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A systematic review of randomized controlled trials and network *meta*-analysis of e-cigarettes for smoking cessation

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ABSTRACT

Aim: E-cigarettes, or nicotine vaping products, are potential smoking cessation aids that provide both nicotine and behavioural substitution for combustible cigarette smoking. This review aims to compare the effectiveness of nicotine e-cigarettes for smoking cessation with licensed nicotine replacement therapies (NRT) and nicotine-free based control conditions by using network *meta*-analysis (NMA).

Methods: We searched PubMed, Web of Science and PsycINFO for randomised controlled trials (RCTs) that allocated individuals to use nicotine e-cigarettes, compared to those that used licensed NRT (e.g., nicotine patches, nicotine gums, etc), or a nicotine-free control condition such as receiving placebo (nicotine-free) e-cigarettes or usual care. We only included studies of healthy individuals who smoked. Furthermore, we identified the latest Cochrane review on NRT and searched NRT trials that were published in similar periods as the e-cigarette trials we identified. NMA was conducted to compare the effect of e-cigarettes on cessation relative to NRT and control condition. Cochrane risk-of-bias tool for randomized trials Version 2 was used to access study bias.

Results: For the e-cigarette trials, our initial search identified 4,717 studies and we included 7 trials for NMA after removal of duplicates, record screening and assessment of eligibility (Total N = 5,674). For NRT trials, our initial search identified 1,014 studies and we included 9 trials that satisfied our inclusion criteria (Total N = 6,080). Results from NMA indicated that participants assigned to use nicotine e-cigarettes were more likely to remain abstinent from smoking than those in the control condition (pooled Risk Ratio (RR) = 2.08, 97.5% CI = [1.39, 3.15]) and those who were assigned to use NRT (pooled RR = 1.49, 97.5% CI = [1.04, 2.14]. There was a moderate heterogeneity between studies (I^2 = 42%). Most of the e-cigarette trials has moderate or high risk of bias.

Conclusion: Smokers assigned to use nicotine e-cigarettes were more likely to remain abstinent from smoking than those assigned to use licensed NRT, and both were more effective than usual care or placebo conditions. More high quality studies are required to ascertain the effect of e-cigarette on smoking cessation due to risk of bias in the included studies.

1. Introduction

Tobacco cigarettes are responsible for more deaths than any other consumer product in human history. Over 8 million people die prematurely each year due to smoking-related diseases (World Health Organization, 2019). Assisting smokers to quit is thus a global health priority. Nicotine replacement therapy products (NRTs) are front-line smoking cessation aids because they increase the success of quit attempts by reducing nicotine cravings without exposing users to the many harmful chemicals present in tobacco smoke. NRTs approved for smoking cessation include nicotine patches, gum, lozenges, mouthspray, an inhalator and intranasal spray. These products are modestly effective

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compared to placebo (Hartmann-Boyce et al., 2018), but many NRT-assisted quit attempts still result in failure (Alpert et al., 2013).

Nicotine-containing electronic cigarettes [e-cigarettes; also known as Nicotine Vaping Products (NVPs)], may be more effective than licensed NRTs because they deliver nicotine to alleviate withdrawal symptoms (Farsalinos et al., 2014) and also provide a similar behavioural and sensory experience as smoking tobacco products. They are now one of the most popular aids for smoking cessation in many high income countries (Caraballo et al., 2017). Smoker enthusiasm for e-cigarettes has sparked debate about their regulation because of concerns that widespread use could renormalise smoking and increase uptake of e-cigarettes and tobacco cigarettes by young people. It will be decades before evidence of the long-term population effects of e-cigarettes can be obtained, but most modelling suggests that there would be an overall public health benefit from access to nicotine e-cigarettes because the increase in smoking cessation would outweigh potential harms of use by youth (Levy et al., 2018). Conclusions drawn from these studies hinge on two key assumptions: (1) nicotine e-cigarettes are substantially less harmful than smoking and (2) nicotine e-cigarettes helps smokers to stop smoking.

Most scientists agree that e-cigarettes are less harmful than smoking due to the lower levels of carcinogens, toxic metals and other harmful and potentially harmful substances in the vapour compared with tobacco smoke (National Academies of Sciences E, Medicine, 2018). The precise difference in harm between e-cigarettes and combustible cigarettes remains unclear. Some health and medical organisations in the UK have estimated that e-cigarettes are likely to be no >5% the risk of smoking tobacco (McNeill et al., 2018), but some opponents claim that the risk could be higher (Glantz & Bareham, 2018).

Evidence for the effectiveness of e-cigarettes for smoking cessation is also debated. Much of the supportive evidence comes from observational cohort and cross-sectional studies (Hartmann-Boyce et al., 2020) in naturalistic settings. These studies are vulnerable to self-selection biases wherein those who use e-cigarettes might differ fundamentally from those who choose to quit smoking in other ways. Statistical adjustment in observational studies may not control for unobserved differences between participants (i.e., residual confounding) and estimates drawn from observational studies are often larger than those obtained from randomised controlled trials (RCT) examining the same exposure-outcome relationship (Hemkens et al., 2016). Therefore, evidence from well-designed RCTs is essential in evaluating the effectiveness of e-cigarettes.

A recent Cochrane systematic review (Hartmann-Boyce et al., 2020) of the effectiveness of e-cigarettes for smoking cessation identified only three peer-reviewed RCTs (Bullen et al., 2013; Hajek et al., 2019; Lee et al., 2019) comparing e-cigarettes with other NRTs and four peer-reviewed RCTs (Bullen et al., 2013; Caponnetto et al., 2013; Halpern et al., 2018; Holliday et al., 2019) that compared e-cigarettes with nicotine-free control conditions. This review concludes that nicotine e-cigarettes are effective for smoking cessation, compared to NRTs and nicotine-free control conditions. Despite a relatively small numbers of trials, separate *meta*-analyses were conducted to compare e-cigarette trials vs other NRTs and to compare e-cigarette trials vs nicotine-free control conditions.

