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using a secure password-protected web-based system
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation allocation schedule will be generated by a statistician with no other involvement in the study to achieve concealment of allocation."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Nature of study precluded blinding; different levels of support across intervention arms
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition < 50%
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported

Humair 2014
Study characteristics

Methods	Design: Prospective cohort Recruitment: People attending an outpatient clinic Setting: University hospital outpatient clinic, Switzerland Study start date/end date: Not specified
Participants	Total N: 17 Inclusion criteria: <ul style="list-style-type: none"> Wish to reduce tobacco use or had failed to stop smoking using varenicline, bupropion or NRT in past Inclusion based on specific population characteristic: No Mean 23 cpd, 82% had a psychiatric illness Motivated to quit: Yes E-cigarette use at baseline: Not specified
Interventions	EC: Cig-a-like Offered an EC with nicotine 59% also reported using NRT or varenicline in addition to EC

Humair 2014 (Continued)

Outcomes	Smoking cessation and reduction by at least 30% at 12 months (self-report) Adverse events No significant side effects
Study funding	Not specified
Author declarations	Not specified
Notes	Abstract only, hence little detail available Not clear if EC was provided by clinic or if participants had to buy their own

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers lost to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Ikonomidis 2018
Study characteristics

Methods	Design: (acute phase) Randomized cross-over assignment (outcomes measured within hours of the intervention and hence do not meet the criteria of 1 week or more); chronic phase: non-randomized, single-group assignment Recruitment: Hospital smoking cessation unit Setting: Hospital smoking-cessation unit, Greece Study start date: 31 January 2017; Study end date: Estimated completion date: December 2021
Participants	Total N: 90 Inclusion criteria: <ul style="list-style-type: none"> Active conventional cigarette smoker Adults 18 to 60 years Exclusion criteria: <ul style="list-style-type: none"> Health condition adversely affected by smoking, history or presence of cardiovascular disease Inclusion based on specific population characteristic: No 54% women; mean age 50.2; mean cpd 23.4; mean FTND: Not reported

Electronic cigarettes for smoking cessation (Review)

Ikonomidis 2018 (Continued)

Motivated to quit: Yes – recruited from smoking cessation unit

E-cigarette use at baseline: Not reported

Interventions	<p>EC: not clear</p> <p>E cigarette details: In the chronic phase, all 70 participants were instructed to replace their conventional cigarettes (con-cig) with an e-cig containing nicotine (12 mg/dL (e-cig fluid with nicotine concentration of 12 mg/mL (propylene glycol 74.3%, glycerin 20%, flavouring 4.5%, nicotine 1.2%))) for 1 month</p>
Outcomes	<p>1 month; Self-report and objective measures</p> <p>Cessation: Self-report cessation at 1 month. CO measured at 1 month. Cessation data not used as < 6 months</p> <p>Adverse events and biomarkers:</p> <ul style="list-style-type: none"> • Exhaled CO concentration • Heart rate; blood pressure <p>Other outcomes measured:</p> <ul style="list-style-type: none"> • Oxidative stress as assessed by malondialdehyde (MDA) plasma concentrations • Aortic stiffness as assessed by pulse wave velocity (PWV) and augmentation index (AIX75)
Study funding	This study was supported by a grant from the Hellenic Cardiology Society and Hellenic Society of Lipidology and Atherosclerosis.
Author declarations	None
Notes	New for 2020 update. Acute phase of trial not relevant for the review as very short-term outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and differential levels of support given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Objective measures used for all outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	70 participants and 20 controls recruited – no dropout
Selective reporting (reporting bias)	Unclear risk	NCT record states that chronic endothelial integrity, platelet aggregation and high-shear stress-dependent platelet function would be assessed but is not reported in this research letter – however study estimated completion date is December 2021, so perhaps data not ready for publication or limited capacity in the research letter – not the primary publication

Ikonomidis 2018 (Continued)

Other bias	Unclear risk	Few details – written as commentary. Trial registration suggests this is an on-going study
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Ioakeimidis 2018
Study characteristics

Methods	Design: Randomized controlled trial Recruitment: Not specified Setting: Hospital, Greece. Study start date/Study end date: Not specified
Participants	Total N: 54 N per arm: Arm 1: 27; Arm 2: 27 Inclusion criteria: <ul style="list-style-type: none"> • ≥ 10 cpd • Motivation to quit • Hospitalized with acute coronary syndrome (ACS) • 18 or older Exclusion criteria: <ul style="list-style-type: none"> • Prior EC use • History of neuropsychiatric disorders • Prior varenicline use or use of SC pharmacotherapy at time of ACS • Cardiogenic shock or renal impairment • Hepatic impairment prior to ACS • Excessive alcohol use or current use of marijuana or non-cigarette tobacco products Inclusion based on specific population characteristic: People who have experienced acute coronary syndrome 65% women; mean age 52; mean cpd 21; mean FTND 5.6 Motivated to quit: Yes E-cigarette use at baseline: No prior EC use
Interventions	EC: information on whether cig-a-like or refillable not provided Both arms given "low intensity counselling" Intervention 1: 12-week use of EC 12 mg/ml nicotine Intervention 2: 12-week varenicline
Outcomes	Weeks: 4, 12, 24 Cessation: 7-day PP at 24 weeks, self-report Adverse events and biomarkers: Unclear how these were reported. Abstract says no SAEs, poster implies this may have just been CV or neuropsychiatric SAEs. Abstract says nothing about AEs but nausea and sleeping disorders given in table in poster. Implies (S)AEs collected during treatment period only

loakeimidis 2018 (Continued)

Other outcomes measured: Not specified

Study funding	Not reported
Author declarations	Not reported
Notes	New for 2020 update. Abstract and poster only; limited data available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not specified but equal amounts of contact and support between arms so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-report only but equal amounts of contact between arms, no reason to suspect differential misreport
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Abstract/poster only so not able to judge
Other bias	High risk	Abstract and poster only. Two different figures presented for quit rate in EC arm (no difference in those presented in varenicline arm) between abstract and poster. Poster percentage aligns with figure, so using that (16.5%) as opposed to abstract figure (32.5%). Contacted authors but no reply. Calculated n quit based on percentages but unclear what denominators were; EC calculates back to whole number for EC but not for varenicline

ISRCTN14140672
Study characteristics

Methods	Design: Prospective cohort 4-centre pragmatic cluster feasibility trial Recruitment: At homeless centres Setting: 4 homeless centres in the UK Study start date: 1 October 2018; Study end date: 31 March 2020
Participants	Total N: 80 N per arm: EC 48; UC 32

ISRCTN14140672 (Continued)

Inclusion criteria:

- Adults who smoke (18 and over) accessing homeless support services on a regular basis and also known to staff
- Self-reported daily smokers only with smoking status also confirmed by support staff
- Smoking status was also biochemically verified by exhaled CO breath

Exclusion criteria:

- Non-smokers, or those reporting using another smoking cessation aid at the current time
- Anyone below the age 18 years, reporting pregnancy, or unable to consent, e.g. currently intoxicated or unable to speak English
- All those not well known to centre staff were ineligible

Inclusion based on specific population characteristic: people accessing homeless centres

35% women; mean age 42.7; mean cpd 20; mean FTND: FTCD 5.51

Motivated to quit: “varied considerably; large majority expressed a desire to quit smoking in the near future”

E-cigarette use at baseline: Not specified

Interventions	<p>EC: Refillable</p> <p>Usual care: Written information on quitting smoking (adapted from NHS Choices); signposting to the local stop-smoking service (SSS) by centre staff</p> <p>Intervention: as usual care, plus refillable EC provided once with e-liquid provided 1 x wk for 4 wks, Aspire PockeX (tank style), choice of 3 flavours (fruit, menthol, tobacco) and 2 nicotine strengths (12 mg/mL or 18 mg/mL). Written info for EC use and support from centre staff, who met once a week to provide e-liquid and troubleshoot EC use</p>
Outcomes	<p>Weeks: 4, 12, 24; Clinic visits and self-report</p> <p>Cessation: CO-validated sustained at 24 weeks</p> <p>Adverse events and biomarkers: Self-reported negative effects in EC arm only – each participant asked to rate on scale so cannot meta-analyse; exhaled CO; unintended consequences</p> <p>Other outcomes measured:</p> <p>Qualitative process evaluation; costs; self-reported positive and negative affects; recruitment rates; retention; EC/other tobacco/nicotine product use at study end; HRQoL; healthcare service utilisation; other drug use/dependence; unintended consequences</p>
Study funding	<p>This study is funded by the National Institute for Health Research Public Health (project reference: 17/44/29)</p>
Author declarations	<p>SC, AF, JL, CB, AT, DR, IU, LB, SP have no competing interests. PH has received research grant from and provided consultancy to Pfizer. LD has provided consultancy for the pharmaceutical industry relating to the development of smoking cessation products</p>
Notes	<p>New for 2020 update. Authors provided information prior to peer review</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	High risk Intention was to randomize but were unable to due to practical constraints.

ISRCTN14140672 (Continued)

		Quote: "Thus the actual allocation of centres to each arm was a pragmatic decision based on centre readiness and staff/researcher availability though we balance potential confounders and differences in environment by ensuring each cluster (EC and UC) contained one day centre and one residential unit."
Allocation concealment (selection bias)	Unclear risk	Quote: "Participants joined after cluster randomisation... Allocation was concealed to participants until after the baseline assessment." But unclear if allocation was concealed for those recruiting, and allocation would have been known to new participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and different levels of support between arms, so performance bias cannot be ruled out
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cessation (primary outcome) biochemically validated
Incomplete outcome data (attrition bias) All outcomes	High risk	13/48 (27.1%) lost to follow-up in the intervention arm and 20/32 (62.5%) lost to follow-up in the control arm at 24 weeks
Selective reporting (reporting bias)	Low risk	All anticipated outcomes reported

Kumral 2016

Study characteristics

Methods	<p>Design: Prospective randomized clinical trial</p> <p>Recruitment: All patients admitted to a smoking cessation clinic at the Department of Otorhinolaryngology-Head and Neck Surgery, Okmeydanı Training and Research hospital</p> <p>Setting: Smoking cessation clinic, Turkey</p> <p>Study start date: March 2013; Study end date: November 2013</p>
Participants	<p>Total N: 98 but analysis excludes 16 from intervention and 10 from control who did not stop smoking; thus 72 analysed</p> <p>N per arm: EC: 58 (42 analysed); Non-EC 40 (30 analysed)</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Smoked at least one pack of cigarettes a day for at least 5 years. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> History of allergic rhinitis, chronic sinusitis, vasomotor rhinitis, asthma, malignancy, or surgery in upper respiratory tract; Age under 18; Use of psychoactive drugs <p>Inclusion based on specific population characteristic: No</p> <p>44% women; mean age 36; mean cpd and mean FTND not specified</p>

Kumral 2016 (Continued)

Motivated to quit: "All patients were willing to quit smoking"

E-cigarette use at baseline: Not specified

Interventions	<p>EC: Unclear</p> <p>EC arm: "used EC to quit smoking" – allowed to select brand and flavour, used "medium density" liquid (11 - 12 mg/ml) (no further detail given)</p> <p>Non-EC arm: Received cognitive behavioural therapy (no further detail given)</p>
Outcomes	<p>3 Months</p> <p>Sino-nasal outcome test (SNOT-22) via self-administered questionnaire, to evaluate changes in subjective symptoms. Saccharin transit test to evaluate nasal mucociliary clearance (MCC) function which authors state is "an important defence mechanism"</p>
Study funding	Not specified
Author declarations	Not specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients participating in the study were randomly divided into two groups; EC smokers (group 1) and non-EC smokers (group 2)." No further detail provided
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded. The trial is described as single-blinded and outcome assessors were blinded. No placebo used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcome data, participants not blinded and unequal amounts of support between arms
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rate not clear. Only analysed people who quit
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Lee 2018
Study characteristics

Methods	Randomized parallel-assignment double-blind pilot trial Setting: San Francisco Veterans Affairs Medical Center (SFVAMC), USA
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Electronic cigarettes for smoking cessation (Review)

Lee 2018 (Continued)

Recruitment: veterans awaiting surgery
 Recruitment: In VA hospital presenting for surgery
 Study start date: August 2015; Study end date: May 2016

Participants	<p>Total N: 50</p> <p>N per arm: NRT: 30; END: 20</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Presented to the anaesthesia preoperative clinic for elective surgery 3 or more days before surgery Currently smoked more than 2 cigarettes per day, having smoked at least once in the last 7 days <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Exclusively used other forms of tobacco or marijuana only Pregnant or breastfeeding Unstable cardiac condition Currently using smoking cessation pharmacotherapy Were already enrolled in a smoking cessation trial Currently used e-cigarettes on a daily basis <p>Inclusion based on specific population characteristic: Patients awaiting elective surgery</p> <p>10% women; mean age 54; mean cpd 14; mean FTND 3.3</p> <p>Motivated to quit: Not specified</p> <p>E-cigarette use at baseline: Not specified but excluded daily users</p>
Interventions	<p>EC: Cig-a-like</p> <p>Both groups receive: i) referral to the California Smokers' Helpline, ii) brief advice lasting less than 2 minutes, iii) a brochure from the ASA about quitting smoking before surgery</p> <p>EC arm: 6-week supply of NJOY e-cigarettes (disposable, first generation). Instructed to use Bold (4.5%) ad lib for 3 weeks, then Gold (2.4%) ad lib for 2 weeks and then study (0%) ad lib for final week. Number of ECs issued corresponded to baseline cpd, assuming 1 EC = 10 cigarettes. Asked to refrain from the use of all study products at the end of 6 weeks</p> <p>NRT arm: 5-week Nicoderm CQ patches, 1 week placebo patches. Dose based on cpd at baseline: ≥ 10 cpd, 21 mg/day for 3 weeks, 14 mg/day for 1 week, 7 mg/day for 1 week, 0 mg/day for 1 week. < 10 cpd at baseline: 14 mg/day for 3 weeks, 7 mg/day for 2 weeks, 0 mg/day for 1 week</p>
Outcomes	<p>30 Days (phone), 8 Weeks (in person), 6 Months (phone)</p> <p>Cessation: 7-day PP at 30 days (not validated), 8 weeks (CO-validated), 6 months (not validated). Smoking cessation for at least 48 hours on day of surgery (CO-validated)</p> <p>Adverse events and biomarkers:</p> <ul style="list-style-type: none"> Adverse events, side effects, and surgical complications by self-report at 30 days, 8 weeks At 8 weeks exhaled CO, FEV1 and FVC <p>Other outcomes measured:</p> <ul style="list-style-type: none"> Attitudes and usage Salivary cotinine Smoking reduction

Lee 2018 (Continued)

Study funding	“This work was funded by internal UCSF Department of Anesthesia and Perioperative Care funds (San Francisco, California, United States of America) and the UCSF Resource Allocation Program grant, administered by the Helen Diller Family Comprehensive Cancer Center developmental funds from the National Cancer Institute Cancer Center Support Grant (P30 CA 82103-16). E-cigarettes were purchased from NJOY using these funds. NJOY had no involvement in the design, execution, or analysis of the study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.”	
Author declarations	“The authors declare there are no competing interests”	
Notes	3 NRT participants used EC, 2 EC participants used nicotine patch Study listed as ongoing study NCT02482233 in the 2016 review update	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomization was computer-generated, with randomly permuted block sizes of 3 or 6, in a 2:1 ratio using the ralloc program”
Allocation concealment (selection bias)	Low risk	Quote: “Allocation was concealed by consecutively numbered, sealed, opaque envelopes”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded but both interventions active with equal amounts of support so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-report only at 6 months and participants not blinded to condition, but similar level of support given to both groups so differential misreport judged unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 NRT and 1 ENDS loss to follow-up at 6 months
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Lee 2019

Study characteristics	
Methods	Design: Randomized controlled trial Recruitment: Recruited from motor company. Setting: Motor company, medical office in Korea Study start date: 5 January 2012; Study end date: 31 August 2012
Participants	Total N: 150 N per arm: EC: 75; NRT: 75 Inclusion criteria:

Lee 2019 (Continued)

- Male
- At least 10 cpd in previous year
- Smoked for at least 3 years
- Motivate to stop smoking entirely or reduce consumption

Exclusion criteria:

- Past history of serious clinical disease
- Attempted to stop smoking in past 12 months by using NRTs

Inclusion based on specific population characteristic: No

0% women; mean age 42.3; mean cpd: Not reported, 1.01 packs per day; mean FTND 4.05

Motivated to quit: Yes, or to reduce

E-cigarette use at baseline: Not specified

Interventions	<p>EC: Refillable</p> <p>Both arms received 50 mins education session on smoking cessation and use of smoking cessation aids in medical office (no further detail given). Asked to return to medical office every 4 weeks (to 24 weeks?) for “evaluation and counselling by an independent health practitioner”</p> <p>Arm 1: 50-min education sessions on smoking cessation and the use of smoking-cessation aids, instructed to visit the medical office each month for evaluation and counselling by a health practitioner who was unaffiliated with the study. Participants supplied with eGo-CTM EC (nicotine 0.01 mg/mL) from Ovale in 12-wk supply</p> <p>Arm 2: As (1) but instead of EC given 2 mg nicotine gum in 12-wk supply</p>
Outcomes	<p>12, 24 weeks (in person)</p> <p>Cessation: continuous abstinence from 9 - 24 weeks, exhaled CO < 10 ppm, negative urine cotinine</p> <p>Adverse events and biomarkers: Yes but just note ‘adverse events’</p> <p>Other outcomes measured: 7-day PPA, cigarette reduction</p>
Study funding	“none”
Author declarations	“none declared”
Notes	Study listed as ongoing study KCT0001277 in the 2016 review update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “computer-generated randomization sequence with a block size of 2”
Allocation concealment (selection bias)	Low risk	Quote: “The enrolment and assignment of all subjects were performed by a clinical research coordinator not involved in the study”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded but both interventions active with equal amounts of support, so performance bias judged unlikely

Lee 2019 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants not blinded but results biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	61/75 NRT and 71/75 EC FU at 24 weeks
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Lucchiari 2020
Study characteristics

Methods	Design: Randomized parallel-assignment double-blind trial Recruitment: Participants enrolled in lung cancer-screening programme Setting: Early lung cancer detection programme (Cosmos II) at European Institute of Oncology, Italy Study start date: September 2014; Study end date: January 2016
Participants	Total N: 210 N per arm: 70 participants per arm Inclusion criteria: <ul style="list-style-type: none"> • Participants are involved in the COSMOS II study • Participants are 55 years or more and have smoked at least 10 cigarettes a day for the past 10 years • Participants wish to reduce tobacco smoking (motivational score higher than 10) who are not treated at a smoking centre • Signed informed consent Exclusion criteria: <ul style="list-style-type: none"> • Symptomatic cardiovascular disease • Symptomatic severe respiratory disease • Regular psychotropic medication use • Current or past history of alcohol abuse • Use of smokeless tobacco or NRT • Participation in another antismoking programme in the current year Inclusion based on specific population characteristic: 55 years of age or older 37% women; mean age 62.8; mean cpd 19.38; mean FTND 4.37 Motivated to quit: yes E-cigarette use at baseline: Excluded people who smoke who had ever regularly used e-cigarettes for more than 1 week alone or in combination with tobacco cigarettes
Interventions	EC: Cig-a-like Both arms received “low intensity counselling” – phone at week 1, 4, 8 and 12, approx. 10 mins each

Lucchiari 2020 (Continued)

Nicotine EC arm: e-cigarette kit and 12 10-mL liquid cartridges (8 mg/mL nicotine concentration). During the first week, participants could use the e-cigarette ad libitum. At the end of the first week, asked to use only EC for the next 11 weeks

Nicotine-free EC (placebo) arm: Nicotine-free EC – same as above but with nicotine-free EC

Outcomes	<p>Months 3, 6 and 12 (but only 3- and 6-month data available)</p> <p>Cessation: Continuous abstinence for previous month, CO \leq 7 ppm</p> <p>Adverse events and biomarkers: FOR EC ARMS ONLY:</p> <ul style="list-style-type: none"> • Exhaled CO • Leicester Cough Questionnaire (LCQ) • Respiratory symptoms (self-report) • Side effects using checklist <p>Other outcomes measured:</p> <ul style="list-style-type: none"> • Motivational questionnaire • HADS • EC use
Study funding	This study was supported by a grant from Fondazione Umberto Veronesi (FUV)
Author declarations	The authors declare no conflicts of interest
Notes	Listed as ongoing study Lucchiari 2016 (NCT02422914) in 2016 review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization list using a permuted block design (40 blocks of 6 subjects randomly assigned to 1 of the 3 treatment arms) had been previously prepared by independent personnel."
Allocation concealment (selection bias)	Low risk	Double-blind, active and placebo e-cigarettes labelled by independent personnel, researcher and participants blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind" for nicotine vs no nicotine EC but limited info given; however, as similar levels of support across arms performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Approx. 73% followed up in each group at 6 months, very little difference between groups
Selective reporting (reporting bias)	High risk	Paper states data also collected at 12 m but this is not presented and unclear why. Paper states CO collected but data not presented

Martner 2019

Study characteristics

Methods

Design: A nonconcurrent multiple baseline across participants design. Three phases were included: Baseline, EC, and EC + CM. Half the participants received the EC phase following baseline; the other half received EC + CM following baseline

Recruitment: Community

Setting: Set-up meetings occurred at the University of Florida Behavioral Health and Technology Research Clinic, USA

Study start date/Study end date: Not specified.

Participants

Total N: 12

Inclusion criteria:

- 18 - 65 years old
- Smoked ≥ 2 years
- Smoked ≥ 8 cpd on average
- Smoked in the past 24 hours
- Expressed a desire to quit smoking (yes/no)
- Had reliable access to the internet and a computer or smartphone
- Breath CO ≥ 10 ppm at set-up

Exclusion criteria:

- Current or previous medical condition that would pose an increased risk to participation
- Use of benzodiazepines, cocaine, or opiates in the previous 6 months
- Smoke marijuana more than twice a month
- Exposed to elevated CO levels (e.g. spouse smokes in house)
- Pregnant or expected to become pregnant in the next 6 months

58.3% women; mean age 37.5; mean cpd 16.25; mean FTND 5

Motivated to quit: Expressed a desire to quit smoking.

E-cigarette use at baseline: 3 participants never tried an EC prior to the study; 2 owned an EC but quit using it more than a month prior to the study; remaining 7 had tried an EC more than a year prior to the study but never owned one

Interventions

EC: Refillable

All participants provided with smokio electronic cigarettes (second-generation ECs) and V2 e-liquid with a concentration of 24 mg/ml (2.4%) of nicotine. Researchers provided participants with a copy of the National Cancer Institute's brochure *Clearing the Air* (<http://smokefree.gov>). Then researchers and participants read through a manual that described the study procedures, and showed participants how to use the software to measure CO and how to use the EC

Participants initially received EC without contingency for a period of 14 days following the quit attempt. If participants failed to reduce CO levels during this phase, they received contingency management in addition to EC

Outcomes

4 weeks

Adverse events and biomarkers: Adverse events collected in 4-day smoking behaviour questionnaires; eCO

Other outcomes measured: acceptability and use of EC; overall experience of study

Martner 2019 (Continued)

Study funding	"The study was supported in part by crowd-sourced funding enabled by Experiment.com. Preparation of this paper was supported in part by Grant P30DA029926."	
Author declarations	"The authors declare no conflicts of interest."	
Notes	N of 1 (within-participants randomized design, not between groups). New for 2020 update.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details provided.
Selective reporting (reporting bias)	Unclear risk	AEs measured in behavioural change questionnaire but not reported

McRobbie 2015

Study characteristics	
Methods	Design: Prospective cohort Recruitment: advertisements in free London newspapers Setting: Smokers' clinic, East London, UK Study start date: February 2013; Study end date: September 2013
Participants	Total N: 40 Inclusion criteria: <ul style="list-style-type: none"> • People who smoke daily who want to quit • Aged 18 and older Exclusion criteria: <ul style="list-style-type: none"> • Pregnant and breastfeeding women • Current serious medical illness • EC use for more than 1 week in the past 45% women, mean age 47 (SD 12), mean cpd 19 (SD 10), mean FTND 5.2 (SD 2.8), 65% in full-time employment Motivated to quit: Yes E-cigarette use at baseline: Excluded those who had used EC for more than 1 week in the past
Interventions	EC: Cig-a-like

McRobbie 2015 (Continued)

Participants attended baseline session 1 week prior to their TQD. On the TQD, participants were provided with an EC (Green Smoke, 1st generation device, 2.4% nicotine cartridges). 2 cartridges a day were supplied initially, with the supply adjusted to actual use later. Attended 4 weekly follow-up sessions and received standard behavioural support

Outcomes

Cigarette consumption and CO readings collected at each session. Urine sample for cotinine and 3-HPMA analysis collected at baseline and 4 weeks post-TQD

Change in urinary 3-HPMA (ng/mg creatinine) at 4 weeks

Change in urinary cotinine (ng/mg creatinine) at 4 weeks

Change in CO at 4 weeks

Study funding

"This study was funded by a grant given to P. Hajek, H. McRobbie, and M.L.Goniewicz from the UK Medicines and Healthcare Products Regulatory Agency (MHRA). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact."

Author declarations

"H. McRobbie is Clinical Director at The Dragon Institute; reports receiving commercial research grant from Pfizer; and has received speakers bureau honoraria from Johnson&Johnson and Pfizer. M.L. Goniewicz reports receiving commercial research grant from Pfizer. P. Hajek has received speakers bureau honoraria from and is a consultant/advisory board member for the manufacturers of stop-smoking medications. No potential conflicts of interest were disclosed by the other authors."

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/40 participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported

Meier 2017

Study characteristics

Methods	Design: Randomized cross-over trial (e-cig vs placebo)
	Recruitment: via local media outlets
	Setting: Community, USA
	Study start date/Study end date: Not specified.
Participants	Total N: 24

Meier 2017 (Continued)

Inclusion criteria:

- ≥ 18 ,
- People who smoke daily (≥ 10 cpd)
- Not interested in quitting in next 30 days
- English-speaking
- Interested in using EC

Exclusion criteria:

- Using cessation meds
- Use of ECs in last 6 m
- Exhaled CO < 6 ppm,
- History of CV trauma or uncontrolled hypertension
- Pregnant

Inclusion based on specific population characteristic: No

25% women; mean age 48.5; mean cpd 16.3; FTND not reported

Motivated to quit: No (eligibility criteria was to not want to quit in next 30 days)

E-cigarette use at baseline: 8/24 (33%) had previously tried an EC, avg 9.4 months since last use, avg length of use 3.6 days

Interventions

EC: Cig-a-like

Smoked “as usual” for 1 week followed by 2 weeks of either placebo or active 1st generation EC BluCig starter kit with up to 7 cartridges (prefilled, with either active 16 mg or 0 mg nicotine solution)

Participants were instructed “this e-cig may or may not contain nicotine; we ask that you try it at least once, but use it however you like; smoke regular cigarettes as you wish.” Shown how to charge the device and sampled the product during the visit. Provided a handout on how to use the product (e.g., switching cartridges) and general information about ECs

Outcomes

1 week in each condition, in person

Adverse events and biomarkers:

- Adverse events, not clear how collected
- Exhaled CO

Other outcomes measured:

- Vaping
- Regular smoking
- Perceived reward from ECs
- Intentions/confidence to quit
- Cotinine
- Withdrawal symptoms

Study funding

“..supported by grants P01 CA138389, P30 CA138313 (Hollings Cancer Center Support Grant) from the National Cancer Institute of the National Institutes of Health and UL1 TR000062 from the National Center for Advancing Translational Science of the National Institutes of Health. BWH was supported by K12DA031794”

Author declarations

“KMC has received grant funding from the Pfizer, Inc., to study the impact of a hospital-based tobacco cessation intervention. He also receives funding as an expert witness in litigation filed against the tobacco industry. We have no other declarations of interests to declare”

Meier 2017 (Continued)

Notes New for 2020 update.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomized to receive either an active or placebo EC first", no further information provided.
Allocation concealment (selection bias)	Unclear risk	Refer to 'Random sequence generation'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants and research staff conducting sessions were blinded to dose. All cartridges were pre-loaded by the manufacturer. Labeling was removed by a research team member not involved in participant contact to mask placebo versus active ECs. We restricted flavor options to regular tobacco flavor or menthol to most closely match usual cigarette brand flavor profile and reduce unwanted variance in product"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants and research staff conducting sessions were blinded to dose. All cartridges were pre-loaded by the manufacturer. Labeling was removed by a research team member not involved in participant contact to mask placebo versus active ECs. We restricted flavor options to regular tobacco flavor or menthol to most closely match usual cigarette brand flavor profile and reduce unwanted variance in product"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

NCT02417467
Study characteristics

Methods	Design: RCT Recruitment: "from the general population" Setting: Canada Study start date: November 2016; Study end date: December 2019
Participants	Total N: 376 N per arm: Nicotine E-cigs + counselling: 128; Non-nicotine E-cigs +counselling: 127; Counselling: 121 Inclusion criteria: <ul style="list-style-type: none"> • Active smoker, 10 or more cigarettes per day, on average, for the past year • Age of 18 years or older • Motivated to quit according to the Motivation To Stop Scale (MTSS) (level 5 or higher) • Able to understand and to provide informed consent in English or French • Likely to be available for follow-up (1 year)

NCT02417467 (Continued)

Exclusion criteria:

- Medical condition with a prognosis < 1 year
- Current or recent cancer (less than 1 year in remission)
- Pregnant or lactating female
- Current or recent use (in the past 30 days) of any pharmacotherapy or behavioural therapy for smoking cessation (e.g. Nicotine Replacement Therapies, bupropion, varenicline, or counselling)
- Any e-cigarette use (nicotine or non-nicotine) in the past 60 days, or ever use of any e-cigarette for more than 7 days consecutively
- History of psychosis, schizophrenia, or bipolar disorder
- Less than one month following a myocardial infarction, life-threatening arrhythmia, severe or worsening angina pectoris, or cerebral vascular accident; Use of any illegal drugs in the past year (excluding marijuana)
- Planned use of tobacco products other than conventional cigarettes (e.g. cigarillos, cigars, snuff, shisha, etc.) or marijuana during the study period

47% women; mean age 52; mean cpd 21; mean FTND: Not reported

Motivated to quit: yes

E-cigarette use at baseline: Not reported; but any E-cig use within previous 60 days an exclusion criterion

Interventions	<p>EC: not specified</p> <p>Smoking cessation/relapse prevention counselling provided for all participants for a minimum of 30 minutes at baseline, 10 minutes during telephone follow-ups, and 15 minutes at clinic visits (20 minutes at week 4)</p> <p>1) Nicotine-containing EC: participants expected to self-regulate administration of e-cigarettes. No details about device or dose</p> <p>2) Non-nicotine EC: as above</p> <p>3) Counselling only</p>
Outcomes	<p>Telephone follow-ups at weeks 1, 2, and 8; Clinic visits at weeks 4, 12, 24, and 52. Self-report and biochemical validation</p> <p>Adverse events and biomarkers</p> <p>The number of serious adverse events (SAE) reported over the 12 week treatment period</p> <p>The number of adverse events reported over the 12-week treatment period</p> <p>Other outcomes measured:</p> <ul style="list-style-type: none"> • Change in daily cigarette consumption • The number of dropouts due to side effects of the e-cigarettes over the 12-week treatment period
Study funding	No details
Author declarations	Dr. Wilderman received financial compensation from Pfizer Inc. for his involvement in a smoking cessation study using varenicline. The other authors have no conflicts of interest to declare (extracted from presentation slides_ACC.20 World congress of cardiology)
Notes	<p>Study listed as ongoing study in the 2016 review update</p> <p>Data extracted from presentation slides and clinicaltrials.gov record thus limited detail available</p>

NCT02417467 (Continued)

The primary endpoint was changed from 52 weeks to 12 weeks following the early termination of enrolment (77% of target enrolment) due to a delay in product manufacturing

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Data extracted from slide presentation and registry record – information not reported
Allocation concealment (selection bias)	Unclear risk	Data extracted from slide presentation and registry record – information not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	State quadruple blinding (participant, care provider, investigator, outcomes assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above. Biochemical validation for 12 week abstinence
Incomplete outcome data (attrition bias) All outcomes	Low risk	Retention rate at 12 weeks follow-up: <ul style="list-style-type: none"> Nicotine ECs & counselling: 118/128 = 92% Non-nicotine ECs & counselling = 113/127 = 89% Counselling = 92/121 = 76%
Selective reporting (reporting bias)	Unclear risk	Not all outcomes (AEs) reported as preliminary data in the conference presentation. No results posted on trial registry to date
Other bias	Unclear risk	The primary endpoint was changed from 52 weeks to 12 weeks following the early termination of enrolment (77% of target enrolment) due to a delay in product manufacturing

NCT02648178
Study characteristics

Methods	Setting: Medical centre, USA Recruitment: People with cancer Design: Non-randomized single-group assignment trial Recruitment: Clinical settings, including outpatient clinics and the infusion suite Study start date: June 2016; Study end date: May 2018
Participants	Total N: 19 Inclusion criteria: <ul style="list-style-type: none"> Histological or cytological diagnosis of aerodigestive tract cancers or bladder cancer within the past 5 years (more than 1 tobacco-related malignancy is allowed) AJCC stages I - IV Daily smoking (at least 10 cigarettes per day for 10 years) and breath CO₂ ≥ 8 ppm

NCT02648178 (Continued)

- Does not wish to quit smoking now (anyone wishing to quit smoking will be referred for smoking cessation counselling through the WRJ VAMC or DHMC program)
- May be receiving anti-cancer agents
- Age 18 or older
- Fluent in English
- Patient must be capable and willing to provide informed written consent for study participation
- Able to participate in study visits

Exclusion criteria:

- Cancer surgery planned in the next 9 weeks
- Treatment with radiation planned for the next 9 weeks
- Actively trying to quit smoking, or planning to in the next 30 days. (If a patient reports that they plan to quit smoking in the next 30 days, we will call them after the 30 days to see if they are still trying to quit)
- Any use of e-cigarettes in the past 30 days
- Pregnant or trying to get pregnant

Inclusion based on specific population characteristic: Patients with stage I - IV aerodigestive tract cancers or bladder cancer who smoke daily

42.1% women; mean age: not reported -categories 18 - 65 years: N = 9, > 65 years: N = 10; cpd and FTND: not reported.

