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Longer-term use of electronic cigarettes when provided as a stop smoking aid: Systematic review with meta-analyses

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ABSTRACT

Moderate certainty evidence supports use of nicotine electronic cigarettes to quit smoking combustible cigarettes. However, there is less certainty regarding how long people continue to use e-cigarettes after smoking cessation attempts. We set out to synthesise data on the proportion of people still using e-cigarettes or other study products at 6 months or longer in studies of e-cigarettes for smoking cessation.

We updated Cochrane searches (November 2021). For the first time, we meta-analysed prevalence of continued e-cigarette use among individuals allocated to e-cigarette conditions, and among those individuals who had successfully quit smoking. We updated meta-analyses comparing proportions continuing product use among individuals allocated to use nicotine e-cigarettes and other treatments.

We included 19 studies ($n = 7787$). The pooled prevalence of continued e-cigarette use at 6 months or longer was 54% (95% CI: 46% to 61%, I^2 86%, $N = 1482$) in participants assigned to e-cigarette conditions. Of participants who had quit combustible cigarettes overall 70% were still using e-cigarettes at six months or longer (95% CI: 53% to 82%, I^2 73%, $N = 215$). Heterogeneity in direction of effect precluded meta-analysis comparing long-term use of nicotine e-cigarettes with NRT. More people were using nicotine e-cigarettes at longest follow-up compared to non-nicotine e-cigarettes, but CIs included no difference (risk ratio 1.15, 95% CI: 0.94 to 1.41, $n = 601$). The levels of continued e-cigarette use observed may reflect the success of e-cigarettes as a quitting tool. Further research is needed to establish drivers of variation in and implications of continued use of e-cigarettes.

1. Introduction

Smoking is the leading cause of preventable death worldwide, accounting for 8 million deaths annually, and motivating national smoke-free goals (World Health Organisation, 2021). The UK aims to be smoke free by 2030 (OHID, Office for Health Improvements and Disparities, 2021) and >50 German public health and civil society organisations are calling on Germany to be smoke free by 2040 (DFKZ, D.K., Deutsches Krebsforschungszentrum, 2021). New Zealand is committed to lowering its national smoking rate to 5% by 2025 (NZ, New Zealand Ministry of Health, 2021). Effective quit aids and less harmful forms of nicotine delivery such as nicotine replacement therapy (NRT) and e-cigarettes have been identified as tools with which to achieve these goals (McNeill et al., 2021).

Abbreviations: EC, Electronic cigarette or e-cigarette; NRT, Nicotine replacement therapy; RCT, Randomised controlled trial; SRNT, Society for Research on nicotine and tobacco.

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E-cigarette use and regulation vary considerably by geographic location. Although e-cigarette use has increased since they came onto the market 15 years ago (ASH, Action on Smoking and Health, 2021; McNeill et al., 2018; McNeill et al., 2021), the overall global prevalence of e-cigarette use is low (World Health Organisation, 2021). E-cigarette sales are projected to rise across the world with the exception of African countries where projected sales are low and remain stable (World Health Organisation, 2021). New designs of e-cigarette devices are being developed. Older cig-a-likes have been replaced by newer pod e-cigarettes that use nicotine salts, disposable e-cigarettes, and refillable tank e-cigarettes; the latter are the most popular type of e-cigarette in England (McNeill et al., 2021). Restrictions on e-cigarette sales, flavors and nicotine content vary globally, as seen with recent flavor bans in some US states. In the UK, nicotine content and advertising are restricted and e-cigarettes are promoted as a harm reduction tool to help people quit combustible cigarettes. In England, e-cigarettes were used by 27% of the adult population in a quit attempt over the past 12 months, and are more popular than nicotine replacement therapy (NRT) which was used by 18% of those trying to quit (McNeill et al., 2021). Of those people who successfully quit smoking long-term, English data show that overall 11% continue to use e-cigarettes, compared to only 3% who continue to use NRT (Kock et al., 2022). In Australia e-cigarettes are only available on prescription (World Health Organisation, 2021). The sale of e-cigarettes is banned in some countries, such as India, Qatar, Lebanon and North Korea (World Health Organisation, 2021).

Findings from our Cochrane review showed moderate certainty evidence that more people successfully quit smoking using nicotine e-cigarette than using NRT or non-nicotine e-cigarettes (Hartmann-Boyce et al., 2021). By 'moderate certainty' we mean that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it will differ. The main limitation of the evidence base is the small number of RCTs, often with low event rates. However, new studies are emerging and may increase certainty regarding the effectiveness of e-cigarettes for quitting combustible cigarette smoking.

Interest has been building into long-term use trajectories of e-cigarettes when used as a combustible cigarette smoking cessation aid. This is of interest for a number of reasons – longer term use of nicotine e-cigarettes compared to other pharmacotherapies may drive their success as a quit smoking aid by preventing relapse to smoking. However, although agreed to be considerably safer than traditional cigarettes, e-cigarettes are not risk free, and concerns remain about the safety of their long-term use, including in people who have quit smoking (McNeill et al., 2021). Little is known about how long people use e-cigarettes when using them as a smoking cessation aid. Long-term use has been observed with NRT products and seems to be dependent on the speed of nicotine delivery. The proportion of clients provided with these products and still using them at one year ranges from negligible rates in the case of patches, through over 5% in the case of oral NRT products, to over 10% in the case of nasal nicotine spray (Hajek et al., 1988; Hajek and McRobbie, 2007; Hajek et al., 1999; Sutherland et al., 1992; West et al., 2000). We wanted to explore if similar patterns were present in e-cigarette users, and therefore set out to review and synthesise available data on the proportion of people using e-cigarettes at six months or longer, in isolation or compared to other smoking cessation aids, following their provision within trials as a stop-smoking aid. We also looked at the proportion of participants still using e-cigarettes among successful quitters in the e-cigarette arms at 6 months or longer. The latter is new and not covered by the Cochrane review; comparisons with other treatments are explored here in more detail than in the Cochrane review (Hartmann-Boyce et al., 2021).

2. Methods

This analysis builds on our living systematic review of e-cigarettes for smoking cessation, with new and updated analyses (Hartmann-Boyce et al., 2021). As this is a systematic review, ethical approval was not required.

