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Smoking cessation in individuals who use vaping as compared to traditional nicotine replacement therapies; a systematic review and meta-analysis

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Dr Pound conceptualized and designed the study, carried out the analyses, interpreted the data, drafted the initial manuscript, reviewed, and revised the manuscript.
Mrs Zhang participated in the conceptualization and design of the study, carried out the analyses, interpreted the data, participated in drafting the initial manuscript, reviewed and revised the manuscript.
Ms Kodua participated in the conceptualization and design of the study, and reviewed the manuscript.
Dr Sampson participated in the design of the study, developed the search strategies, reviewed, and revised the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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ABSTRACT

Objectives: Despite the aggressive marketing of electronic nicotine device systems (ENDS) as smoking cessation tools, the evidence of their effectiveness is mixed. We conducted a systematic review of randomized controlled trials to determine the effect of ENDS on cigarette smoking cessation, as compared to other types of nicotine replacement therapies (NRT).

Methods: We included randomized controlled trials in which any type of ENDS was compared to any type of NRT, in traditional cigarette users. We searched MEDLINE, Embase, and the CENTRAL Trials Registry of the Cochrane Collaboration using the Ovid interface, as well as ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform trials registries regardless of study completion status. We used the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) for each outcome of interest. The primary outcome was smoking cessation. Secondary outcomes included smoking reduction, harms, withdrawal, and acceptance of therapy. A random-effect model was used, and data were pooled in meta-analyses where appropriate.

Results: Six studies were retained from an initial 270. Most outcomes were judged to be at high risk of bias. The overall quality of evidence was graded as 'low' or 'very low'. Pooled results showed no difference in smoking cessation (RR 1.42 [0.97, 2.09]), proportion of participants reducing smoking consumption (RR 1.25 [0.79, 1.98]), mean reduction in cigarettes smoked per day (MD 1.11 [-0.41, 2.63]), or harms (RR 0.96 [0.76, 1.20]), between groups.

Discussion: We found no difference in smoking cessation, harms, and smoking reduction between e-cigarette and NRT users. However, the quality of the evidence was low. Further research is needed before widespread recommendations can be made with regards to the use of ENDS. Research is also needed to investigate the long-term effects of ENDS, as well as optimal dosing.

Systematic review registration number: protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO) on February 27th, 2020. Registration number pending.

Strengths and limitations of this study

- This study provides up to date meta-analyses of direct comparisons of vaping with nicotine replacement therapy for smoking cessation, studied through randomized controlled trials.
- We examined harms associated with vaping, which are becoming increasingly concerning.
- This study makes extensive efforts to obtain unreported data from investigators.
- Careful consideration is given to the potential impact of risk of bias and methodological heterogeneity.
- As we included only RCTs, many studies that used weaker study designs were ineligible for this review.

SUMMARY OF FINDINGS TABLE

Nicotine-containing Electronic cigarettes (ENDS) vs Nicotine Replacement Therapies (NRT) for smoking cessation

Population: Current smokers at enrolment into trials

Intervention: Nicotine-containing e-cigarettes

Comparison: Nicotine-replacement therapies

Outcomes ENDS as compared to NRT	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Cessation	RR 1.42 [0.97, 2.09]	1800 (5 studies)	⨁⨁ OO[1,2] low	
Smoking reduction				
Proportion of people decreasing cigarette consumption by 50%	RR 1.25 [0.79, 1.98]	1460 (4 studies)	⨁⨁ OO[1,2] low	
Mean decrease in cigarettes per day	MD 1.11 [-0.41, 2.63]	633 (3 studies)	⨁⨁ OO[1,2] low	
Adverse events (AEs)	RR 0.96 [0.76, 1.20]	758 (4 studies)	⨁ OOO[1,2,3] Very low	No severe adverse events related to investigated products were reported
Withdrawal symptoms	Summary data not available	4 studies	⨁ OOO[1,2,3] Very low	Withdrawal measures included Minnesota Nicotine Withdrawal Scale, QSU scores, frequency of urge and strength of urge score, and pre-specified symptoms of depressed mood, irritability, restlessness, and hunger