Motivated to quit: No (inclusion criterion)

E-cigarette use at baseline: Not specified but EC use within 30 days is an exclusion criterion

Interventions

EC: Cig-a-like and refillable

Instructed on use of EC, and given a supply that is "approximately equivalent to their current nicotine intake". Given Halo Triton EC (leak-proof refillable tank system) or Halo G6 leak proof prefilled cartomizers. Began participants with 18 mg/ml and moved nicotine content up or down based on participant preference. Choice of flavours, provided for 9 weeks

Outcomes

Weeks 3, 6, 9, 12. Self-report at clinic visits

Adverse events and biomarkers:

- Averse events assessed with a checklist for commonly-occurring side effects from e-cigarettes and nicotine products
- Exhaled carbon dioxide
- Expired carbon monoxide
- Urine propylene glycol
- Urine 4- (methylnitrosamino)-1-(3-pyridyl)-1butanol (NNAL) 40 and 1- hydroxy naphthalene (1-HOP)

Other outcomes measured:

- Timeline Follow-Back Questionnaire (TLFB)
- EC appeal assessed with attitudinal ratings, on a 5-point Likert-type scale
- e-cigarette ease of use, satisfaction, and enjoyment, and willingness to continue to purchase e-cigarettes in the future
- Change in daily cigarette smoking given 10 or more E-cig sessions
- Average number of E-cigs used per day
- The co-ordinators will conduct and audiorecord a 10 - 15-minute qualitative interview at 9 weeks soliciting perceptions about e-cigarettes to be transcribed and analyzed for common themes that could be useful in developing the larger intervention
- urine nicotine and cotinine

Study funding

Not reported – data extracted from clinical trial registry record

NCT02648178 (Continued)

Author declarations	Not reported – data extracted from clinical trial registry record	
Notes	Study listed as ongoing study in the 2016 review update	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized, single-group assignment
Allocation concealment (selection bias)	High risk	Not randomized, single-group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	19 enrolled; 10 participants followed up at 12 weeks
Selective reporting (reporting bias)	Unclear risk	The following measures were not reported: exhaled carbon dioxide; urine propylene glycol; urine nicotine, cotinine, NNAL and 1- hydroxy naphthalene (1-HOP), and Timeline Follow-Back Questionnaire (TLFB). Data at 6, 12 months also not reported

NCT02918630

Study characteristics	
Methods	Design: RCT Recruitment: Clinics Setting: SMI clinics, USA Study start date: October 2016; Study end date: August 2017
Participants	Total N: 7 N per arm: NRT: 4; EC+NRT 3 Inclusion criteria: <ul style="list-style-type: none"> • Be diagnosed with schizophrenia (or other SMI, not clear) • Be in stable medical condition (DSM-V) • Report smoking ≥ 10 tobacco cigarettes/day • Present a breath CO ≥ 10 ppm • Report wanting to reduce their cigarette smoking • Be fluent in English • Have a stable living situation Exclusion criteria: <ul style="list-style-type: none"> • Be currently pregnant or breastfeeding • Report wanting to quit smoking in the immediate future • Test positive for illicit drugs except THC • Have any illness, medical condition, or use of medications, which in the opinion of the study physicians would preclude safe or successful completion of the study, or both

NCT02918630 (Continued)

Inclusion based on specific population characteristic: Yes - SMI (schizophrenia and schizoaffective disorder, bipolar disorder, or PTSD)

43% women; mean age 48.3; mean cpd: NR; mean FTND: NR

Motivated to quit: Wanted to quit or reduce their cigarette smoking but did not want to quit in the immediate future (this was an exclusion criterion) NB – trial registry states wanted to reduce and protocol states wanted to quit or reduce as inclusion criteria

E-cigarette use at baseline: Not specified

Interventions	<p>EC: Refillable</p> <p>Both arms received a nicotine patch 21 mg for 4 weeks</p> <p>EC + NRT: 4 weeks: 1) a 3.3 V, 1000 mAh battery; and 2) a 1.5 Ohm, dual-coil cartomizer (SmokTech; Shenzhen, China). Nicotine concentrations 36 mg/ml. Verbal and written instructions on how to use and maintain the e-cigarettes at Week 1 visit</p> <p>NRT arm: NRT only</p>
Outcomes	<p>5 weeks</p> <p>Cessation: n/a but “change in smoking”</p> <p>Adverse events and biomarkers:</p> <p>Breath CO, COPD-related symptoms, EC side effects (e-cig side effects questionnaire), AEs, SAEs</p> <p>Other outcomes measured:</p> <p>Urinary cotinine, cpd, tobacco dependence, craving, withdrawal symptoms, desire to quit, confidence to quit, EC dependence, EC use, satisfaction with EC, nicotine dependence, schizophrenia symptoms (brief psychiatric rating scale), cognitive domains associated with schizophrenia (MATRICS consensus cognitive battery), changes in positive symptoms of schizophrenia (scale for the assessment of positive symptoms), changes in negative schizophrenia symptoms (scale for the assessment of negative symptoms), suicide ideation (Columbia Suicide Severity Rating Scale)</p>
Study funding	Not reported
Author declarations	Not reported
Notes	New for 2020 update. Information from http://clinicaltrials.gov registry and unpublished protocol; discrepancies between the two in terms of trial methods. Feasibility for future NIH grant application. Intended to recruit 20 participants but only 7 started and completed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	“double-blind” but “open-label” elsewhere, no further info given

NCT02918630 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	Schizophrenia and COPD outcomes not reported.
Other bias	Unclear risk	Some discrepancies between clinicaltrials record and protocol linked to from record, including when NRT started and inclusion criteria (just schizophrenia or all SMI). Target sample size was 20 but only 7 people recruited

Nides 2014
Study characteristics

Methods	Design: Open-label non-comparative study Recruitment: Study site database and community advertisements Setting: Clinical Trials Unit, USA Study start date: April 2013; Study end date: 10 July 2013
Participants	Total N: 29 Inclusion criteria: <ul style="list-style-type: none"> • Age 18 - 65 years • Good health • BMI 18 - 35 • Smoking 10+ cpd • CO > 10 ppm Exclusion criteria: <ul style="list-style-type: none"> • Pregnancy or breastfeeding • Other drug dependency • Use of any psychiatric or opioid medications • EC within the previous 14 days • Use of NRT in last 30 days • Want to reduce or quit smoking within the next 30 days Exclusion criterion: EC within the previous 14 days; use of NRT in last 30 days 44% women; mean age 43; mean cpd 20.1; mean FTND 4.5 Motivated to quit: no E-cigarette use at baseline
Interventions	EC: Cig-a-like Participants attended 3 clinic visits at 1-week intervals

Nides 2014 (Continued)

Visit 1: Baseline

Visit 2: Provided with 1st generation type - 'NJOY® King Bold' (NJOY, Inc. Scottsdale, AZ), with 26 mg nicotine. Used ad libitum for 20 minutes in the clinic, then ad libitum use over the next week. Recorded use of regular cigarettes and puffs on EC

Visit 3: Participants abstained from all sources of nicotine for 12 hours prior to visit

Outcomes	Adverse events
Study funding	Funding for this study was provided by NJOY, Inc., Scottsdale, AZ
Author declarations	Dr Nides has received compensation from NJOY, Inc. and GlaxoSmithKline. Dr Leischow has received compensation from GlaxoSmithKline, Pfizer, and Cypress Bioscience. Mr Simmons and Ms Bhatler have no conflict of interest to report
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants dropped out between visits 1 and 2
Selective reporting (reporting bias)	Low risk	Planned comparisons reported

Oncken 2015
Study characteristics

Methods	Design: Randomized cross-over study Recruitment: Newspaper advertisements, radio announcements, and from local general medicine practices Setting: Lab-based study, Connecticut, USA Study start date: October 2012; Study end date: June 2015
Participants	Total N: 27 Inclusion criteria: <ul style="list-style-type: none"> • non-treatment-seeking people who smoke who were willing to try EC for 2 weeks and abstain from conventional cigarette smoking • 18 – 55 years of age who smoked at least 10 cpd Exclusion criteria:

Oncken 2015 (Continued)

- Pregnant
- Previous myocardial infarction or stroke
- Uncontrolled hypertension (blood pressure (BP) > 160/100)
- Insulin-dependent diabetes
- COPD or current asthma
- Known allergy to propylene glycol

45% women; mean age 42; 70% white; 15% Hispanic, 15% black; mean cpd 16; 45% had tried EC at baseline, 50% smoked menthol cigarettes

Motivated to quit: No

E-cigarette use at baseline: Not specified

Interventions	EC: Cig-a-like Prescribed Joye eGo-C (www.joyetech.com) and e-Juice (18 mg/mL nicotine) procured from American eLiquid (www.americanliquid.com) Cross-over study between menthol-flavoured and non-menthol tobacco-flavoured EC. Requested not to smoke their regular cigarettes during study period, but most (60%) reported intermittently smoking cigarettes during study	
Outcomes	Follow-up at 1 wk and 2 wks BP, heart rate, body plethysmography, static lung volumes and airways resistance (Raw) and specific conductance (sGaw) – taken at lab visits after abstaining from EC for at least 2 hrs, then taken again after inhaling EC and repeated 5 mins later Adverse events also reported but method for measuring not stated Also measured nicotine concentrations, rates of cigarette and EC use	
Study funding	This project was supported by Academic Enhancement funds from the Department of Medicine at the University of Connecticut Health Center (to CO) and the Clinical Research Center at the University of Connecticut Health Center	
Author declarations	CO is currently receiving study medication (nicotine inhaler and placebo) from Pfizer pharmaceuticals for an NIH funded of nicotine inhaler for smoking cessation during pregnancy	
Notes		
Risk of bias		
	Bias	Authors' judgement Support for judgement
	Random sequence generation (selection bias)	Unclear risk Method not stated; Quote: "Subjects were then randomly assigned to use the menthol or plain e-cigarette cartridge for one week, switching to the other cartridge for the second week"
	Allocation concealment (selection bias)	Unclear risk No detail given
	Blinding of participants and personnel (performance bias) All outcomes	Low risk No detail given on blinding but equal levels of support between arms, so performance bias judged unlikely
	Blinding of outcome assessment (detection bias)	Low risk Some subjective outcomes but equal levels of support between arms so differential misreport judged unlikely

Oncken 2015 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	20/27 followed up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Pacifici 2015
Study characteristics

Methods	Design: Uncontrolled pre-post pilot study Recruitment: Word of mouth Setting: Hospital-based smoking cessation clinic, Italy Study start date/end date: Not specified
Participants	Total N: 34 Inclusion criteria: <ul style="list-style-type: none"> Adults who smoke, unwilling to quit smoking tobacco cigarettes and who have never tried a quit-smoking protocol or have refused any smoking cessation treatment, or both Exclusion criteria: <ul style="list-style-type: none"> None stated Inclusion based on specific population characteristic: No 47.1% women, mean age 40.6, mean cpd 21.5 no EC use at baseline, not motivated to quit
Interventions	EC: Refillable Participants were given commercially-available EC (AVATAR device, Battery 550 mAh/3.9 V, W: 7.8, cartomizer with 2, 2 ohm resistance, tank capacity 1.5 mL, temperature of the aerosol: 55/65 degrees), 2 different chargers for each EC and PUFFIT e-liquids with nicotine content matching the individual nicotine daily intake and tobacco and/or other flavours freely chosen by each participant W1: nicotine-free e-liquid W2&3: Own EC with personal nicotine dosage, encouraged to use as substitute for traditional cigarettes W4: Encouraged to forego all traditional cigarettes Throughout: assistance at any time of day from centre staff with any EC-related problem, plus follow-up group sessions and smartphone messaging application Behavioural support: Multi-component medically-assisted training programme with monitoring of nicotine intake as a biomarker of correct EC use, including information about general working principles, safety and risks of EC, together with medically-assisted face-to-face training on how to correctly use the device to absorb nicotine vapour

Pacifici 2015 (Continued)

Outcomes	Follow-up at 1, 4 and 8 m Cessation (measure not defined) Adverse events Exhaled CO, COT, 3-HCOT concentration cpd
Study funding	The authors thank Renata Solimini, Adele Minutillo, Emilia Marchei and Maria Concetta Rotolo for their technical assistance. This work was supported by the Department of Therapeutic Research and Medicines Evaluation Istituto Superiore di Sanità, Roma, Italy
Author declarations	The authors declare no conflict of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not controlled
Allocation concealment (selection bias)	High risk	Not controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed up
Selective reporting (reporting bias)	High risk	AEs measured but not reported

Polosa 2011
Study characteristics

Methods	Design: Prospective cohort Recruitment: Advertisements in local hospital in Catania, Italy Setting: not specified Study start date: February 2010; Study end date: June 2010
Participants	Total N: 40, hospital staff Inclusion criteria: <ul style="list-style-type: none"> • Healthy people who smoke • 18 - 60 years old • smoking \geq 15 cpd for at least the past 10 years, and not wanting to quit smoking at any time in the next 30 days Exclusion criteria:

Polosa 2011 (Continued)

- History of alcohol and illicit drug use
- Psychiatric illness
- Recent myocardial infarction
- Angina pectoris
- High blood pressure (BP > 140 mmHg systolic or 90 mmHg diastolic, or both)
- Diabetes mellitus
- Severe allergies
- Poorly-controlled asthma or other airways diseases

35% women, mean age 42.9 (SD 8.8), median cpd 25 (IQR 20 - 30), median FTND 6.0 (IQR 6 - 8)

Motivated to quit: No

E-cigarette use at baseline: Not specified

Interventions	<p>EC: Cig-a-like</p> <p>Seen at baseline, given EC ('Categoria' brand) with an initial 4-week supply of 7.4 mg nicotine cartridges. Instructed to use ad libitum up to 4 cartridges per day. EC cartridges supplied at months 1, 2, and 3</p> <p>No instruction on cessation or reduction was provided</p>
Outcomes	<p>Follow-up at 1, 2, 3, 6, 18 and 24 months where cigarette consumption, CO, and AEs were measured, incl. 30-day PP CO-validated abstinence at 6 months and CO-validated abstinence at 18 and 24 months (not otherwise defined)</p> <p>Adverse events</p>
Study funding	<p>"We wish to thank Arbi Group Srl (Milano, Italy) for the free supplies of 'Categoria' e-Cigarette kits and nicotine cartridges as well as their support. We would also like to thank the study participants for all their time and effort and LIAF (Lega Italiana AntiFumo) for the collaboration"</p>
Author declarations	<p>"None of the authors have any competing interests to declare, but RP has received lecture fees from Pfizer and, from Feb 2011, he has been serving as a consultant for Arbi Group Srl. Arbi Group Srl (Milano, Italy), the manufacturer of the e-Cigarette supplied the product, and unrestricted technical and customer support. They were not involved in the study design, running of the study or analysis and presentation of the data"</p>
Notes	<p>Smoking cessation services provided to those who spontaneously asked for assistance with quitting. These participants were excluded from the study protocol</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	13/40 were lost to follow-up, but used ITT analysis
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Polosa 2014b

Study characteristics

Methods	<p>Design: Prospective cohort study</p> <p>Recruitment: Volunteers, leaflets, cessation service kiosk in hospital</p> <p>Setting: Smoking cessation clinic, Italy</p> <p>Study start date: January 2013; Study end date: November 2013</p>
Participants	<p>Total N: 50</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Healthy people who smoke • 18 – 60 years old • Smoking \geq 15 conventional cpd for at least 10 years • Unwilling to quit <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • none stated <p>40% women, mean age 41, mean cpd 25, mean FTND 6.0</p> <p>No EC use at baseline, not motivated to quit</p>
Interventions	<p>EC: Refillable</p> <p>2nd generation devices (personal vaporisers - PVs): EGO/CE4 model, filled with tobacco aroma e-Liquid containing 9 mg/ml nicotine; instructed to use the study products ad libitum (up to a maximum of 5 ml/day; i.e. half vial)</p> <p>Behavioural support:</p> <p>Participants were instructed how to charge, fill, activate and use the EC. Key troubleshooting was addressed and phone numbers were supplied for assistance. "No emphasis on encouragement, motivation and reward for the smoking cessation-related efforts were provided during the study."</p>
Outcomes	<p>4, 8, 12 and 24 wks</p> <p>30-day PP verified by CO \leq 10 ppm</p> <p>Adverse events</p> <p>Cpd, exhaled CO, reduction rates, product usage, and opinions of the EC products</p>
Study funding	<p>"The authors wish to thank FlavourArt (Oleggio, NO, Italy; www.flavourart.it). Authors wish to thank LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti Smoking League) for supporting this research"</p>
Author declarations	<p>"RP has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has also served as a consultant for Pfizer and Arbi Group Srl, an Italian distributor of e-Cigarettes. RP is currently scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti Smoking League). PC, MM, JBM, and CR have no relevant competing interest to declare in relation to this work"</p>

Polosa 2014b (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not controlled
Allocation concealment (selection bias)	High risk	Not controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	76% followed up, ITT analysis used, no significant differences in baseline characteristics between completers and those lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Polosa 2015
Study characteristics

Methods	Design: Prospective cohort Recruitment: Professional retail staff in participating vape shops Setting: 7 vape shops in Catania province, Italy Study start date/end date: Not specified
Participants	Total N: 71 Inclusion criteria: <ul style="list-style-type: none"> Adults who smoke (≥ 18) making first purchase at participating vape shop (definition of smoker not stated) Exclusion criteria: <ul style="list-style-type: none"> none stated 38% women, mean age 41.7, mean cpd 24.9, mean FTND 5 No EC use at baseline
Interventions	EC: Refillable Instructed how to charge, fill, activate and use EC; key troubleshooting advice provided; phone number available for technical support "Encouraged to use these products in anticipation of reducing the number of cig/day smoked"
Outcomes	6 and 12 m follow-up 30-day PPA via self-report Details of product purchase

Polosa 2015 (Continued)

Sustained 50% and 80% reduction in cpd from baseline

Study funding	Authors wish to thank the local participating Vape Shops and LIAF, Lega Italiana Anti Fumo (Italian acronym for the Italian Anti-Smoking League) for supporting this research
Author declarations	Riccardo Polosa has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has also served as a consultant for Pfizer and Arbi Group Srl, an Italian distributor of e-Cigarettes. Riccardo Polosa is currently scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League). Jacques Le-Houezec is a consultant for Johnson & Johnson France, a manufacturer of nicotine replacement therapy, and was reimbursed for travel and accommodation to present at a conference in Shenzhen (China) organised by the e-cig manufacturer association (CECMOL). Pasquale Caponnetto and Fabio Cibella have no relevant conflict of interest to declare in relation to this work

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not controlled
Allocation concealment (selection bias)	High risk	Not controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	69% follow-up at 12 m. Participants lost to follow-up considered as continuing smokers
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Pratt 2016
Study characteristics

Methods	<p>Design: Observational study – uncontrolled experimental study</p> <p>Recruitment: community mental health centre through self-referral and clinician referrals</p> <p>Setting: community mental health centre (USA)</p> <p>Study start date: October 2013; Study end date: June 2014</p>
Participants	<p>Total N: 19 (21 originally recruited, however 2 participants did not return for any weekly visits so 19 analysed)</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Age ≥ 18 • Primary DSM-IV axis I diagnosis, based on chart review and confirmation by the community mental health centre team psychiatrist, of schizophrenia, schizoaffective disorder, or bipolar disorder • SMI defined by at least moderate impairment in multiple domains of life functioning due to mental illness • Smoking at least 10 cigarettes per day • History of failed treatment-facilitated quit attempts

Pratt 2016 (Continued)

- Voluntary informed consent for participation

Exclusion criteria:

- Current use of e-cigarettes
- Medical instability
- Primary diagnosis of dementia or significant cognitive impairment defined as a Mini Mental Status Examination (MMSE) score < 24

Inclusion based on specific population characteristic: Psychiatrically stable, in-treatment, people who smoke with a schizophrenia spectrum disorder or bipolar disorder

68% women; mean age 42; mean cpd: Only cigarettes per week reported: 192 (SD = 159.3). This would be an average of 27 cpd; mean FTND 5.5

Motivated to quit: “None of the participants was actively engaged in a quit attempt during the study”

E-cigarette use at baseline: E-cig use was an exclusion criterion

Interventions

EC: Cig-a-like

E-cigarette details: (NJOY brand) based on each participant's level of use of combustible tobacco. Each e-cigarette cartridge was approximately equivalent to 2 packs of combustible cigarettes. Trained research interviewers instructed participants on the proper use of e-cigarettes

Outcomes

Week 1, 2, 3, 4

Adverse events and biomarkers:

- Breath CO level
- Possible side effects

Other outcomes measured:

- Use of tobacco products
- Fagerström nicotine dependence scores
- Appeal of EC
- Level of enjoyment of EC
- Satisfaction with EC compared with usual combustible tobacco
- Willingness to purchase EC

Study funding

“Financial support to purchase the e-cigarettes and pay small stipends to the participants in this unfunded pilot study came from Dr. Mary Brunette's discretionary reserve account.”

Author declarations

“All authors declare that they have no conflicts of interest”

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias)	Low risk	2 dropouts (9.5%) failed to return to clinic. Analysis based on 19 participants

Pratt 2016 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
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Pulvers 2018

Study characteristics

Methods	<p>Design: Observational uncontrolled experimental study</p> <p>Recruitment: Community</p> <p>Setting: Visits took place in University labs, USA</p> <p>Study start date: January 2015; Study end date: April 2015</p>
Participants	<p>Total N: 40</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Being 18 years of age or older • Cigarette smoking on at least 4 days of the past 30 days for at least 1 year • Never using EC regularly (less than 25 lifetime uses) • Not having used EC on more than 3 of the past 30 days • Being willing to switch from smoking regular cigarettes to ECs • Fluency in English • Having regular access to a telephone and transportation to attend appointments • Being willing to abstain from using marijuana during the study <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Any use of other tobacco products (OTPs) including smokeless tobacco, cigarillos, pipes, cigars, hand-rolled cigarettes, and hookah in the past 30 days • Being currently in a smoking cessation programme or another clinical trial • Past 30 day use of nicotine replacement therapy or medication which aids smoking cessation including bupropion, clonidine, nortriptyline, or varenicline • Having uncontrolled asthma, severe allergies, or diabetes mellitus • Currently taking prescription medication for emotional distress, depression, or other psychological problems • Current dependence on a substance other than nicotine • Presence of any cardiovascular or pulmonary illnesses in the past 6 months • For women, pregnancy or plans to become pregnant in the next 6 months <p>Inclusion based on specific population characteristic: No</p> <p>27% women; mean age 30.08; mean cpd 8.76; FTND not reported</p> <p>Motivated to quit: over half either did not intend to quit at all or did not intend to quit in the next 6 months 22/40 (55%)</p> <p>E-cigarette use at baseline: Inclusion criteria included the following:</p> <ul style="list-style-type: none"> • Never using EC regularly (less than 25 lifetime uses) • Not having used EC on more than 3 of the past 30 days
Interventions	EC: Refillable

Pulvers 2018 (Continued)

2nd generation EC starter kit with 2 e-Go C batteries (3.7 volts/650 MaH), a USB connection cord, an AC adapter, and a carrying case, and a supply of Saturn V4i atomizers (2.4 ohms) filled with liquid in their preferred flavour (28 atomizers total; 2/day). Provided 24 mg/mL dosage vegetable glycerin liquid in a tester sample to all participants. Those who reported the 24 mg was too strong were provided 12 mg/mL dosage liquid. The first session included brief education, training, action planning for making a complete switch to EC. A referral to the California Smokers' Helpline was made at the final visit (week 4).

Outcomes

3 lab visits (baseline, week 2, and week 4) and 2 phone visits (week 1 and week 3). Biological samples were taken at all 3 in-person visits (baseline, week 2, and week 4). However, due to budgetary restrictions, only the baseline and week 4 biological data were analysed

Adverse events and biomarkers:

- Biochemical measures only: Breath samples were taken with a Micro + (Bedfont, Haddonfield, NJ) to measure CO
- Urine samples taken to test for change in tobacco toxicant exposure by following measures:
 - * concentrations of NNAL measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS)
 - * metabolites of a panel of potentially toxic VOCs, including benzene (PMA), ethylene oxide (HEMA), N-nitrosodimethylamine (MMA), acrylonitrile (CNEMA), acrolein(3-HPMA), propylene oxide (2-HPMA), acrylamide (AAMA), and crotonaldehyde (HPMMA) measured by LC–MS/MS,2

Other outcomes measured:

Cotinine, change in tobacco consumption (CPD using TLFB interview), change in frequency of EC use, change in nicotine dependence and attitudes/behaviour, change in 30-day nicotine exposure

Study funding

“This study was funded by the University of Minnesota (JSA), P30 DA012393 (NLB), P50 CA180890 (NLB), and California State University San Marcos (KP).”

Author declarations

“Benowitz is a consultant to pharmaceutical companies that market smoking cessation medications and has been an expert witness in litigation against tobacco companies. The other authors have no conflicts of interest.”

Notes

New for 2020 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	37/40 provided follow-up data
Selective reporting (reporting bias)	Low risk	All outcomes reported

Smith 2020
Study characteristics
Electronic cigarettes for smoking cessation (Review)

Smith 2020 (Continued)

Methods	<p>Design: Double-blind randomized controlled trial</p> <p>Recruitment: Recruited from the local area via advertising on craigslist social media</p> <p>Setting: Laboratory and electronic diaries, USA</p> <p>Study start date/Study end date: Not specified.</p>
Participants	<p>Total N: 30</p> <p>N per arm: PG/VG ratio 70/30 = NR; PG/VG ratio 50/50 = NR; PG/VG ratio 0/100 = NR</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • adults age \geq 18 who have been smoking at least 5 cigarettes daily for the past year (expired CO > 8) • usual brand is non-menthol • use of ENDS on 5 or fewer lifetime occasions • regular use of e-mail or smartphone ownership with capacity to receive SMS text and internet access (necessary for electronic diaries) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • unwilling to use ENDS as part of the trial • use of smokeless, hookah, or tobacco products other than cigarettes \geq 10 days in the past 30 days • pregnant, trying to become pregnant, or breastfeeding • recent history of cardiovascular distress in the last 3 months (arrhythmia, heart attack, stroke, uncontrolled hypertension) • current use of cessation medications • another household member currently enrolled in the study (to prevent contamination of e-liquid assignment during sampling) <p>30% women; mean age 43.7; mean cpd 18.5; mean FTND 5.4</p> <p>Motivated to quit: Not specified</p> <p>E-cigarette use at baseline: Participants had used an e-cigarette an average of 1.6 times in their life, and no one reported use in the last 30 days</p>
Interventions	<p>EC: Cig-a-like</p> <p>EC provided for 1 week. All aspects of the ENDS device and e-liquid were held constant between groups with the exception of PG/VG ratio:</p> <p>PG/VG ratio 70/30; PG/VG ratio 50/50; PG/VG ratio 0/100. Ego-T 1100 mAh battery and disposable cartomizers (510 Smoketech, 1.5-Ω dual coil). E-liquid was tobacco-flavoured (Classic Tobacco, American E-liquid) and contained 18 mg nicotine/ml</p>
Outcomes	<p>1 week; 2 lab visits pre and post and participant diaries</p> <p>Adverse events and biomarkers: Participants provided a CO sample at each visit</p> <p>Other outcomes measured: cpd, ENDS puffs</p>
Study funding	<p>Funding for this project was provided by pilot funding from the National Cancer Institute (P01CA200512 to K.M.C.). Salary support provided by the National Institute on Drug Abuse (K12DA031794 to T.T.S., K23DA041616 to B.W.H.)</p>
Author declarations	<p>M.J.C. has received consulting honoraria from Pfizer. K.M.C. has received payment as a consultant to Pfizer, Inc., for service on an external advisory panel to assess ways to improve smoking cessation delivery in health care settings. He also has served as paid expert witness in litigation filed against the tobacco industry</p>

Smith 2020 (Continued)

Notes Additional data provided from authors. New for 2020 update.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At the conclusion of the lab visit, participants were randomized and assigned to take home one of the three e-liquids to use at home for a 1-week sampling period (10 participants/ratio)." Quote: "Participants were randomly assigned to receive one e-liquid to take home for 1 week." (no further detail given)
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "PG/VG ratio was blinded from participant and staff members who conducted experimental sessions."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of participants at follow-up not reported, but this may be due to the 1-week follow-up and it seems that all participants (excluding 1 participant who was not randomised) were followed up
Selective reporting (reporting bias)	Unclear risk	No protocol. Few details for CO measurements, just percentage change for each group, but mean CO data provided by author on request

Stein 2016
Study characteristics

Methods	Design: Non-controlled open-label experimental study Recruitment: A flyer posted at a large methadone maintenance treatment programme Setting: Methadone maintenance treatment programme, USA Study start date: April 2015; Study end date: Not specified
Participants	Total N: 12 Inclusion criteria: <ul style="list-style-type: none"> • current moderate or heavy cigarette use (10+ cpd for at least 12 months prior to enrolment) • current MMT for at least 3 months • ready to make a smoking quit attempt in the next 14 days • plan to remain on MMT for at least 12 weeks Exclusion criteria: <ul style="list-style-type: none"> • used e-cigarettes on more than 2 of the past 30 days • currently used medications that may reduce smoking (bupropion, varenicline, NRT)

Stein 2016 (Continued)

- had unstable medical or psychiatric conditions (past-month suicidal ideation or past-year suicide attempt, hospitalization for myocardial infarction or stroke in the prior 3 months)
- had regular use of marijuana (self-report or positive urine drug test)

Inclusion based on specific population characteristic: People receiving MMT for opioid use disorder

50% women; mean age 45.9; mean cpd 17.8; mean FTND: Not reported

Motivated to quit: yes

E-cigarette use at baseline: Had not used e-cigarettes for more than 2 of the past 30 days

Interventions	EC: Cig-a-like 2 week supply of NJOY e-cigarettes at week 1 (quit day), consisting of 5 packs of NJOY e-cigarettes (15 in total). Participants could request an additional 5 pack (20 in total) for the following 2-week study period, if they ran out before a study visit. Participants instructed to use EC exclusively for a total of 6 weeks (end of treatment). They were referred to the state telephone QuitLine for supportive counselling at the quit-day visit (week 1)	
Outcomes	Participants quit and received e-cigs at week 1. Assessments were carried out at week 3, 5, 7 and 9 Adverse events and biomarkers: <ul style="list-style-type: none"> • “Side effects” of e-cigarettes were recorded. Side effects were rated none, slight, mild, moderate and severe at every assessment visit. An adverse effect possibly related to e-cigarette use was defined as positive if the value at baseline was either none or slight AND the value at any of 3, 5, or 7 weeks was mild or more severe Other outcomes measured: <ul style="list-style-type: none"> • Reduction in the average cpd • E-cig adherence • Nicotine withdrawal 	
Study funding	“MDS is a recipient of National Institute on Drug Abuse Award K24 DA000512. This award funded the project described here.”	
Author declarations	“None declared.”	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No randomization
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “One individual dropped out after week 3 and did not return; another completed all follow-up assessments except week 7.”
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Strasser 2016