2.1. Inclusion criteria

We included randomised controlled trials (RCTs) and randomised crossover trials in which current smokers were randomised to nicotine e-cigarettes as a smoking cessation aid or to a control condition. Throughout this paper 'smoking cessation' refers to the cessation of the use combustible tobacco cigarettes. Eligible controls were as follows: alternative smoking cessation aids including NRT; no intervention; other nicotine e-cigarette; non-nicotine e-cigarettes. Due to a historical paucity of data uncontrolled studies in which all participants were provided with nicotine e-cigarettes were also included; these were combined with data from single arms within RCTs in prevalence analyses (i.e. we did not combine comparative data from RCTs with data from uncontrolled intervention studies) (Hartmann-Boyce et al., 2021). Products could either be provided by the study or bought independently by the participants with the exception of Martinez et al., 2021 where participants used their own e-cigarettes.

To be included in our analyses, studies had to report how many people were still using the study product(s) (e-cigarettes or pharmacotherapy) at six months or more after randomisation. A time period of at least 6 months was chosen as people are advised to use most traditional quitting aids for a period of 12 weeks. Therefore, 6-month use would be considered more sustained long-term use and is a typical measurement point in smoking cessation studies. Where this was not reported but the authors indicated that information on this outcome was collected, we contacted the authors directly for further information.

2.2. Searches

We searched the Cochrane Tobacco Addiction Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, ClinicalTrials.gov, and ICTRP from 2004 (when e-cigarettes first became available) to 1st November 2021. For further details on the search strategy see (Hartmann-Boyce et al., 2021).

We searched the reference lists of eligible studies and contacted authors of known trials and other published e-cigarette studies. We also searched abstracts from the Society for Research on Nicotine and Tobacco (SRNT) 2021 Annual Meeting and the *E*-SRNT September 2021 meeting.

Text was translated and authors contacted where necessary. Two review authors independently screened titles and abstracts, and then full texts of potentially relevant papers. We resolved any disagreements by discussion or with a third reviewer.

2.3. Data analysis

Data were extracted and risk of bias was assessed using a pre-piloted data extraction form and the Cochrane Risk of Bias Tool v1 (Higgins, 2011). We considered risk of selection bias, detection bias and attrition bias. We resolved any disagreements by discussion or with a third review author. We extracted data on: publication details, study design, setting, participant characteristics, intervention and control conditions, primary and secondary outcomes, funding source, and declarations of interest. We characterised e-cigarette type as: cartridge (cig-a-like devices, mainly with relatively low nicotine delivery compared to other types, cartridges designed for single use); refillables (which includes tank systems); and pods (nicotine salts, such as JUUL).

We based the proportion of people continuing to use the study product on the number of people available for follow-up rather than the number randomised. We used complete case data and did not attempt to impute missing values as there is no evidence to support other assumptions.

We calculated prevalence of continued e-cigarette use for the nicotine e-cigarette arms from each study, and pooled these in a random

effects meta-analysis. We also calculated the proportion of people who were abstinent from combustible tobacco cigarettes in the e-cigarette arms and, of these, the proportion that were still using e-cigarettes and pooled this data in a random effects meta-analysis. Prevalence meta-analysis was performed using the 'metaprop' function of the 'meta' package in R version 3.6.1 (Balduzzi and Schwarzer, 2019). Studies were grouped by e-cigarette type. We also updated comparisons from the Cochrane review related to our outcome of interest using RevMan Web: nicotine e-cigarette vs NRT; nicotine e-cigarette vs non-nicotine e-cigarette (Review Manager (RevMan), 2020). For these comparative analyses, fixed effects models were used, as per the original review (Hartmann-Boyce et al., 2021). We present results as risk ratios (RRs) with 95% confidence intervals (CI).

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; we considered a value >50% as evidence of substantial heterogeneity (Higgins et al., 2003).

We narratively report results from studies that could not be included in meta-analyses.

3. Results

Of the 65 studies eligible for the main Cochrane review ($N = 17,277$), 19 ($N = 7797$) reported information on study product use at ⩾6 months follow-up (Fig. 1) and were eligible for inclusion in this review. Authors of five of these studies provided the data on request (Baldassarri et al., 2018; Eisenberg et al., 2020; Lee et al., 2018; Polosa et al., 2011; Russell et al., 2021).

3.1. Characteristics of included studies

Table 1 presents information on study type, e-cigarette intervention type, study country, participant group and motivation to quit. In summary, 13 of the 19 studies were RCTs, one study was a non-randomised cluster trial, and five studies were uncontrolled intervention studies. Six studies took place in the UK, six in USA, three in Italy, two in New Zealand and one in each of Australia, and Canada. In four studies participants were not motivated or planning to quit. In seven studies participants were motivated to quit smoking. One study was carried out among participants who found quitting hard (Myers Smith et al., 2022). Motivation to quit was unclear or not reported in the remaining studies. In Martinez 2021, the participants were dual combustible cigarette and