Acceptance of therapy	Summary data not available	4 studies	⨁ OOO[1,2,3] Very low	Acceptance defined as wanting to recommend product to friends, helpfulness, taste, satisfaction, psychological reward, enjoyment of sensation, aversion, and ability to reduce craving depending on study

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level because of risk of bias
[2]Downgraded one level because of heterogeneity
[3]Downgraded one level because of imprecision of results

INTRODUCTION

Despite a significant lack of rigorous pharmacological testing, the use of electronic nicotine device systems (ENDS), otherwise known as vaping devices, has been aggressively marketed as an effective method to quit smoking. In Canada, 32% of current and former smokers report having used ENDS as a smoking cessation aid. In addition to delivering nicotine to the user, ENDS are thought to replace some of the habitual behaviours and sensations associated with smoking, such as the action of bringing a cigarette to the mouth. By doing so, ENDS may provide coping mechanisms that other traditional nicotine replacement therapies (NRT) do not offer, and therefore may help with the behavioural component of smoking reduction and cessation.[2] While vaping is believed to be less harmful than cigarette smoking, a large number of emerging reports on the health impacts of vaping are worrisome. In addition, the evidence on the effectiveness of ENDS as a smoking cessation aid is mixed.

In 2016, a meta-analysis of 20 studies found that people using ENDS had a 28% reduction in the odds of stopping cigarette smoking as compared to those not using ENDS.[3] However, in a 2019 recent randomized controlled trial (RCT), individuals randomized to nicotine-containing e-cigarettes were more likely to abstain from smoking at one year compared to individuals randomized to nicotine patches (18% compared to 9.9%, RR 1.83; 95% CI 1.30 to 2.58).[4] A Cochrane review[5] found that nicotine-containing e-cigarettes were more effective than non-nicotine containing e-cigarettes for smoking cessation, but was not able to compare ENDS products to traditional NRT.

Little information is known about the long-term health impacts of ENDS. Reports of acute toxicity have recently captured the public's attention. In late 2019 and early 2020, "e-cigarette, or vaping, product use-associated lung injury" (EVALI) caused 2807 illnesses and 68 deaths in the US,[6] and 19 cases in Canada.[7] Other short-term adverse events reported with the use of ENDS include cardiovascular changes such as increased heart rate and blood pressure, cough, wheeze,[8] and mucus production.[9] Burn injuries have also been reported, as well as fatalities from drinking or injecting the e-liquid.[8]

There is no long-term data available on the relationship between ENDS and oral, respiratory, and cardiovascular health, as well as cancer. There is however available data linking the chemicals present in e-liquids with cellular DNA damage and carcinogenicity.[9,10] There is some evidence that the use of ENDS is associated with asthma exacerbations.[11] No human long-term data exist on the use of ENDS in pregnancy and their impact on the developing fetus.

Given the large number of smokers using ENDS as a potential smoking cessation tool, there is a need to review and synthesize the evidence of trials examining a head to head comparison of ENDS versus traditional NRT for smoking cessation.

Objective

The objective of this review is to systematically review the evidence found in RCTs to determine the effect of electronic nicotine delivery systems (ENDS) on cigarette smoking cessation in smokers, as compared to other types of nicotine replacement therapies (NRT).

METHODS

Protocol and registration

The protocol for this systematic review was submitted to International Prospective Register of Systematic Reviews (PROSPERO) on February 27th, 2020 (registration pending) and uploaded as a preprint on Open Science Framework (OSF) Preprints on May 12th 2020.[12]

Criteria for study inclusion

Study Characteristics:

RCTs in which ENDS were compared to non-electronic NRT in smokers were included. We restricted our inclusion to RCTs to minimize the risk of bias. No language limits were imposed. No date limits were imposed either, although we did not anticipate studies published prior to 2003, since this is when the first e-cigarette was invented.[13] There was no geographical restriction of studies.