Study characteristics

Methods	<p>Design: Randomized, factorial trial (Participants were randomized to one of the 5 brands of e-cigarettes – although only 4 brands analysed)</p> <p>Recruitment: Media ads</p> <p>Setting: Recruitment from the community, study took place at University, USA.</p> <p>Study start date/Study end date: Not specified.</p>
Participants	<p>Total N: Analysis based on 24 (28 originally recruited, but the first 4 participants enrolled experienced malfunctioning NJOY e-cigs and withdrew – the project was removed from the market before the 5th participant was randomised)</p> <p>N per arm: blu: 6; Green Smoke: 6; V2: 6; White Cloud: 6</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Age 18 to 65 and self-reported smoking at least 10 cigarettes per day. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Use of other tobacco or nicotine-containing products, including e-cigarettes (no more than 3 previous episodes of use and not currently using) • Current diagnosis or evidence of substance abuse or dependence or major depression • Current or history of psychotic or bipolar disorder • History of suicide attempt • History of cancer or cardiovascular disease • Uncontrolled hypertension • Use of smoking cessation medications • Any current plans to try to quit smoking • Current pregnancy or lactation <p>Inclusion based on specific population characteristic: Not applicable</p> <p>29% women; mean age 43.3; mean cpd 17; mean FTND 3.7</p> <p>Motivated to quit: Participants had no current plans to try to quit smoking (eligibility criterion)</p> <p>E-cigarette use at baseline: No more than 3 previous episodes of use and not currently using (eligibility criterion)</p>
Interventions	<p>EC: Cig-a-like</p> <p>All participants received nicotine EC and were instructed to use them exclusively for 9 days</p> <p>The 5 brands selected, including brand reported nicotine levels, were: (1) NJOY (18mg nicotine) – this brand was discontinued and not analyzed as the e-cigs provided malfunctioned; (2) V2, 18 mg nicotine; (3) Green Smoke, 18.9 - 20.7 mg nicotine; (4) blu, 20 - 24mg nicotine; and (5) White Cloud, 23 - 24 mg nicotine. Each brand advertised the delivery of the same level of nicotine (appropriate for about a pack/day smoker), provided the standard tobacco flavour (no other flavours made available), and used a disposable cigarette-like device</p>
Outcomes	<p>Day 10 is the only testing point of interest for us but participants were also tested at days 1 and 5</p> <p>Adverse events and biomarkers:</p> <ul style="list-style-type: none"> • breath CO

Strasser 2016 (Continued)

- direct effects of nicotine (e.g. dizzy, nauseas, headache) - visual analogue scale with a single word scored from 0 (not at all) to 100 (extremely). Total scores were summed such that higher scores indicated negative responses

Other outcomes measured:

- e-cigarette use
- direct effects of the e-cigarette (e.g. satisfying, calming, pleasant, smoke another right now) - visual analogue scale with a single word scored from 0 (not at all) to 100 (extremely). Total scores were summed such that higher scores indicated positive responses
- cotinine
- withdrawal and craving

Study funding	“National Cancer Institute (NCI) of the National Institutes of Health (NIH) and FDA Center for Tobacco Products (CTP) under Award Number P50CA179546, as well as grants from the National Cancer Institute (P50 CA143187, P30 CA16520, and P30 DA12393)”
Author declarations	“Dr Benowitz has served on scientific advisory boards for Pfizer and GlaxoSmithKline related to smoking cessation medications and has been an expert witness in litigation against tobacco companies. Dr Schnoll receives medication and placebo free of charge from Pfizer and has provided consultation to Pfizer and GlaxoSmithKline. These companies had no involvement in this study. Dr Strasser has received funding through the Pfizer GRAND program, an independent peer-reviewed grant program funded through Pfizer (2008-2011); all investigators have received funding from the United States National Institutes of Health”

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although participants were randomized to different brands of EC, no description on how randomization was carried out
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of whether groups were blind to other conditions, but given similar levels of support between arms, so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear whether any blinding took place, some outcomes were measured using objective measures and there was no difference in contact between arms
Incomplete outcome data (attrition bias) All outcomes	High risk	For blu, Green Smoke, and V2 groups, 83% of participants completed the 10-day study; only 33% of participants randomized to White Cloud completed the 10-day study; meaning loss to follow-up was considerably higher in this group
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Tseng 2016
Study characteristics
Electronic cigarettes for smoking cessation (Review)

Tseng 2016 (Continued)

Methods	<p>Design: 2-arm; double-blind placebo-controlled RCT</p> <p>Recruitment: Advertisements placed in Craigslist as well as flyers distributed on the street and placed in New York City venues with details for how to contact study staff.</p> <p>Setting: Community, USA</p> <p>Study start date: July 2014 – 2015 (month unclear); Study end date: Not specified</p>
Participants	<p>Total N: 99 (100 were randomized but 1 participant randomized to the control arm was found to be ineligible between randomization and baseline)</p> <p>N per arm: Nicotine EC: 50; Placebo EC: 49</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • age 21 – 35 (confirmed with some form of identification document) • daily smoker • smoked ≥ 10 cigarettes a day (verified by a CO level of ≥ 8 ppm) • interested in reducing cigarette consumption • able to provide consent • had a cell phone and was willing/able to receive text messages and counselling on their cell phone • willing to use an EC for 3 weeks <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Pregnant and/or breastfeeding • had a history of asthma, other airways diseases, or heart disease • were currently using smoking cessation medications (including other forms of NRT, bupropion, or varenicline), or enrolled in a smoking cessation programme or another cessation trial. • Use of EC in the past 14 days or any other tobacco products (pipe, cigar, cigarillos, snuff, chewing tobacco, rolling tobacco, or hookah/shisha) in the past 30 days • having a moderate to severe drug use disorder defined as a score of at least 5 on the Drug Abuse Screening Test-10 and/or a hazardous or active alcohol use disorder defined as at least 7 for men and at least 5 for women on the Alcohol Use Disorders Identification <p>Inclusion based on specific population characteristic: Young adults</p> <p>32.3% women; mean age 28.43; mean cpd 14.33; FTND not measured but time to first cigarette was measured categorically. The mode category was 6 - 30 mins (39/99; 41.5%) Smoking behavioural dependence scale (11 items): mode category 'Moderate' (51/99; 51.5%)</p> <p>Motivated to quit: Readiness to quit (1 – 10 scale, 1 – 8 apply to current people who smoke): 5.57 ± 1.49</p> <p>E-cigarette use at baseline: No use of e-cigs in past 14 days (eligibility criterion)</p>
Interventions	<p>EC: Cig-a-like</p> <p>E-cigarette details:</p> <p>3 weeks of disposable 4.5% nicotine NJOY, King Bold (NJOY, Inc, Scottsdale, AZ) which resemble conventional cigarettes. NJOY also manufactured the non-nicotine placebo EC. Both nicotine and placebo ECs were tobacco-flavoured. The products were purchased by the investigators and provided to the participants free of charge</p> <p>Other stop-smoking pharmacotherapies: None</p> <p>Behavioural support:</p> <p>Prior to receiving the ECs, participants were required to complete a 20- to 30-minute telephone counselling session with a trained tobacco cessation counsellor. The purpose of the telephone counselling was to review current smoking patterns and offer behavioural and environmental change strategies.</p>

Tseng 2016 (Continued)

These included specific smoking reduction options, such as eliminating cigarettes at work and in the home, carrying only those cigarettes needed for that day, dropping cigarettes associated with less intense triggers first, avoiding smoking triggers, and other strategies to manage urges.¹⁸ Participants were asked to reduce the number of cigarettes smoked daily by at least 50% of the total number of cigarettes smoked per day at baseline. To mimic real-life EC use, minimum EC use instruction was provided. Participants were encouraged to replace cigarettes with as much or as little use of an EC as needed in order to reduce nicotine withdrawal symptoms

Outcomes	Week 1, 3 Cessation: Not applicable Adverse events and biomarkers: adverse events and symptoms related to EC use Other outcomes measured: <ul style="list-style-type: none"> • self-reported reduction of at least 50% in the number of cpd • percentage reduction in number of cpd • Use of ECs • satisfaction with ECs
Study funding	“This work was supported by the National Center for Advancing Translational Sciences at the National Institutes of Health (grant number UL1TR000038).”
Author declarations	“None declared”
Notes	Study listed as ongoing study NCT02628964 in the 2016 review update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “computer generated”
Allocation concealment (selection bias)	Unclear risk	Quote: “...was concealed from research assistants. Blinding of the allocation of nicotine or placebo EC was ensured by the identical appearance of the ECs”. However, not enough information given on how allocation was concealed at the point of randomization
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Blinding of the allocation of nicotine or placebo EC was ensured by the identical appearance of the ECs”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Blinding of the allocation of nicotine or placebo EC was ensured by the identical appearance of the ECs”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Nicotine EC Itfu: 10/50; Placebo EC Itfu: 10/49
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Valentine 2018

Study characteristics

Methods	<p>Design: Open-label prospective cohort study</p> <p>Recruitment: Recruited from within the Department of Veterans Affairs (VA) Connecticut Healthcare System by word of mouth</p> <p>Setting: Receiving psychiatric services from Department of Veterans Affairs healthcare system, USA</p> <p>Study start date/Study end date: Not specified.</p>
Participants	<p>Total N: 50 (sample analyzed for primary outcomes on week 1 completers – N = 43)</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Without an immediate intention to stop smoking • Smoking history of at least 5 cigarettes a day for the past year <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Current untreated medical or psychiatric or substance use disorders, or both, as determined by a review of the veteran's electronic medical record • current use of nicotine replacement or other cessation pharmacotherapies • use of e-cigarettes or smokeless tobacco products for more than 2 of the past 30 days <p>Inclusion based on specific population characteristic: Military veteran people who smoke who had no immediate intention to stop smoking and were currently receiving psychiatric services from the Department of Veterans Affairs healthcare system.</p> <p>7% women; mean age 56.9; mean cpd 16.6; mean FTND 4.9</p> <p>Motivated to quit: Had no immediate intention to stop smoking</p> <p>E-cigarette use at baseline: E-cigarettes or smokeless tobacco products may have been used for less than 2 of the past 30 days</p>
Interventions	<p>EC: Refillable</p> <p>All given eVic Supreme (Joyetech), "a commercial, variable-power, tank-type device". 6.5 mL tank (Delta 23, Joyetech) and a C3 triple coil atomizer head (Joyetech) with a total resistance of 1.8 ohms. Participants could choose flavour (menthol or tobacco) and nicotine concentration (12 or 24 mg/mL).</p> <p>Participants taught how to use EC, with additional materials dispensed as needed. Participants were informed that they could use the study e-cigarette or regular tobacco cigarettes, or both, ad libitum during study participation</p>
Outcomes	<p>Week 1, 2, 3, 4, 8 (Weekly lab visits and 1 month follow-up)</p> <p>Adverse events and biomarkers: Alveolar (breath) CO levels (ppm)</p> <p>Other outcomes measured:</p> <ul style="list-style-type: none"> • Number of cpd • The frequency of e-cigarette use (mean days/week) • The amount of money spent on combustible cigarettes (US dollars/week) • Fagerström Test of Nicotine Dependence • Contemplation Ladder • E-cigarette questionnaire (assessed changes in perceptions about e-cigarettes (e.g. harmfulness, benefits, cost), motivations to use (or not use) them, and the reasons for e-cigarette or combustible cigarette preferences) (measured at baseline and follow-up) • Cotinine

Valentine 2018 (Continued)

Study funding "This research was supported by the New England Mental Illness Research, Education and Clinical Center and the U.S. Department of Veterans Affairs. Statistical analyses, biochemical assays, and analyses of e-cigarette solutions were supported by the Administrative and Laboratory cores of P50DA036151 (Yale TCORS) from the National Institutes of Health and the U.S. Food and Drug Administration Center for Tobacco Products. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or of the U.S. Food and Drug Administration."

Author declarations "Ralitza Gueorguieva, PhD, discloses consulting fees for Palo Alto Health Sciences and Mathematica Policy Research and a provisional patent submission by Yale University: Chekroud, A. M., Gueorguieva, R., & Krystal, K. H. "Treatment Selection for Major Depressive Disorder" (filing date June 3, 2016, USPTO docket number Y0087.70116US00). The authors report no other financial relationships with commercial interests."

Notes New for 2020 update.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled cohort study
Allocation concealment (selection bias)	High risk	Uncontrolled cohort study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up: 31/50 at week 8
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial record.

Van Staden 2013
Study characteristics

Methods Design: Single-group within-subject design
 Recruitment: Participants from a military hospital in South Africa
 Setting: South Africa
 Study start date/ end date: Not specified

Participants Total N: 15, mean age 38 years, smoked 20 cpd (range 10 - 30), for an average of 17 years (range 5 - 27)
 Total N: 13 completed the study (5 women)
 Inclusion criteria:

- Adults who smoke daily, of at least 10 cpd

Exclusion criteria:

- History of lung disease

Inclusion based on specific population characteristic: No

Van Staden 2013 (Continued)

Motivated to quit: Not specified

E-cigarette use at baseline: Not specified

Interventions	EC: Cig-a-like Participants were asked to use an EC only for 2 weeks (i.e. no cigarettes) EC: 'Twisp eGo' cartridge 0.8 ml containing 0.0144 mg of nicotine
Outcomes	The following measurements were taken at baseline and 2-week follow-up: <ul style="list-style-type: none"> Blood pressure and pulse Arterial and venous COHb and blood oxygen saturation
Study funding	"We are grateful for the sponsorship of the eGo e-cigarette packs by Twisp and also for the valuable advice and laboratory assistance given by Col. (Dr) J Lubbe, Chemical Pathologist, 1 Military Hospital, Pretoria with regard to the measurement of the cotinine levels. We also wish to acknowledge Professor Martin Veller for his insightful contributions during the preparation of this manuscript and also Dr Richard van Zyl-Smith for his assistance and review."
Author declarations	"The sponsor of the Twisp e-cigarette had no role in the design and conduction; the collection, analysis and interpretation of the study; or in the preparation, review or approval of the manuscript."
Notes	Dropouts (N = 2) were due to illness (headache and fever) and undertaking a military course associated with high stress and exposure to others smoking, making it difficult to abstain from cigarettes The paper states that the EC cartridge contained 0.8 ml of solution with 0.0144 mg of nicotine. This would be an unusually low concentration of nicotine and we have assumed an error in units where milligrams should have been grams (0.0144 grams of nicotine would make the concentration 18 mg/ml)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/15 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Veldheer 2019
Study characteristics

Methods	Design: Randomized parallel-assignment double-blind trial Setting: USA (2 sites) Recruitment: Community advertisements
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Veldheer 2019 (Continued)

Study start date: June 2015; Study end date: June 2018.

Participants

Estimated enrolment: 520

Total N: 263 in this analysis (520 planned overall; THIS INCLUDES ONLY THOSE FOLLOWED UP AT 1 AND 3 MONTHS)

N per arm: sub: 72; EC: 191

Inclusion criteria:

- Age 21 - 65
- Smoke > 9 cigarettes per day for at least 1 year
- Smoke regular filtered cigarettes or machine-rolled cigarettes with a filter
- CO measurement > 9 ppm at baseline
- No serious quit attempt in the prior 1 month. This includes use of any FDA-approved smoking cessation medication (varenicline, bupropion (used specifically as a quitting aid), patch, gum, lozenge, inhaler, and nasal spray) in the past 1 month as an indication of treatment-seeking
- Not planning to quit in the next 6 months
- Interested in reducing cigarette consumption
- Willing to attend visits weekly and monthly over a 9-month period (not planning to move, not planning extended vacation, no planned surgeries)
- Read and write in English
- Able to understand and consent

Exclusion criteria:

- Pregnant and/or nursing women
- Unstable or significant medical condition in the past 12 months (recent heart attack or some other heart conditions, stroke, severe angina including high blood pressure if systolic > 159 or diastolic > 99 observed during screening)
- Immune system disorders, respiratory diseases (exacerbations of asthma or COPD, require oxygen, require oral prednisone), kidney (dialysis) or liver diseases (cirrhosis), or any medical disorder/medication that may affect participant safety or biomarker data
- Use of any non-cigarette nicotine delivery product (pipe, cigar, dip, chew, snus, hookah, e-cigs, strips, sticks) in the past 7 days
- Uncontrolled mental illness or substance abuse or inpatient treatment for these in the past 6 months
- History of difficulty providing or unwilling to provide blood samples (fainting, poor veins, anxiety)
- No surgery requiring general anaesthesia in the past 6 weeks
- Use of an e-cig for 5 or more days in the past 28 days or any use in the past 7 days
- Use of marijuana or any illicit drug/prescription drugs for non-medical use daily/almost daily, or weekly in the past 3 months per NIDA Quick Screen
- Use of hand-rolled, roll-your-own cigarettes
- Known allergy to propylene glycol or vegetable glycerin
- Other member of household is currently participating/participated in the study

58% women; mean age 47; mean cpd 18; mean FTND: Not specified

Motivated to quit: Interested in reducing cigarette intake but not planning to quit in next 6 months

E-cigarette use at baseline: None

Interventions
EC: Cig-a-like

For 24 wks:

1) **Cigarette substitute:** QuitSmart cigarette substitute - plastic tube looks like a real cigarette, designed to provide the same draw resistance as a smoker's usual cigarette. No drug delivery. 2 cigarette substitutes and a product manual are provided to participants following randomization and replace-

Veldheer 2019 (Continued)

ment products are provided throughout the intervention period (24 weeks). At baseline, associated user manual, research staff explain how to use product. Reduction goal to 50% at weeks 0 and 1, 75% at weeks 2 and 4, continue reducing onwards from there

2) **EC with no nicotine:** EGO e-cigarette. Cartomizers containing 0 mg/ml nicotine provided throughout the intervention period (24 weeks) Associated user manual, research staff explain how to use product.

3) As (2) but 8 mg/ml nicotine

4) As (2) but 36 mg/ml nicotine

Outcomes	<p>Months 1, 3, 6, 9; (only 1 and 3 month available at time of extraction)</p> <p>Cessation: Conventional tobacco product use measured but measures not clear</p> <p>Adverse events and biomarkers:</p> <ul style="list-style-type: none"> • Adverse events • Lung function • Blood pressure, pulse • CO, “exhaled breath condensate biomarkers of oxidative stress, glutathione and 8 Isoprostanes” – incl. carcinogenic nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK; via its metabolite NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) in urine], expired air carbon monoxide (CO), and nicotine (via its metabolite cotinine in urine) <p>Other outcomes measured:</p> <ul style="list-style-type: none"> • Weight • Cotinine • Tobacco use
Study funding	<p>This study was funded by the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) under Award Number P50DA036105. The content is solely the responsibility of the authors and does not necessarily represent the views of the NIH or FDA. The project [publication] was supported by CTSA award No. UL1TR000058 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.</p>
Author declarations	<p>JF has done paid consulting for pharmaceutical companies involved in producing smoking cessation medications, including GSK, Pfizer, Novartis, J&J, and Cypress Bioscience. TE is a paid consultant in litigation against the tobacco industry and is named on a patent application for a device that measures the puffing behavior of electronic cigarette users. There are no competing interests to declare for other authors</p>
Notes	<p>Preliminary data from RCT; full results not yet available</p> <p>EC arms pooled in preliminary data available to us at time of writing</p> <p>Authors provided outcome data; Study listed as ongoing study Lopez 2016 in the 2016 review update</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “the assignment codes are made from separate randomization lists created in advance by the statistician for each site stratum.”
Allocation concealment (selection bias)	Low risk	Quote: “Once a participant has been confirmed eligible for randomization, a computer procedure will assign the participant to the next condition on the list automatically.”

Veldheer 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded for non-EC arms but given similar level of support/product, so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded for non-EC arms but given similar level of support/product, so differential misreport judged unlikely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dataset only includes those followed up at 1 and 3 months, which excludes 140 participants; breakdown by arm not provided
Selective reporting (reporting bias)	High risk	Results paper just preliminary results with all EC arms collapsed. Protocol and NCT record list different outcomes and study lengths.

Wadia 2016
Study characteristics

Methods	Design: Uncontrolled experimental study Recruitment: Dental hospital staff were recruited – not specified how Setting: Dental hospital, UK Study start date: April 2015; Study end date: December 2015
Participants	Total N: 20 (18 of the 20 attended the reassessment visit) Inclusion criteria: <ul style="list-style-type: none"> • 18 - 65 years old • Systemically healthy • Smoked at least 10 cigarettes per day for at least 5 years • had at least 24 natural teeth (excluding third molars) and had no probing pocket depths over 4 mm at any site • did not wish to quit Exclusion criteria: <ul style="list-style-type: none"> • Participants were excluded if they had a systemic condition known to exacerbate or modulate periodontitis (for example, diabetes) • antibiotics had been taken in the previous 3 months • anti-inflammatory drugs or other medication likely to affect the periodontal tissues were taken routinely • if they were pregnant or a nursing mother % women, age, cpd and FTND: not specified. Motivated to quit: enrolled people who smoke who did not intend to quit smoking, but were prepared to attempt to substitute smoking with the use of e-cigarettes for 2 weeks E-cigarette use at baseline: not specified
Interventions	EC: Refillable

Wadia 2016 (Continued)

Participants provided with a blu PROTM e-cigarette kit (Electric Tobacconist®), an extra bottle of blu PRO Tobacco™ e-Liquid (Electric Tobacconist) and written instructions. The e-Liquid was Classic Tobacco-flavoured and contained 18 mg of nicotine (medium strength). The participants agreed to substitute their regular smoking habits with the use of e-cigarettes for 2 weeks. They were asked to make a note of any cigarette smoking during the 2 weeks if complete abstinence was unsuccessful

Outcomes	2 weeks Adverse events and biomarkers: adverse effects Other outcomes measured: <ul style="list-style-type: none"> • Cigarette use • Dental outcomes
Study funding	Not specified
Author declarations	Not specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No randomization
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Walele 2018
Study characteristics

Methods	Design: RCT (short-term, Cravo 2016) followed by cohort study (Walele 2018) in which all participants were given nicotine EC Recruitment: Community Setting: 2 centres in the UK (Covance Clinical Research Unit Ltd, Leeds and Simbec Research Ltd, Wales) Study start date: December 2013; Study end date: December 2016
Participants	420 participants Inclusion criteria differ per study phase: Cravo 2016 (short-term RCT): <ul style="list-style-type: none"> • 21 - 65 years of age

Walele 2018 (Continued)

- BMI 18 - 35 kg/m²
- 5 - 30 cigarettes per day for at least 1 year (self-reported)
- in good health (determined by medical history, a physical examination, a 12-lead ECG, lung function tests and clinical laboratory evaluations)
- Established people who smoke (urinary cotinine \geq 3 and exhaled CO \geq 6 ppm)

Additional criteria for Walele 2018 (participants from Cravo 2016):

- Participants assessed by PI as being compliant in Cravo 2016 (e.g. having attended outpatient visits and having been compliant with study procedures)
- Participants had to be willing to use the study product as the only nicotine-containing product for the duration of the study, and, as deemed by PI, had to have no clinically significant abnormalities in 12-lead electrocardiogram, vital signs, spirometry and clinical laboratory assessments in the preceding study
- In addition, participants who were assigned to the conventional cigarette (CC arm) in Cravo 2016 had to be established people who smoke CCs, which was assessed by urinary cotinine levels (a score of 3 and above on a NicAlert™ test strip was considered positive), eCO levels (a readout > 6 ppm was considered positive) and by review of a smoking history questionnaire

Exclusion criteria:

Cravo 2016:

- Use of NRT, snuff or chewing tobacco in 14 days previous, or intended to use during study
- Trying to stop smoking or considering quitting
- Clinically-significant illness or disorder, history of drug or alcohol abuse within 2 years prior to study start
- Woman of “childbearing potential” unwilling to use “acceptable contraceptive measure” during study

Walele 2018 (participants from Cravo 2016):

- People who had taken or received any form of NRT, snuff or chewing tobacco during the previous study or intended to use it during this study, were excluded
- People with relevant illness history
- People with history of drug or alcohol abuse
- People with lung function test or vital signs considered unsuitable
- People who are trying to stop smoking
- Women who are pregnant, or unwilling to use acceptable contraceptive method for the duration of the study

Cravo 2016

Total N: 419 randomized, 408 analysed (excludes 11 who were excluded prior to any product use)

N per arm: EVP: 306; Control: 102

45% women; mean age 34.6; Mean cpd: most 11 - 20 cpd (56% int, 62% control); Mean FTND: most moderate (57% int, 54% cont)

Motivated to quit: No

E-cigarette use at baseline: Not excluded based on prior EC use

Walele 2018

Total N: 209 (147 pre-EVP group; 62 pre-CC group)

45% women; mean age 36.6; mean cpd 2.6 (data from figure): Not reported; FTND: Not reported

Motivated to quit: As reported for Cravo 2016

Walele 2018 (Continued)

E-cigarette use at baseline: Not reported

Interventions

EC: Cig-a-like
Cravo 2016

EC: EVP prototype (2.0% nicotine), developed by Fontem Ventures B.V. (Amsterdam, the Netherlands). Instructed to only use EVP for study period. It consisted of a rechargeable battery (voltage range of 3.0e4.2 V), an atomiser and a capsule (small cartridge) containing e-liquid. The capsules were replaceable and the battery and atomiser were reusable. Could choose between two different e-liquids, which differed solely in their flavour: a menthol-flavoured e-liquid with 2.0% nicotine (2.7 mg nicotine/capsule) and a tobacco-flavoured e-liquid with 2.0% nicotine (2.7 mg nicotine/capsule)

Control: Used their own usual conventional cigarette brand

Walele 2018

E-cigarette details: Commercially available Puritane™ (closed system EVP) consists of a lithium-ion rechargeable battery and a replaceable cartomiser comprising of an e-liquid reservoir pre-filled by the manufacturer, a heating element and a mouthpiece; 1.6% nicotine (16 mg/g) Available in tobacco or menthol. 2 weeks before baseline, participants had a familiarisation session with Puritane™, where they could see and try the EVP

Outcomes

Cravo 2016: Weeks 1, 2, 4, 6, 8, 10 and 12

Walele 2018: starting on the last day of the previous trial): Months 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24

Study centre visits for assessments

Adverse events and biomarkers:

- “adverse events” (coded using Medical Dictionary for Regulatory Activities version 16.1, 2013, collected via diary cards and questionnaires)
- vital signs (systolic and diastolic blood pressure, pulse rate and oral temperature)
- lung function (FEV, FEF, PEF, FEV)
- urine biomarkers (nicotine equivalents (NEQs: nicotine, cotinine, nicotine-N-glucuronide, cotinine-Nglucuronide, trans 3'-hydroxycotinine and trans 3'-hydroxycotinine glucuronide); S-PMA; 3-HPMA; PG; total NNAL (NNAL β NNAL-glucuronide)); exhaled CO
- blood COHb

Other outcomes measured:

- Number of conventional cigarettes smoked
- EVP capsules used
- ECG (categorised them as normal, abnormal-not clinically significant (NCS) or abnormal-clinically significant (CS))
- MWS-R (revised Minnesota Nicotine Withdrawal Scale)
- QSUBrief (Brief Questionnaire of Smoking Urges) questionnaires
- clinical chemistry (blood levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), sodium, potassium, chloride, calcium, inorganic phosphate, glucose, urea nitrogen (BUN), total bilirubin, creatinine, total protein, albumin, cholesterol (HDL, LDL, and total));clinical haematology (white blood cell count (WBC), red blood cell count (RBC), haemoglobin, haematocrit (PCV), mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), platelet count, differential WBC);urinalysis (pH, protein, glucose, ketones, urobilinogen, blood and specific gravity)

Study funding

Cravo 2016

"This work was funded and supported by Fontem Ventures B.V. Imperial Brands plc is the parent company of Fontem Ventures B.V. the

Walele 2018 (Continued)

manufacturer of the EVP prototype used in this study"

Walele 2018

"This work was funded and supported by Fontem Ventures B.V. Imperial Brands Group plc is the parent company of Fontem Ventures B.V., the

manufacturer of the EVP used in this study"

Author declarations

Cravo 2016

"Dr. Cravo has nothing to disclose. Mrs Martin reports personal fees from Fontem Ventures B.V. during the conduct of the study; personal fees from Tobacco and pharmaceutical industries outside the submitted work. Dr. Sharma reports other from Fontem Ventures B.V. during the conduct of the study. Dr. Bush reports other from Fontem Ventures B.V. during the conduct of the study. Mrs Savioz reports personal fees from Fontem Ventures B.V. during the conduct of the study; personal fees from Tobacco and pharmaceutical industries outside the submitted work. Mr Craige has nothing to disclose. Mr Walele has nothing to disclose."

Walele 2018 (copied from Transparency documents)

"Dr. Koch reports other from Fontem Ventures B.V., during the conduct of the study; Dr. Martin reports personal fees from Fontem Ventures B.V., during the conduct of the study; personal fees from Tobacco and pharmaceutical industries, outside the submitted work; Dr. O'Connell has nothing to disclose. Dr. Bush reports other from Fontem Ventures B.V., during the conduct of the study; Dr. Savioz reports personal fees from Fontem Ventures B.V., during the conduct of the study; personal fees from Tobacco and pharmaceutical industries, outside the submitted work; Dr. Walele has nothing to disclose."

Notes

Sponsor: Imperial Tobacco Group PLC

Study listed as ongoing studies NCT02029196 and NCT02143310 in 2016 review update. Treated as single study in this review due to including

the same participants, and no time lag between studies

"The same subjects who participated in our previous clinical trial (ClinicalTrials.gov, #NCT02029196) conducted in the same centres, with another EVP (Cravo et al., 2016), were invited to participate the study by Walele 2018. All volunteering subjects were assigned to switch to using Puritane™, a closed system EVP, for two years, starting on the last day of the previous trial (End of Study [EoS] visit), which corresponded to the baseline visit of Walele 2018."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed using an Interactive Web Response System (IWRS; Almac Clinical Technologies)"
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed using an Interactive Web Response System (IWRS; Almac Clinical Technologies)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label, no blinding, differential levels of support/product use so performance bias cannot be ruled out
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label, no blinding, with differential levels of support/product use and subjective outcomes

Walele 2018 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Cravo: 286/306 int (4.5% ltfp) and 101/102 (1% ltfp) control completed study but all who received product included in analysis. In EVP group, 14 withdrew consent, 2 experienced AEs, 1 death, 3 "other". CC group 1 AE Walele 2018: High 209/387 enrolled for study Walele 2018. A total of 102 participants (48.8%; EVP: 75/145 (51%); CC: 27/61 (43.5%) completed the study
Selective reporting (reporting bias)	Low risk	Cravo 2016: Low All anticipated outcomes reported (study registered prior to study completion) Walele 2018: Low All anticipated outcomes reported (study registered prior to study completion)

Walker 2020

Study characteristics

Methods	Design: RCT Recruitment: National media advertising Setting: Community based, New Zealand Study start date: Recruitment between March 2016; Study end date: Aug 2018
Participants	N per arm: Patches-only group: 125; Patches plus nicotine e-cigarette group: 500; Patches plus nicotine-free e-cigarette group: 499 Inclusion criteria: <ul style="list-style-type: none"> • Eligible if they were living in New Zealand • 18 years or older • smoked tobacco (amount not specified) • Motivated to quit in the next 2 weeks • Able to provide verbal consent • Prepared to use any of the trial treatments • Had access to a telephone Exclusion criteria: <ul style="list-style-type: none"> • Pregnant or breastfeeding women • Had used an e-cigarette for smoking cessation for more than 1 week anytime in the past year • Currently using smoking cessation medication • Enrolled in another cessation programme or study • Self-reported a history of severe allergies • Poorly-controlled asthma • Cardiovascular event in the 2 weeks before enrolment • Only 1 participant per household was permitted. 69% women; mean age 41.6; mean cpd 17.3; mean FTND 5.2 Motivated to quit: yes

Walker 2020 (Continued)

E-cigarette use at baseline: Not reported but use of an e-cigarette for smoking cessation for more than 1 week anytime in the past year was an exclusion criterion

Interventions
EC: Refillable

Moderate-intensity behavioural support was available for all participants immediately after randomization, then once a week for 6 weeks. This support consisted of 10 – 15 mins of withdrawal-oriented behavioural support and advice on using their allocated treatment, delivered proactively over the phone by researchers who had received standardized training in delivery of such support. Assigned to:

- 1) **Nicotine patch** for 14 weeks including 2 week prequit. 21 mg, 24-hr nicotine patch (Habitrol)
- 2) **Nicotine patch and nicotine-free EC** for 14 weeks. As 1, plus 14-week supply at no cost. A 2nd generation eVOD (Kangertech, Shenzhen GuangDong, China) starter kit, with a choice of 1 of 2 tobacco e-liquid flavours. Advised to start using the e-cigarette 2 weeks before their quit date, as and when necessary or desired, and in accordance with the manufacturer's written instructions, to become familiar with its use Participants were instructed to stop smoking from their quit date and continue with their allocated treatment for 12 weeks (ad libitum use of the e-cigarette), irrespective of any lapses to smoking
- 3) **Nicotine patch and nicotine EC** for 14 weeks. As above, but 18 mg/mL nicotine

Outcomes

Quit date, 1, 3, 6 and 12 months

Continuous abstinence at 6 months with CO validation

Adverse events and biomarkers: Known side-effects associated with e-cigarette use and nicotine patch use; SAEs

Other outcomes measured:

- Relapse
- Self-reported treatment adherence
- Tobacco withdrawal symptoms and urge to smoke
- Urge to vape
- Self-reported weight
- Concomitant medication
- Treatment cross-over
- Use of other smoking cessation support or medication
- Continued use of allocated treatment past 14 weeks
- Changes in shortness of breath, cough, asthma, COPD, and mental health problems
- Belief in ability to quit and remain tobacco-free
- Smoking identity and views on their allocated treatment for smoking cessation and whether they would recommend it to other people who smoke who want to quit
- In people still smoking at each follow-up call, outcomes were number of cigarettes smoked per day and reduction in smoking
- Participants allocated e-cigarettes were asked about their urge to vape; whether they changed devices or e-liquid, or both; whether they accessed any e-cigarette support

Study funding

Funding: Health Research Council of New Zealand. "The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication."