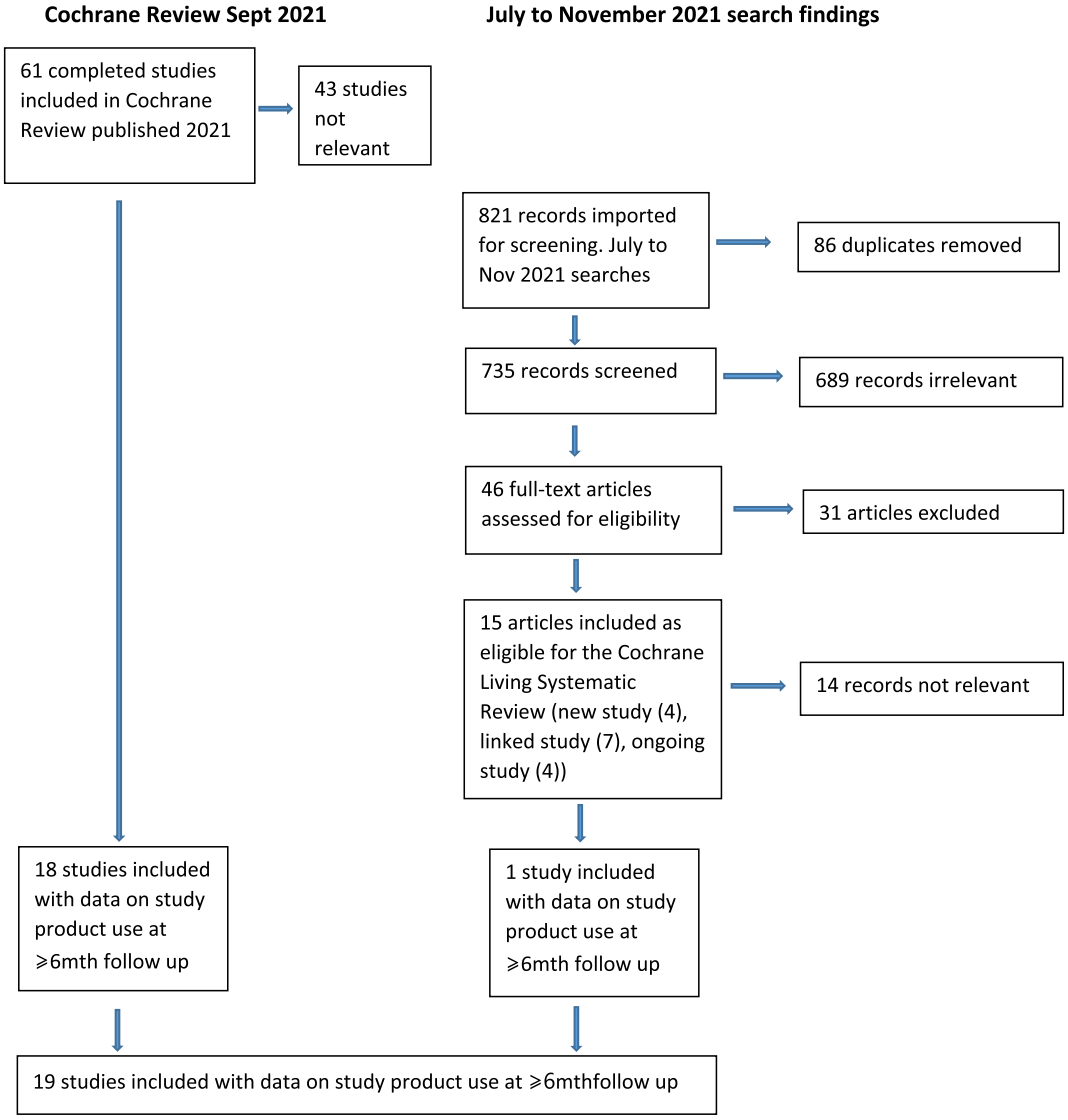

Fig. 1. Flow diagram of studies with data on study product use at longest follow up, ⩾ 6mth.

Table 1
Studies with information on e-cigarette use at 6+ months follow up. Data for the most intensive arm or single arm included.

Study ID	Study design	Comparison	Length of FU in months (from baseline)	Number at FU	% still using EC (n)	Number in arm reported here randomised at baseline	Total study N	Type of EC: Cig-a-like; refillable; pod.	More detailed description of EC	Country	Motivated to quit combustible cigarettes Y/N	Quit rates for tobacco cigarettes in arm reported here (ITT)	Of those who quit tobacco cigarettes % using ECs where available	Of those who did not quit tobacco cigarettes % using ECs where available
Baldassarri et al., 2018	RCT	EC + nicotine patch vs non-nicotine EC + nicotine patch.	6	13	23% (3)	20	40	EC: Refillable	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 (24 mg/ml nicotine strength, 70/30 propylene glycol/ vegetable glycerin, tobacco flavor). (other non-nicotine EC arm not shown)	USA	Y	20% (4/20)	50% (2/4)	5% (1/20)
Begh et al., 2021	RCT	EC vs standard care	8	148	35.14 (52)	164	325	EC: Refillable	Aspire PockeX all-in-one e-cigarette, 2 × 0.6 Ω coils and 1 × 1.2 Ω coil, 3 nicotine e-liquids in 18 mg/ml (blueberry, menthol) and 12 mg/ml (mixed fruit) strength	UK	N	4.3% (7/164)	71.4% (5/7)	
Bell et al., 2017	Pragmatic, uncontrolled, mixed-methods trial	n/a	6	26	92.31 (24)	30	30	EC: Refillable	Innokin Endura T18® vaporiser kit, Innokin Endura T22® vaporiser kit, 4 spare coils, 1 wall charger, 10 × 10-mL bottles of Nicophar® 12 mg nicotine e-liquid. Supplies to last 12 weeks	Australia	Y	26.6% (8/30)		
Bullen et al., 2013	RCT	EC vs nicotine patches vs placebo EC.	6	241	29% (71)	289	657	EC: Cig-a-like	Elusion e-cigarette, nicotine Cartridges containing 10–16 mg nicotine per mL	New Zealand	Y	7.3% (21/ 289)	38% (8/21)	
Caponnetto et al., 2013	Prospective cohort	n/a	12	14	64.29 (9)	14	14	EC: Cig-a-like	"Categoria" e-cigarette, Arbi group Srl, Milano, Italy	Italy	NS	14% (2/14)		
Cobb et al., 2021 [linked to Veldheer 2019] Data from Foulds 2021	RCT	EC vs non-nicotine EC AND higher vs lower nicotine content. (randomised parallel-assignment double-blind trial)	6	130	47.69 (62)	130	390	EC: Treat as refillable [cartridge. eGO e-cigarette second generation EC]	ENDS 36 mg/mL nicotine. EGO e-cigarette. Cartomizers containing 36 mg/ml nicotine provided throughout the intervention period (24 weeks)	USA	N	7.7% (10/ 130) 28 day abstince. 10.8% (14/ 130) 7 day abstinence ITT	86% (12/14)	
Dawkins et al., 2020	Prospective cohort four-Centre pragmatic cluster feasibility	Cluster EC vs usual care (written information,	6	35	77.14 (27)	48	80	EC: Refillable	Aspire PockeX (tank style), choice of 3 flavors (fruit, menthol, tobacco) and 2 nicotine strengths	UK	People interested in using EC to quit were eligible,	6.25% (3/48)	NS	

(*continued on next page*)

Table 1 (*continued*)