In this paper, we attempt to improve the estimation of the effect of e-cigarettes on smoking cessation by using random-effect network *meta*-analysis (Mills et al., 2013; Schwarzer et al., 2015). This cutting-edge technique allows estimation using one single *meta*-analytic model, and incorporates both direct and indirect evidence for effect estimation. For example, the effect of e-cigarettes vs nicotine-free control conditions on smoking cessation can be estimated through a direct comparsion between e-cigarettes and nicotine-free control condition, and an indirect comparison by firstly comparing the e-cigarettes vs NRTs and then NRTs vs nicotine-free control (see Fig. 1). The latter indirect comparison allows incorporation of estimates from the larger body of research that compares NRTs and nicotine-free control (Hartmann-Boyce et al., 2018). The network *meta*-analytic model then combines estimates from both direct and indirect comparison to form a final estimate. Similarly, the effect of e-cigarettes vs NRTs can be estimated through a direct comparison between e-cigarettes and NRTs and an indirect comparison through e-cigarette vs control and control vs NRTs. Since many more studies can be incorporated in the effect estimation through the inclusion of the indirect pathway, this method could potentially yield more accurate effect estimates.

The key aim of this study is to synthesise the current knowledge about the efficacy of e-cigarettes for smoking cessation from RCTs that compare nicotine e-cigarettes with medicinally licensed NRTs (Hajek et al., 2019) or control conditions, and estimate the effect of e-cigarettes vs NRTs and e-cigarettes vs nicotine-free control condition (nicotine-free e-cigarettes or behavioural counselling) through network *meta*-analysis.

2. Method

2.1. Protocol and registration

The systematic review was conducted in accordance with PRISMA guidelines. This was part of a larger project with a prospectively registered protocol (PROSPEROCRD42020 169 165; Appendix 1). In this review, we focused on the first primary outcome in our protocol, namely, the change of smoking status from smoker to abstinence, and only focused on RCTs. The extracted data and analysis codes are available on GC's GitHub account (https://github.com/gckc123/ecig_quitting_review). All results are fully reproducible in R using the provided data and code.

2.2. Eligibility criteria

2.2.1. Nicotine E-cigarette trials

We included studies published in English that met the following inclusion criteria: 1) Study design: randomised controlled trial; 2) Sample

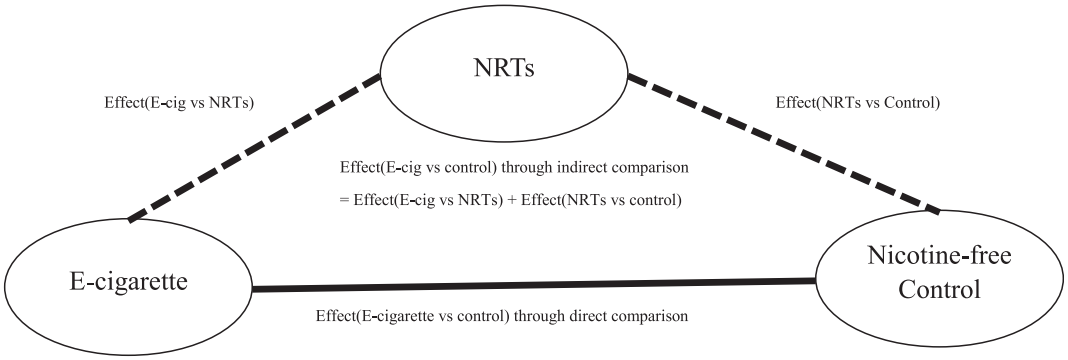

Fig. 1. Conceptual diagram of a network *meta*-analysis comparing E-cigarettes with nicotine-free control condition.

population: general population who smoke tobacco; 3) Exposure and comparison: nicotine e-cigarette compared with nicotine-free control condition (e.g., placebo e-cigarette or non-pharmacological support such as brief counselling) or NRTs (e.g., nicotine patch, nicotine gum, etc.). Trials that compared the additional effect of nicotine e-cigarettes on top of NRT (e-cigarette + NRT vs NRT) were excluded (Walker et al., 2020) because the exposure e-cigarette with NRT is not comparable to most existing trials; 4) Outcome: smoking abstinence at the end of the study (unless the study specified a follow-up time as the primary measurement time point).

2.2.2. Nrt trials

We included studies published in English that met the following inclusion criteria: 1) Study design: randomized controlled trial; 2) Sample population: general population who smoke tobacco; 3) Exposure and comparison: NRT compared with nicotine-free control condition (e.g., placebo or non-pharmacological support such as brief counselling); 4) Outcome: smoking abstinence at the end of the study. The earliest RCT study on e-cigarettes was published in 2013. To ensure comparability, we only included NRT trials that were published since 2013 so that the social context, norms, and culture around smoking would be comparable for both the e-cigarette and NRT trials. Sensitivity analysis was performed by including additional NRT trials published between 2011 and 2013.

2.3. Search strategy

We have done two separate searches, one for Nicotine E-cigarette Trials and one for NRT trails.

2.3.1. Nicotine E-cigarette trials

We searched PubMed, Web of Science and PsycINFO for studies published after 2003 to coincide with the introduction of e-cigarettes in consumer markets. The search was performed between Feburary 2020 and April 2020. The search and data extraction was completed by two authors (DS and AS). The detailed search strategy and search terms are provided in Appendix 5.

2.3.2. Nrt trials

We employed a three-stage search strategy. First, we searched the Cochrane Database of Systematic Reviews for the most recent review on the effectiveness of NRT for smoking cessation (Hartmann-Boyce et al., 2018) and extracted the relevant original studies from this review. Second, we performed additional searches in PubMed and Google Scholar after the search date of this review for: i) systematic reviews and ii) original studies. Third, we searched Google Scholar for studies that cited the Cochrane review. The search and data extraction was completed by two authors (CL and TS; see Appendix 6 for search strategy).