Author declarations

NW, CB, MV, GL, ML, and VP report grants from the Health Research Council of New Zealand, during the conduct of the study. NW, CB, MV, and VP report grants from Pfizer, outside of the submitted work. GL chairs the organisation End Smoking New Zealand, which advocates for harm reduction approaches to tobacco control. E-cigarettes were purchased from a New Zealand e-cigarette online retailer (NZVAPOR, <https://www.nzvapor.com/>), e-liquid was purchased from Nicopharm, Australia (<https://>

Walker 2020 (Continued)

www.nicopharm.com.au/), and nicotine patches were supplied by the New Zealand Government via their contract with Novartis (Sydney, Australia). NZVAPOR also provided, at no cost to participants, on-line and phone support regarding use of the e-cigarettes. Neither NZVAPOR nor Nicopharm have links with the tobacco industry. None of the above parties had any role in the design, conduct, analysis, or interpretation of the trial findings, or writing of this publication.

Notes Study listed as ongoing study NCT02521662 in the 2016 review update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization sequence
Allocation concealment (selection bias)	Low risk	Quote: "We ensured allocation concealment because the statistician who generated the random allocation was not the person randomising participants."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants and researchers collecting outcome data were masked to the nicotine content of the e-liquid" but those allocated to patch only would be aware they did not have an E-cigarette Quote: "Third, while we attempted to minimise detection bias by masking the nicotine content of the e-liquid, we were only 30% successful, and thus some bias in favour of nicotine e-cigarettes could have occurred."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 50% lost to follow-up, similar rates of attrition between groups (within 20%)
Selective reporting (reporting bias)	Unclear risk	CO-verified abstinence at 12 months stated as a secondary outcome but data are not reported in the main text. However, state in the appendix that too few people in each group were followed up to 12 months (36/1124) so no data are presented for this time point

AE: adverse event; BMI: body mass index; CO: carbon monoxide; COT: cotinine; cpd: cigarettes per day; EC: electronic cigarette; ENDS: electronic nicotine delivery system; FTND: Fagerström Test for Nicotine Dependence; HRQoL: health-related quality of life; IQR: interquartile range; ITT: intention-to-treat; LTFU: lost to follow-up; MMT: methadone maintenance treatment; NEC: nicotine electronic cigarette; NRT: nicotine replacement therapy; PEC: placebo electronic cigarette; PP(A): point prevalence (abstinence); ppm: parts per million; SAE: serious adverse event; SD: standard deviation; SMI: serious mental illness; TQD: target quit date; UC: usual care

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adkison 2013	Although this study uses a prospective cohort design, no data on EC use were collected at baseline, with EC use data only being available at follow-up
Al-Delaimy 2015	Observational study with no intervention provided - included in previous versions, but excluded from 2020
Anonymous 2019	Commentary of included study (not primary study)

Study	Reason for exclusion
Battista 2013	Short-term EC use only
Bianco 2019	Ineligible intervention
Biener 2015	Cohort study, but EC use evaluated retrospectively only
Biondi-Zoccai 2019	Less than 1 week follow-up
Borderud 2014	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Brose 2015	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Brown 2014a	Cross-sectional survey
Bullen 2010	Short-term EC use only
Bullen 2018	Withdrawn trial registry
Caponnetto 2019	Ineligible intervention
Chaumont 2018	Less than 1 week follow-up
Chaumont 2019	Ineligible intervention
Chausse 2015	Ineligible study design
Choi 2014	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Chorti 2012	Short-term EC use only
Collins 2019	Ineligible intervention
Cook 2019	Commentary of included study (not primary study)
Cox 2019a	Short-term abstinence only (< 6 months)
Czogala 2012	Short-term EC use only
D'Ruiz 2017	Less than 1 week follow-up
Dawkins 2012	Short-term EC use only
Dawkins 2013a	Short-term EC use only
Dawkins 2014	Short-term EC use only
Douptcheva 2013	Longitudinal study, but no data are reported for smoking cessation or reduction or for adverse events
Dutra 2014	Cross-sectional survey
Eissenberg 2010	Short-term EC use only

Study	Reason for exclusion
Elena Cavarretta 2019	Less than 1 week follow-up
Etter 2014	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Farsalinos 2012	Short-term EC use only
Farsalinos 2013a	Included people that had already stopped smoking conventional cigarettes
Farsalinos 2013b	Short-term EC use only
Farsalinos 2013c	Short-term EC use only
Farsalinos 2013d	Short-term EC use only
Flouris 2012	Short-term EC use only
Flouris 2013	Short-term EC use only
Gmel 2016	Cohort study, but EC use only evaluated retrospectively
Gottlieb 2019	Commentary of included study (not primary study)
Grana 2014b	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
James 2016	Follow-up at 12 weeks, AE data not collected
Kasza 2013	Longitudinal study, but no data are reported for smoking cessation or reduction or for adverse events
Kouretas 2012	Short-term EC use only
Kousta 2019	Commentary of included study (not primary study)
Lechner 2015	Less than 1 week follow-up
Lee 2014	Cross-sectional survey
Manzoli 2015	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Marini 2014	Short-term EC use only
Mayor 2019	Commentary of included study (not primary study)
Meltzer 2017	Ineligible intervention
Miura 2015	Tests a device which is not an EC
NCT02487953a	Withdrawn trial registry
NCT02487953b	Withdrawn trial registry
NCT03036644	Less than 1 week follow-up

Study	Reason for exclusion
NCT03575468	Ineligible intervention
NCT04107779	Less than 1 week follow-up
Nolan 2016	Short-term abstinence only (< 6 months)
Palamidas 2014	Short-term EC use only
Pearson 2012	Longitudinal study, but no data are reported for smoking cessation or reduction or for adverse events
Pokhrel 2013	Cross-sectional survey
Polosa 2014a	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Popova 2013	Cross-sectional survey
Prochaska 2014	RCT but no EC intervention provided - included in previous versions, but excluded from 2020
Russo 2018	Ineligible study design
Schober 2014	Short-term EC use only
Siegel 2011	Retrospective survey of 222 EC users that responded to a survey sent to 5000 new users of the 'Blu' EC. Likely to be a self-selected sample
Song 2020	Ineligible patient population
St.Helen 2020	Wrong intervention
Stein 2019	Commentary of included study (not primary study)
Stower 2019	Ineligible study design
Tsikrika 2014	Short-term EC use only
Tucker 2018	Short-term abstinence only (< 6 months)
Tzatzarakis 2013	Short-term EC use only
Vakali 2014	Short-term EC use only
Valentine 2016	Less than 1 week follow-up
Van Heel 2017	Ineligible study design
Vansickel 2010	Short-term EC use only
Vansickel 2012	Short-term EC use only
Vansickel 2013	Short-term EC use only
Vardavas 2012	Short-term EC use only

Study	Reason for exclusion
Vickerman 2013	Cross-sectional survey
Voos 2019	Less than 1 week follow-up
Voos 2020	Ineligible study design
Wagener 2014	EC use for up to 1 week, but does not report on any adverse events
Walele 2016a	RCT but follow-up too short
Walele 2016b	RCT but follow-up too short
Yan 2015	Ineligible study design
Yuki 2017	Less than 1 week follow-up
Zhang 2019	Commentary of included study (not primary study)

EC: electronic cigarette

Characteristics of ongoing studies [ordered by study ID]

ACTRN12617001324303

Study name	Vaporised nicotine products versus oral forms of nicotine replacement therapy (NRT) products for tobacco smoking cessation among low-socioeconomic status (low-SES) people who smoke
Methods	Parallel, single-blinded, randomized controlled trial Setting: Australia Recruitment: Not stated.
Participants	Target sample size: 868 Inclusion criteria: <ul style="list-style-type: none"> • At least 18 years of age • Current daily smoker • Motivated and willing to make a quit attempt using medications (NRT/VNP) • Speak English • Able to provide verbal informed consent • Receipt of government pension or allowance (proxy for low-SES) • Have a phone we contact them on; • Willing to complete 2 telephone check-in calls and baseline and follow-up telephone interviews The term “current smoker” in this trial will refer to those who use either factory-made or roll-own cigarettes. Exclusion criteria: <ul style="list-style-type: none"> • Women who are pregnant, breastfeeding or planning to become pregnant in the next 12 months • Current users of smoking cessation medications (i.e. NRT, bupropion [Zyban], clonidine, nortriptyline, electronic nicotine cigarettes) • Those who are participating in another smoking cessation programme or study

ACTRN12617001324303 (Continued)

People will also be excluded if they report any of the following medical conditions in the previous 3 months: serious chronic lung diseases, arrhythmia, heart attack, stroke, or severe angina

Interventions

Vaporised nicotine product (VNP) arm:

- Innokin Endura T18 Personal Vaporizer
- e-liquid nicotine (18mg/ml nicotine) for 8 weeks
- Quitline behavioural support
- 3 flavours will be offered: tobacco, strawberry, menthol
- Permitted to use the study product ad libitum throughout the day and encouraged to stop smoking completely, or reduce smoking if unable to stop completely
- Participants will be provided with detailed instructions on how to use the e-cigarette device effectively

Oral nicotine replacement therapy (NRT) arm:

- 2 mg or 4 mg nicotine gum/lozenge for 8 weeks
- Quitline behavioural support
- Those receiving the lozenge will be instructed to use 9 - 15 lozenges per day, approximately 1 every 2 hours or when they have an urge to smoke
- Those receiving the gum will be instructed to use 10 to 20 pieces per day for the 2 mg gum and 4 to 10 pieces per day for the 4 mg gum, approximately 1 every 2 hours or when they have an urge to smoke
- Participants will be provided with detailed instructions on how to use the NRT effectively and encouraged to stop smoking completely, or reduce smoking if unable to stop completely

Outcomes

Primary outcome: Carbon monoxide-verified six-month continuous abstinence (smoking not more than 5 cigarettes) from the quit date (8 months from baseline)

Secondary outcomes measured at 2-week and 6-week check-in calls and 8-month follow-up

- Self-reported 7-day point prevalence abstinence
- Self-reported continuous abstinence: defined as self-report of smoking not more than 5 cigarettes from the designated quit date
- Self-reported number of cpd among people continuing to smoke
- Self-reported 30-day PPA at each follow-up (self-report of having smoked no cigarettes (not even a puff))
- Mean reduction in number of cigarettes smoked per day based on participant self-report
- Proportion of participants that achieved a 50% reduction of baseline cigarette consumption based on participant self-report (8 months only)
- Self-reported continued use of nicotine products to assess maintenance use and dual use (8 months only)

Weekly text message surveys and check-in calls 2 weeks and 6 weeks into the treatment period. These check-in calls will also assess smoking status, short-term outcomes, and adverse events at these time points

Starting date

Anticipated start date: 30 April 2019

Contact information

Richard P Mattick, r.mattick@unsw.edu.au

Alexandra Aiken, a.aiken@unsw.edu.au

Notes

ACTRN12618000408280

Study name	A pragmatic randomized partial cross-over clinical trial of nicotine vaporizers added to standard care for smoking cessation and relapse prevention (CARP) among priority populations with comorbidities
Methods	<p>Randomized controlled trial</p> <p>Setting: Australia</p> <p>Recruitment: Not stated</p>
Participants	<p>Target sample size: 810</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Diagnosed with or receiving treatment for a priority health conditions in the past 12 months • Aged 18+ years • Currently smoke 10+ cigarettes per day • Has capacity to consent, able to understand participant materials and follow study instructions and comply with study procedures (e.g. sufficient English language ability, able to operate the vaporiser device) • Willing to make a quit attempt at baseline according to randomized condition (Condition A to make quit attempt with nicotine vaporizer; Condition B to make quit attempt without nicotine vaporizer) • Has a referral to Quitline counselling and smoking cessation support programme (standard care) but has not begun quit attempt (Note: Quitline referral can occur at time of study enrolment) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Already begun quit attempt (i.e. post-quit day) at time of enrolment into trial or currently enrolled in another smoking cessation clinical trial or using varenicline or bupropion or used a nicotine vaporizer product in the last 30 days. NOTE: Use of nicotine replacement products not supplied in the trial (e.g. as part of quitline support) is not an exclusion criterion • Currently pregnant or breast-feeding or an intention to be during trial participation period; <ul style="list-style-type: none"> * A urinary pregnancy test will be required where pregnancy is suspected * Participants will be advised appropriate contraception should be used to avoid pregnancy during the trial with ongoing contraception options discussed • Has experienced cardiac-related chest pain, or another cardiovascular event or procedure in the last month, such as heart attack, stroke, insertion of stent, bypass surgery • Hospitalized for a mental health condition in the last 30 days • Currently being treated with oxygen therapy • Diagnosed terminal illness (such as cancer) or debilitating condition that will limit ability to fully participate as determined by preregistration responses from participant or opinion of enrolling clinician
Interventions	<ul style="list-style-type: none"> • Arm 1 Referral to Quitline telephone smoking cessation counselling + Nicotine patches (15 mg/16-hr) delivered at baseline + refillable nicotine vaporizer device (2 x kits) + nicotine vaporising liquid (in high and low strength - high strength: nicotine 1.8% in Vegetable Glycerine and purified water; low strength: nicotine 0.6% in Vegetable Glycerine and purified water). 1 patch to be applied daily to skin for up to 84 days. The vaporizer with nicotine liquid is to be used as needed up to 3.5 mL per day to treat withdrawal symptoms for up to 2 years (concurrently with patches for the first 84 days) to assist smoking cessation and relapse prevention. Participants start on high-strength nicotine liquid and may decrease their dose to low strength to assist with dose reduction prior to stopping use of the vaporizer. • Arm 2 Referral to Quitline telephone smoking cessation counselling + Nicotine patches (15 mg/16-hr) + participant's choice of either nicotine gum or nicotine lozenges (up to 800 x 4 mg pieces to be used up to 8 per day) delivered at baseline. Between 6 - 9 months post-baseline - participants in Arm 2 who are smoking (either failed to quit or relapsed) will be offered: refillable nicotine vaporizer (2 x kits) + nicotine vaporizing liquid (in high and low strength - high strength: nicotine 1.8% in Vegetable Glycerine and purified water; low strength: nicotine 0.6% in Vegetable

ACTRN12618000408280 (Continued)

Glycerine and purified water) to make a second quit attempt. Participants start on high-strength nicotine liquid and may decrease their dose to low strength to assist with dose reduction prior to stopping use of the vaporizer at the discretion of the participant. Participants will have until 2 years from baseline to use the vaporizer for smoking cessation and relapse prevention

Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> Continuous abstinence from smoking from weeks 12 to 26 assessed at 26 weeks from baseline by self-report. Participants that self-report abstinence from smoking will be asked for a urine specimen for bioconfirmation. Urine specimens will be batch-tested for anabasine and cotinine at 6,12 and 21 month time points from baseline <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Continuous abstinence from smoking from weeks 12 to 52, assessed at week 52 from baseline Continuous abstinence from smoking from weeks 12 to 104, assessed by self-report at week 104 from baseline Continuous abstinence from smoking from weeks 40 to 52, assessed by self-report at 52 weeks from baseline Continuous abstinence from smoking from weeks 92 to 104, assessed by self-report at 104 weeks from baseline Number of adverse events measured by self-report at 12 weeks and 26 weeks from baseline <p>Abstinence is assessed through study-specific survey questions in Module CS Combustible Smoking Questions – administered through electronic survey or structured telephone interview. Participants that self-report abstinence from smoking will be asked for a urine specimen for bioconfirmation. Urine specimens will be batch-tested for anabasine and cotinine at 6,12 and 21 month time points</p>
Starting date	5 June 2018
Contact information	Malcolm Brinn, m.brinn@uq.edu.au Coral Gartner, c.gartner@uq.edu.au
Notes	

Begh 2019

Study name	<p>Examining the effectiveness of general practitioner and nurse promotion of electronic cigarettes versus standard care for smoking reduction and</p> <p>abstinence in hardcore smokers with smoking-related chronic disease: protocol for a randomized controlled trial</p>
Methods	<p>Individually randomized, blinded, 2-arm trial</p> <p>Setting: General practices, England</p> <p>Recruitment: Primary care registries</p>
Participants	<p>Target sample: 320 (160 per arm)</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Participant is willing and able to give informed consent for participation in the study Aged 18 years or above

Begh 2019 (Continued)

- Current smoker with a value of at least 10 ppm for exhaled CO and smokes a minimum of 8 cigarettes/8 g of tobacco per day (including pipe, cigars or tobacco roll-ups)
- Diagnosed with 1 or more of the following chronic conditions: ischaemic heart disease, peripheral vascular disease, hypertension, diabetes mellitus (type 1 and type 2), stroke, asthma, COPD, chronic kidney disease, depression, schizophrenia, bipolar disorder or other psychoses

Exclusion criteria:

- GP believes that switching to e-cigarettes would not benefit the patient given their current medical condition
- Currently using e-cigarettes, nicotine replacement therapy or other cessation therapies (e.g. bupropion, nortriptyline or varenicline)
- Plans to stop smoking before or at the annual review
- Currently enrolled in another smoking-related study or other study where the aims of the studies are incompatible
- Cannot consent due to mental incapacity
- Pregnant, breastfeeding or planning to become pregnant during the course of the study

Interventions

- Control: No additional support beyond standard care
- Intervention: will receive GP- or nurse-led brief advice about e-cigarettes, **an e-cigarette starter pack** with accompanying practical support booklet, and telephone support from experienced vapers and online video tutorials

Outcomes

Months 2, 8

Primary outcomes:

- 7-day PPA from smoked tobacco at 2 months; Self-reported abstinence from smoking—not even a puff—in the past 7 days, accompanied by a salivary anabasine concentration of < 1 ng/ml; exhaled CO as verification of abstinence (CO < 10 ppm) used, as necessary.

Secondary outcomes:

- Smoking reduction
- 7-day PPA and prolonged abstinence at 8 months;
- Participant recruitment and follow-up,
- Participant uptake and use of e-cigarettes,
- Nicotine intake,
- Contamination of randomization and practitioner adherence to the delivery of the intervention

Starting date

November 2016

Contact information

Rachna Begh, rachna.begh@phc.ox.ac.uk

Notes

Berlin 2019

Study name

Randomized, placebo-controlled, double-blind, double-dummy, multicentre trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine: the ECSTROKE trial protocol

Methods

3-arm randomized, placebo-controlled, multicentre, double-blind, double-dummy, parallel groups, phase III type trial

Setting: Smoking cessation clinics of both academic and community hospitals

Berlin 2019 (Continued)

Recruitment is either local (a) directly by the centres or centralized (b) using a web page and a centralized study-specific phone number and email address

- People who smoke intending to quit smoking are recruited by advertisement in pharmacies, physicians' offices situated in the catchment area of each investigator's centre, by local newspapers and in public places of the centres' healthcare facilities
- Candidates to participate can register by the study's website, unique email address and phone number. Registration is followed by a phone screening before dispatching to the study centres. Only 1 person by household will be recruited

Participants

Estimated enrolment: 650 participants

Inclusion criteria:

- People who smoke, at least 10 cpd (factory-made or roll-your-own) in the past year
- Aged 18 – 70 years
- Motivated to quit, defined as a score > 5 on a visual rating scale ranging from 0 (not motivated at all) to 10 (extremely motivated)
- Signed written informed consent
- Understanding and speaking French
- Women of childbearing age can be included if they use an effective contraceptive method: either hormonal contraception or an intrauterine device started at least 1 month before the first research visit
- Individual affiliated to a health insurance system
- Previous failure of NRT for smoking cessation

Exclusion criteria:

- Any unstable disease condition within the last 3 months defined by the investigator as major change in symptoms or treatments, such as recent myocardial infarction, unstable or worsening angina, severe cardiac arrhythmia, unstable or uncontrolled arterial hypertension, recent stroke, cerebrovascular disease, obliterative peripheral arterial disease, cardiac insufficiency, diabetes, hyperthyroidism, pheochromocytoma, severe hepatic insufficiency, history of seizures, severe depression, COPD
- Any life-threatening condition with life expectancy of < 3 months
- Alcohol use disorder defined as a score ≥ 10 on the Alcohol Use Disorders Identification Test (AUDIT)-C questionnaire (see below)
- Abuse of or dependence on illegal drugs in the last 6 months, revealed by medical history
- Regular use of tobacco products other than cigarettes
- Current or previous (last 6 months) use of EC
- Pregnant women
- Breastfeeding women
- Protected adults
- Current or past 3 months participation in another interventional research
- Current or past 3 months use of smoking cessation medication such as varenicline, bupropion, NRTs
- Known lactose intolerance (placebo tablets contain lactose)
- Hypersensitivity to the active substance or to any of the excipients
- Known severe renal failure

Interventions

A) **EC without nicotine** (ECwoN) plus placebo tablets of varenicline (0.50mg) administered by oral route: placebo condition;

B) **EC with nicotine** (ECwN) plus placebo tablets of varenicline: ECwN condition. V

C) Reference: ECwoN plus 0.5 mg varenicline tablets: **varenicline condition**. Varenicline administered according to the marketing authorisation

Berlin 2019 (Continued)

E-cigarette details:

- EC device Mini iStick kit (20 W) Eleaf, clearomiser: GS Air M with resistance of 1.5 ohm. To keep the blinding, the clearomizer's Pyrex window is of grey colour not allowing to distinguish the colouration of the e-liquid containing nicotine. Liquid for EC is manufactured by GAIATREND SARL (www.gaiatrend.fr/fr/)
- All participants will be delivered a short manual and a video specifically developed for this study explaining the use of EC. At each visit, participants receive verbal counselling about the use of the EC device and answers to their questions about handling the EC device

Behavioural support:

- Brief behavioural smoking cessation counselling for all participants is administered at all visits by the investigators specialised in smoking cessation. It is based on the national guidelines for smoking cessation

Treatment duration: 1 week + 3 months

Outcomes	Week 2, 4, 8, 10, 12, 24 after target quit day Primary outcome: <ul style="list-style-type: none"> • Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9 – 12) of the treatment period of 3 months Secondary outcomes: <ul style="list-style-type: none"> • Safety profile • PPA rate • CAR confirmed by urinary anabasine concentration • Changes in cpd consumption • Craving for tobacco and withdrawal symptoms with respect to baseline
Starting date	17 October 2018
Contact information	Ivan Berlin, ivan.berlin@aphp.fr
Notes	

Caponnetto 2014

Study name	Smoking cessation and reduction In schizophrenia (the SCARIS study)
Methods	3-arm prospective 12-m randomized controlled trial investigating efficacy and safety of EC Setting: psychiatric and smoking cessation centres, Italy Recruitment: local newspapers and radio/television advertisements
Participants	153 participants Inclusion criteria <ul style="list-style-type: none"> • Schizophrenic in stable phase of illness • Smoked at least 10 cpd over previous 5 years • Aged 18 - 65 • In good general health • Not currently attempting to quit smoke or wishing to do so in next 6m

Caponnetto 2014 (Continued)

	Exclusion criteria <ul style="list-style-type: none"> • Use smokeless tobacco or NRT • Pregnant or breastfeeding • Current or recent (1 yr) history of drug or alcohol abuse • Other significant co-morbidities
Interventions	12-wk supply of: <ul style="list-style-type: none"> • EC, high nicotine (24 mg) • EC, no nicotine (0 mg, with tobacco aroma) • PAIPO nicotine-free inhalator
Outcomes	Follow-up visits at 4, 8, 12, 24 and 52 wks Outcome measures: <ul style="list-style-type: none"> • Smoking cessation • Smoking reduction ($\geq 50\%$ from baseline) • Adverse events • Quality of life • Neurocognitive functioning • Participant perceptions and satisfactions with products
Starting date	September 2014
Contact information	Pasquale Caponnetto, p.caponnetto@unict.it
Notes	

Fraser 2015

Study name	An open-label randomized pragmatic policy trial examining effectiveness of short-term use of nicotine replacement therapy (NRT) vs short- or long-term use of NRT vs short- or long-term use of NRT or electronic nicotine delivery systems for smoking cessation in cigarette smokers
Methods	Phase 3 blinded RCT Setting: Australia Recruitment: commercial market research panel
Participants	Target sample size: 1600 <ul style="list-style-type: none"> • Current daily smoking (at least 6 cpd) • Can read and understand English • Agree to try samples of nicotine products • Willing to complete surveys • 18 years or older Exclusion criteria: <ul style="list-style-type: none"> • If currently treated for serious medical condition, • Pregnant or planning to become pregnant or breastfeed in next 12 m

Fraser 2015 (Continued)

Interventions	<ul style="list-style-type: none"> a) Factsheet explaining relative harm of NRT compared to smoking, free sample of NRT, participant chooses preferences, has free for 3 wks then offered at subsidised rate for further 6 m b) As (a), but with additional information provided c) As (a), but additional information on electronic cigarettes and emphasis on cessation, and may select electronic cigarettes as well as NRT
Outcomes	<p>6 m and 12 m, self-report</p> <ul style="list-style-type: none"> Continuous abstinence NRT and EC use Interest in quitting smoking and in quitting NRT Cigarette consumption Product orders and use Quit attempts
Starting date	February 2014
Contact information	Coral Gartner, c.gartner@uq.edu.au
Notes	

ISRCTN13288677

Study name	Can electronic cigarettes and nicotine replacement treatment help reduce smoking in smokers who struggle to quit?
Methods	<p>Pilot single-centre randomized control trial</p> <p>Setting: Queen Mary University of London, UK</p> <p>Recruitment method not specified.</p>
Participants	<p>Target sample size: 200</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> 18 years or older Able to provide written informed consent History of failed quit attempts using stop-smoking medications or stop smoking services, or both Willing to use their allocated harm-reduction strategy for at least 4 weeks <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Women who are pregnant or breastfeeding Unable to read/write/understand English Currently using EC or any stop-smoking products Taking part in other interventional research Have a strong preference to use or not to use NRT or EC
Interventions	<p>1) NRT arm:</p> <ul style="list-style-type: none"> Will be shown and explained the NRT products available and encouraged to choose a product or product combination that suits their needs Will receive a letter of recommendation as per standard practice and collect their chosen products at local pharmacies

ISRCTN13288677 (Continued)

- Product use will be supervised and adjusted (if required) as part of the behavioural support package. As per local standard practice, NRT will be provided for up to 8 weeks

2) **EC arm:**

- Will be shown and explained different EC products commonly used and asked to obtain the product of their choice, either using a voucher for up to GBP 35 to purchase EC at a local vape shop, purchase from other suppliers and claim a refund of up to GBP 35 upon providing a valid receipt, or choose from a limited selection at the smoking cessation clinic
- Will be encouraged to try different products and liquids if the first purchase does not meet their needs, but after the initial purchase, participants will fund further supplies themselves (this is to mimic the provision of starter packs, an approach that is most likely to be used by routine services)

Outcomes	<p>Participants contacted by phone at 1 week, 4 weeks and 24 weeks after the initial screening session</p> <p>Primary outcomes:</p> <ul style="list-style-type: none"> • Cigarette consumption per day, assessed by self-report in the follow-up survey created for the purpose of the study at 1, 4 and 24 weeks post-quit date/preparation date. Those who report \geq 50% smoking reduction will be validated with a CO reading in the clinic <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Use of allocated harm-reduction strategies • Strategy ratings • Changes in smoking behaviour • Proportion of people still using allocated strategy at 6 months
Starting date	January 2017
Contact information	Marzena Orzol, m.orzol@qmul.ac.uk
Notes	

Klonizakis 2017

Study name	Smokers making a quit attempt using e-cigarettes with or without nicotine or prescription nicotine replacement therapy: impact on cardiovascular function (ISME-NRT) - a study protocol
Methods	<p>Pragmatic, 3-group, randomized, assessor-blinded, single-centre trial</p> <p>Setting: Centre for Sport and Exercise Science (CSES) of Sheffield Hallam University, UK</p> <p>Recruitment: From the community in the wider Sheffield area will be by: i) low-cost newspaper and post-office advertisement, ii) posters in local pharmacies, libraries, mosques, churches, and clubs, iii) social media or search engine advertisement (Facebook, Google ads) iv) notices in newsletters or participation in outreach events of community organisations (such as Sheffield U3A and AGE UK), iv) a study website, and v) out-reach events in local ethnic community centres or places of worship</p>
Participants	<p>Estimated enrolment: 258 participants (86 participants arm)</p> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Age > 18 years of either sex • People who smoke (at least 10 cpd for the past year) • Willing (by declaration) to attempt quit smoking by using the NHS services or e-cigarettes <p>Exclusion Criteria:</p>

Klonizakis 2017 (Continued)

	<ul style="list-style-type: none"> • Inability to walk • Recent (within 6 months) cardiovascular disease event (e.g. stroke, myocardial infarction) or cardiac surgery • Insulin-controlled diabetes mellitus or with co-existing skin conditions, leg ulcers, vasculitis or deep venous occlusion (as these may affect their cardiovascular function) • Pregnancy • Requiring major surgery during the course of the study) • Contra-indications/unsuitability for NRT • Current daily use of e-cigarettes • Currently undertaking a cessation attempt supported by a smoking cessation clinic • Unable to give informed consent
Interventions	<ul style="list-style-type: none"> • a) Complimentary e-cigarette equipment and refills (Tornado V5, Joyetech, Shenzhen, China) at allocation stage, together with instructions on the correct usage of e-cigarettes. They will also receive behavioural support for a 3-month period. The nicotine strength of Group A cartridges will be up to 18 mg/ml nicotine strength • b) As a), but with nicotine-free liquid • c) Referral to NHS smoking cessation clinics and will receive NRT in conjunction with behavioural support
Outcomes	<p>Follow-up: Within 3 days of “quit date”, 3 and 6 months past quit date</p> <p>Outcome measures:</p> <ul style="list-style-type: none"> • Macro-vascular function (FMD assessment) • Micro-vascular function • Smoking status at 3 and 6 months, self-reported and biochemically validated by exhaled air measurement of < 10 ppm CO • Change in CVD risk using Q-risk assessment • Health Economic effects using EQ5D-L • Total cholesterol and High Density lipoprotein via fingerprick blood sample • Participant experiences' assessment
Starting date	24 April 2017
Contact information	Markos Klonizakis, m.klonizakis@shu.ac.uk
Notes	

NCT01842828

Study name	Spain-UK-Czech E-cigarette Study (SUKCES)
Methods	<p>Randomized controlled trial, open-label pilot study</p> <p>Setting: smoking cessation clinics in London, Madrid and Prague</p> <p>Recruitment: via smoking cessation clinics</p>
Participants	<p>220 people who smoke, seeking help to quit</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • 18 or older • Want help to quit

NCT01842828 (Continued)

	Exclusion criteria: <ul style="list-style-type: none"> • Pregnant or breastfeeding; • Enrolled in other research; • Currently using EC
Interventions	<ul style="list-style-type: none"> • Standard care plus 4 wks EC supply • Standard care only
Outcomes	<ul style="list-style-type: none"> • CO-validated continuous abstinence at 4 and 24 wks post-TQD • Withdrawal symptoms at 1 and 4 wks post-TQD • EC use • EC taste and satisfaction compared to conventional cigarettes • Adverse events
Starting date	December 2013
Contact information	Peter Hajek, p.hajek@qmul.ac.uk
Notes	

NCT01989923

Study name	Smoking cessation in women with gynaecological conditions
Methods	Randomized controlled trial, open-label feasibility study Setting: hospital clinic, USA Recruitment: in clinic
Participants	30 women who smoke with cervical dysplasia Inclusion criteria: <ul style="list-style-type: none"> • Women who smoke at least 10 cpd over past year • Diagnosis of cervical dysplasia, cervical cancer, and lower genital tract dysplasia and cancer • Aged 18 - 65 Exclusion criteria: <ul style="list-style-type: none"> • Previous diagnoses or treatment for cancer (except for non-melanoma skin cancer) • Stroke, heart disease, heart attack, or irregular heart beat • Pregnancy and lactation • Plan to continue to use other nicotine as well as study products • Uncontrolled hypertension • Using other stop-smoking medication • Taking prescription medicine for depression or asthma
Interventions	<ul style="list-style-type: none"> • NRT patch (21 mg for first 3 wks, 14 mg for 2nd 3 wks) plus nicotine gum (2 mg) or lozenges (2 mg) for 6 wks • EC device ('Blu' Cig) with refills to last 6 wks, number provided based on packs smoked a day x 1.5. Strength of EC reduced at 3 wks Both groups receive identical cessation counselling

NCT01989923 (Continued)

Outcomes	At 6 and 12 wks via survey: <ul style="list-style-type: none"> • Cpd • PPA at 7 and 30 days • Smoking cessation • Participants' attitudes and beliefs towards treatments • Adherence
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Starting date	June 2013
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Contact information	Laura A Beebe, laura-beebe@ouhsc.edu
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Notes	
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NCT02004171

Study name	Electronic cigarettes or nicotine inhaler for smoking cessation
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Methods	Randomized controlled trial, open-label safety/efficacy study Setting and recruitment not specified, USA
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Participants	40 participants Inclusion criteria: <ul style="list-style-type: none"> • 18 - 60 years old • Meet DSM-IV criteria for nicotine dependence • Seeking treatment for smoking cessation • smoking at least 15 cpd Exclusion criteria: <ul style="list-style-type: none"> • DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder • Current diagnosis of major depressive disorder • Current diagnosis for other psychiatric disorders that may require intervention over course of study • Receiving treatment for nicotine dependence • Pregnancy, lactation, or chance of pregnancy • Unstable medical condition • Substance abuse diagnosis • Use of cannabis or alcohol on more than 20 days in past 30 days • Suicide risk
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Interventions	4 wks: <ul style="list-style-type: none"> • ECs (2nd generation) with 24 mg nicotine cartridges, 1 - 2 cartridges daily • Nicotine inhaler with 10 mg cartridges, max 16 cartridges per day
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Outcomes	Over 4 wks: <ul style="list-style-type: none"> • cpd • Withdrawal • Benefits from smoking cessation (breathing, sense of taste and smell, physical fitness) • Adverse events
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NCT02004171 (Continued)

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Starting date	December 2013
Contact information	Barney Vaughan, vaughan@nyspi.columbia.edu
Notes	

NCT02124187

Study name	Smoking cessation and reduction in depression (SCARID)
Methods	3-arm prospective 12-m randomized controlled trial investigating efficacy and safety of ECs
Participants	<p>129 participants</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Diagnosis of major depressive disorder (MDD) (according to DSM-5 criteria) • Smoke ≥ 10 cpd (for at least the past 5 years) • age 18 - 65 years • In good general health • Unwilling to quit smoking in the next 30 days <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Use of smokeless tobacco or NRT or other smoking cessation therapies • Pregnancy or breastfeeding • Current or recent (< 1 yr) past history of alcohol or drug abuse or both • Active suicidal intention • Other significant co-morbidities according to the Investigator's clinical assessment (e.g. cancer, acute myocardial infarction, unstable angina, severe cardiac arrhythmia, recent cerebrovascular incident, or severe atherosclerosis)
Interventions	<p>12-wk supply of:</p> <ul style="list-style-type: none"> • EC 24 mg nicotine • EC 0 mg nicotine • Nicotine-free inhalator
Outcomes	<p>Follow-up visits at 4, 8, 12, 24 and 52 wks</p> <p>Outcome measures:</p> <ul style="list-style-type: none"> • Smoking cessation • Smoking reduction ($\geq 50\%$ from baseline) • Adverse events • Quality of life • Neurocognitive functioning • Participant perceptions and satisfaction with products
Starting date	February 2015
Contact information	Pasquale Caponnetto p.caponnetto@unict.it

NCT02124187 (Continued)

Notes

NCT02261363

Study name	A mixed-method EMA assessment of cognition and behaviour among new ENDS users: an observational cohort study
Methods	Observational cohort study Setting: community Recruitment: volunteers
Participants	Estimated enrolment: 120, 100 not intending to quit in next 30 days, 20 intending to quit Selected inclusion criteria: <ul style="list-style-type: none"> • Aged 18 years or older • Daily smoker with at least 5 years of established daily smoking not taking smoking cessation medications • Have not used an ENDS product (electronic cigarette) in the last 30 days • Be interested in trying an ENDS • Not have heart disease/uncontrolled blood pressure • Not have psychosis/suicidal thoughts • Not be currently enrolled in an alcohol treatment programme
Interventions	Unclear whether participants will be encouraged to use EC or not
Outcomes	Wks 1 - 3: Primary: <ul style="list-style-type: none"> • Cigarette use • EC use Secondary: <ul style="list-style-type: none"> • Motivation to quit
Starting date	August 2014
Contact information	Jennifer Pearson, American Legacy Foundation
Notes	May not be eligible

NCT02398487

Study name	Head-to-head comparison of personal vaporizers versus cig-a-like: prospective 6-month randomized control design study (VAPECIG 2)
Methods	Randomized parallel-assignment open-label trial Setting: Italy, community
Participants	Estimated enrolment: 200

Electronic cigarettes for smoking cessation (Review)

NCT02398487 (Continued)

Inclusion criteria:

- (People who smoke) in good general health
- Committed to follow trial procedures

Exclude if:

- Recent vaping history (stopped vaping < 3 months ago)
- Use of any other form of non-combustible nicotine-containing products (chewable tobacco or nicotine replacement therapy)
- Symptomatic cardiovascular disease
- Clinical history of asthma and COPD
- Regular psychotropic medication use
- Current or past history of alcohol abuse
- Use of smokeless tobacco or nicotine replacement therapy
- Pregnancy or breastfeeding.