Study ID	Study design	Comparison	Length of FU in months (from baseline)	Number at FU	% still using EC (n)	Number in arm reported here randomised at baseline	Total study N	Type of EC: Cig-a-like; refillable; pod.	More detailed description of EC	Country	Motivated to quit combustible cigarettes Y/N	Quit rates for tobacco cigarettes in arm reported here (ITT)	Of those who quit tobacco cigarettes % using ECs where available	Of those who did not quit tobacco cigarettes % using ECs where available
	trial. Non randomised	signposting to stop smoking services).							(12 mg/mL or 18 mg/mL). (EC provided once with e-liquid provided 1 x wk. for 4 weeks)		but 'did not need to be motivated to quit.'			
Eisenberg et al., 2020	RCT	3 arm RCT: EC + counselling vs non-nicotine EC + counselling vs counselling (control).	6	100	37 (37)	128	376	EC: Cig-a-like	Rechargeable base with prefilled, disposable, tobacco-flavored liquid cartridges (15 or 0 mg nicotine/mL), which were produced specifically for use in clinical studies (purchased from NJOY Inc., Scottsdale, Arizona). 21 cartridges at baseline with additional cartridges supplied as needed.	Canada	Y	17.2% (22/128)		
Ely, 2013	Prospective cohort	n/a	6	44	45.46 (20)	48	48	EC: Cig-a-like	Participants were provided with written information on "blu cig" and "smoke tip" (the two e- brands recommended for this program)	USA	Y	44% (21/48)	33% (7/21)	
Hajek et al., 2019	RCT	EC vs NRT	12	356	48.60 (173)	439	886	EC: Refillable	Starter pack (1 kit, aspire UK) provided along with 30 ml bottle of tobacco Royale flavor e-liquid, concentration 18 mg/ml.	UK	NS	18% (79/439)	80% (63/79)	
Holliday et al., 2019	RCT	EC vs control	6	29	72.4 (21)	40	80	EC: Refillable	(Vype eTank clearomizer). Provided with an approximately 2-week supply of e-liquid (20 ml) with a choice of flavor (blended tobacco, crisp mint, dark cherry and Vpure (flavorless)) and nicotine strength (0 mg/ml, 6 mg/ml, 12 mg/ml, 18 mg/ml)	UK	NS	15% (6/40)		
Lee et al., 2018	Randomised parallel-assignment double-blind pilot trial	EC vs nicotine patches	6	18	16.67 (3)	20	30	EC: Cig-a-like	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	USA	NS	25% (5/20)		
Martinez et al., 2021	RCT	No self-help, generic self-help, or self-help	24	361	67.60	575	2896	EC: Participants	ASSESS. Participants used their own type and brand of EC. Participants were	USA	Did not select for this. 26% were planning to	40%		

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Table 1 (*continued*)

Study ID	Study design	Comparison	Length of FU in months (from baseline)	Number at FU	% still using EC (n)	Number in arm reported here randomised at baseline	Total study N	Type of EC: Cig-a-like; refillable; pod.	More detailed description of EC	Country	Motivated to quit combustible cigarettes Y/N	Quit rates for tobacco cigarettes in arm reported here (ITT)	Of those who quit tobacco cigarettes % using ECs where available	Of those who did not quit tobacco cigarettes % using ECs where available
		instructing use of EC as a quit smoking aid						own type and brand of EC	dual users of nicotine EC and combustible tobacco cigarettes.		quit in next 30 days.			
Myers Smith et al., 2022	RCT	EC vs NRT	6	60	53.33 (32)	68	135	EC: Refillable	Refillable EC products (Innokin T18E, Smok, and TECC mini with variable voltage). Instructed to obtain one of these, or another product of their choice, together with initial samples of e-liquid with the strength and flavor of their choice, either via a voucher for up to £40 at a local vape shop that agreed to provide this service, or via other suppliers, and claim a refund against their receipt of up to £40.	UK	Study participants find quitting difficult	19.1% (13/68)	84.6% (11/13)	
Pacifici et al., 2015	Uncontrolled pre-post pilot study	n/a	8	34	76.47 (26)	34	34	EC: Refillable	AVATAR device, battery 550 mAh/3.9 V, W: 7.8, cartomizer with 2, 2 Ω 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 flavors freely chosen by each participant	Italy	N	52.9% (18/34)	100% (18/18)	
Polosa et al., 2011	Prospective cohort	n/a	6	27	81.48 (22)	40	40	EC: Cig-a-like	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	Italy	N	22.5% (9/40)	66.67% (6/9)	
Pulvers et al., 2020	RCT	EC vs continued smoking	6	96	57.29 (55)	125	186	EC: Pod	JUUL (5% nicotine); choice of flavors (menthol, mango, cool mint, Virginia tobacco); given 1 pod per pack of cigarettes; given a 2-week	USA	Y	26.4% (33/125)	69.7% (23/33)	25.6% (32/125)

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Table 1 (*continued*)

Study ID	Study design	Comparison	Length of FU in months (from baseline)	Number at FU	% still using EC (n)	Number in arm reported here randomised at baseline	Total study N	Type of EC: Cig-a-like; refillable; pod.	More detailed description of EC	Country	Motivated to quit combustible cigarettes Y/N	Quit rates for tobacco cigarettes in arm reported here (ITT)	Of those who quit tobacco cigarettes % using ECs where available	Of those who did not quit tobacco cigarettes % using ECs where available
									supply at baseline and then a further 4-week supply at week-2 visit.					
Russell et al., 2021	RCT	EC vs NRT. And nicotine salt EC vs free base nicotine EC	6	124	50 (62)	145	426	EC: Pod	MyBlu +NSPs. A closed system pod e-vapour product (mybluTM) containing nicotine salt e-liquid pods (NSPs) (in other arm not shown here: Freebase nicotine e-liquid pods (FBNPs).	UK	NS	30.3% (44/145)	NR	NR
Walker et al., 2020	RCT	EC with and without nicotine in combination with nicotine patches	6	317	56.47 (179)	500	1124	EC refillable + nicotine patch	A 2nd generation eVOD (Kangertech, Shenzhen GuangDong, China) starter kit, with a choice of 1 of 2 tobacco e-liquid flavors.	New Zealand	Y	7% (35/500)		

Footnote to Table 1: EC refers to nicotine electronic cigarettes. EC = e-cigarette.

e-cigarette users.

Seven studies had additional notable inclusion criteria. Dawkins et al. 2021 included people experiencing homelessness (Dawkins et al., 2020). The participants of the Begh 2021 study had long-term conditions (such as heart disease, hypertension, diabetes, stoke) (Begh et al., 2021). The participants of the study by (Bell et al., 2017) were HIV positive. Lee's 2018 study (Lee et al., 2018) was among veterans awaiting surgery and (Holliday et al., 2019) was among patients with periodontitis. The participants in (Caponnetto et al., 2013) had a diagnosis of schizophrenia. The (Pulvers et al., 2020) study exclusively recruited African American and Latinx participants.

Twelve studies used refillable-type e-cigarettes, six studies cig-a-likes, two studies pods, and in one study, participants used their own e-cigarette devices, (Table 1). One study directly compared a freebase nicotine to a salt-based nicotine device (Russell et al., 2021).

Another study recruited dual users at baseline (Martinez et al., 2021). This study tested a behavioural intervention where participants were provided with self-help booklets, specifically targeting dual users that encouraged them to use their e-cigarettes. This intervention was compared to a generic smoking cessation self-help booklet and an assessment-only study arm.