2.4. Risk of bias assessment

Three investigators (DS, TZ and CL) independently assessed the risk of bias for the included studies using the Cochrane risk-of-bias tool for randomized trials Version 2 (Higgins et al., 2011). Studies were assessed within 5 specified domains: 1) randomisation; 2) deviations from intended interventions; 3) missing outcome data; 4) risk of bias in measurement of outcome; and 5) risk of bias in selection of the reported results. There was a high level of agreement in the initial quality assessments between the raters (>80% rating scores across all studies), and consensus was reached for all studies after discussion.

2.5. Analysis

Random-effect network *meta*-analysis (NMA) was used to compute the pooled risk ratio (RR) for the three comparisons: (i) nicotine e-cigarette vs NRT; (ii) nicotine e-cigarette vs control condition; and (iii) NRT vs control condition. In this study, we focused on the comparison, nicotine e-cigarette vs NRT and nicotine e-cigarette vs control condition, and adjusted for multiple comparison using a significance level of 0.025.

NMA computes the pooled RR from all direct and indirect comparisons (Mills et al., 2013; Schwarzer et al., 2015). For example, to derive the pooled RR comparing nicotine e-cigarette and control condition, NMA utilizes RR estimates from studies comparing these two conditions to calculate a pooled direct RR (i.e., studies with a group of participants randomized to use a nicotine e-cigarette and a group assigned to a control condition). NMA also utilizes RR estimates from studies that compared nicotine e-cigarette and NRT, and studies that compared NRT and a control condition to calculate a pooled indirect RR. Both direct and indirect RRs are then combined to form an overall pooled RR. A key assumption of NMA is that the indirect estimate between any two conditions does not differ from the direct estimate (consistency assumption). This assumption will be examined by a decomposition of the heterogeneity statistics and tested using the Q-statistics (Schwarzer et al., 2015). A statistically significance Q-statistics indicates significant inconsistency between direct and indirect effect. Publication bias was assessed using comparison-adjusted funnel plots and Egger's test (Schwarzer et al., 2015). A symmetrical funnel plots and a non-statistically significant results fron Egger's test indicated low risk of publication bias. All analyses were performed in R and StatsNotebook (Chan, 2020) using the package *netmeta* (Schwarzer et al., 2015).

We performed three sets of sensitivity analyses: 1) excluding pilot studies; 2) including additional NRT studies published between 2011 and 2013, and 3) excluding E-cigarette studies with follow-up less than 6 months so that the follow-up period will be more similar between the E-cigarette trials and the NRT trials. Results from these sensitivity analyses are shown in Appendix 3.

3. Results

3.1. Study selection

3.1.1. E-cigarette trials

We identified 4717 studies from PubMed, Web of Science and PsycINFO. After removal of duplicates, record screening and assessment of eligibility, we included 7 e-cigarette trials in the subsequent network *meta*-analysis. Two trials had multiple arms comparing nicotine e-cigarettes with NRT and a control condition (Bullen et al., 2013; Halpern et al., 2018) so these two trials also contributed estimates to the comparison between NRT and control condition in the NMA. The PRISMA flow diagram for this search is shown in Appendix 2a.

3.1.2. Nrt trials

We have identified 133 trials from an existing Cochrane review (Hartmann-Boyce et al., 2018) and 167 trials from other reviews, and 714 studies from PubMed and Google Scholar search. After removal of duplicates, record screening and assessment of eligibility, we included 9 trials for subsequent network *meta*-analysis. The PRISMA flow diagram for this search is shown in Appendix 2b.

3.2. Study characteristics

3.2.1. Nicotine E-cigarette trials

Study characteristics of the 7 e-cigarette trials are shown in Table 1. All trials were from high-income countries; two from the USA (Halpern et al., 2018; Carpenter et al., 2017), two from Italy (Caponnetto et al., 2013; Masiero et al., 2019), one from New Zealand (Hartmann-Boyce et al., 2018), one from the UK (Hajek et al., 2019), and one from Korea (Lee et al., 2019). Two were multi-arm trials comparing nicotine e-cigarette use against a nicotine-free control condition and NRT (Bullen et al., 2013; Halpern et al., 2018); three compared nicotine e-cigarette use against a nicotine-free control condition (Caponnetto et al., 2013;

Table 1
Characteristics of E-cigarette trials.