Interventions	Comparison between 2 types of EC; 'personal vaporizers' and 'cig-a-like'
Outcomes	24 weeks: <ul style="list-style-type: none"> • Smoking cessation • smoking reduction
Starting date	October 2014
Contact information	Riccardo Polosa
Notes	

NCT02487953

Study name	Electronic nicotine delivery systems (ENDS) as a smoking cessation treatment
Methods	Randomized parallel-assignment double-blind trial Setting: Smoking cessation research centre, USA Recruitment: volunteers
Participants	Estimated enrolment: 300 Inclusion criteria: <ul style="list-style-type: none"> • Have no known serious medical conditions • Smoke an average of at least 10 cpd • Have an expired-air CO reading of at least 15 ppm • Able to read and understand English • Express a desire to quit smoking in the next 30 days • Higher than median rating of enjoyment of airway sensory effects of inhaling smoke on Cigarette Evaluation Questionnaire Exclusion criteria: multiple related to baseline health status
Interventions	<ul style="list-style-type: none"> • Nicotine EC + nicotine patch • Nicotine EC + placebo patch

NCT02487953 (Continued)

- Placebo (non-nicotine) EC + nicotine patch

Nicotine patches will be provided for 2 weeks before TQD and 8 weeks after at full dose then dose weaning for 4 weeks

EC will be provided for 1 week before TQD and 8 weeks after, then instructed to reduce

Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> • Abstinence at 4 - 8 weeks from TQD <p>Secondary:</p> <ul style="list-style-type: none"> • Abstinence at 9 - 12 weeks, 13 - 16 weeks, 6 months <p>All abstinence validated by CO</p>
Starting date	January 2016
Contact information	Al Salley: al.salley@duke.edu. PI Jed Rose
Notes	

NCT02527980

Study name	E-cigarettes: dynamic patterns of use and health effects
Methods	<p>Prospective observational study</p> <p>Setting: community, USA</p> <p>Recruitment: People who smoke and dual EC and cigarette users</p>
Participants	<p>Estimated enrolment: 450</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • ≥ 18 years old • No plans to quit smoking and/or EC use in the next 30 days • Not currently taking smoking cessation medication • Not currently in treatment for psychosis or bipolar disorder • Participants must report either that they have: smoked at least 5 cpd for the past 6 months and not used EC within the last 3 months ("exclusive smokers") or used nicotine-containing EC at least once a week for the past month and have smoked at least 5 cpd for the last 3 months ("dual users")
Interventions	"We will conduct a 2-year longitudinal cohort study comprising participants who smoke exclusively CCs (n = 175) and dual users of e-cigs and CCs (n = 275)"
Outcomes	"We will use state-of-the-art ecological momentary assessments to determine: 1) dynamic patterns of e-cig and CC use and related outcomes (e.g. dependence, withdrawal symptoms, CC quit attempts and quitting success); 2) episodic (affective, contextual, social) and stable person-factor (lifestyle factors, demographics) variables that covary meaningfully with e-cig and CC use and related outcomes; 3) biomarkers of tobacco and carcinogen exposure as well as other health-related outcomes (e.g. reduced pulmonary function)."
Starting date	September 2015

NCT02527980 (Continued)

Contact information PI Megan Piper

Notes

NCT02590393

Study name The role of nicotine and non-nicotine alkaloids in e-cigarette use and dependence

Methods Randomized parallel-assignment double-blind trial

Setting: Smoking research clinic, USA

Recruitment: volunteers

Participants Estimated enrolment: 375

Inclusion criteria:

- Have no known serious medical conditions
- Are 18 - 65 years old
- Smoke an average of at least 10 cpd
- Have smoked at least 1 cumulative year
- Have an expired air CO reading of at least 10 ppm
- Are able to read and understand English

Exclude if: multiple, related to baseline health status

 Interventions

- Switch to standard **nicotine EC** use for 8 wks
- Switch to **ECs with same nicotine but very low non-nicotine alkaloid levels**
- Switch to **ECs with very low nicotine** and non-nicotine alkaloids

 Outcomes

Primary:

- CO levels at 8 wks

Secondary:

- EC use
- EC solution use
- cigarette use, at 8 wks

Starting date May 2016

Contact information Jed Rose

Notes "This is not a smoking cessation study; People who smoke will not be asked to quit smoking, and e-cigarettes will not be used as a medical device or therapy."

NCT02635620

Study name Changes in lung function parameters, bronchial reactivity, state of health and smoking behaviour associated with changing from conventional

NCT02635620 (Continued)

	smoking to electronic cigarettes
Methods	<p>Prospective observational study</p> <p>Setting: Community, Germany</p> <p>Recruitment: Vape shops and smoking cessation clinics</p>
Participants	<p>Estimated enrolment: 80</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Smoking \geq 5 years • Smoking \geq 10 cpd • No intention to stop smoking within the last 3 months • Using EC with nicotine • No infection of airways at the time of measurements • EC group: intending to use EC • Control group: smoking cessation in the framework of a clinical conducted programme <p>Exclude if:</p> <ul style="list-style-type: none"> • pregnancy or breastfeeding • not speaking German • known allergy • acute psychiatric diseases, suicidal tendency • drug/substance/alcohol abuse • severe internal diseases
Interventions	<p>Comparison between:</p> <ul style="list-style-type: none"> • People who smoke who intend to start EC use for the first time • 2) People who smoke who intend to quit smoking within a clinical conducted smoking cessation programme
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> • Lung function • QoL • Respiratory tract inflammation
Starting date	October 2015
Contact information	Tobias R��ther
Notes	

NCT03589989

Study name	The ESTxENDS Trial- Electronic Nicotine Delivery Systems (ENDS/Vaporizer/E-cigarette) as an aid for smoking cessation. (ESTxENDS)
Methods	<p>Randomized, parallel-assignment, open-label trial</p> <p>Setting: Switzerland</p>

NCT03589989 (Continued)

Recruitment: Not specified

Participants	<p>Estimated Enrolment: 1172</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Informed consent as documented by signature • Persons aged 18 or older • Currently smoking 5 or more cigarettes a day for at least 12 months • Willing to try to quit smoking within the next 3 months • Persons providing a valid phone number, a valid email address and/or a valid postal address. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Known hypersensitivity or allergy to contents of the e-liquid • Participation in another study with investigational drug within the 30 days preceding the baseline visit and during the present study where interactions are to be expected • Women who are pregnant or breastfeeding • Intention to become pregnant during the course of the scheduled study intervention, i.e. within the first 6 months of the study • Persons having used ENDS regularly in the 3 months preceding the baseline visit • Persons having used nicotine replacement therapy (NRT) or other medications with demonstrated efficacy as an aid for smoking cessation such as varenicline or bupropion within the 3 months preceding the baseline visit • Persons who cannot attend the 6-month follow-up visit for any reason • Cannot understand instructions delivered in person or by phone, or otherwise unable to participate in study procedures
Interventions	<ul style="list-style-type: none"> • a) ENDS (vaporizer/e-cig) and smoking cessation counselling will receive: <ul style="list-style-type: none"> • ENDS and nicotine-containing e-liquids, which they will be allowed to use ad libitum • Smoking cessation counselling: provided in person at the first clinical visit and then over the phone at the target quit date 1 week later and again at weeks 2, 4 and 8 after the target quit date. After 6 months, participants will be asked to come to a final clinical visit • Participants will be allowed to additionally use nicotine replacement therapy • b) Control group will receive smoking cessation counselling only as provided for a). Participants will be allowed to additionally use nicotine replacement therapy
Outcomes	<p>Primary outcome: Continuous smoking abstinence at 6 months post-quit date measured by:</p> <ul style="list-style-type: none"> • Self-report of having smoked no cigarettes from quit date, validated by urinary levels of anabasine. If anabasine is missing, validation by exhaled carbon monoxide (CO). <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Continuous smoking abstinence at 6 months post-quit date <ul style="list-style-type: none"> * Self-report of having smoked no cigarettes from quit date, validated by urinary levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol). If NNAL is missing, validation by urinary levels of anabasine or exhaled carbon monoxide (CO) • Self-reported smoking abstinence allowing a 2-week `grace period' at 4, 8 weeks and 6 months post quit date • Validated smoking abstinence allowing a 2-week `grace period' at 6 months post quit date <ul style="list-style-type: none"> * validated by urinary levels of anabasine. If anabasine is missing validation by exhaled CO * validated by urinary levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol). If NNAL is missing, validation by urinary levels of anabasine or exhaled CO • Self-reported smoking abstinence allowing up to 5 cigarettes at 1, 2, 4, 8 weeks and 6 months post-quit date

NCT03589989 (Continued)

- Validated smoking abstinence allowing up to 5 cigarettes at 6 months post-quit date:
 - * validated by urinary levels of anabasine. If anabasine is missing validation by exhaled CO
 - * validated by urinary levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol). If NNAL is missing, validation by urinary levels of anabasine or exhaled CO
- Self-reported 7-day PPA at 1, 2, 4, 8 weeks and 6 months post-quit date
- Validated 7-day PPA at 6 months post-quit date
 - * Confirmation of having smoked no cigarettes in the past 7 days, validated by urinary levels of anabasine. If anabasine is missing validation by exhaled CO
 - * Confirmation of having smoked no cigarettes in the past 7 days, validated by urinary levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol). If NNAL is missing, validation by urinary levels of anabasine or exhaled CO
- Number of cpd at baseline, target quit date, 1, 2, 4, 8 weeks and 6 months post-quit date, self-reported
- Change in number of cpd at baseline, 6 months post-quit date, self-reported. Successful reduction defined as 50% reduction in cpd
- Use of any other smoking cessation products (NRT) at 1, 2, 4, 8 weeks and 6 months post-quit date, self-reported
- Withdrawal at baseline and 6 months
- Fagerström Test for Nicotine Dependence at baseline and 6 months
- Swiss EQ-5D at baseline and 6 months
- Use of any ENDS at 1, 2, 4, 8 weeks and 6 months post-quit date, self-reported
- Most common adverse events using ENDS at 1, 2, 4, 8 weeks and 6 months post-quit date

Starting date	16 July 2018
Contact information	Reto Auer, reto.auer@biham.unibe.ch Anna Schöni, anna.schoeni@biham.unibe.ch
Notes	Linked trials: NCT03603340; NCT03603353; NCT03612336; NCT03612375; NCT03612453; NCT03612544; NCT03632421; NCT03938298

NCT03700112

Study name	An open-label, randomized cross-over study comparing nicotine pharmacokinetics of seven electronic cigarette products and one traditional cigarette across two delivery (10 puff and ad-libitum) conditions, in healthy adult smokers.
Methods	Open-label, randomized cross-over trial Setting and recruitment not specified, New Zealand
Participants	Estimated enrolment: 24 Inclusion criteria: <ul style="list-style-type: none"> • Male or female aged 18 to 60 years of age inclusive • BMI between 18 to 35 kg/m² inclusive • Healthy based on medical history and screening assessments, in the opinion of the Investigator • Current smoker of at least 8 cigarettes per day on average • Has been smoking for at least 12 months prior to screening. Brief periods of non-smoking (e.g. up to ~7 consecutive days due to illness, trying to quit, participation in a study where smoking was prohibited) are permitted at the discretion of the Investigator • Able to participate, and willing to give written informed consent and comply with study restrictions

NCT03700112 (Continued)

Exclusion criteria:

- Clinically-relevant medical or psychiatric disorder, in the opinion of the Investigator
- Clinically-significant abnormality on screening ECG
- Sustained blood pressure recordings at screening of < 90 mmHg or > 150 mmHg for systolic blood pressure, or < 50 mmHg or > 90 mmHg for diastolic blood pressure
- Sustained resting heart rate of > 100 or < 40 beats per minute at screening
- Positive result for urine drugs of abuse test or alcohol breath test at screening. If a positive urine drug test is observed, and it is believed the positive urine test is due to prescription drugs, the PI should obtain documentation that a) confirms the person's use of the prescribed medication, and b) the prescribed medication will cause a false positive drug test
- Clinically-significant abnormality in laboratory test results at screening, in the opinion of the Investigator
- Exposure to an investigational drug in a clinical trial within 1 month prior to Assessment Day 1
- Blood or plasma donation of > 500 mL within 1 month prior to Assessment Day 1
- Positive urine pregnancy test at screening or Assessment Day 1 in women
- Any clinically-significant concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the participant in this study

Interventions

- JUUL Virginia Tobacco flavoured 5.0% ENDS; consumed using 10 puffs delivery method, ad-libitum
- PMI iQOS Heat sticks - Regular consumed using 10 puffs delivery method, ad-libitum
- Reynolds VUSE Solo ENDS - Original consumed using 10 puffs delivery method, ad-libitum
- Imperial MyBlu ENDS - Original consumed using 10 puffs delivery method, ad-libitum
- Altria MarkTen ENDS - Bold Classic consuming using 10 puffs delivery method, ad-libitum
- MLV PHIX ENDS - Original Tobacco consumed using 10 puffs delivery method, ad-libitum
- NJOY Daily EXTRA ENDS - Rich Tobacco consumed using 10 puffs delivery method, ad-libitum
- Altria Marlboro combustible cigarette - Red consumed using 10 puffs delivery method, ad-libitum

Outcomes

Day 48

Outcomes:

- Nicotine PK parameters calculated from the individual plasma concentrations
- Exhaled CO
- Level of user satisfaction measured by Modified Product Evaluation Scale
- Characterize consumption of 8 x E-cigarettes/cigarettes products by collecting total number of puffs for each e-cigarette

Starting date

7 December 2018

Contact information

Study director: Concetta Carbonaro

Responsible party: Juul Labs, Inc.

Notes

NCT03962660

Study name

Harm reduction for tobacco smoking with support of tobacco-replacing electronic nicotine delivery systems (HaRTS-TRENDS)

Methods

Parallel, randomized controlled trial

NCT03962660 (Continued)

Setting: USA

Recruitment: from prominent Housing First programs serving chronically homeless people who are often multiply affected by psychiatric, medical and substance-use disorders. The proposed sample will be recruited from a highly vulnerable and marginalized population in a tight-knit urban community

 Participants

Estimated enrolment: 94

Inclusion criteria:

- Having a history of chronic homelessness according to the widely-accepted federal definition
- Being a current DESC client living in 1 of DESC's participating permanent supportive housing projects
- Being between 21 - 65 years of age
- Being a daily smoker (> 4 cigarettes/day in the past year with a breath CO \geq 6 ppm or salivary cotinine test at level 1 if CO < 6 ppm)
- Having adequate English language skills to understand verbal information and communicate in the study

Exclusion Criteria:

- Use of other tobacco products besides cigarettes \geq 9 days in the past month
- Refusal or inability to consent to participation in research
- Constituting a risk to the safety and security of other clients or staff.

 Interventions

- Intervention: HaRTS-TRENDS: 4 individual sessions delivered in the context of the interventionist's pragmatic harm-reduction mindset paired with a compassionate, advocacy-oriented "heart-set" or style. It comprises the delivery of 4 manualized components, including
 - * a) participant-led tracking of preferred smoking outcomes,
 - * b) elicitation of participants' harm-reduction goals and their progress toward achieving them,
 - * c) discussion of the relative risks of various nicotine delivery systems,
 - * d) instruction in using ENDS. Additionally, HaRTS-TRENDS entails provision of commercially available ENDS.
- Standard care: The 4-session, individual standard care control condition entails the well-documented and evidence-based 5 As intervention (i.e. Ask about nicotine use, Assess use, Advise to quit smoking, Assist with exploring current smoking/planning smoking cessation, Arrange follow-up). Part of arranging follow-up is the recommendation to call the smoking quit line, which can supply additional counselling and nicotine replacement therapy

 Outcomes

Primary outcomes, measured across the 12-month follow-up:

- Biologically-verified nonsmoking (i.e. self-reported nonsmoking if corresponding CO measure is < 8) in the past 7 days
- Urinary concentration of a tobacco-specific nitrosamine

Secondary outcomes, measured across the 12-month follow-up:

- Self-reported smoking intensity is the mean number of cigarettes participants report smoking per day in the 7 days prior to the assessment
- Self-reported smoking frequency is the number of days participants report smoking in the 7 days prior to the assessment
- CO level
- Urinary cotinine
- FEV1%
- 10-item Clinical COPD Questionnaire
- EQ-5D-5L

Other outcomes:

NCT03962660 (Continued)

- Smoking craving
- Side effects of ENDS

Starting date	9 May 2019
Contact information	Tatiana M Ubay, tatiubay@uw.edu
Notes	

NCT04063267

Study name	Electronic cigarettes as a harm reduction strategy in individuals with substance use disorder
Methods	Parallel, randomized trial Recruitment/Setting: Not specified
Participants	Estimated enrolment: 240 Inclusion criteria: <ul style="list-style-type: none"> • Smokes at least 10 cpd • Meet DSM-V AUD and/or OUD within the past year, interested in reducing cpd • Able to provide consent • Use a cell phone, are willing/able to receive and respond to daily text messages about their cigarette use and e-cigarette use on their cell phone • Provide 1 additional contact, and are willing to use an e-cigarette for 3 weeks Exclusion criteria: <ul style="list-style-type: none"> • Pregnant and/or breast feeding (self-reported) • Currently using smoking cessation medications (including other forms of NRT, bupropion, or varenicline) • enrolled in a smoking cessation programme or another cessation trial • Have used an e-cigarette in the past 14 days • Have used any other tobacco products (pipe, cigar, cigarillos, snuff, chewing tobacco, rolling tobacco, or hookah/shisha) in the past 30 days • Report having a history of asthma, other airways diseases, or heart disease
Interventions	E-cigarettes arm: <ul style="list-style-type: none"> • Participants will be encouraged to substitute e-cigarettes for combustible cigarettes in order to reduce nicotine withdrawal symptoms Nicotine Replacement Therapy arm: <ul style="list-style-type: none"> • Nicotine patches and gum to last them the first week based on their baseline recorded smoking. Participants will be advised to use both a 21 mg nicotine patch and 4 mg nicotine for cravings
Outcomes	Proportion of participants who achieve 50% reduction in cpd at 3 weeks
Starting date	15 September 2019
Contact information	NYU Langone Health, Scott.Sherman@nyulangone.org
Notes	

NTR6224

Study name	Electronic cigarettes: an intervention for dual-users
Methods	<p>RCT</p> <p>Setting: The Netherlands</p> <p>Recruitment: Not specified.</p>
Participants	<p>Target sample size: 100</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Dual-users (people who smoke tobacco cigarettes and vape e-cigs) who have the intention to completely and exclusively switch to vaping e-cigs within six months <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Non-smoker Dual-users who have used e-cigarettes for less than 3 months
Interventions	<p>Intervention arm will contain the following elements, will have 3 contact moments (after intake).</p> <ul style="list-style-type: none"> Providing correct information about the expected health effects of “dual use” vs. completely switching (pros and cons for both short and long term), including corrective information about the harm of nicotine Broadening practical knowledge about the different kinds of e-liquids and e-cigs and the optimal use of these Components aimed at increasing motivation (offering perspective on success) and self-efficacy (how to handle situations in which people still smoke tobacco cigarettes) <p>Control/waiting group</p>
Outcomes	<p>Questionnaires that identify:</p> <ul style="list-style-type: none"> Smoking/vaping behaviour (number of tobacco cigarettes that are still smoked) and by biological validation of smoking cessation through eCO-measurements <p>Questionnaire assessing:</p> <ul style="list-style-type: none"> In which situations do people still smoke tobacco cigarettes What amount of e-liquid do people still use, etc.
Starting date	1 March 2018
Contact information	Karolien Adriaens, karolien.adriaens@kuleuven.be
Notes	

BMI: body mass index; CAR: continuous abstinence rate; CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; cpd: cigarettes per day; CVD: cardiovascular disease; EC: electronic cigarette; ECG: electrocardiogram; FTND: Fagerström Test for Nicotine Dependence; NNAL: carcinogen found in tobacco smoke; NRT: nicotine replacement therapy; PP(A): point prevalence (abstinence); QoL: quality of life; TQD: target quit date; wk: week; yr: year

DATA AND ANALYSES

Comparison 1. Nicotine EC versus NRT

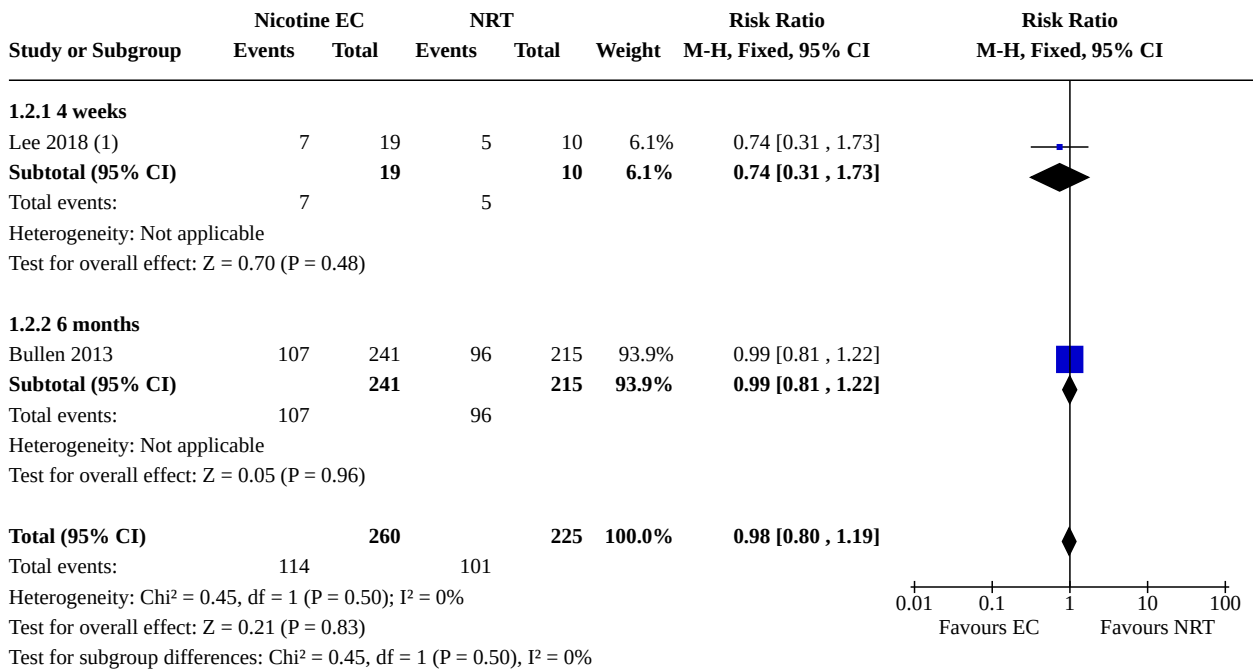
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Smoking cessation	3	1498	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.25, 2.27]
1.2 Adverse events	2	485	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.80, 1.19]
1.2.1 4 weeks	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.31, 1.73]
1.2.2 6 months	1	456	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.81, 1.22]
1.3 Serious adverse events	2	727	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.77, 2.41]
1.3.1 4 weeks	1	29	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.2 1 year	1	698	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.77, 2.41]
1.4 Carbon monoxide (ppm)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 8 weeks	2	136	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-1.94, 0.62]
1.5 Heart rate (bpm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6 Systolic blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 Blood oxygen saturation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 3-HPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9 NNAL (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10 2-HPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11 HMPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 PheT (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.12.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13 CEMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.14 AAMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.14.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.15 FEV1 (ml)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.15.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.16 FEV1/FVC (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.16.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Nicotine EC versus NRT, Outcome 1: Smoking cessation

Study or Subgroup	EC		NRT		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Bullen 2013	21	289	17	295	27.2%	1.26 [0.68 , 2.34]	
Hajek 2019	79	438	44	446	70.6%	1.83 [1.30 , 2.58]	
Lee 2018	5	20	1	10	2.2%	2.50 [0.34 , 18.63]	
Total (95% CI)		747		751	100.0%	1.69 [1.25 , 2.27]	
Total events:	105		62				
Heterogeneity: Chi ² = 1.21, df = 2 (P = 0.55); I ² = 0%							
Test for overall effect: Z = 3.46 (P = 0.0005)							
Test for subgroup differences: Not applicable							

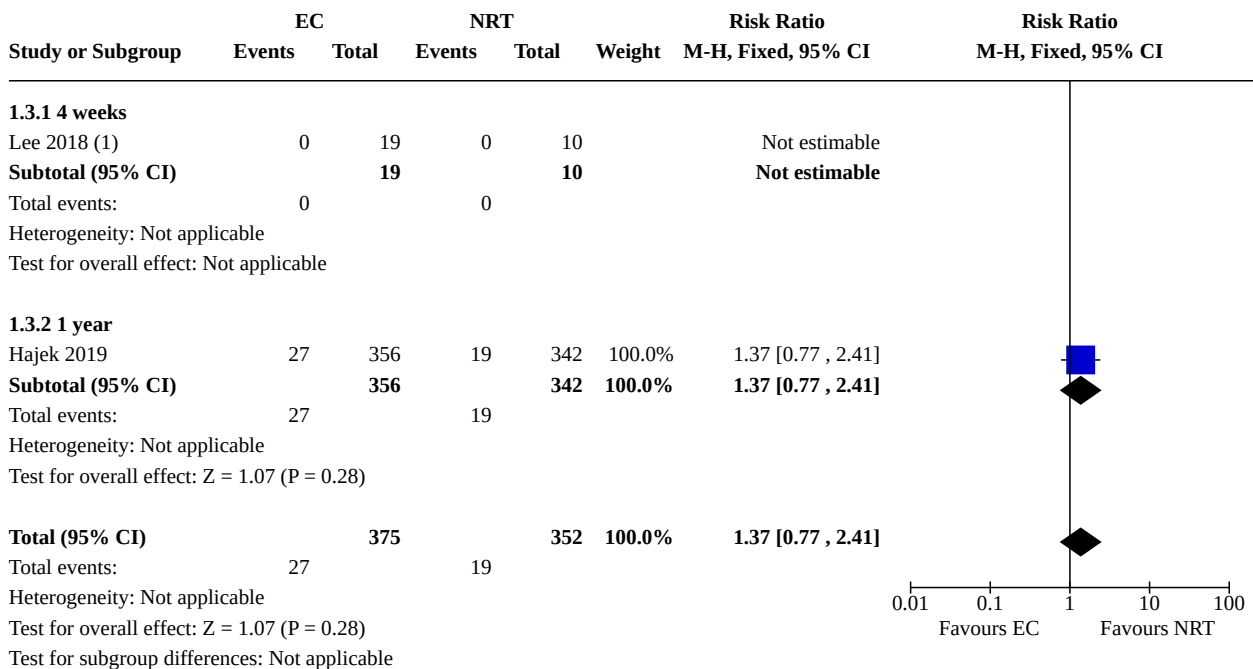
Analysis 1.2. Comparison 1: Nicotine EC versus NRT, Outcome 2: Adverse events



Footnotes

(1) Data at 4 weeks post-operation; time from baseline not defined and likely to differ between participants

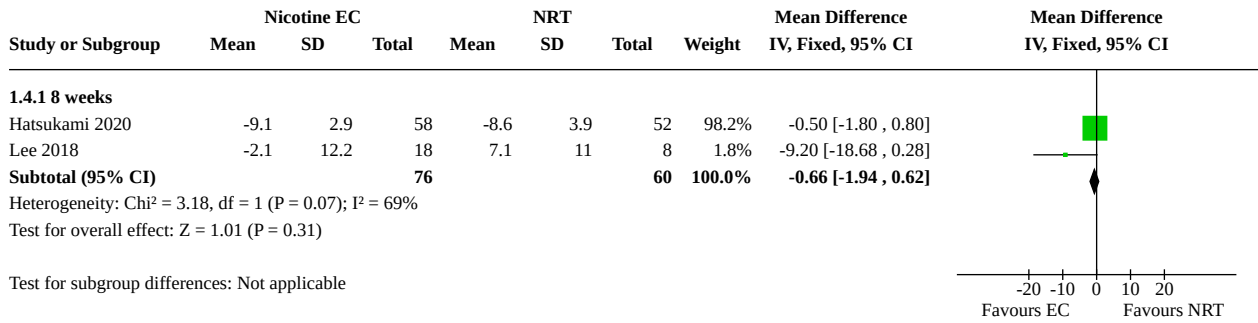
Analysis 1.3. Comparison 1: Nicotine EC versus NRT, Outcome 3: Serious adverse events