Of the 19 included studies, three studies received e-cigarette industry support (Caponnetto et al., 2013; Polosa et al., 2011; Russell et al., 2021) and one did not specify their funding source (Ely, 2013). The remainder were conducted independently of the e-cigarette industry.

3.2. *Risk of Bias*

See Table 2 for risk of bias summaries, which presents the review authors' judgements about each risk of bias item for each included study. Overall, we judged five of the included studies to be at low risk of bias (Bullen et al., 2013; Cobb et al., 2021; Hajek et al., 2019; Lee et al., 2018; Martinez et al., 2021) across all domains assessed. Selection bias was only relevant for the studies with more than one arm, of these only (Dawkins et al., 2020) was at high risk of bias and (Russell et al., 2021) was at unclear risk of bias. For attrition bias 17 studies were at low risk of bias, two studies (Baldassarri et al., 2018) and (Dawkins et al., 2020) were at high risk of attrition bias.

3.3. *Use of e-cigarette at six months or longer*

3.3.1. *Prevalence*

We pooled data on proportion of people using e-cigarettes at six months or longer, combining data from the intervention arms of 16 studies ($n = 1482$) in which participants were given a nicotine e-cigarette at study start, and no other pharmacotherapy. We sub-grouped data by e-cigarette type (cig-a-like; refillable e-cigarette; pod).

Baldassarri et al., 2018 and Walker et al., 2020 were not included in the meta-analysis as e-cigarettes were used in combination with nicotine patches. Martinez et al., 2021 was not included as the participants provided their own e-cigarettes. In these three studies >50% of participants in relevant arms were using e-cigarettes at 6 months or longer, (57.5%, 56.5%, and 67.6%, respectively).

The pooled prevalence was 0.54 (95% CI 0.46–0.61, $I^2 = 86\%$, $p < 0.01$), indicating that on average 54% of participants given nicotine e-cigarettes at study start were still using e-cigarettes at six months or longer (Fig. 2). In 9 studies, at least 50% of participants were still using e-cigarettes at 6 months or longer. However, the high statistical heterogeneity detected ($I^2 = 86\%$), unexplained by subgroup analysis or by length of follow-up, indicates substantial unexplained variation between studies. Looking at this by subgroup, data was highly heterogeneous for cig-a-likes ($I^2 = 84\%$, 6 studies, $n = 444$) and for refillable e-cigarettes ($I^2 = 85\%$, 8 studies, $n = 818$).

The prevalence of e-cigarette use at 6+ months ranged from 0.17 (95% CI 0.04–0.41, $n = 18$)(Lee et al., 2018) to 0.92 (95% CI 0.75–0.99,

Table 2
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Study ID	Random sequence generation (selection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)
Baldassarri et al., 2018	Low	Low	High
Begh et al., 2021	Low	Low	Low
Bell et al., 2017	NA	NA	Low
Bullen et al., 2013	Low	Low	Low
Caponnetto et al., 2013	NA	NA	Low
Cobb et al., 2021	Low	Low	Low
Dawkins et al., 2020	High	Low	High
Eisenberg et al., 2020	Low	Low	Low
Ely, 2013	NA	NA	Low
Hajek et al., 2019	Low	Low	Low
Holliday et al., 2019	Low	Low	Low
Lee et al., 2018	Low	Low	Low
Martinez et al., 2021	Low	Low	Low
Myers Smith et al., 2022	Low	Low	Low
Pacifici et al., 2015	NA	NA	Low
Polosa et al., 2011	NA	NA	Low
Pulvers et al., 2020	Low	Low	Low
Russell et al., 2021	Unclear	Low	Low
Walker et al., 2020	Low	Low	Low

Footnote to Table 2: Studies were judged to be at low risk of bias overall if judged low risk across all domains assessed, at high risk of bias if assessed at high risk in one or more domains, and at unclear risk where no domains were judged to be at high risk but at least one was judged to be at unclear risk.

$n = 26$) (Bell et al., 2017). Lee was a small study ($N = 30$) with 18 participants followed up in the cig-a-like e-cigarette arm among veterans awaiting surgery. Bell 2017 used refillable e-cigarettes. Bell 2017 was a one-armed study among people who were HIV positive, and was also small (N = 30 and 26 at longest follow up).

3.3.2. *Quit rates in those using e-cigarettes and proportion using e-cigarettes at six months or longer among successful quitters*

Table 1 presents data on the proportion of people who quit combustible tobacco cigarettes in the e-cigarette arms and, where available, the proportion in this group who are still using e-cigarettes. In the e-cigarette arm quit rates range from 4.3% in Begh et al., 2021 to 52.9% in Pacifici et al., 2015. We pooled data on the proportion of people continuing to use e-cigarettes at 6 months or longer who had quit combustible cigarettes in the nicotine e-cigarette arms, Fig. 3. Data were combined from the intervention arms of 9 studies ($n = 215$) in which participants were given a nicotine e-cigarette at study start, and no other pharmacotherapy. The pooled prevalence was 0.70 (95% CI 0.53–0.82, $I^2 = 73\%$, $p < 0.01$), indicating that on average 70% of participants who had quit combustible cigarettes using a nicotine e-cigarette were still using e-cigarettes at six months or longer (Fig. 3). We sub-grouped data by e-cigarette type (cig-a-like; refillable e-cigarette; pod); proportions were higher in the refillable (81%) and pod (70%) groups than the older cig-a-likes where this was 40%. For the pooled analysis heterogeneity was high $I^2 = 73\%$, however, this appeared to be explained by device type (test for subgroup differences $p < 0.01$), for cig-a-likes the I^2 was 29% (3 studies, $n = 51$) and for refillable e-cigarettes the I^2 value was zero (5 studies, $n = 131$). Only one study contributed to the pod group (Pulvers et al., 2020).

3.3.3. *Direct comparisons*

3.3.3.1. Nicotine e-cigarettes vs NRT. Data from five studies ($n = 1635$) comparing nicotine e-cigarettes with NRT were highly heterogeneous in the direction of effect and hence we do not present pooled results (Fig. 4). In Hajek et al., 2019 (refillable, $n = 698$) more people were using nicotine e-cigarettes than NRT at 12 months, with CIs excluding no difference (RR 8.75, 95% CI 5.58 to 13.75). Similarly, in Myers Smith et al., 2022 (refillable, $n = 106$), and Bullen 2013, (cig-a-like, $n = 465$) more people were using nicotine e-cigarettes than NRT at 6 months, and CIs again excluded no difference (Myers Smith RR 3.64, 95% CI 1.77 to 7.50; Bullen RR 3.75, 95% CI 2.27 to 6.12). By contrast, in Russell et al., 2021 (pod, $n = 348$) found no difference in proportion of participants still using study product at longest follow-up (RR 1.09, 95% CI 0.79 to 1.51; RR 1.00, 95% CI 0.71 to 1.40). One smaller study (Lee et al., 2018) (cig-a-like, $n = 30$) showed a higher proportion of participants still using NRT, but had wide CIs (RR 0.75, 95% CI 0.15 to 3.72.