Study Population:

All traditional cigarette users were included, regardless of age, amount of traditional cigarette use, and motivation to quit.

Intervention of interest:

The intervention of interest comprised all types, models, and brands of ENDS.

Comparators:

All included studies compared ENDS with non-electronic NRT. NRT comprised, but were not limited to, nicotine patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strips, microtabs, and combination of products.

Outcome measures:

The primary outcome measure is traditional cigarette smoking cessation defined as abstinence from traditional cigarette smoking for any time period, as reported in each included study, regardless of whether abstinence is self-reported or biochemically validated.
Secondary outcomes include reduction in the number of traditional cigarettes smoked in any given time period, adverse events, withdrawal symptoms, and participants' acceptance of therapy. We had planned on collecting quit attempts information but none of the studies reported on this outcome.

Settings:

All health care and community settings were included.

Study Identification

The following databases were searched: MEDLINE (1946 to June 2020), Embase (1947 to June 2020) and the CENTRAL Trials Registry of the Cochrane Collaboration (May 2020 Issue) using the Ovid interface. The MEDLINE search was limited using the Cochrane Highly Sensitive Search Strategy and the Embase search was limited using the recommended limit for controlled

trials.[14] Searches were developed by a librarian experienced in systematic reviews, using a method designed to optimize term selection.[15] ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) trials registries were searched for registered intervention studies, regardless of their completion status. Electronic search strategies are presented in Supplementary Material 1. The reference lists of included studies and any applicable review studies were searched.

Authors of protocols identified through registries were contacted electronically, to request data for the review. In addition, clinical experts in the field of vaping and smoking cessation were contacted to enquire about any unpublished research fulfilling our inclusion criteria.

Selection of Studies

Records retrieved by the electronic search were downloaded and imported into a Reference Manager database for duplicate removal, and then uploaded to Covidence. Throughout the review, newly identified records were integrated into the set for screening.

Each title and abstract was independently screened by two review authors (from CP, JZ, and ATK) against the eligibility criteria.[14] Full text of all studies deemed potentially eligible was obtained and reviewed independently by two of the same review authors to determine eligibility. For screening, data extraction, and risk of bias assessment, disagreements were resolved by discussion, and with a third reviewer when needed.

Data extraction and management

For studies that fulfilled the inclusion criteria, two reviewers (CP, JZ) extracted the data into an electronic data collection form, which was piloted by both reviewers (Supplementary Material 2). The data collection was revised, based on feedback from the reviewers. Study authors were contacted electronically to obtain relevant but unavailable data.

Risk of bias assessment for included studies

Two reviewers (CP, JZ) independently conducted the risk of bias assessment for each study at the outcome level using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[16]

Measures of treatment effect

Dichotomous data was analyzed by calculating the risk ratio, using the longest follow-up time reported, as well as the 95% confidence interval. The risk ratio (RR) for smoking cessation was calculated as such:

$$RR = \frac{N\ of\ subjects\ abstaining\ from\ smoking\ in\ intervention \Big/ N\ of\ subjects\ in\ intervention}{N\ of\ subjects\ abstaining\ from\ smoking\ in\ control \Big/ N\ of\ subjects\ in\ control}$$

Continuous data for the secondary outcomes were analyzed through mean differences between groups as the same scales were used. In the case of studies with multiple arms, we only extracted data for the groups relevant to this review.

Data synthesis

We provide a narrative synthesis of the included studies. Where appropriate, data have been pooled for meta-analyses, and random effects were used for all analyses in RevMan.[14] The inverse-variance random-effects and the mean difference approach (using standard deviations and sample sizes) were used for dichotomous and continuous outcomes, respectively, to assign the weight given to each study. Participants with missing data were considered as still smoking.[5] The proportion of adverse events reported was based on the number of people available for outcome assessment. For the reduction of the number of cigarettes smoked, missing values were assumed to be zero.