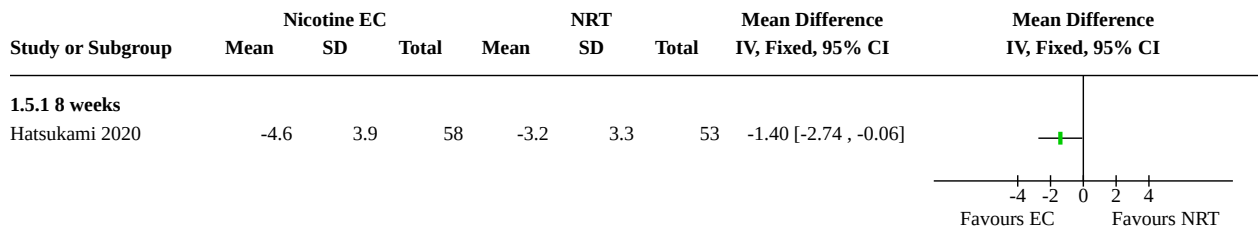
Footnotes

(1) Data at 4 weeks post-operation; time from baseline not defined and likely to differ between participants

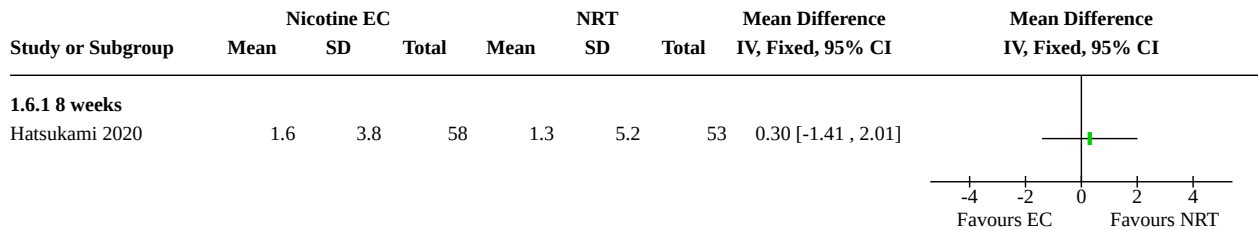
Analysis 1.4. Comparison 1: Nicotine EC versus NRT, Outcome 4: Carbon monoxide (ppm)



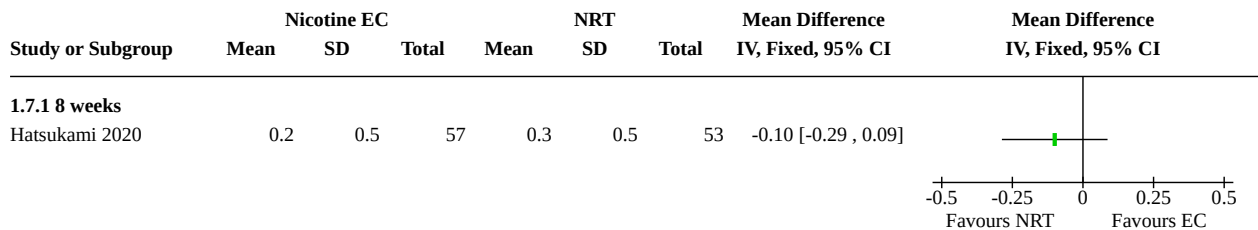
Analysis 1.5. Comparison 1: Nicotine EC versus NRT, Outcome 5: Heart rate (bpm)



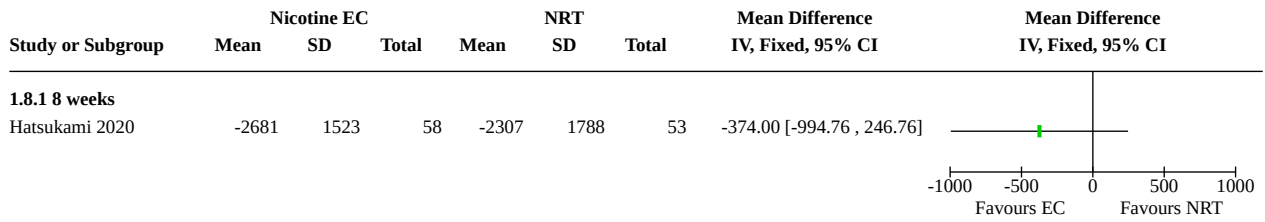
Analysis 1.6. Comparison 1: Nicotine EC versus NRT, Outcome 6: Systolic blood pressure



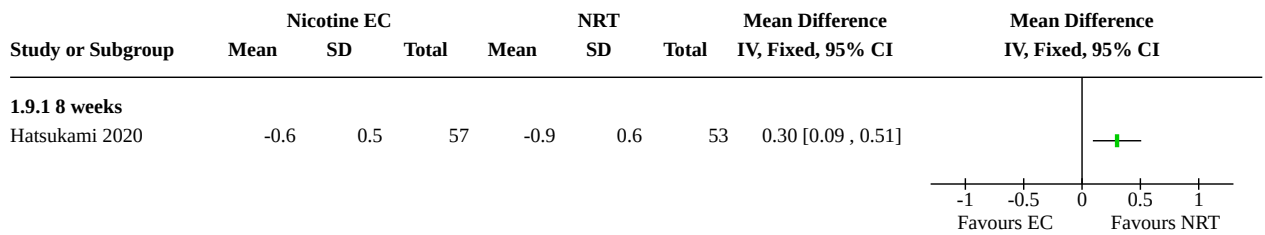
Analysis 1.7. Comparison 1: Nicotine EC versus NRT, Outcome 7: Blood oxygen saturation



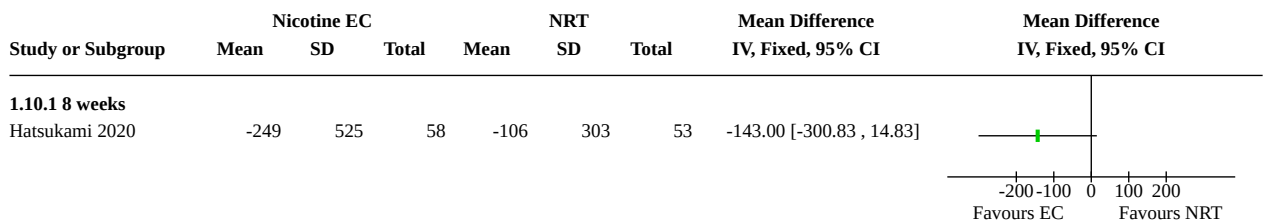
Analysis 1.8. Comparison 1: Nicotine EC versus NRT, Outcome 8: 3-HPMA (pmol/mg creatinine)



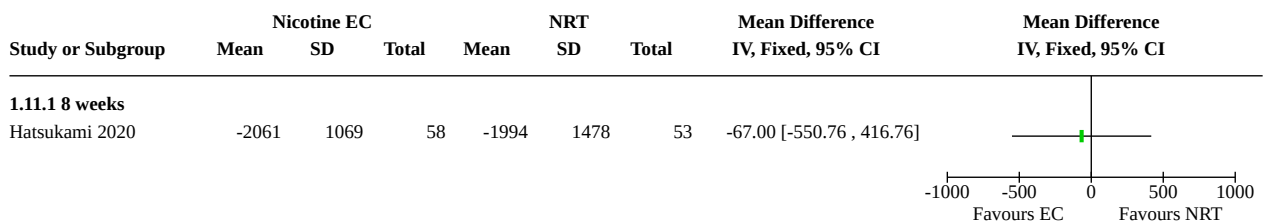
Analysis 1.9. Comparison 1: Nicotine EC versus NRT, Outcome 9: NNAL (pmol/mg creatinine)



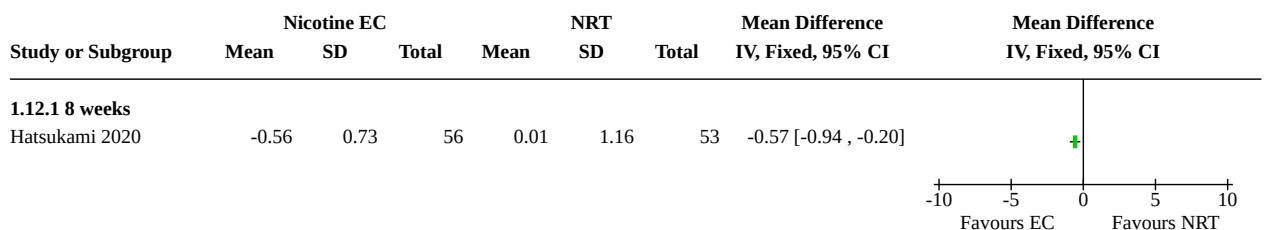
Analysis 1.10. Comparison 1: Nicotine EC versus NRT, Outcome 10: 2-HPMA (pmol/mg creatinine)



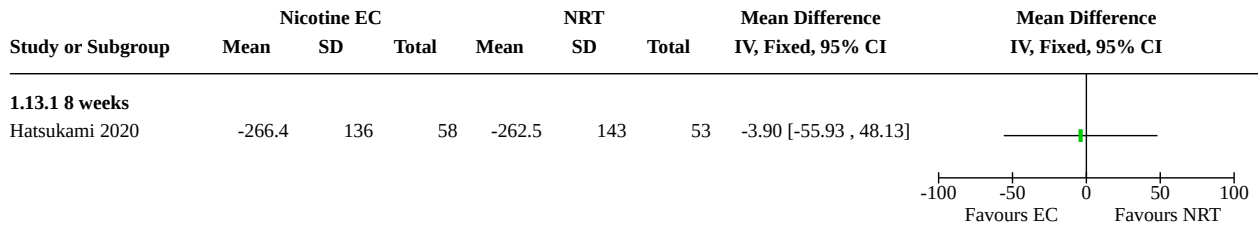
Analysis 1.11. Comparison 1: Nicotine EC versus NRT, Outcome 11: HMPMA (pmol/mg creatinine)



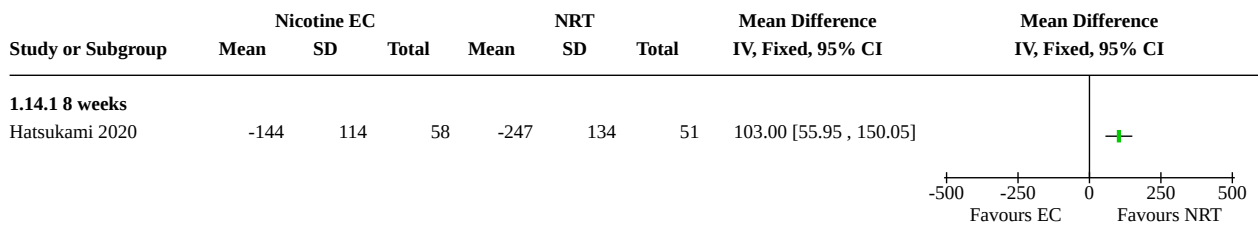
Analysis 1.12. Comparison 1: Nicotine EC versus NRT, Outcome 12: PheT (pmol/mg creatinine)



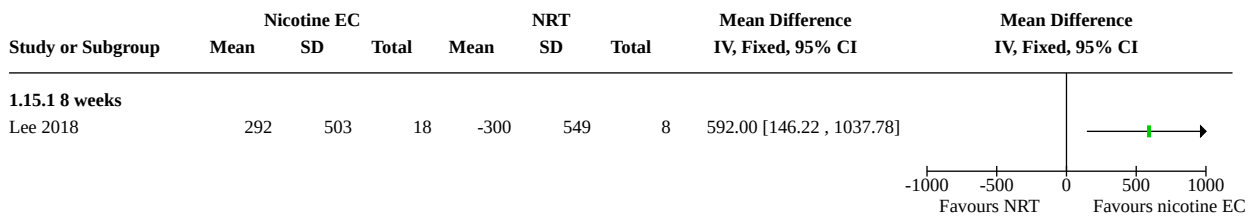
Analysis 1.13. Comparison 1: Nicotine EC versus NRT, Outcome 13: CEMA (pmol/mg creatinine)



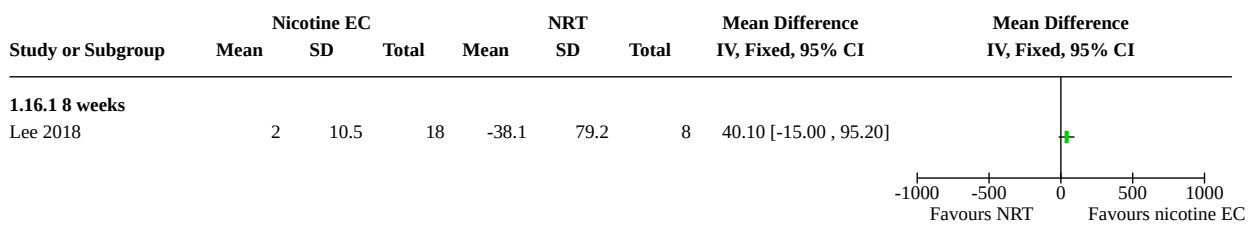
Analysis 1.14. Comparison 1: Nicotine EC versus NRT, Outcome 14: AAMA (pmol/mg creatinine)



Analysis 1.15. Comparison 1: Nicotine EC versus NRT, Outcome 15: FEV1 (ml)



Analysis 1.16. Comparison 1: Nicotine EC versus NRT, Outcome 16: FEV1/FVC (%)



Comparison 2. Nicotine EC versus varenicline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.2 Serious adverse events	1	54	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.1 12 weeks	1	54	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 2.1. Comparison 2: Nicotine EC versus varenicline, Outcome 1: Smoking cessation

Study or Subgroup	Nicotine EC		Varenicline		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ioakeimidis 2018	4	27	13	27	0.31 [0.11, 0.82]	

Analysis 2.2. Comparison 2: Nicotine EC versus varenicline, Outcome 2: Serious adverse events

Study or Subgroup	Nicotine EC		Varenicline		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.2.1 12 weeks							
Ioakeimidis 2018 (1)	0	27	0	27		Not estimable	
Subtotal (95% CI)		27		27		Not estimable	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		27		27		Not estimable	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

Footnotes

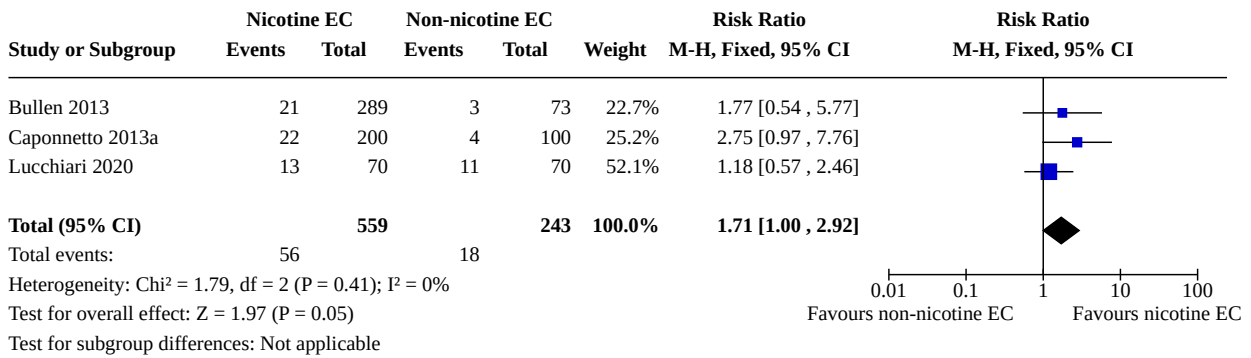
(1) n followed up not reported; n randomised used as denominators

Comparison 3. Nicotine EC versus non-nicotine EC

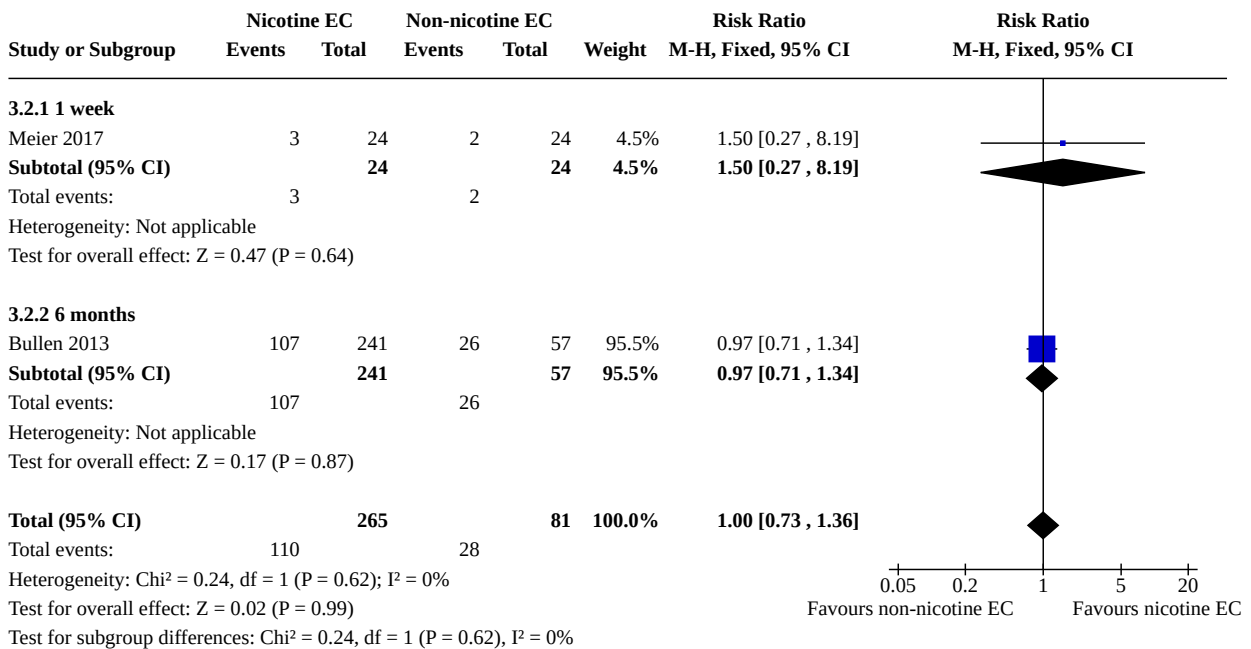
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Smoking cessation	3	802	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.00, 2.92]
3.2 Adverse events	2	346	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.73, 1.36]
3.2.1 1 week	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.27, 8.19]
3.2.2 6 months	1	298	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.71, 1.34]
3.3 Serious adverse events	4	494	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.19]

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
3.3.1 1 week	1	48	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3.2 4 weeks	1	74	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3.3 12 weeks	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.19]
3.3.4 1 year	1	117	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Carbon monoxide (ppm)	2	171	Mean Difference (IV, Fixed, 95% CI)	-2.44 [-3.91, -0.97]
3.4.1 2 weeks	1	25	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-3.00, 2.20]
3.4.2 12 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-5.18, -1.62]
3.5 Heart rate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6 Systolic blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.7 FeNO (ppb)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.7.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.8 FEV1 (l)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.8.1 12 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.9 FVC (l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.9.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.10 FEV1/FVC	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.10.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

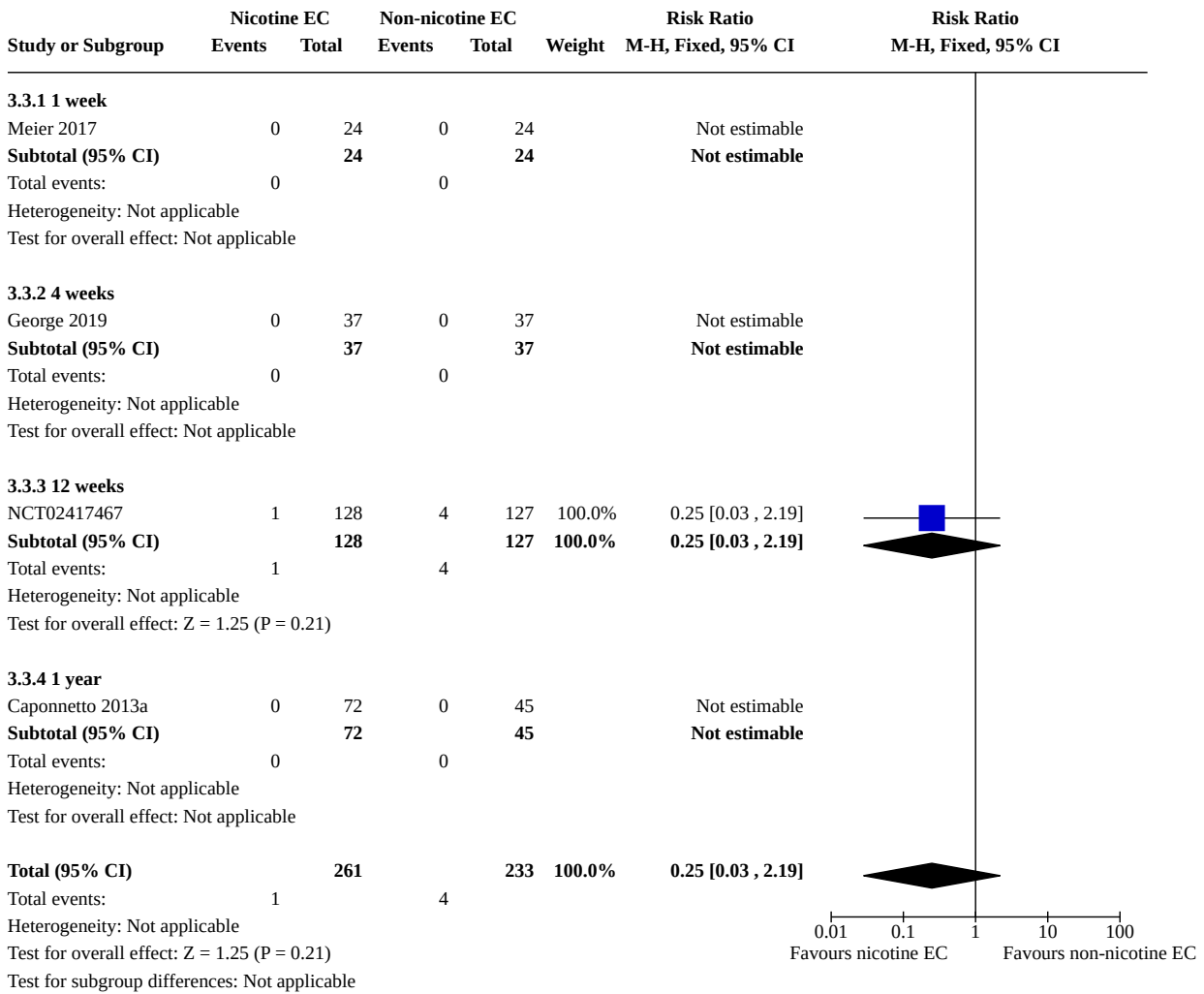
Analysis 3.1. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 1: Smoking cessation



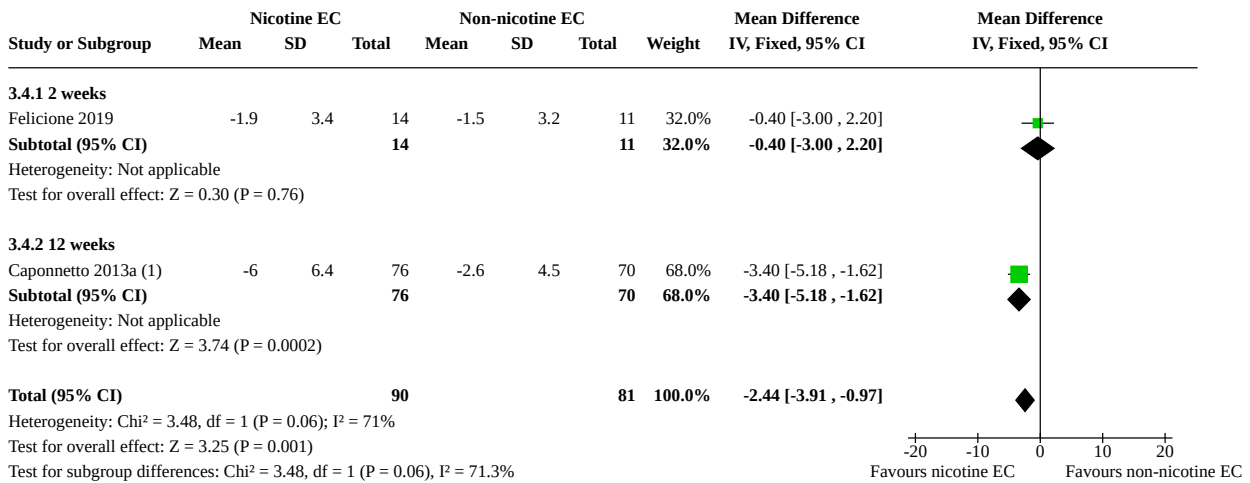
Analysis 3.2. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 2: Adverse events



Analysis 3.3. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 3: Serious adverse events



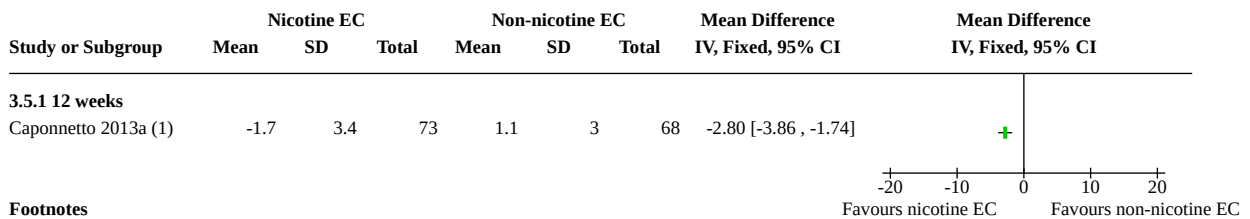
Analysis 3.4. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 4: Carbon monoxide (ppm)



Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

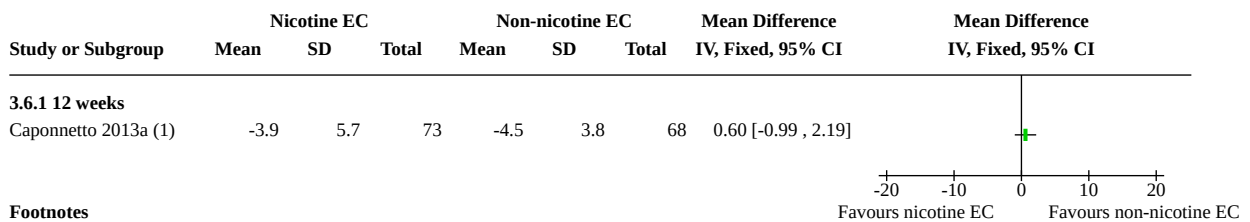
Analysis 3.5. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 5: Heart rate



Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

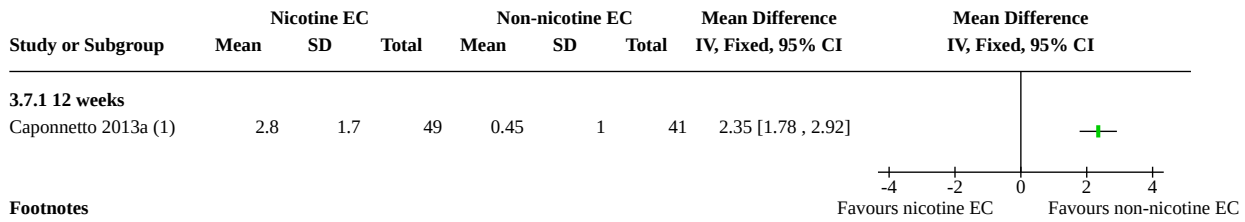
Analysis 3.6. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 6: Systolic blood pressure



Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

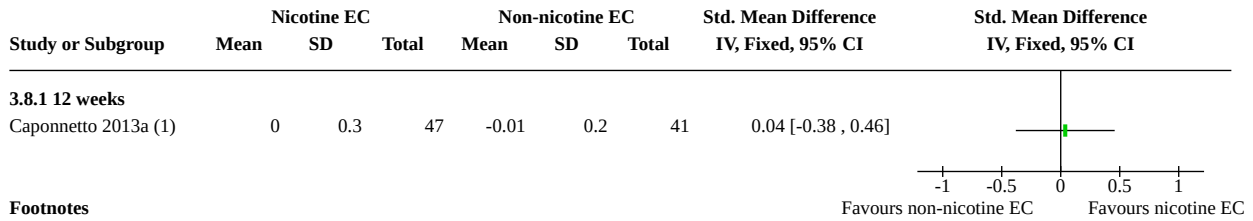
Analysis 3.7. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 7: FeNO (ppb)



Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

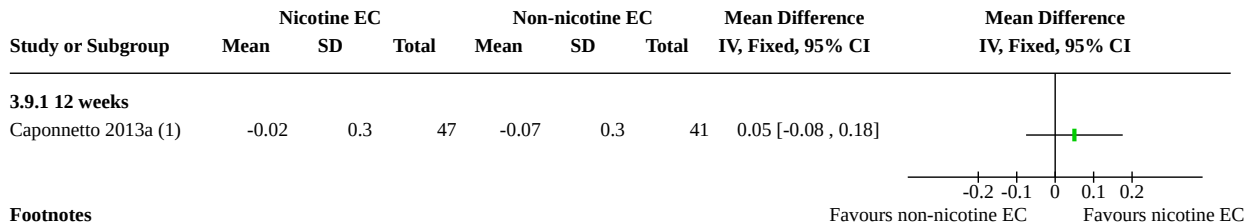
Analysis 3.8. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 8: FEV1 (l)



Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

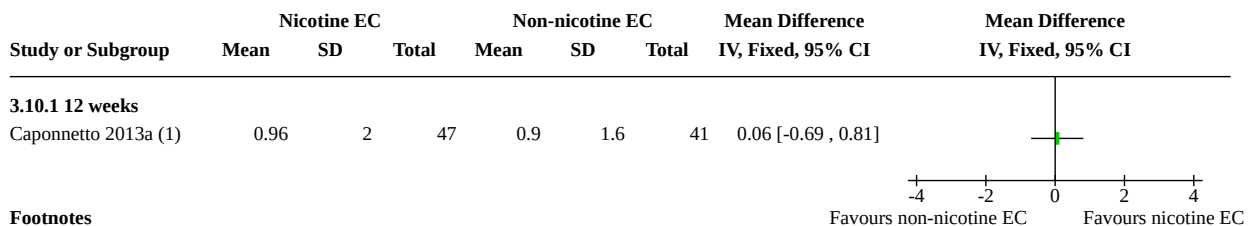
Analysis 3.9. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 9: FVC (l)



Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

Analysis 3.10. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 10: FEV1/FVC



Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

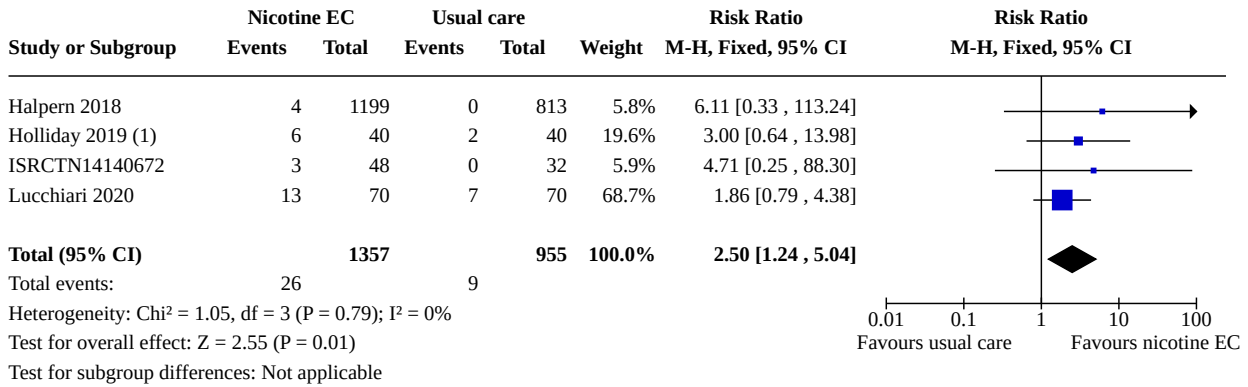
Comparison 4. Nicotine EC versus behavioural support only/no support

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Smoking cessation	4	2312	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [1.24, 5.04]

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Adverse events	3	516	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.04, 1.31]
4.2.1 12 weeks	1	408	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.01, 1.26]
4.2.2 16 weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.67, 2.07]
4.2.3 6 months	1	58	Risk Ratio (M-H, Fixed, 95% CI)	11.00 [0.64, 190.26]
4.3 Serious adverse events	5	842	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.25, 6.96]
4.3.1 4 weeks	1	77	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3.2 12 weeks	2	657	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.25, 6.96]
4.3.3 16 weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3.4 6 months	1	58	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.4 Carbon monoxide (ppm)	5		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.1 3 to 4 weeks	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.2 8 weeks	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.3 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.5 Heart rate (bpm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.5.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6 Systolic blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.7 Blood oxygen saturation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.7.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.8 3-HPMA (SMD)	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.8.1 8 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.8.2 12 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9 NNAL (SMD)	3		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9.1 3 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9.2 8 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
4.9.3 12 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.10 2-HPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.10.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.11 HMPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.11.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.12 PheT (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.12.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.13 CEMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.13.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.14 AAMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.14.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.15 S-PMA (nanograms)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.15.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.16 FVC (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.16.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.17 FEV1 (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.17.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.18 FEF 25-75 (litres/second))	1	387	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.10, 0.30]
4.18.1 12 weeks	1	387	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.10, 0.30]
4.19 PEF 25-75 (litres/minute)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.19.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