3.3.3.2. Nicotine e-cigarettes vs non-nicotine e-cigarettes. Three studies compared nicotine e-cigarettes with non-nicotine e-cigarettes (Bullen et al., 2013; Cobb et al., 2021; Eisenberg et al., 2020). Pooled data showed more people using e-cigarettes in the nicotine arm, but CIs were wide and included no difference (RR 1.15, 95% CI 0.94 to 1.41, $n = 601$, $I^2 = 30\%$, $n = 874$, Fig. 5).

The study by Walker et al., 2020 comparing nicotine e-cigarettes + patches with non-nicotine e-cigarettes + patches (excluded from our meta-analysis) showed that more people continued to use nicotine e-cigarettes + patches (56.5%, 179/317) than non-nicotine e-cigarettes + patches (49.4%, 152/308) (Walker et al., 2020). At six months, 40.4% of the patches-only arm ($n = 52$) were still using patches. In the patches + nicotine e-cigarettes group ($n = 317$), 22% were using patches only, 45% were using e-cigarettes only, and 11% were using both patch and e-cigarettes. In the patches + non-nicotine e-cigarettes group ($n = 308$), 29% were still using patches, 36% were using e-cigarettes only, and 13% were using both patches and e-cigarettes.

Baldassarri also compared nicotine e-cigarettes + patches with non-nicotine e-cigarettes + patches, and hence was also excluded from the meta-analysis (Baldassarri et al., 2018). At 6 months 23% (3/13) people continued to use e-cigarettes in the nicotine e-cigarette arm and 47% (9/19) continued to use e-cigarettes in the non-nicotine arm. At 6 months 20% (4/20) in the nicotine e-cigarette arm and 10% (2/20) in the non-nicotine arm had quit combustible cigarettes. In both groups of those who had successfully quit 50% were using e-cigarettes.

3.3.3.3. High- versus low-nicotine e-cigarette devices. Cobb et al., 2021 compared high (36 mg/mL nicotine) to low (8 mg/mL) nicotine content e-cigarettes. More participants in the high nicotine arm 47.7% (62/230) continued to use e-cigarettes at 6 months compared to the low nicotine arm 37.7% (49/130).

3.3.3.4. Nicotine salt e-cigarettes vs freebase nicotine e-cigarettes. One study contributed data to the comparison of nicotine salt e-cigarettes vs freebase nicotine e-cigarettes (Russell et al., 2021). Study product use was similar between arms, as seen in Fig. 4.

3.3.3.5. E-cigarettes versus usual care. Two studies reported on participants using e-cigarettes in both nicotine e-cigarette and usual care arms (where participants were not assigned to specific study products) (Begh et al., 2021; Dawkins et al., 2020). Begh looked at e-cigarette use at 8 months; more people in the e-cigarette arm reported using e-cigarettes

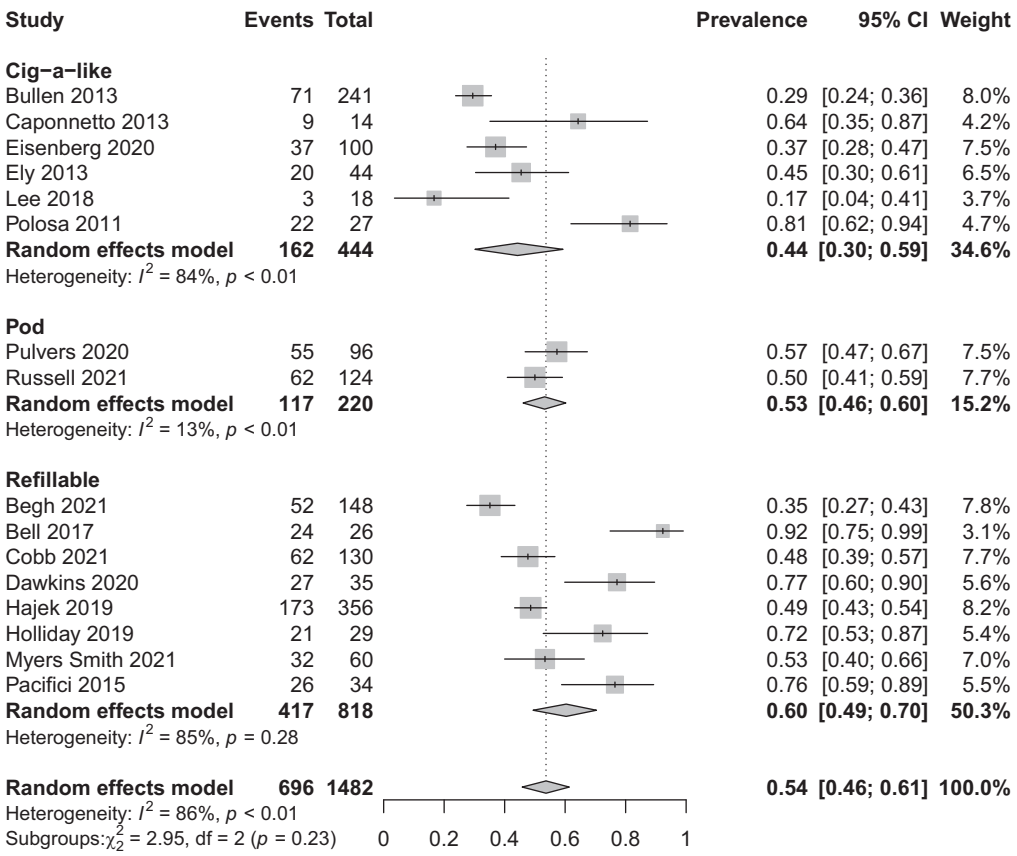

Fig. 2. Prevalence of e-cigarettes use at 6+ months grouped by device type.
Footnote to Fig. 2: Dawkins 2020 was a cluster randomised study, the clustering effect could not be determined, the majority of participants in the e-cigarette group reported here were recruited from the same centre (out of two recruitment sites).

than in the usual care arm (35.1% (52/148) of the e-cigarette arm compared to 9.8% (14/143) in the usual care arm). In Dawkins 2020, at 6 months 27/34 (79.4%) participants followed up in the e-cigarette arm compared to 10/12 (83.3%) participants in the usual care arm were using e-cigarettes.