Assessment of heterogeneity

A p value of 0.10 for the chi-squared test (Cochrane Q) and an I^2 value of >50% were used as indicators of substantial heterogeneity. This however needs to be interpreted with caution given the small number of studies available for the meta-analysis. Clinical and methodological diversity was also explored.

We planned to assess reporting/publication bias using funnel plots of effect estimate against standard error, and testing for funnel plot asymmetry, however, the number of included studies was too low (<10).

We also planned on conducting a number of sensitivity analyses to determine the robustness of the results of the meta-analyses; subgroup analyses to investigate potentially modifying factors such as age and smoking intensity; as well as meta-regression to study the impact of covariates such as motivation to quit smoking, provision of training, and other factors,[17] but minimum data thresholds were not met.

We present a 'Summary of Findings' table for all outcomes. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias)[14] to assess the quality of evidence for each outcome and to draw conclusions about the robustness of evidence within this review.

RESULTS

Our initial bibliographic search yielded 270 records, and after screening and full-text review, we retained 6 RCTs. An updated search conducted in June 2020 yielded an additional 116 records (for a total of 386 records), none of which were included after screening (Figure 1).

We identified six RCTs (Bullen 2013,[18] Eisenhofer 2015,[19] Hajek 2019,[4] Hatsukami 2019,[20] Lee SH 2019,[21] Lee SM 2018[22]). Of these, five contributed data to our primary outcome of smoking cessation.[4,18,20-22] Four studies[4,18,21,22] examined cessation at 6 months or longer, while one[20] examined short term cessation (< 6 months). Table 1 includes the salient features of the

included studies. A more detailed description of included studies can be found in Supplementary Material Table 3.

Table 1. Characteristics of included studies

Author and year of publication	Design	Country	Number of participants	Main eligibility criteria	Intervention	Comparator	Main outcome of interest
Characteristics of RCTs measuring smoking cessation at 6 months or later							
Bullen, 2013[17]	3-group, parallel, single center	Australia	657 total, 584 included in this review (2 of 3 groups)	≥ 18 years, smoked ≥ 10 cigarettes per day in the past year, motivated to quit	First-generation e-cigarette x 12 weeks	Nicotine patch x 12 weeks	Continuous abstinence 6 months after quit day
Hajek 2019[4]	2-group, parallel, multi-centre	United Kingdom	884	Adults with no strong preference towards e-cigarette or NRT	Any type of e-cigarette	Any nicotine-replacement therapy	Continuous abstinence 52 weeks after quit day
Lee SH, 2019[20]	2-group, parallel, single center	Republic of Korea	150	≥ 18 years, smoked ≥ 10 cigarettes per day in the past year, motivated to quit	e-cigarette x 24 weeks	Nicotine gum x 24 weeks	Continuous abstinence 24 weeks after quit day
Lee SM, 2018[21]	2 group, parallel, single center	USA	30	Adults, smoked ≥ 2 cigarettes per day in the past year, smoked at least once in last 7 days	e-cigarette x 6 weeks	Nicotine patch x 5 weeks, then placebo patch x 1 week	7-day point prevalence abstinence at 6 months
Characteristics of RCT measuring smoking cessation earlier than 6 months							
Hatsukami, 2019[19]	4 group, parallel, multi-center	USA	264 total, 152 included in this review (2 of 4 groups)	≥ 18 years, smoked ≥ 5 cigarettes per day	e-cigarettes	Nicotine gum or nicotine lozenge	7-day point prevalence abstinence at 8 months
Characteristics of RCT measuring other outcomes							

Eisenhofer, 2015[18]	2-group, parallel, single center	USA	11	Veterans who met criteria for tobacco disorder	e-cigarettes x 3 weeks	Nicotine patch x 3 weeks	Reduction in number of cigarettes smoked per day at 3 weeks

Risk of bias in included studies

We assessed risk of bias for each included study. A detailed report of the risk of bias assessment can be found in Supplementary Material Table 4.
Figures 2a, 2b, 2c, 2d, and 2e illustrate the risk of bias for each outcome.