First author (publication year)	Sampling criteria	Sampling population and setting	Follow-up length (weeks/ months)	Abstinence rate by treatment condition (N that quit/N in treatment condition)	E-cigarette/E-liquid use	Abstinence assessment	Overall risk of bias
Bullen et al. (2013)	Aged 18 or older; smoked at least 10 cigarettes per day in past year; motivated to quit.	Community sample drawn from Auckland, New Zealand.	6 months	Nicotine EC: 7.27% (21/289) Nicotine patches: 5.76% (17/295) Placebo e-cigarette: 4.11% (3/73)	Elusion e-cigarettes; 16 mg/mL liquid nicotine concentration (independently verified as 10–16 mg)	Self-reported abstinence over the follow-up period (allowing for ≤ 5 cigarettes in total); verified at 6-month follow-up by exhaled CO	Low risk
Caponnetto et al. (2013)	Aged 18–70; smoked at least 10 cigarettes per day for at least the past 5 years; in good health; not currently attempting to quit or wishing to do so in next 30 days.	Community sample recruited via newspaper advertisements in Catania, Italy.	12 months	Nicotine EC: 13% (13/100) Placebo e-cigarette: 4% (4/100)	Categoria 401 e-cigarettes; containing 7.2 mg (2.27% total volume)	Self-reported complete abstinence; verified via exhaled CO	Low risk
Carpenter et al. (2017)[b]	18 years or older; current smoker of at least 5 cigarettes per day for >1 year; no current use of e-cigarettes; not currently seeking treatment for smoking.Participants were excluded if they had recent history of cardiovascular distress or major current psychiatric impairment.	Community sample recruited from south-eastern USA.	16 weeks	Nicotine EC: 9.52% (2/21) Usual care: 4.55% (1/22)	BluCig e-cigarettes; 24 mg/mL nicotine concentrations across groups	Self-reported smoking status; verified via exhaled CO	High risk
Hajek et al. (2019)	Adult smokers that were not pregnant or breastfeeding, and not using e-cigarettes or NRT at the time of the trial.	Community sample recruited via NHS stop-smoking services in the UK and social media.	12 months	Nicotine EC: 18.04% (79/438) Participants' choice of NRTs: 9.87% (44/446)	Aspire One Kit and One Kit 2016 e-cigarettes; 18 mg/mL nicotine concentration. Participants provided with starter kit and sourced on e-liquid for the remainder of the trials.	Self-reported abstinence (no >5 cigarettes from 2 weeks after quit date); verified via exhaled CO.	Low risk
Halpern et al. (2018)[a]	18 years or older; reported current smoking on a health risk assessment within the preceding year.	Employees of US companies enrolled in the Vitality wellness program.	6 months	Nicotine EC: 1.00% (12/1199) Combination of NRTs: 0.50% (8/1588) Usual care: 0.12% (1/813)	NJOY e-cigarettes; 1–1.5% nicotine	Self-reported abstinence recorded at 1, 3- and 6-months; verified via urine cotinine level (and secondary verification via blood carboxyhemoglobin)	Some concerns
Lee et al. (2019)	Males over 18 years; smoked at least 10 cigarettes a day during the preceding year; smoked for at least 3 years; motivated to quit or reduce smoking. Participants were excluded if they had past medical history of serious clinical disease or had attempted to stop smoking in preceding 12 months.	Employees of a motor company in the Republic of Korea.	24 weeks	Nicotine EC: 21.33% (16/75) Nicotine gum: 28.00% (21/75)	eGO-C Ovale; 0.01 mg/mL liquid nicotine concentration	Self-reported abstinence, verified via exhaled CO and urine cotinine	Some concern
Masiero (2017)	Aged 55 or over; smoked at least 10 cigarettes per day for past 10 years;	Individuals enrolled in long-term lung cancer detection program	3 months	Nicotine EC: 21.43% (15/70)	eGO-CE4 PIEFFE; 8 mg/mL liquid nicotine concentration	Self-reported abstinence over the past month;	High risk

(*continued on next page*)

Table 1 (*continued*)

First author (publication year)	Sampling criteria	Sampling population and setting	Follow-up length (weeks/ months)	Abstinence rate by treatment condition (N that quit/N in treatment condition)	E-cigarette/E-liquid use	Abstinence assessment	Overall risk of bias
	high motivation to quit; not enrolled in other cessation programs.	(COSMOS II) at the European Institute of Oncology in Milan, Italy.				verified at follow-up via exhaled CO	
	Participants were excluded if they had severe cardiovascular or respiratory symptoms; used psychotropic medication; had a current or past history of alcohol abuse; any use of NRTs or e-cigarettes.			Low-intensity telephone counselling: 8.57% (6/70)			

[a]This is a five-arm study. Data from two intervention arms, cessation aids with reward incentives and cessation aids with redeemable deposits, were not included in this *meta*-analysis. [b]Pilot study.

Carpenter et al., 2017; Masiero et al., 2019) and two compared nicotine e-cigarette use against licensed NRTs (Hajek et al., 2019; Lee et al., 2019). One was a pilot study (Carpenter et al., 2017). The combined sample size was 5674. Three of the studies had a low risk of bias (Bullen et al., 2013; Hajek et al., 2019; Caponnetto et al., 2013), two had some concerns (Lee et al., 2019; Halpern et al., 2018) and two were classified as high risk (Carpenter et al., 2017; Masiero et al., 2019). Individual domain ratings for the risk of bias assessment are shown in Appendix 4.

3.2.2. Nrt trials

The study characteristics of the 9 NRT trials are shown in Table 2. Three trials involved participants from multiple countries (Anthenelli et al., 2016; Tønnesen et al., 2012; Lerman et al., 2015), two from the US (Fraser et al., 2014), one from Hong Kong (Cheung et al., 2020), one from Canada (Cunningham et al., 2016), one from Iran (Heydari et al., 2012), one from The Netherlands (Scherphof et al., 2014), and one from Finland (Tuisku et al., 2016). One was a pilot study (Cheung et al., 2020). The combined sample size was 6080. Two of the studies had a low risk of bias, six had some concerns and one had a high risk or bias. The detailed risk of bias assessments is shown in Appendix 4.

3.3. Pooled effects

Results from NMA indicated that participants in the nicotine e-cigarette condition were more likely to remain abstinent than those in the control condition (pooled RR = 2.09, 97.5% CI = [1.39, 3.15]), and those in an NRT condition (pooled RR = 1.49, 97.5% CI = [1.04, 2.14]) after adjusting for multiple comparisons. The I^2indicates that 42% of variation across studies was due to heterogeneity. Fig. 2 shows a forest plot of the decomposition of estimates computed from the direct and indirect comparison. All the direct and indirect estimates were largely consistent, and Z-tests indicated that these effects were not significantly different in the three comparisons (all p-values > 0.30). An overall test indicated no evidence of inconsistency between direct and indirect estimates, $Q(3) = 1.13$, $p = .769$. Fig. 3 shows the comparison-adjusted funnel plots. The plot is largely symmetrical, and Egger's test also indicated that there was no evidence of asymmetry ($p = .706$), suggesting an absence of publication bias.

3.4. Sensitivity analysis

We performed three sets of sensitivity analyses. First, we excluded pilot studies (one e-cigarette trial and one NRT trial). The results were similar to the main analysis and the same conclusion was drawn. Second, we included additional NRT trials that were published between 2011 and 2013. The comparison between nicotine e-cigarette and NRT conditions became non-significant in this sensitivity analysis after adjusting for multiple comparison, although the effect size estimate was similar (pooled RR = 1.45, 97.5% CI = [0.98, 2.15]). This result was likely due to increased heterogeneity ($I^2 = 50.5\%$) from the inclusion of the additional studies which inflated the standard error of the estimates. Furthermore, it should be noted that the lower bound of the multiple-comparison-adjusted CI was just below one and the effect size was still substantial in this model. Third, we excluded studies with less than 6 months follow-up and the results were similar to the main analysis and the same conclusion was drawn.