In Martinez et al., 2021, in which all participants were using e-cigarettes at baseline and participants were randomised to no self-help, generic self-help, or self-help instructing use of e-cigarettes as a quit smoking aid, there was no evidence that the e-cigarettes self-help increased the proportion of people still using e-cigarettes at 24 months (67.6% no self-help, 66.1% generic self-help, 64.1% in the e-cigarette booklet arm).

4. Discussion

This is the most comprehensive review – and to the best of our knowledge, the only meta-analyses to date - of continued e-cigarette use after its provision as a stop-smoking intervention in a trial setting. Nineteen of 65 studies eligible for the Cochrane review of electronic cigarettes for smoking cessation (Hartmann-Boyce et al., 2021) provide data on number of participants still using e-cigarette at six months or longer. Our new meta-analysis including data from 16 of these studies showed that, of people within trials provided with a nicotine e-cigarette for smoking cessation, on average 54% were still using a nicotine e-cigarettes at six months or longer. Our updated meta-analyses of direct comparisons found slightly more people assigned to nicotine e-cigarettes than to non-nicotine e-cigarettes were using e-cigarettes at six months or longer, but CIs were wide and included no difference. Statistical heterogeneity precluded meta-analysis in the comparison of e-cigarettes with NRT, but in three of the five studies, more people in the e-cigarette arm were still using their assigned study product than in the NRT arm. We report that on average 70% of participants who had quit combustible cigarettes using a nicotine e-cigarette were still using e-cigarettes at six months or longer (Fig. 3). Nine studies contributed to this analysis and the observed heterogeneity appeared to be explained by device type, with use higher in newer e-cigarette devices.

A number of limitations need to be considered when interpreting these results. A minority of studies report on the outcome of e-cigarette or study product use at six months or longer follow up, limiting our ability to gain a full understanding of e-cigarette use trajectories after their provision as a stop smoking aid within a trial. In addition, longest follow-up was 24 months, and only one study had this follow-up length (Pacifici et al., 2015). Our main findings are also limited by unexplained statistical heterogeneity. Differences in prevalence of e-cigarettes use were not explained by e-cigarette device type apart from in e-cigarette use among successful quitters. Here, it is unclear if it is differences in e-cigarette device or in some other correlated variable – for example date of study conduct – that could be driving the observed differences. There is also inconsistency in the results for the comparison of e-cigarettes vs NRT, with some studies showing more people using e-cigarettes than NRT at longest follow up and others not showing a difference. This heterogeneity could be driven by many factors, including the heterogeneous populations included in this analysis, for example, differences in motivation to quit. Nicotine delivery and flavors, as well as the intensity and duration behavioural support, may have also influenced results. Further research, in different populations and using different devices, is needed to assess the generalizability of the results presented here – we would anticipate substantial variation in longer-term use based on both user and product characteristics.

Our review also has a number of strengths. We followed Cochrane

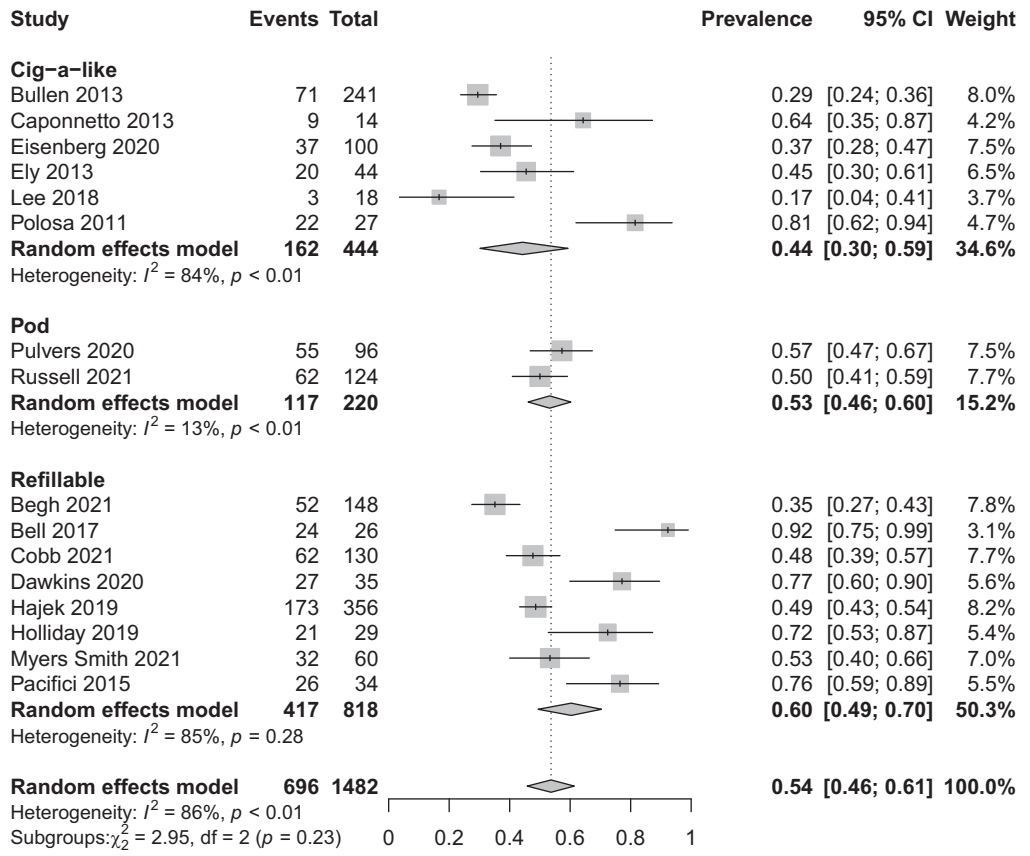

Fig. 3. Prevalence of e-cigarette use at 6+ months among successful quitters in the nicotine e-cigarette arm grouped by device type.