Effect of Interventions

Smoking cessation

Five of the six studies reported on smoking cessation.[4,18,20-22] When comparing e-cigarettes to NRT in the context of smoking cessation, there was no significant difference between groups in verified self-reported continuous abstinence at 6 months (21/289 vs 17/295, RR 1.26 [0.68, 2.34], p=0.46) in the Bullen 2013[18] study, and in continuous abstinence from 9 to 24 weeks (16/75 vs 21/75, RR 0.76 [0.43, 1.34], p = 0.344) in the Lee SH 2019[21] study. In addition, the Lee SM 2018[22] study showed no difference between groups for the 7-day point prevalence abstinence at 6 months in the context of perioperative smoking cessation (5/20 vs 1/10, RR 2.50 [0.34, 18.63], p = 0.63).

In the Hajek 2019[4] study, self-reported, verified continuous abstinence at 1 year was found to be higher in the e-cigarette group (79/438 vs 44/446, RR 1.83 [1.30, 2.58], P<0.001), and smoking cessation assessed by 7-day point prevalence at 8 weeks in the Hatsukami 2019[20] trial was also higher in the e-cigarette group (25/76 vs 13/76, RR 1.92 [1.07, 4.37], p = 0.039).

We combined data from all 5 studies comparing smoking cessation between e-cigarettes and NRT and obtained a pooled RR of 1.42 [0.97, 2.09].

Smoking reduction

All six studies[4,18-22] assessed smoking reduction. Bullen 2013,[18], Eisenhofer,[19] Hajek 2019,[4] and Lee SM 2018[22] reported the proportion of participants reducing smoking by at least 50%. While Lee SH 2019[21] also reported on this outcome, the size of the reduction was not specified. Bullen 2013[18] and Lee SH 2019[21] reported an absolute reduction, and Hatsukami 2019[20] reported a relative reduction in cigarettes per day from baseline.

In the Bullen 2013 study,[18] mean cigarette consumption at 6 months decreased by 9.7 (SE 0.4) in the e-cigarette group, and by 7.7 (SE 0.4) in the NRT group. Mean difference between groups was 1.9 (SE 0.6) (p = 0.002). After excluding people who successfully quit smoking, the RR of decreasing cigarette smoking by at least 50% when comparing the e-cigarette to the NRT groups was 1.61 [1.31, 1.99].

Eisenhofer 2015[19] compared week 3 to week 1, and showed that both e-cigarettes (t = 5.3, p = 0.013) and NRT (t = 3.4, p = 0.015) significantly reduced (~50%) self-reports of cigarettes smoked in the previous 24 hours. This was confirmed by significant reductions of breath CO levels in both groups No additional information could be obtained from the abstract and none of the authors could be reached.

In the Hajek 2019[4] study, 44 of 345 participants in the e-cigarette group, and 29 of 393 participants in the NRT group experienced a carbon monoxide-validated reduction in smoking of ≥ 50% in participants without abstinence between weeks 26 and 52, yielding a relative risk of smoking reduction of 1.73 (1.11-2.70).

Hatsukami 2019[20] defined smoking reduction by the estimated ratio of cigarettes smoked at 8 weeks as compared to baseline, with a result of 0.25 (0.17, 0.37) in the e-cigarette group, and 0.29 (0.21, 0.39) in the NRT group (p = 0.185). Additional data obtained from the author showed that 19 participants in the e-cigarette group and 22 participants in the NRT group reduced smoking consumption by 50% (RR 0.86 [0.51, 1.46]) at 8 weeks, and that mean cigarette consumption decreased by 9.22 (SD 7.95) in the e-cigarette group, and by 7.61 (SD 8.27) in the NRT group. The mean difference between groups was 1.61 [-0.97, 4.19].