3.5. Discussion

There are two key findings from this systematic review and network *meta*-analysis:

(1) Participants randomised to receive nicotine e-cigarettes were 49% more likely to remain abstinent from smoking than those who received NRTs.
(2) Those randomised to receive nicotine e-cigarettes were 109% more likely to remain abstinent from smoking than those in control conditions where no nicotine was supplied.

These findings are largely consistent with evidence from observational studies that nicotine e-cigarettes are effective in facilitating smoking cessation (Malas et al., 2016). However, our findings need to be interpreted with caution. First, one of the seven e-cigarette trials was a pilot study and four had a sample size of 100 or fewer participants per treatment condition. These results might, therefore, not be generalisable to the wider population. Many studies had relatively short follow-up periods of 6 months or less, and therefore we had limited data on long term abstinence. While there is clear evidence that NRTs assist smoking cessation (Hartmann-Boyce et al., 2018), relapse rates remain high (Alpert et al., 2013). The pragmatic trial by Hajek and colleagues (Hajek et al., 2019) provided some insight into how smokers may use e-cigarettes over a longer timeframe. Participants who used e-cigarette were 83% more likely to be abstinent from smoking at 12 months than those who were randomised to receive NRT; and that among those who remained abstinent, 80% of e-cigarette users continued to vape compared with 9% of the NRT users who continued to use NRT. This finding suggests that e-cigarettes may be a more acceptable longer-term substitute for cigarette smoking than NRT.

Another limitation is that overall, there is a moderate level of heterogeneity in the trials in this study. This is likely due to the considerable

Table 2
Characteristics of NRT trials.

First author (reference year)	Sampling criteria	Sampling population and setting	Length of follow-up (months)	Abstinence rate by treatment condition (Smokers who quitted/ Smokers in treatment condition)	Abstinence assessment	Overall risk of bias
Anthenelli et al. (2016)[b]	Smoked an average of > 10 cigarettes/day, 18–75 years, exhaled MO > 10 ppm at screening	Patients recruited from investigators' clinics; through newspapers, radio, television advertising, and fliers and posters from 16 countries, including US	6	Nicotine patch: 18.5% (187/1013) Placebo: 10.5% (106/1009)	Self-reported abstinence for 9–12 weeks with no exhaled carbon monoxide concentration >0 ppm	Low risk
Cunningham et al. (2016)	Smoked an averaged of >10 cigarettes/day, 18+ years	Community sample recruited from telephone survey in Canada	6	Nicotine patch: 2.8% (14/500) Nicotine-free control (Not receiving anything): 1.0% (5/499)	Self-reported abstinence with biochemical validation (however, only 50.9% had useable saliva samples)	Some concerns
Cheung et al. (2019)[a]	Smoked an average of >10 cigarettes/day, 18+ years, Chinese language literate, not used NRT for past 3 months, no severe heart condition, not pregnant and breastfeeding	Community sample recruited from outdoor smoking hotspots in urban areas in Hong Kong	6	Nicotine patch and gum: 16.0% (8/50) Brief medication counselling: 16.0% (8/50)	Self-reported 7-day point prevalence of abstinence	High risk
Fraser et al. (2014)	Smoked an average >4 cigarettes/day, 18+ years, interest to quit smoking in next 30 days but not actively engaged in quitting, phone & home internet access, no prior use of smokefree.gov website, no allergies to NRT, not pregnant	Community sample who spontaneously accessed the website smokefree.gov	7	Lozenges: 29.1% (151/518) Combination of messaging, brochures and Quitline counselling: 26.9% (139/516)	Self-reported abstinence in past 7 days at 7mo follow-up	Some concerns
Heydari et al. (2012)	Smokers willing to quit	Patients recruited from tobacco cessation clinics in Tehran, Iran.	6	Nicotine Patch: 25.0% (23/92) Brief advice: 6.6% (6/91)	Self-reported abstinence at 6 months follow-up verified with exhaled carbon monoxide measurement	Some concerns
Lerman et al. (2015)	Smoked an average of >10 cigarettes/day for ≥6 months, 18–65 years, exhaled MO > 10 ppm	Community sample recruited through advertisements for a free smoking cessation programs in US and Canada.	6	Nicotine patch: 16.5% (69/418) Placebo: 12.3% (50/408)	Self-reported abstinence at 6 months f/up; biologically verified in person for those self-reporting abstinence (CO less than 8 ppm)	Some concerns
Scherphof et al. (2014)	Smoked ≥ 7 cigarettes/day, 12–18 years, no major physical health problems, parent awareness of smoking behaviours, and motivated to quit smoking	Student sample recruited from school visits in Netherlands.	6	Nicotine patch: 4.4% (6/135) Placebo: 6.6% (8/122)	Self-reported abstinence in past 30 days at 6mo f/up with biochemical verification	Some concerns
Tønnesen et al. (2012)	18+ years, daily cigarette smoker for the last 3 years or more (no lower limit in number of daily cigarettes), expired carbon monoxide level ≥10 ppm after at least 15 smoke-free min, motivated and willing to completely stop smoking, female participants of child-bearing potential to use a medically acceptable method of birth control	Community sample recruited from local newspapers advertisements in Denmark and Germany	12 6	Nicotine mouth spray: 13.8% (44/318) Placebo: 5.6% (9/161)	Self-reported with carbon monoxide-verified continuous abstinence rates at 1 year follow-up	Low risk

(*continued on next page*)

Table 2 (*continued*)