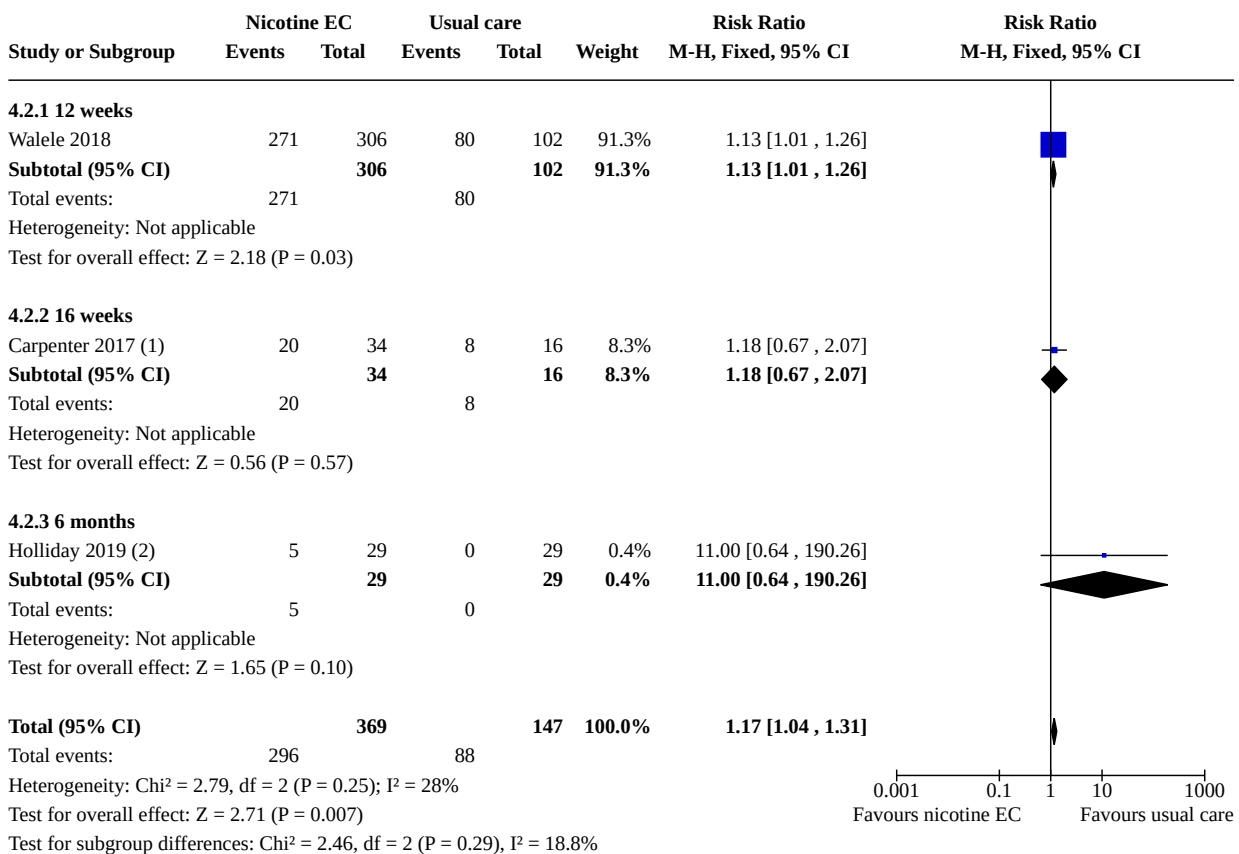
Analysis 4.1. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 1: Smoking cessation



Footnotes

(1) Although participants were given a choice of nicotine concentration including 0 mg, none of the participants chose the non-nicotine e-liquid

Analysis 4.2. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 2: Adverse events

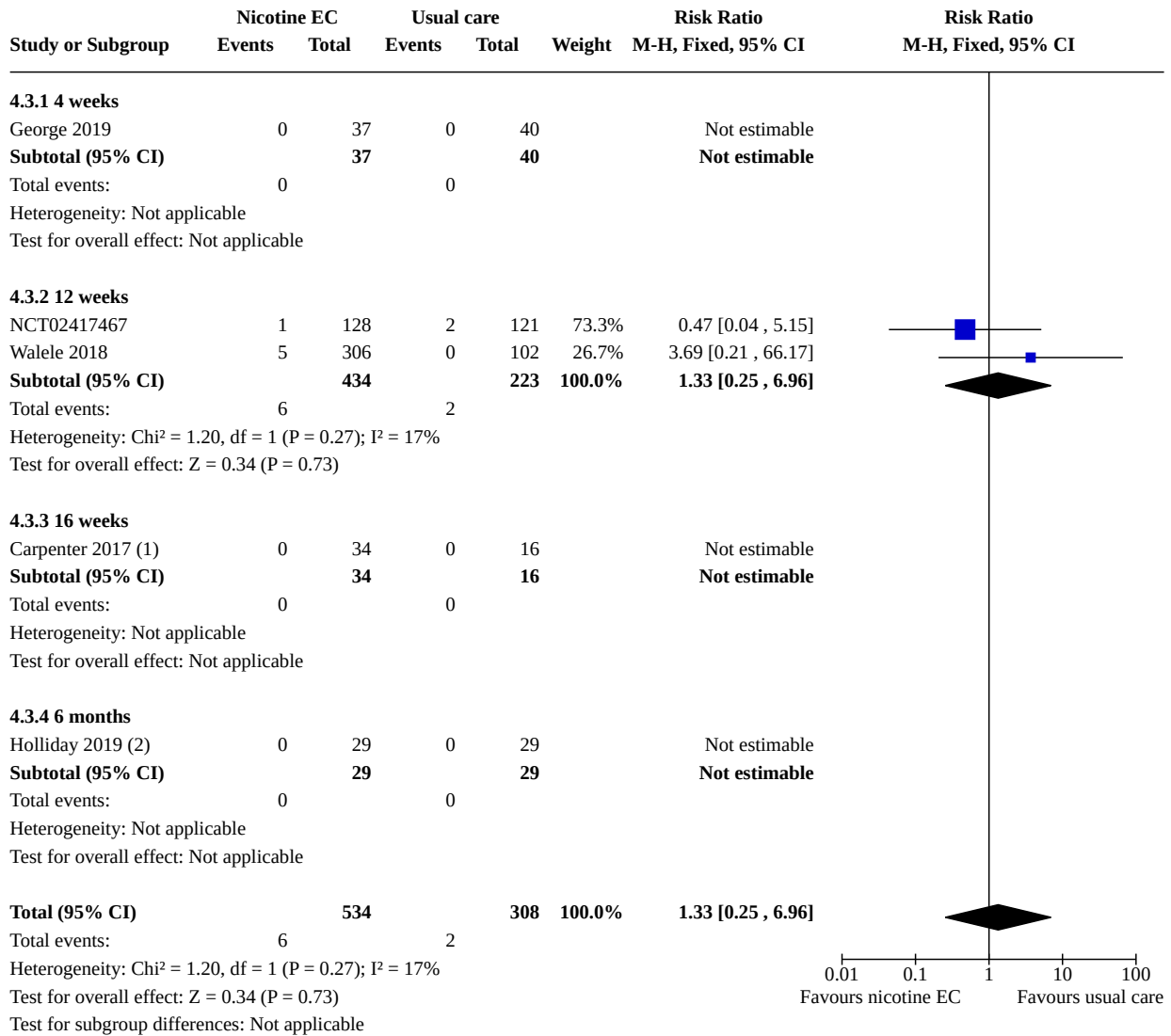


Footnotes

(1) 24mg EC arm included here; 16mg data reported elsewhere

(2) Participants offered choice of nicotine or no-nicotine EC; all chose nicotine-containing EC

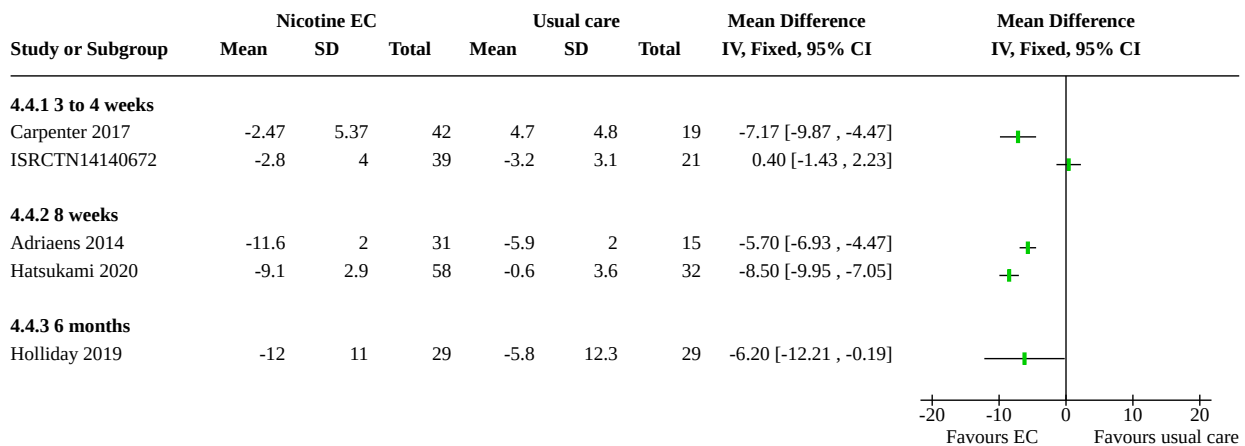
Analysis 4.3. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 3: Serious adverse events



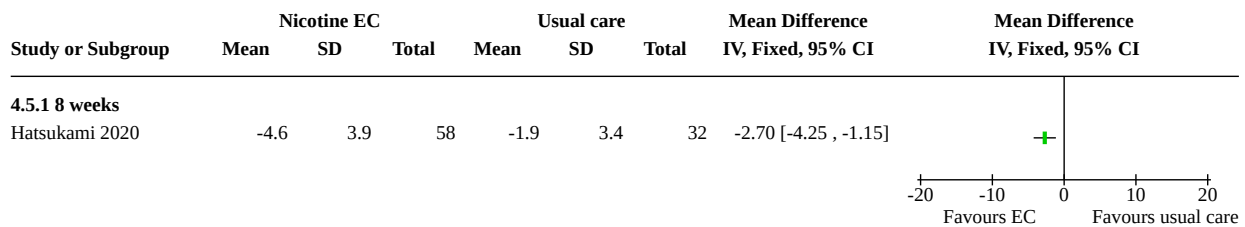
Footnotes

- (1) Data from 24mg arm (0 events in 16mg arm as well)
- (2) Participants offered choice of nicotine or no-nicotine EC; all chose nicotine-containing EC

Analysis 4.4. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 4: Carbon monoxide (ppm)



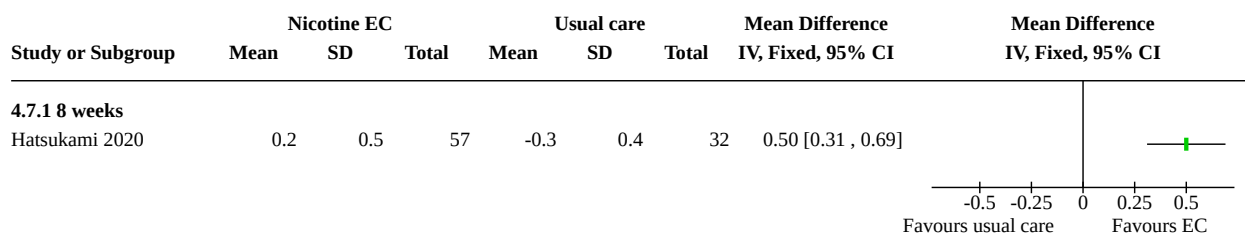
Analysis 4.5. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 5: Heart rate (bpm)



Analysis 4.6. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 6: Systolic blood pressure



Analysis 4.7. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 7: Blood oxygen saturation



Analysis 4.8. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 8: 3-HPMA (SMD)

Study or Subgroup	Nicotine EC			Usual care			Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.8.1 8 weeks								
Hatsukami 2020 (1)	-2681	1523	58	1142	1846	32	-2.31 [-2.86 , -1.75]	
4.8.2 12 weeks								
Walele 2018 (2)	-530	1272.5	284	96	1142.9	100	-0.50 [-0.73 , -0.27]	

Footnotes

- (1) measured as pmol/mg creatinine
- (2) Measured as micrograms

Analysis 4.9. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 9: NNAL (SMD)

Study or Subgroup	Nicotine EC			Usual care			Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.9.1 3 weeks								
Carpenter 2017 (1)	1.59	79.2	41	-21.3	96.5	19	0.27 [-0.28 , 0.81]	
4.9.2 8 weeks								
Hatsukami 2020 (2)	-0.6	0.5	57	-0.2	0.3	31	-0.90 [-1.36 , -0.44]	
4.9.3 12 weeks								
Walele 2018 (3)	-76	189.2	284	6	163.3	100	-0.45 [-0.68 , -0.22]	

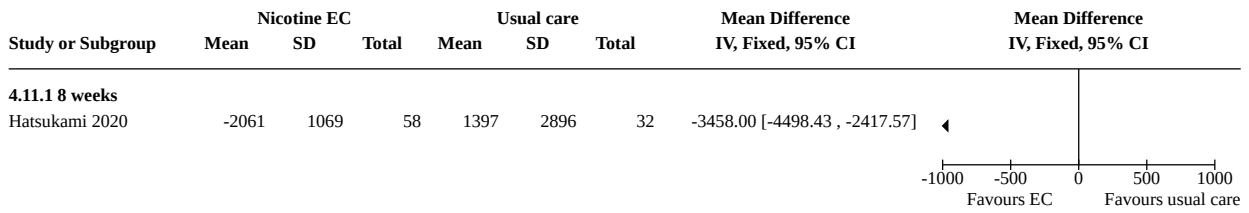
Footnotes

- (1) Measured as pg/ml
- (2) Measured as pmol/mg creatinine
- (3) Measured as nanograms

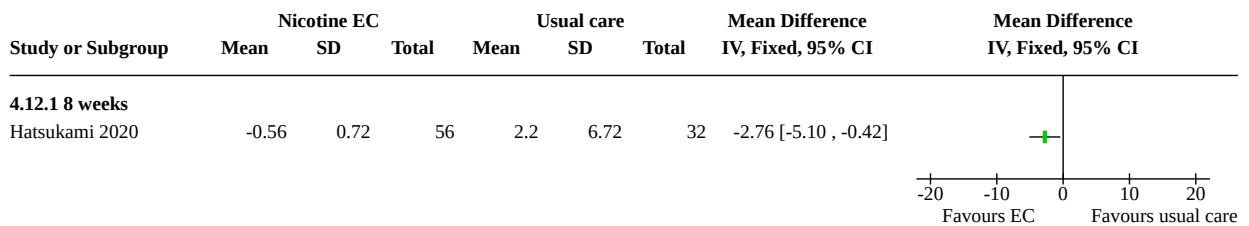
Analysis 4.10. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 10: 2-HPMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC			Usual care			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.10.1 8 weeks								
Hatsukami 2020	-249	525	58	264	1424	32	-513.00 [-1024.55 , -1.45]	

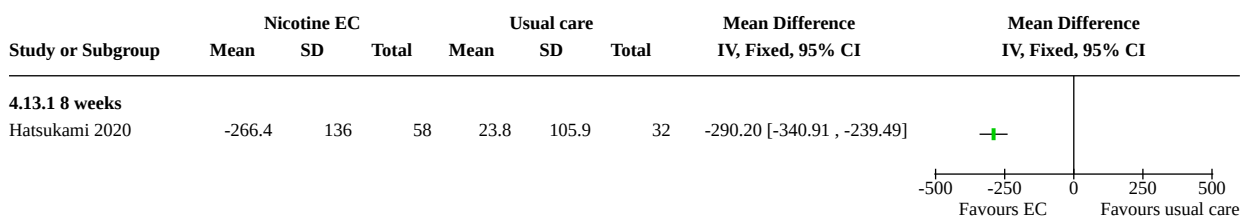
Analysis 4.11. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 11: HMPMA (pmol/mg creatinine)



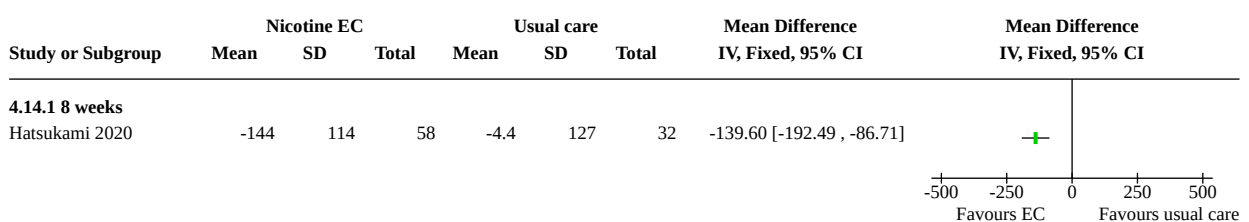
Analysis 4.12. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 12: PheT (pmol/mg creatinine)



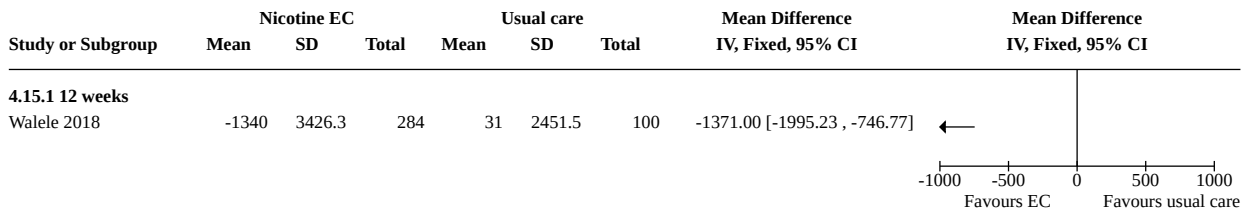
Analysis 4.13. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 13: CEMA (pmol/mg creatinine)



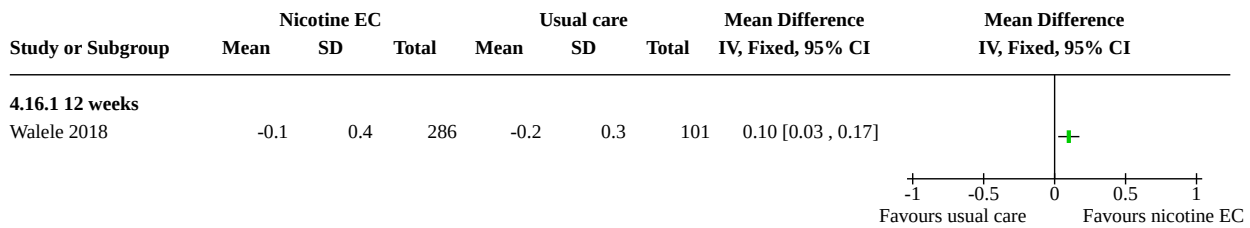
Analysis 4.14. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 14: AAMA (pmol/mg creatinine)



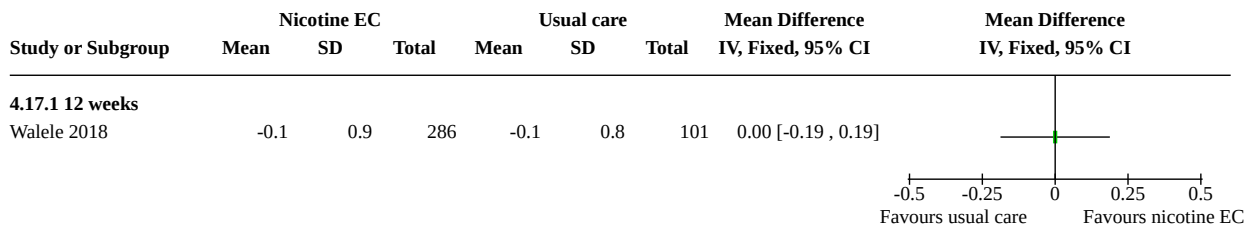
Analysis 4.15. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 15: S-PMA (nanograms)



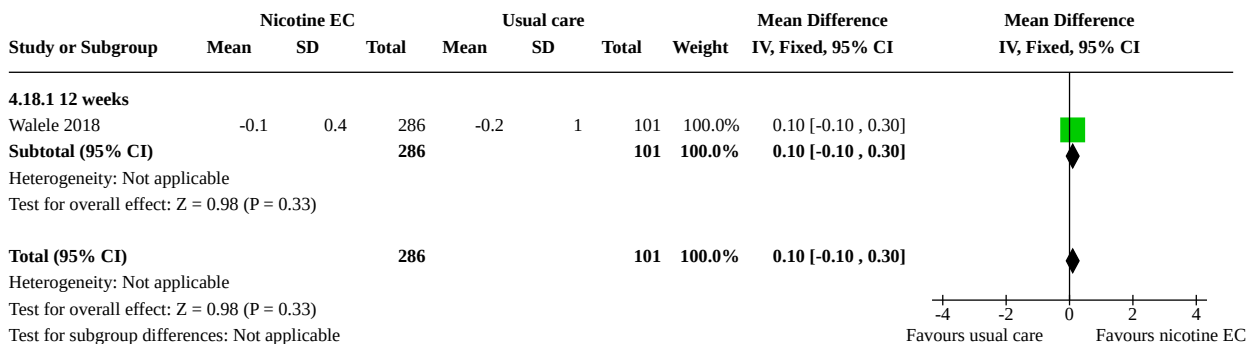
Analysis 4.16. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 16: FVC (litres)



Analysis 4.17. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 17: FEV1 (litres)



Analysis 4.18. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 18: FEF 25-75 (litres/second)



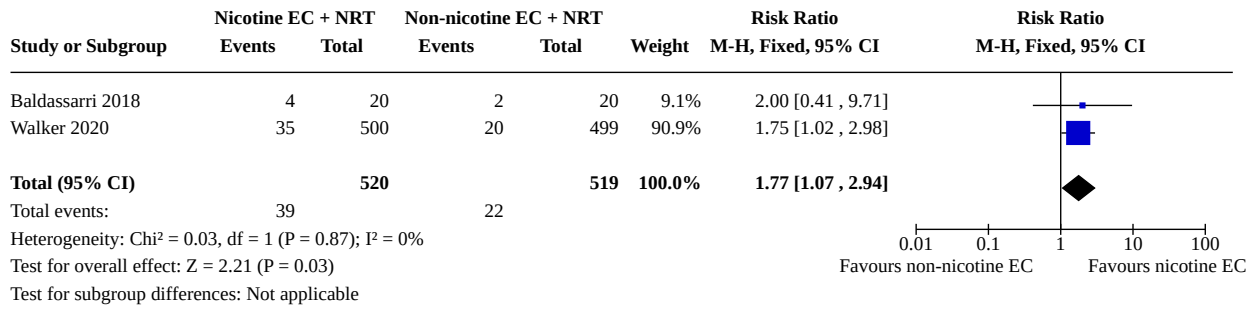
Analysis 4.19. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 19: PEF 25-75 (litres/minute)

Study or Subgroup	Nicotine EC			Usual care			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.19.1 12 weeks Walele 2018	11.7	75.9	286	18.8	103.6	101	-7.10 [-29.14, 14.94]	

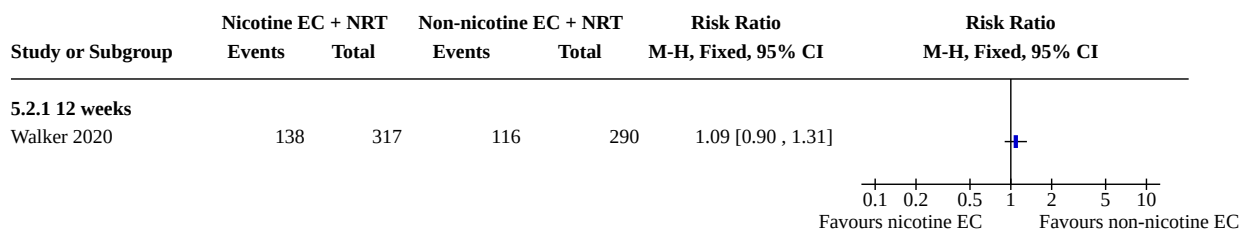
Comparison 5. Nicotine EC + NRT versus non-nicotine EC + NRT

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Smoking cessation	2	1039	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.07, 2.94]
5.2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.2.1 12 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.3 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.3.1 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.4 Carbon monoxide (ppm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.4.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.5 FeNO (ppb)	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-7.23, 6.51]
5.5.1 6 months	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-7.23, 6.51]
5.6 FEV1 (%)	1	32	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.01, 0.10]
5.6.1 6 months	1	32	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.01, 0.10]
5.7 FVC (%)	1	32	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.03, 0.09]
5.7.1 6 months	1	32	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.03, 0.09]

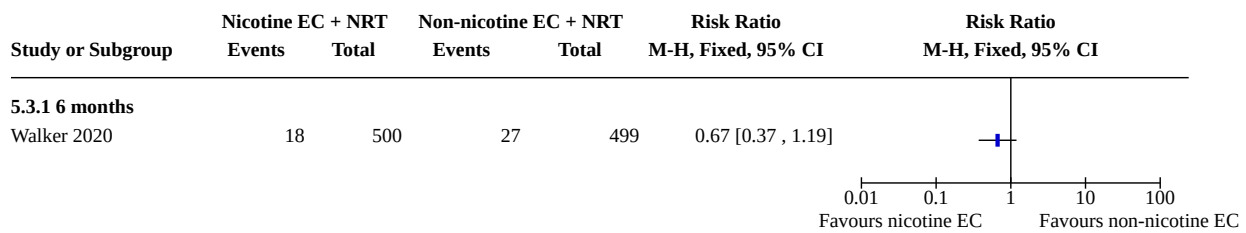
Analysis 5.1. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 1: Smoking cessation



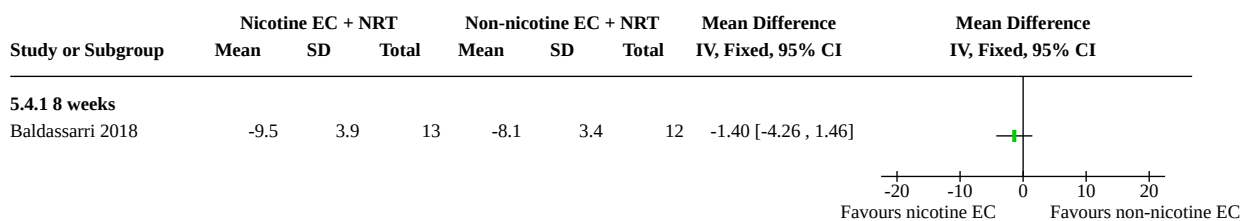
Analysis 5.2. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 2: Adverse events



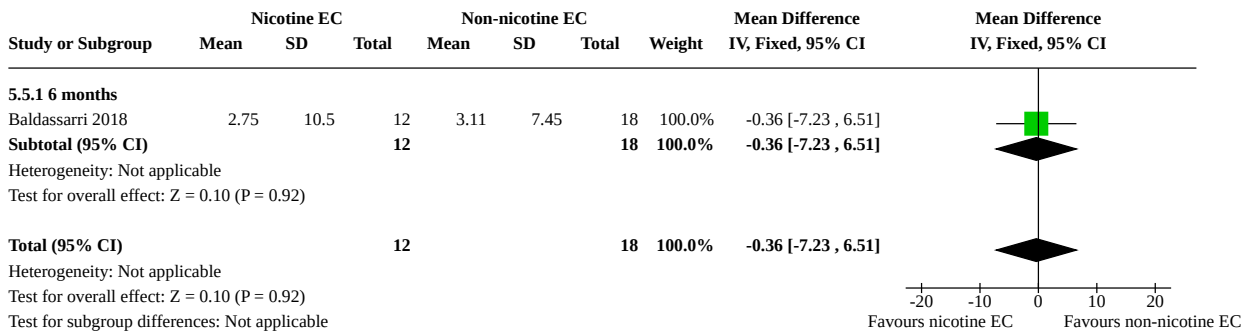
Analysis 5.3. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 3: Serious adverse events



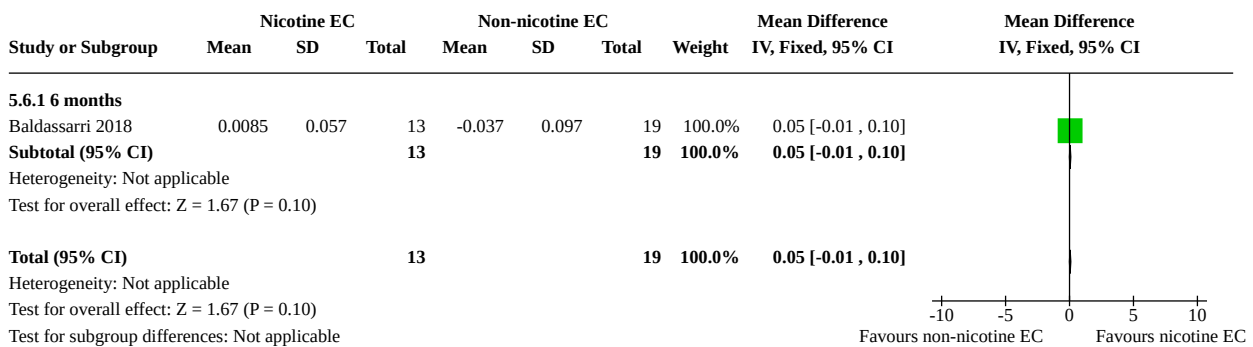
Analysis 5.4. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 4: Carbon monoxide (ppm)



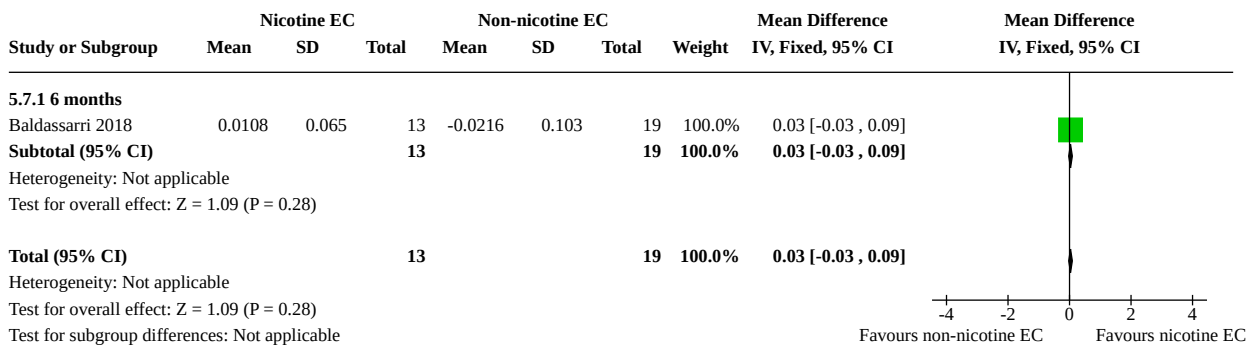
Analysis 5.5. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 5: FeNO (ppb)



Analysis 5.6. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 6: FEV1 (%)



Analysis 5.7. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 7: FVC (%)

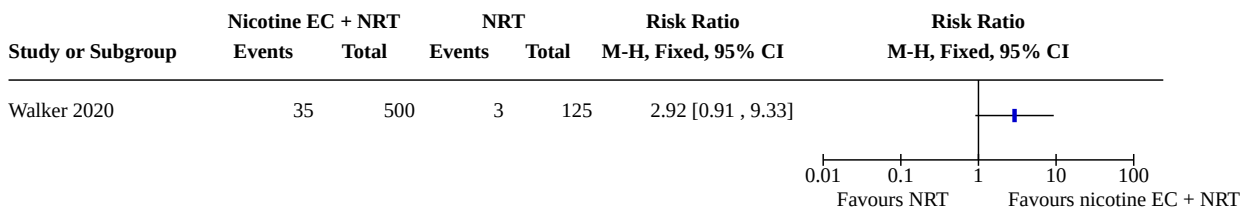


Comparison 6. Nicotine EC + NRT versus NRT

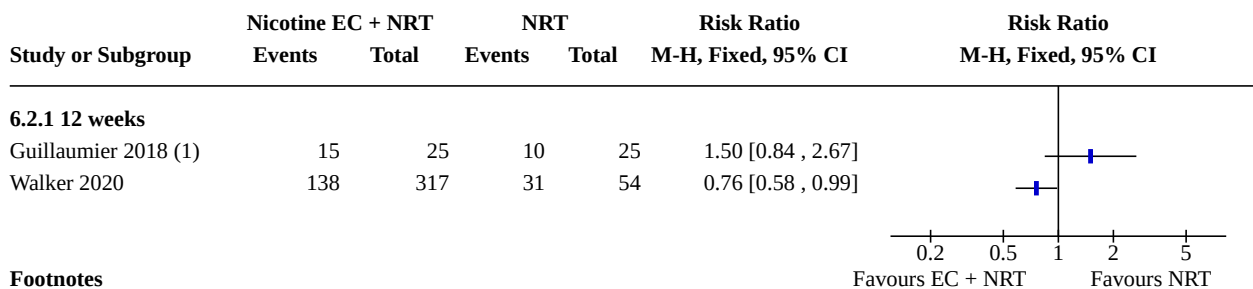
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2.1 12 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Serious adverse events	4	930	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.60, 3.31]
6.3.1 5 weeks	1	7	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3.2 12 weeks	2	298	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [0.48, 9.28]
6.3.3 6 months	1	625	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.39, 3.27]