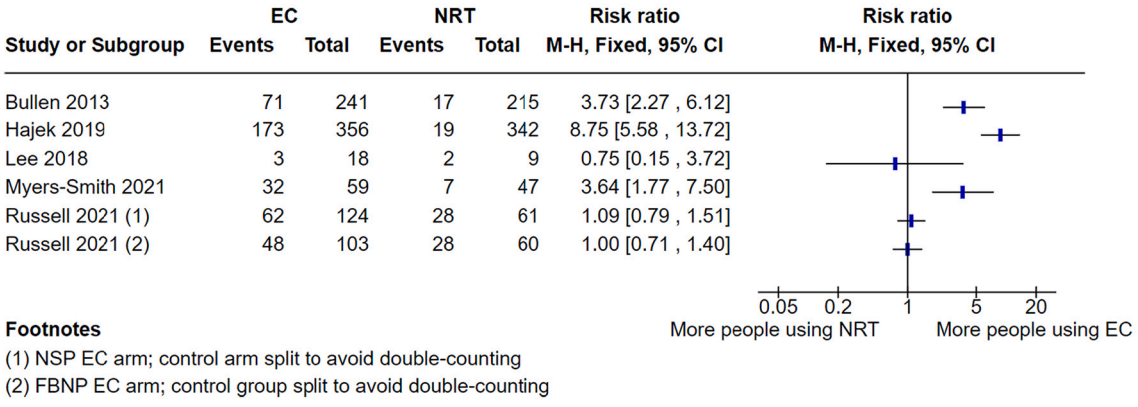

Fig. 4. Continued study product use at 6+ months, nicotine e-cigarettes versus NRT.
Footnote to Fig. 4: One additional study compared to the Cochrane analysis (Myers Smith et al., 2022).

methods and requested and obtained additional unpublished data from authors. Our findings from intervention studies are consistent with observational data. The PATH cohort study found that approximately two-thirds of e-cigarette users who successfully quit smoking continued to use e-cigarettes (Chen et al., 2020). A link with continued e-cigarettes use and attempts to quit combustible cigarettes was demonstrated in a two-year observational study carried out in a nationally representative sample of US smokers, in which long-term use of e-cigarettes was associated with a higher rate of quitting (Zhuang et al., 2016). This was also shown when long-term e-cigarette use was compared with long-term NRT use in a UK cross-sectional and prospective survey, the Smoking Toolkit Study. Here, long-term use of e-cigarettes and long-term use of NRT were found to be almost exclusively among current or ex-smokers (Jackson et al., 2019).

There is moderate certainty evidence that e-cigarettes are more effective in helping people to stop using combustible cigarettes for six months or longer than using NRT or non-nicotine e-cigarettes (Hartmann-Boyce et al., 2021). Longer-term use of nicotine e-cigarettes compared to other stop smoking interventions may in part drive, or at least, reflect their success as a quit smoking aid by preventing relapse to smoking. However, this interpretation must be carefully balanced against concerns regarding the health effects of longer-term e-cigarette use. Though our Cochrane review found no evidence of serious harm from using e-cigarettes as a stop-smoking aid, a key limitation to this evidence is the short length of follow-up in the majority of studies. Expert consensus is that, though considerably safer than combustible

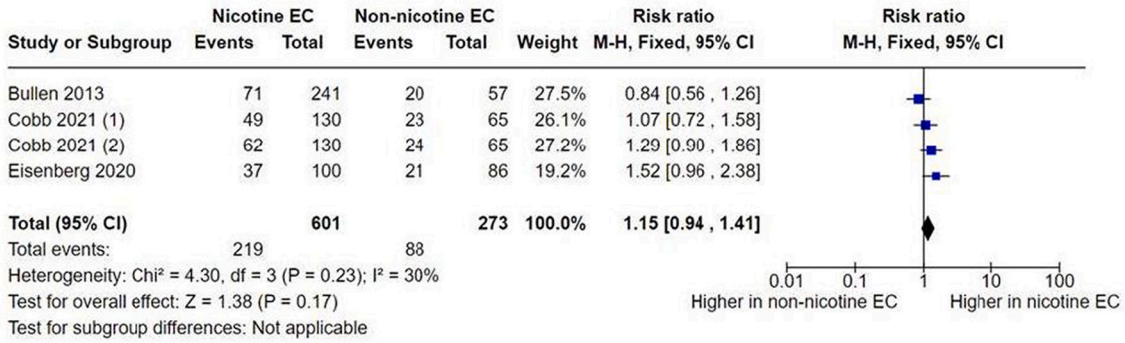

Fig. 5. Continued study product use at 6+ months, nicotine e-cigarettes versus non-nicotine e-cigarettes.
Footnote to Fig. 5: (1) 8 ng/ml; control group split to avoid double-counting. Data provided as ITT with n randomised as denominator; those not followed up assumed to be not using study product (2) 36 mg/ml; control group split to avoid double-counting. Data provided as ITT with n randomised as denominator; those not followed up assumed to be not using study product.
One additional study compared to the Cochrane analysis (Myers Smith et al., 2022).

cigarettes, e-cigarettes are not risk free (McNeill et al., 2021).

The short length of follow up also does not allow comment on whether e-cigarettes will be used for years or indeed for life. Longer-term studies will be needed to provide information on this important outcome as well as the longer-term health implications of continued vaping.

If on-going vaping prevents relapse, this would likely provide a benefit compared to continued use of combustible cigarettes. However, it has also been posited that ongoing vaping could facilitate relapse; more data are needed to investigate this (Barufaldi et al., 2021; Dai and Leventhal, 2019; Everard et al., 2020). Once people have moved away from combustible cigarettes to e-cigarettes, it will be important to monitor whether continued e-cigarette use at six months is a transitional effect, or whether people continue to use e-cigarettes over the following years. Careful consideration needs to be given regarding whether, when, and how to introduce interventions to help this population stop using e-cigarettes without prompting relapse to smoking.

E-cigarettes have a role to play as a harm reduction tool in public health policy and in disease prevention globally. Future studies should measure and report e-cigarette use (e-cigarette registry) (King's College London, 2022). Further research into long-term e-cigarette use should use individual patient data to test whether longer-term use of e-cigarettes is related to smoking cessation, relapse, socially stratifying characteristics, and e-cigarette characteristics including length of use and device type. Comparison of relapse rates in tobacco abstainers who do and do not use e-cigarettes would also be informative. If people continue to use e-cigarettes longer-term it is important to have accurate information on the harms caused by e-cigarettes and research into this is encouraged.

5. Conclusions

In the studies included in this review just over half of people given nicotine e-cigarettes at study start were found to be still using e-cigarettes at six or more months follow up. Of successful quitters, 70% were found to still be using e-cigarettes at six months or more. Future studies need to collect and report data on continued e-cigarette and study product use, including longer-term data beyond six months to assess whether the use of e-cigarettes and other study products is transitional or persistent.

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Author contributions

JHB, NL & ARB conceived the idea. ARB & AT extracted data on use of e-cigarettes at longest follow up. All authors have contributed to data extraction. TF carried out the statistical analysis. ARB and JHB wrote the initial draft and all authors contributed to the writing and editing of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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