First author (reference year)	Sampling criteria	Sampling population and setting	Length of follow-up (months)	Abstinence rate by treatment condition (Smokers who quitted/ Smokers in treatment condition)	Abstinence assessment	Overall risk of bias
Tuisku et al. (2016)	18–26 years, smoked daily for at least the past month and smoked ≥100 cigarettes in their life, motivated to quit smoking	Community sample recruited from community media, colleges and army in Finland.		Nicotine patch: 20.2% (19/94) Placebo: 15.1% (13/86)	Self-reported smoking abstinence at 6mo follow-up; verified by saliva cotinine	Some concerns

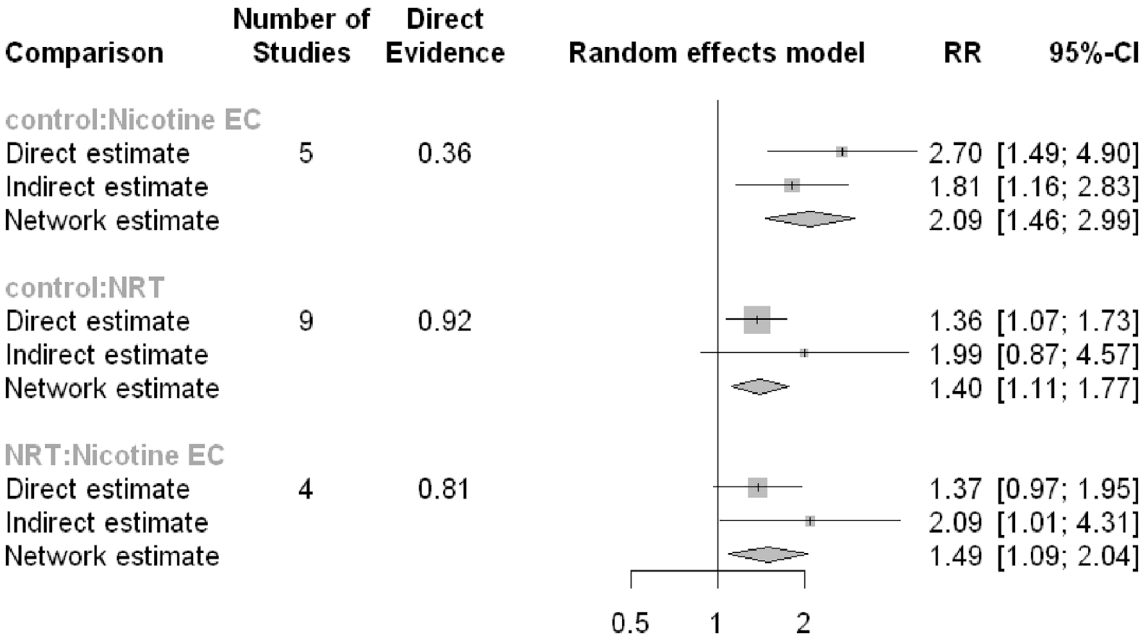

Fig. 2. Forest plot of estimate decomposition into direct and indirect effect and overall effect (Risk ratio) estimates.

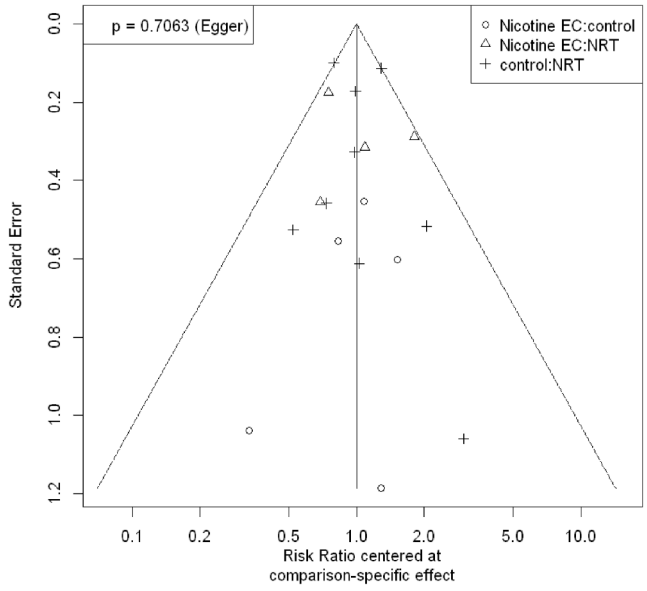

Fig. 3. Comparison adjusted funnel plot with Egger's test for assessing publication bias. A symmetrical funnel plot (data points spread relatively even on both side of the vertical line) and a non-statistically significant Egger's test indicate the absence of evidence for publication bias.

variation in e-cigarettes and NRT products used in different trials, and the possibility that effectiveness may vary between these products. Furthermore, the e-cigarettes used in trials in this study were first- or second-generation devices, and our estimates might not be generalisable to newer devices now used by smokers. It is possible that later generation of the device can deliver nicotine more efficiently, thus improving the effectiveness to reducing craving. There is also consideration variability in follow-up period of ths studies. While the same conclusion was reached in the sensitivity analysis without studies with short follow-up (less than 6 months), the long term effectiveness of e-cigarette on reducing combustible cigarette smoking is unclear because the longest follow-up in all included studies was 12 months. There was also variation in the control condition. For example, some studies used nicotine-free cigarettes and some provided phone counselling. Lastly, there is an over-reliance in the existing literature on carbon monoxide as a biomarker to verify smoking cessation. Combustion of organic matter produces carbon monoxide (CO) as a byproduct. CO can be measured via exhaled breath or in blood as an indicator of recent smoke absorption from combustible tobacco products. Exhaled CO is widely used in clinical trials and experimental studies as it can be measured easily using relatively inexpensive handheld devices. Furthermore, as CO is a measure of the combustion of tobacco, it is not influenced by the use of non-combustible products such as e-cigarettes, NRTs or tobacco products such as snuff. A major drawback of CO, however, is that this biomarker has a relatively short half-life of 2–16 h (Benowitz et al., 2020), which is influenced by physical activity (Hawkins, 1976) and will return a false positive if an individual smokes cannabis (Moolchan et al., 2005). Given this short half-life, measures of CO in breath or blood are able to detect

smoking within 1–2 days. For longer term discrimination, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) is a tobacco metabolite that can be detected in urine for two months or longer following the discontinuation of combustible tobacco use (Hecht et al., 1999). As such, NNAL is able to discriminate e-cigarette use from combustible tobacco, and would be a more valid biomarker for long-term abstinence. The cost of NNAL analysis is, however, considerably higher than for other biomarkers with no existing reliable immunoassays (Benowitz et al., 2020), which may limit the applicability of NNAL.