Analysis 6.1. Comparison 6: Nicotine EC + NRT versus NRT, Outcome 1: Smoking cessation



Analysis 6.2. Comparison 6: Nicotine EC + NRT versus NRT, Outcome 2: Adverse events



Footnotes

(1) NRT not matched between arms

Analysis 6.3. Comparison 6: Nicotine EC + NRT versus NRT, Outcome 3: Serious adverse events

Study or Subgroup	Nicotine EC + NRT		NRT		Weight	Risk Ratio		Risk Ratio	
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI		
6.3.1 5 weeks									
NCT02918630	0	3	0	4		Not estimable			
Subtotal (95% CI)		3		4		Not estimable			
Total events:	0		0						
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									
6.3.2 12 weeks									
Guillaumier 2018 (1)	1	25	0	25	5.6%	3.00 [0.13 , 70.30]			
NCT02417467	4	127	2	121	22.9%	1.91 [0.36 , 10.21]			
Subtotal (95% CI)		152		146	28.5%	2.12 [0.48 , 9.28]			
Total events:	5		2						
Heterogeneity: Chi ² = 0.06, df = 1 (P = 0.80); I ² = 0%									
Test for overall effect: Z = 1.00 (P = 0.32)									
6.3.3 6 months									
Walker 2020	18	500	4	125	71.5%	1.13 [0.39 , 3.27]			
Subtotal (95% CI)		500		125	71.5%	1.13 [0.39 , 3.27]			
Total events:	18		4						
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.22 (P = 0.83)									
Total (95% CI)		655		275	100.0%	1.41 [0.60 , 3.31]			
Total events:	23		6						
Heterogeneity: Chi ² = 0.52, df = 2 (P = 0.77); I ² = 0%									
Test for overall effect: Z = 0.79 (P = 0.43)									
Test for subgroup differences: Chi ² = 0.47, df = 1 (P = 0.50), I ² = 0%									

Footnotes

(1) NRT not matched between arms

Comparison 7. Higher versus lower nicotine content

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Serious adverse events	1	72	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.1.1 1 year	1	72	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 Carbon monoxide (ppm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.2.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.3 Heart rate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.3.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.4 Systolic blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
7.4.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.5 FeNO (ppb)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.5.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.6 FEV1 (l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.6.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.7 FVC (l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.7.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.8 FEV1/FVC	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.8.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

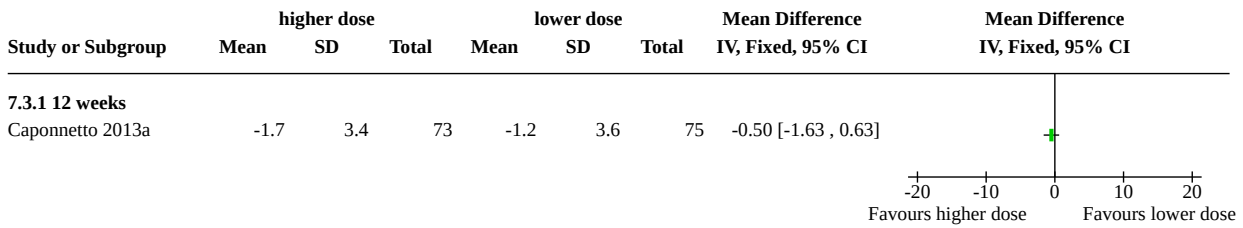
Analysis 7.1. Comparison 7: Higher versus lower nicotine content, Outcome 1: Serious adverse events

Study or Subgroup	Higher nicotine content		Lower nicotine content		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
7.1.1 1 year							
Caponnetto 2013a	0	35	0	37		Not estimable	
Subtotal (95% CI)		35	0	37		Not estimable	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		35	0	37		Not estimable	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

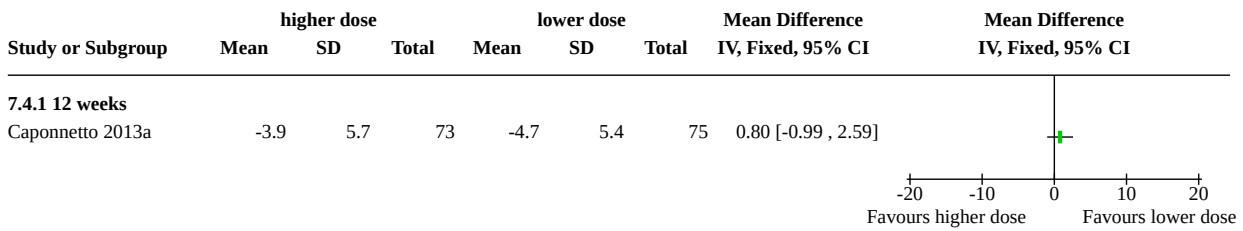
Analysis 7.2. Comparison 7: Higher versus lower nicotine content, Outcome 2: Carbon monoxide (ppm)

Study or Subgroup	higher dose			lower dose			Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
7.2.1 12 weeks								
Caponnetto 2013a	-6	6.4	76	-5.8	3.4	79	-0.20 [-1.82, 1.42]	

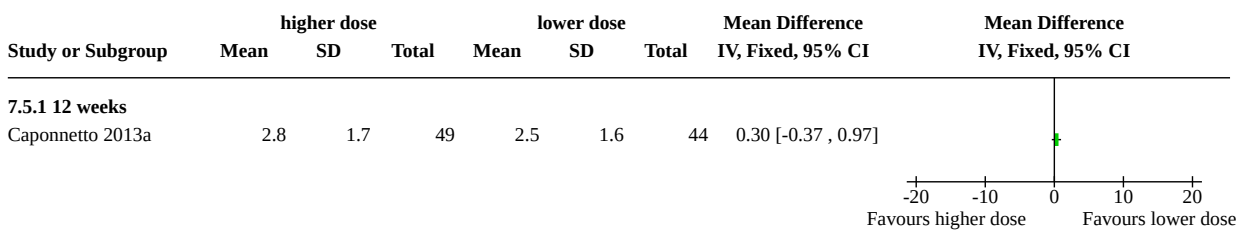
Analysis 7.3. Comparison 7: Higher versus lower nicotine content, Outcome 3: Heart rate



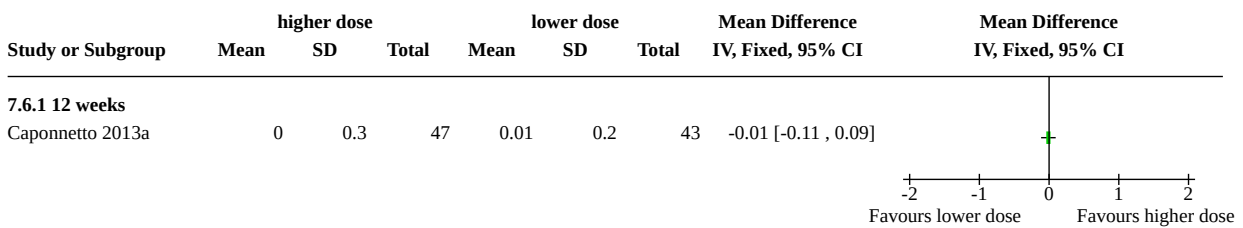
Analysis 7.4. Comparison 7: Higher versus lower nicotine content, Outcome 4: Systolic blood pressure



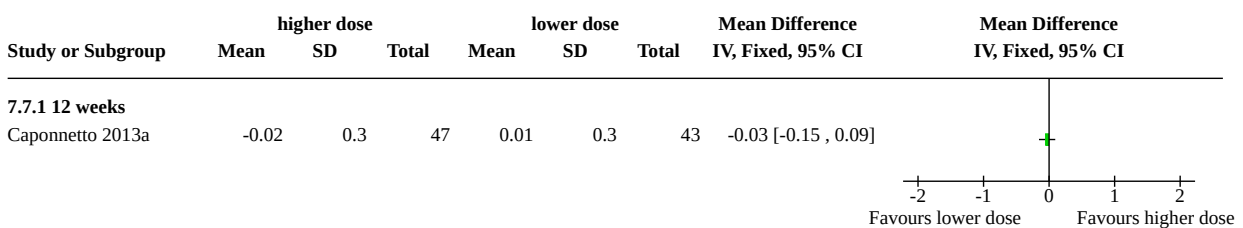
Analysis 7.5. Comparison 7: Higher versus lower nicotine content, Outcome 5: FeNO (ppb)



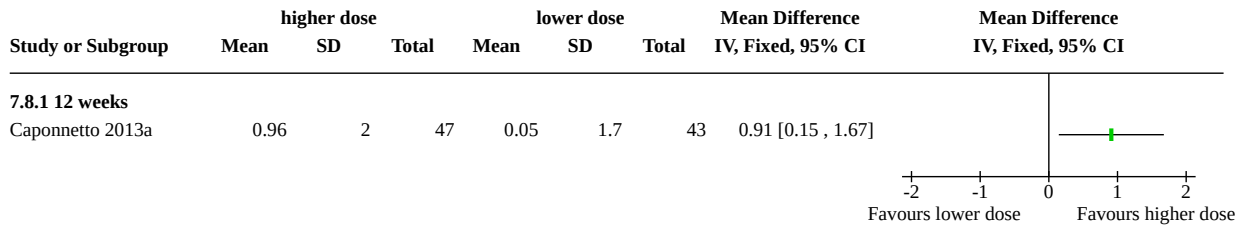
Analysis 7.6. Comparison 7: Higher versus lower nicotine content, Outcome 6: FEV1 (l)



Analysis 7.7. Comparison 7: Higher versus lower nicotine content, Outcome 7: FVC (l)



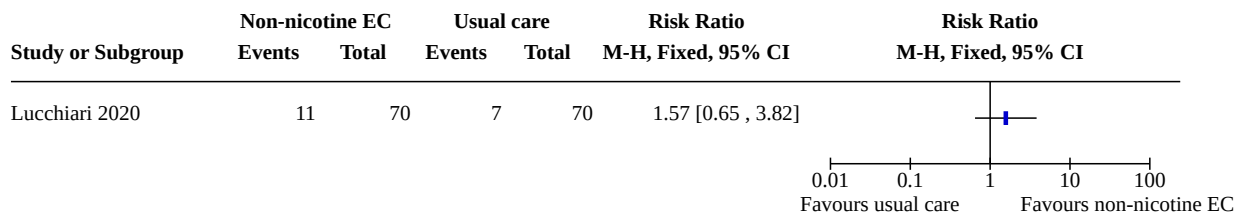
Analysis 7.8. Comparison 7: Higher versus lower nicotine content, Outcome 8: FEV1/FVC



Comparison 8. Non-nicotine EC versus behavioural support only/no support

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

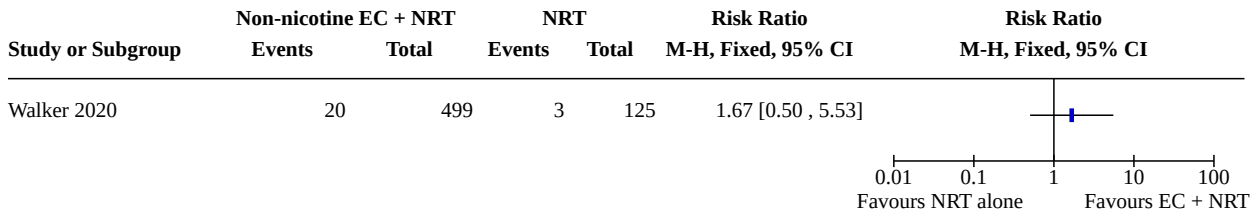
Analysis 8.1. Comparison 8: Non-nicotine EC versus behavioural support only/no support, Outcome 1: Smoking cessation



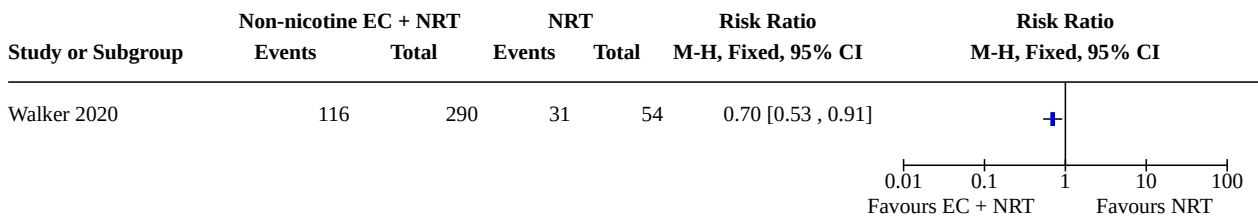
Comparison 9. Non-nicotine EC + NRT versus NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.3 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.3.1 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

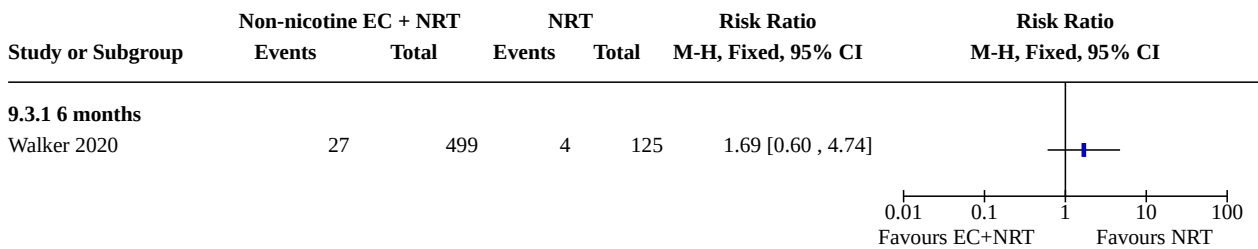
Analysis 9.1. Comparison 9: Non-nicotine EC + NRT versus NRT, Outcome 1: Smoking cessation



Analysis 9.2. Comparison 9: Non-nicotine EC + NRT versus NRT, Outcome 2: Adverse events



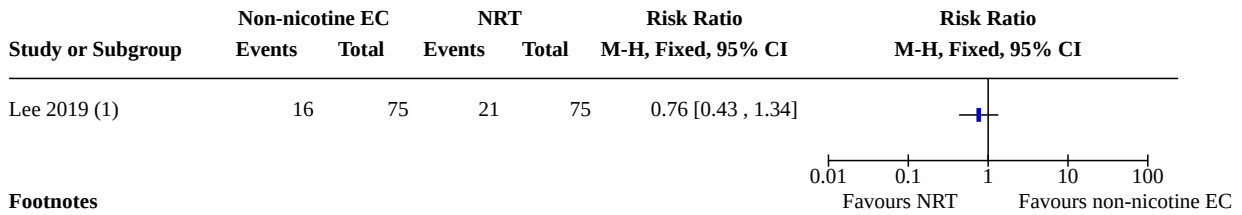
Analysis 9.3. Comparison 9: Non-nicotine EC + NRT versus NRT, Outcome 3: Serious adverse events



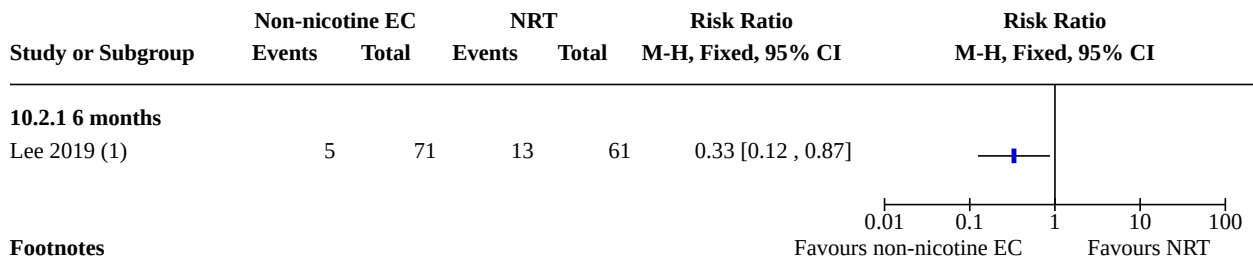
Comparison 10. Non-nicotine EC versus NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2.1 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.3 Serious adverse events	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.3.1 6 months	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

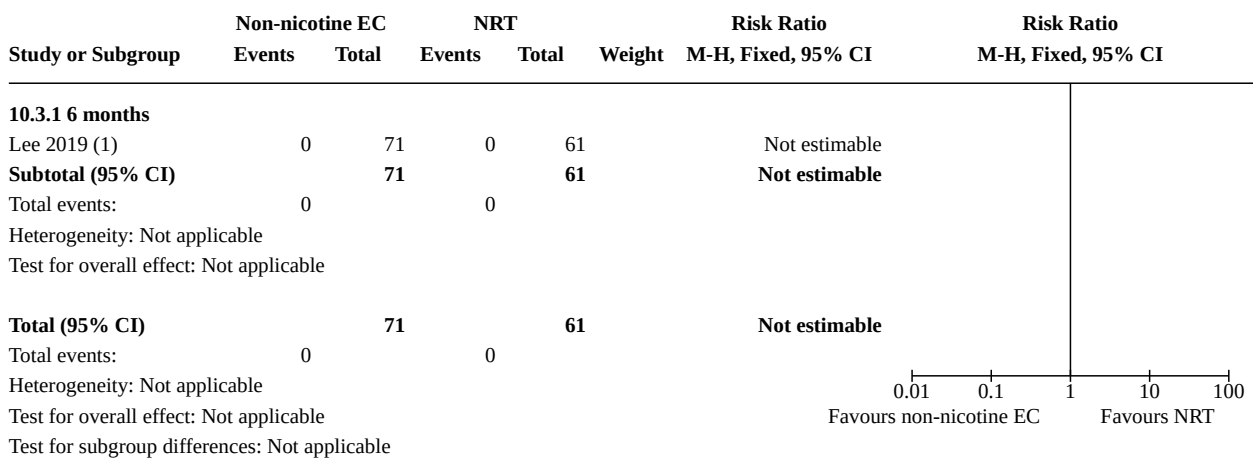
Analysis 10.1. Comparison 10: Non-nicotine EC versus NRT, Outcome 1: Smoking cessation



Analysis 10.2. Comparison 10: Non-nicotine EC versus NRT, Outcome 2: Adverse events



Analysis 10.3. Comparison 10: Non-nicotine EC versus NRT, Outcome 3: Serious adverse events



ADDITIONAL TABLES

Table 1. Summary of proportion of participants abstinent from smoking at 6+ months follow-up: cohort studies of nicotine EC

Study	Motivated or unmotivated to quit smoking?	% abstinent

Table 1. Summary of proportion of participants abstinent from smoking at 6+ months follow-up: cohort studies of nicotine EC (Continued)

Cohort studies		6-month	12-month	18-month	24-month	Notes
Adriaens 2014 ^a	Unmotivated to quit	19.6% (10/51)				Data from 8-month follow-up
Bell 2017	"Willing to attempt to quit"	26.6% (8/30)				
Caponnetto 2013b	Unmotivated to quit		14% (2/14)			
Ely 2013 ^b	Motivated to quit	44% (21/48)				
Pacifici 2015	Unmotivated to quit		53% (18/34)			
Polosa 2011	Unmotivated to quit	23% (9/40)		15% (6/40)	13% (5/40)	
Polosa 2014b	Unmotivated to quit	36% (18/50)				
Polosa 2015	Not defined	42% (30/71)	41% (29/71)			

^aTechnically an RCT but observational for purposes of EC analysis.

^bAll participants (N = 48) used an EC, but 16 also used bupropion and 2 used varenicline.

APPENDICES

Appendix 1. Protocol for living systematic review

Justification for 'Living Review' status

Living systematic reviews (LSRs) offer a new approach to updating reviews, in which the review is continually updated by incorporating relevant new evidence as it becomes available (Brooker 2019). Previous versions of this Cochrane Review of electronic cigarettes (EC) for smoking cessation have informed policy worldwide (Hartmann-Boyce 2016; McRobbie 2014). This update has found high degrees of uncertainty (low- and very low-certainty evidence) for most outcomes, due to the small number of included randomized controlled trials, and the resulting imprecision in effect estimates. This means that some conclusions are likely to change substantially as new evidence emerges.

On average, Cochrane reviews are updated every three to four years. For EC, where the evidence base is rapidly evolving, this schedule impedes the ability of the review to provide the most up-to-date evidence to decision-makers. As EC use, availability, and design changes, policymakers are frequently drawing on this review to inform decisions, so it is imperative that it is up-to-date to ensure decisions are being made on the basis of the entirety of the evidence. Regular updates have the potential to strengthen the existing conclusions of the review or to change conclusions where conflicting evidence or evidence on new outcomes emerges (e.g. comparisons between EC and other interventions; longer-term safety data).

Objective of the change to 'Living Review' status

To implement approved Cochrane LSR methods to provide an up-to-date, accessible, engaging and unbiased review of the evidence on the effect and safety of using EC to quit smoking.

LSR methodological considerations

The methods outlined below are specific to maintaining this review of 'Electronic cigarettes for smoking cessation' as an LSR on the Cochrane Library. These methods will be 'active' immediately upon publication of this update. Core review methods, such as the criteria for considering studies in the review and assessment of risks of bias, are unchanged and are detailed in the main body of the review. Below we outline the methods for which specific considerations apply as a result of the change to 'living' status.

Search methods for identification of studies

We will conduct database searches monthly, beginning December 2020. These searches will be of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, and clinical trial registries, as detailed in the main body of the review. The funders of this LSR – Cancer Research UK (CRUK) - already run monthly searches of the EC evidence and so we will work alongside their health information officer to ensure that we are identifying all the relevant literature with our searches. We will review our search strategies on an ongoing basis every 12 months, as indexing terms and keywords may change, and new search filters may be published. Such changes will be managed by input from experienced information specialists.

Selection of studies

We will immediately screen any new citations retrieved by the monthly searches using [Covidence](#), undertaking dual screening of title and abstract, and then full text, by independent review authors. Where we find multiple citations of the same study we will group them into one study record with a single study ID. One review author (AB) will contact corresponding authors of potentially relevant ongoing studies as they are identified and ask them to advise when results are available, or to share early or unpublished data. Based on the information and projected timescales shared, we will contact corresponding authors on an ongoing basis to retrieve new evidence as it becomes available.

Data synthesis

Whenever we identify new studies relevant to the review, we will extract the relevant data and assess risks of bias as detailed in the main body of the review. We will highlight availability of this new evidence on both the Cochrane Library and on our own dedicated website. We will incorporate the new data into meta-analyses and tables in the Revman ([Review Manager 2020](#)) and supplementary data files, and carry out GRADE assessments ([GRADEpro GDT](#)). We will conduct a full update of the review (full incorporation and interpretation of all new data within the review and re-publishing) when the accumulating evidence leads to changes in any one of:

- The direction of effect or clinical significance of the findings for one or more outcomes;
- The certainty (e.g. GRADE rating) of one or more outcomes;
- The availability of studies investigating new settings, populations, interventions, comparisons or outcomes.

Formal sequential meta-analysis approaches will not be used for updated meta-analyses, in line with Cochrane guidance for LSRs.

Future updates of review methods

The LSR approach acknowledges that reviews may cease to need to be ‘living’ over time, as the review findings become stable, or the question is no longer a priority for decision-makers ([Brooker 2019](#)). Eighteen months into this review’s ‘living’ status (March 2022) we will evaluate the LSR approach, including the likely benefits of and challenges to continuing this methodology for this evidence base, and whether such an approach remains warranted. If the evidence is high certainty for all outcomes and all comparisons at that point, meaning further studies are judged very unlikely to impact the effect estimate, we would consider ceasing living mode for this review. If, as is more likely, some or all outcomes are not yet certain, we will facilitate discussions within the author team and Cochrane, as well as engaging with a wider PPI panel and key decision-makers, e.g. policymakers, in order to determine next steps. If the decision is made to continue in living mode, we will review, and if necessary revise, the living review methods described in this Appendix before continuing.

Appendix 2. Toxins/carcinogen names and abbreviations

Abbreviation	Name
-	1-Hydroxyfluorene
-	1-Hydroxyphenanthrene
-	1-Hydroxypyrene
2-HPMA	2-hydroxypropylmercapturic acid
-	2-Hydroxyfluorene
-	2-Hydroxyphenanthrene
-	2-Naphthol
-	3-, 4-Hydroxyphenanthrenes

(Continued)

3-HPMA	3-hydroxypropylmercapturic acid
-	3-Hydroxyfluorene
AAMA	<i>N</i> -acetyl-S-(carbamoylethyl)-L-cysteine (synonym: 2-carbamoylethylmercapturic acid)
CEMA/CNEMA	2-cyanoethylmercapturic acid; referred to as 'acrylonitrile' in Pulvers 2018
-	Formic acid
HEMA	2-hydroxyethylmercapturic acid
HMPMA/HPMMA	3-hydroxy-1-methyl propylmercapturic acid
MHBMA	2-hydroxy-3-buten-1-ylmercapturic acid
MMA	N-nitrosodimethylamine
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
PheT	Phenanthrene tetraol
PMA	phenylmercapturic acid; referred to as 'benzene' in Pulvers 2018
S-PMA	S-phenylmercapturic acid

Appendix 3. MEDLINE search strategy - 2020 update

1. exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy\$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw.
2. (e-cig\$ or ecig\$ or electr\$ cigar\$ or electronic nicotine).mp. or (vape or vapes or vaporizer or vapourizer or vaporiser or vapouriser or vaper or vapers or vaping).ti,ab. or exp Electronic Nicotine Delivery Systems/
3. (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.
4. exp animals/ not humans.sh.
5. 3 not 4
6. 2 and 5
7. 1 and 2
8. 6 or 7
9. smoking cessation.mp. or exp Smoking Cessation/
10. tobacco cessation.mp. or "Tobacco-Use-Cessation"/
11. (nicotine dependence or tobacco dependence).mp.
12. exp Smoking/th
13. "Tobacco-Use-Disorder"/
14. Smoking reduction/ or Smoking reduction.mp.
15. exp Pipe smoking/ or exp Tobacco smoking/ or exp Tobacco Products/

16. ((quit\$ or stop\$ or ceas\$ or giv\$ or abstain* or abstinen*) adj5 (smoking or smoke* or tobacco)).ti,ab.

17. exp Tobacco/ or exp Nicotine/

18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. 8 and 18

Appendix 4. MEDLINE search strategy - pre-2020

1. e-cig\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. electr\$ cigar\$.mp.
3. electronic nicotine.mp.
4. (vape or vaper or vapers or vaping).ti,ab.
5. 1 OR 2 OR 3 OR 4

Identical terms used for other databases.

Line 4 added to search strategy for 2016 update.

WHAT'S NEW

Date	Event	Description
17 March 2021	Amended	This is a Living Systematic Review. We run and screen searches monthly. Last search date 1st March 2021. In addition to the studies identified from December 2020 to February 2021 we found four new included studies, five new ongoing studies and five papers linked to studies already included in the review. We will incorporate these into the review as part of a future update. The four new included studies are all conference abstracts; three of which were identified from the SRNT 2021 abstract book (SYM2A, SYM2B, PH-353; https://www.srnt.org/page/2021_Meeting). The fourth is available here: http://dx.doi.org/10.1016/j.drugalcdep.2015.07.1091 .

HISTORY

Protocol first published: Issue 11, 2012

Review first published: Issue 12, 2014

Date	Event	Description
4 February 2021	Amended	This is a Living Systematic Review. We run and screen searches monthly. Last search date 1st February 2021. In addition to the studies identified from our December 2020 and January 2021 searches we found one paper linked to a study already included in the review (Lucchiari 2020), and have preliminary results from a study listed as ongoing (Begh 2019). We will incorporate this paper and data into the review as part of a future update.
20 January 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 4th January 2021. In addition to the studies identified from our December 2020 searches we found four new completed studies, one new ongoing study and one paper linked to a study already included in the review. These studies and papers will be incorporated into the review

Date	Event	Description
		at the next update. DOIs for the four new included studies are as follows: Ozga-Hess et al. 2019: 10.1016/j.addbeh.2019.106105 ; Pulvers et al. 2020: 10.1001/jamanetworkopen.2020.26324 ; Scheibein 2020: 10.1186/s12954-020-00406-y ; Yingst et al. 2020: 10.1080/09540121.2019.1687835
15 December 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 1st December 2020. Searches found 3 new completed studies, 11 new ongoing studies and 9 papers linked to studies already included in the review. These studies and papers will be incorporated into the review at the next update. DOIs for the three new included studies are as follows: Czoli et al: 10.1093/ntr/nty174 ; Bonevski et al: 10.1093/ntr/ntaa143 ; Eisenberg et al: 10.1001/jama.2020.18889 .
20 July 2020	New citation required and conclusions have changed	Strength of evidence increased for existing comparisons; new comparisons added
20 July 2020	New search has been performed	New searches run January 2020. 35 new studies added. Living systematic review protocol incorporated
14 December 2016	Amended	Clarification on outcome data from Adriaens - no changes to conclusions
23 June 2016	New search has been performed	Update search run January 2016, 11 new included studies added. Reduction removed as outcome, now covered in Harm Reduction review.
23 June 2016	New citation required but conclusions have not changed	11 new included studies added; no changes to conclusions.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the writing of this review.

For this update, JHB, RB, AT, CN, and NL screened studies and extracted data. JHB and NL entered data for analysis.

As principal investigators of included trials, CB, HMR and PH were not involved with data extraction or 'Risk of bias' assessments.

DECLARATIONS OF INTEREST

RB holds an NIHR grant, however this did not directly fund this current work. She is principal investigator of an ongoing study listed in this review.

CB was principal investigator on the ASCEND e-cigarette trial reported in the Cochrane review and a co-investigator on the ASCEND II trial and several other studies included in the review. CB has provided consultancy for J&J KK (Japan) on NRT products.

ARB's work on this review has been supported by Cancer Research UK Project Award funding. This is not deemed a conflict of interest.

PH provided consultancy for and received research funding from Pfizer, a manufacturer of stop-smoking medications. He was principal investigator on one of the trials included in this review and co-investigator on other relevant studies.

JHB has received support for this work from the Cochrane Review Support Programme and the University of Oxford's Returning Carer's Fund. Neither of these are deemed conflicts of interest.

NL has received payment for lectures on systematic review methodology, and has been an applicant on project funding to carry out priority setting and systematic reviews in the area of tobacco control (NIHR funded). None of this is deemed a conflict of interest.

HM has received honoraria for speaking at smoking cessation educational events and sitting on an advisory board organised by Pfizer.

CN has no known conflicts of interest.

Electronic cigarettes for smoking cessation (Review)

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NR has received royalties from UpToDate, Inc., for chapters on electronic cigarettes and occasional fees from academic hospitals or professional medical societies for lectures on smoking cessation that include discussion of electronic cigarettes. Dr. Rigotti was a member of the committee that produced the 2018 National Academies of Science, Engineering, and Medicine's Consensus Study Report on the Public Health Benefits of E-cigarettes. She was unpaid for this work. Outside the topic of e-cigarettes, Dr. Rigotti has received honoraria from Achieve Life Sciences for consulting about cytisine and travel reimbursement (but no honoraria) from Pfizer for attending advisory boards regarding varenicline.

AT's work on this review has been supported by the Cochrane Review Support Programme and the University of Oxford's Returning Carer's Fund. Neither of these are deemed conflicts of interest.

TT has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Queen Mary University of London, UK
provides salary, office space and library resources for HM and PH
- The University of Auckland, New Zealand
provides salary, office space and library resources for CB
- University of Oxford, UK
Support from Returning Carers' Fund

External sources

- NIHR, UK
Infrastructure award for Cochrane Tobacco Addiction Group and Cochrane Incentive Award

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol did not specify a minimum follow-up period for data on adverse events. As of the 2016 update, we have changed the [Methods](#) section to clarify that we will exclude follow-up data at less than a week.

The original version of this review included reduction as a secondary outcome. The 2016 update removed reduction as an outcome, to bring the review into line with other reviews of cessation treatments produced by the Cochrane Tobacco Addiction Group and to prevent substantial overlap with the update of the Group's review of interventions for harm reduction.

As prespecified in the 2016 update, in the 2020 update we excluded non-intervention studies. In the 2020 update, we also add in an appendix with a protocol setting out our plans to convert this review into a living systematic review in the future.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Cohort Studies; *Electronic Nicotine Delivery Systems; *Nicotine [administration & dosage]; *Nicotinic Agonists [administration & dosage]; Publication Bias; Randomized Controlled Trials as Topic; Smoking [epidemiology]; Smoking Cessation [*methods] [statistics & numerical data]; *Smoking Prevention; Tobacco Use Cessation Devices; Vaping

MeSH check words

Humans; Middle Aged