We know that (1) using e-cigarette is likely to confer substantially lower health risk than smoking tobacco, but the exact health risks of long-term use have not been definitively established, (2) e-cigarettes are likely to be at least as effective as—and based on this network *meta*-analysis probably more effective than—licensed NRTs; and (3) the optimal health behaviour is not to use either e-cigarettes or tobacco cigarettes, but many people who smoke experience difficulty stopping smoking. A recent review by Wang et al (Wang et al., 2020) found e-cigarette were effective for smoking cessation in RCTs, but not in cohort or cross-sectional studies. They concluded e-cigarette should be only provided under medical supervision as part of a cessation program. However, such a conclusion is not justified by their findings. A RCT is an experimental design that is used to determine if e-cigarettes are an effective cessation aid. RCTs to date have not tested whether e-cigarettes should be delivered under medical supervision. Several RCTs were pragmatic trials with minimal supervision from the investigators. For example, in Hajek et al (Hajek et al., 2019), participants were only provided an e-cigarette starter kit with limited supply of e-liquid, and were asked to purchase future e-liquid themselves. They could select different strength of the e-liquid and use other e-cigarette products if they wished to. Another large recent pragmatic trial also demonstrated that using e-cigarettes with NRTs was more effective than using NRTs alone for smoking cessation (Walker et al., 2020). These studies provided some evidence that e-cigarette are an effective cessation aids with no medical supervision. Nonetheless, no RCTs to date were designed to test the effectiveness of e-cigarettes under different level of supervision and therefore no conclusion can be drawn about whether e-cigarettes will be more effective with or without medical supervision.

Given the current evidence about e-cigarette's effectiveness as a cessation aid and with a moderate effect size, a sensible policy would be to encourage smokers who have difficulty quitting tobacco to switch to nicotine e-cigarettes and to concurrently discourage the uptake of e-cigarettes and tobacco smoking among young people. For example, taxation is an effective policy on reducing consumption of consumer products (e.g. tobacco and drinks with high sugar content). A higher tax on combustible tobacco and a lower one on e-cigarette could be used to encourage smokers to shift to e-cigarettes. By providing an effective alternative for cigarette smokers, e-cigarettes could also have potential to be used as a policy lever to phase out combustible cigarette sales, which would further protect youth from taking up smoking (Hefler, 2018).

3.6. Conclusion

Combining well-established evidence from NRT trials and emerging evidence from e-cigarette trials, we found that nicotine e-cigarettes are effective in helping smokers quit smoking. However, most of the e-cigarette trials has moderate or high risk of bias and more high quality studies are required to ascertain the effect of e-cigarette on smoking cessation.

CRediT authorship contribution statement

Gary C.K. Chan: Conceptualization, Formal analysis, Funding acquisition, Project administration. **Daniel Stjepanović:** Conceptualization, Investigation, Methodology, Writing - review & editing, Project administration. **Carmen Lim:** Data curation. **Tianze Sun:** Data curation. **Aathavan Shanmuga Anandan:** Data curation. **Jason P. Connor:** Conceptualization, Writing - review & editing. **Coral Gartner:** Conceptualization, Writing - review & editing. **Wayne D. Hall:** Conceptualization, Writing - review & editing. **Janni Leung:** Conceptualization, Project administration, Writing - original draft.

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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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Appendix A. Supplementary data

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References

World Health Organization (2019). WHO report on the global tobacco epidemic 2019: Offer help to quit tobacco use.

Hartmann-Boyce, J., Chepkin, S. C., Ye, W., Bullen, C., & Lancaster, T. (2018). Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database of Systematic Reviews, 5*.

Alpert, H. R., Connolly, G. N., & Biener, L. (2013). A prospective cohort study challenging the effectiveness of population-based medical intervention for smoking cessation. *Tobacco control, 22*(1), 32–37.

Farsalinos, K. E., Spyrou, A., Tsimopoulou, K., Stefopoulos, C., Romagna, G., & Voudris, V. (2014). Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Scientific Reports, 4*, 4133.

Caraballo, R. S., Shafer, P. R., Patel, D., Davis, K. C., & McAfee, T. A. (2017). Quit methods used by US adult cigarette smokers, 2014–2016. *Preventing Chronic Disease, 14*.

Levy, D. T., Borland, R., Lindblom, E. N., Goniewicz, M. L., Meza, R., Holford, T. R., et al. (2018). Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tobacco Control, 27*(1), 18–25.

National Academies of Sciences E, Medicine. Public health consequences of e-cigarettes: National Academies Press (2018).

McNeill, A., Brose, L. S., Calder, R., Bauld, L., & Robson, D. (2018). Evidence review of e-cigarettes and heated tobacco products 2018. In A report commissioned by Public Health England London: Public Health England (Vol. 6).

Glantz, S. A., & Bareham, D. W. (2018). E-cigarettes: Use, effects on smoking, risks, and policy implications. *Annual Review of Public Health, 39*, 215–235.

Hartmann-Boyce, J., McRobbie, H., Bullen, C., Begh, R., Stead, L. F., & Hajek, P. (2020). Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 10.

Hemkens, L. G., Contopoulos-Ioannidis, D. G., & Ioannidis, J. P. (2016). Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. *bmj, 352*, Article i493.

Bullen, C., Howe, C., Laugesen, M., et al. (2013). Electronic cigarettes for smoking cessation: a randomised controlled trial. *The Lancet, 382*(9905), 1629–1637.

Hajek, P., Phillips-Waller, A., Przulj, D., et al. (2019). A randomized trial of e-cigarettes versus nicotine-replacement therapy. *New England Journal of Medicine, 380*(7), 629–637.

Lee, S.-H., Ahn, S.-H., & Cheong, Y.-S. (2019). Effect of electronic cigarettes on smoking reduction and cessation in Korean male smokers: a randomized controlled study. *The Journal of the American Board of Family Medicine, 32*(4), 567–574.

Caponnetto, P., Campagna, D., Cibella, F., et al. (2013). EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: A prospective 12-month randomized control design study. *PloS one, 8*(6).

Halpern, S. D., Harhay, M. O., Saulsgiver, K., Brophy, C., Troxel, A. B., & Volpp, K. G. (2018). A pragmatic trial of e-cigarettes, incentives, and drugs for smoking cessation. *New England Journal of Medicine, 378*(24), 2302–2310.

Holliday, R., Preshaw, P. M., Ryan, V., et al. (2019). A feasibility study with embedded pilot randomised controlled trial and process evaluation of electronic cigarettes for smoking cessation in patients with periodontitis. *Pilot and feasibility studies, 5*(1).

Mills, E. J., Thorlund, K., & Ioannidis, J. P. A. (2013). Demystifying trial networks and network meta-analysis. *Bmj, 346*, f2914.
Schwarzer, G., Carpenter, J. R., & Rücker, G. (2015). *Meta-Analysis with R*. Springer.
Walker, N., Parag, V., Verbiest, M., Laking, G., Laugesen, M., & Bullen, C. (2020). Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: A pragmatic, randomised trial. *The Lancet Respiratory Medicine, 8*(1), 54–64.
Higgins, J. P. T., Altman, D. G., Gotzsche, P. C., et al. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj, 343*, d5928.
Chan, G. C. K. (2020). StatsNotebook Team. StatsNotebook Version 0.1.0.
Carpenter, M. J., Heckman, B. W., Wahlquist, A. E., et al. (2017). A naturalistic, randomized pilot trial of e-cigarettes: uptake, exposure, and behavioral effects. *Cancer Epidemiology and Prevention Biomarkers, 26*(12), 1795–1803.
Masiero, M., Lucchiari, C., Mazzocco, K., & et al. (2019). E-cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: preliminary results by randomized controlled trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.
Anthenelli, R. M., Benowitz, N. L., West, R., et al. (2016). Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): A double-blind, randomised, placebo-controlled clinical trial. *The Lancet, 387*(10037), 2507–2520.
Tønnesen, P., Lauri, H., Perfekt, R., Mann, K., & Batra, A. (2012). Efficacy of a nicotine mouth spray in smoking cessation: A randomised, double-blind trial. *European Respiratory Journal, 40*(3), 548–554.
Lerman, C., Schnoll, R. A., Hawk, L. W., Jr, et al. (2015). A randomized placebo-controlled trial to test a genetically-informed biomarker for personalizing treatment for tobacco dependence. *The Lancet Respiratory Medicine, 3*(2), 131.
Fraser, D., Kobinsky, K., Smith, S. S., Kramer, J., Theobald, W. E., & Baker, T. B. (2014). Five population-based interventions for smoking cessation: A MOST trial. *Translational Behavioral Medicine, 4*(4), 382–390.
Cheung, Y. T. D., Cheung Li, W. H., Wang, M. P., & Lam, T. H. (2019). Delivery of a nicotine replacement therapy sample at outdoor smoking hotspots for promoting quit attempts: A pilot randomized controlled trial. *Nicotine & Tobacco Research*.
Cunningham, J. A., Kushnir, V., Selby, P., Tyndale, R. F., Zawertailo, L., & Leatherdale, S. T. (2016). Effect of mailing nicotine patches on tobacco cessation among adult smokers: A randomized clinical trial. *JAMA Internal Medicine, 176*(2), 184–190.
Heydari, G., Talischi, F., Tafti, S. F., & Masjedi, M. R. (2012). Quitting smoking with varenicline: Parallel, randomised efficacy trial in Iran. *The International journal of Tuberculosis and Lung Disease, 16*(2), 268–272.
Scherphof, C. S., van den Eijnden, R. J., Engels, R. C., & Vollebergh, W. A. (2014). Long-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: A randomized controlled trial. *Drug and Alcohol Dependence, 140*, 217–220.
Tuisku, A., Salmela, M., Nieminen, P., & Toljamo, T. (2016). Varenicline and nicotine patch therapies in young adults motivated to quit smoking: A randomized, placebo-controlled, prospective study. *Basic & Clinical Pharmacology & Toxicology, 119*(1), 78–84.
Malas, M., van der Tempel, J., Schwartz, R., & et al. (2016). Electronic cigarettes for smoking cessation: a systematic review. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 18(10), 1926-1936.
Benowitz, N. L., Bernert, J. T., Foulds, J., & et al. (2020). Biochemical verification of tobacco use and abstinence: 2019 update. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 22(7), 1086-1097.
Hawkins, L. H. (1976). Blood carbon monoxide levels as a function of daily cigarette consumption and physical activity. *British Journal of Industrial Medicine, 33*(2), 123–125.
Moolchan, E. T., Zimmerman, D., Sehnert, S. S., Zimmerman, D., Huestis, M. A., Epstein, D. H. (2005). Recent marijuana blunt smoking impacts carbon monoxide as a measure of adolescent tobacco abstinence. Substance use & misuse 40(2), 231-240.
Hecht, S. S., Carmella, S. G., Chen, M., et al. (1999). Quantitation of urinary metabolites of a tobacco-specific lung carcinogen after smoking cessation. *Cancer Research, 59*(3), 590–596.
Wang, R. J., Bhadriraju, S., & Glantz, S. A. (2020). E-cigarette use and adult cigarette smoking cessation: A meta-analysis. *American Journal of Public Health*, e1–e17.
Hefler, M. (2018). The changing nicotine products landscape: Time to outlaw sales of combustible tobacco products? *Tobacco Control, 27*(1), 1–2.