In the Lee SH 2019[21] study, mean cigarette consumption decreased at 24 weeks by 6.5 +/- 2.87 (SD) in the e-cigarette group, and by 6.60 +/- 3.75 (SD) in the NRT group (p = 0.974). In addition, 31 out of 75 participants (41.3%) in the e-cigarette group and 19 out of 75 participants (25.3%) in the NRT group reduced their daily cigarette consumption (p = 0.038), but no information on size of smoking reduction is provided. After excluding abstainers, a RR of 1.49 [0.97, 2.31] was obtained for decrease in daily cigarette consumption.

Lastly, in the Lee SM 2018,[22] 1 participant in the END group and 4 participants in the NRT group reduced their cigarette consumption by at least half, resulting in a RR 0.15 [0.02, 1.14].

We combined data from the Bullen 2013,[18] Hajek 2019,[4] Hatsukami 2019[20] and Lee SM 2018[22] studies comparing smoking reduction of at least 50% between e-cigarettes and NRT, as they used similar measures. Pooled results comparing the difference in smoking reduction between the e-cigarette and the NRT groups produced a RR of 1.25, with the line of equivalence falling within the confidence interval [0.79, 1.98].

We also combined data from the Bullen 2013,[18], Hatsukami 2019,[20] and Lee SH 2019[21] comparing mean reduction of cigarettes per day from baseline for ENDs and NRT (Figure 3c). Meta-analysis yielded a MD of 1.11, with the line of equivalence falling within the confidence interval [-0.41, 2.63].

Harms

Five studies reported on harms (Bullen 2013,[18] Hajek 2019,[4] Hatsukami 2019,[20] Lee SH 2019,[21] Lee SM 2018[21]). None of the included studies reported serious adverse events (SAEs) related to e-cigarettes or NRT.

In the Bullen 2013[18] study, 107 participants in the e-cigarette group reported 137 adverse events, while 96 participants in the NRT group (patches) reported 119 events, and, using the number of participants available for analysis at 6 months, there was no difference in the incidence of adverse events between groups (RR 0.99, [0.81, 1,22]). No difference between groups was also observed in the Hatsukami 2019[20] study, where additional data provided by the author showed that 51 of 69 participants in the e-cigarette group and 53 of 72 participants in the NRT group reported adverse events (1.00 [0.82, 1.22]), and in the Lee SM 2018[22] study, where no significant difference in the incidence of adverse events between groups was seen at 8 weeks (RR 1.24 [0.54, 2.84]).

Hajek 2019[4] defined adverse events of interest as nausea, sleep disturbances, and throat and mouth irritation. There were 27 SAEs in the e-cigarette group and 22 in the NRT group, none felt to be related to the intervention or control products. Based on the number of participants available at the 12 month follow-up, e-cigarettes were found to be less likely associated with nausea (RR 0.78 [0.66, 0.92]) and sleep disturbances (RR 0.88 [0.83, 0.95]), but more likely associated with throat/mouth irritation (RR 1.24 [1.13, 1.37]). These numbers however should be interpreted with caution as it was not possible to determine with certainty the denominator from the data.

In the Lee SH 2019 study, [21] 5 participants in the e-cigarette group and 13 participants in the nicotine gum group reported adverse events. There were no SAEs. Based on the number of participants who completed the study, e-cigarettes were less likely to be associated with adverse events (RR 0.13 [0.12, 0.87]).

We combined data from the Bullen 2013,[18] Hatsukami 2019,[20] Lee SH 2019,[21] Lee SM 2018[22] studies comparing harms between e-cigarettes and NRT. Hajek 2019[4] was excluded as they did not clearly report the number of participants that experienced any adverse events and reported only on specific adverse events. Pooled results comparing ENDS to NRT yielded a RR of 0.96 [0.76, 1.20].

Withdrawal symptoms

Four studies reported on the results of withdrawal symptoms (Eisenhofer 2015,[19] Hajek 2019,[4] Hatsukami 2019,[20] and Lee SM 2018[22]) and all used different scales. Eisenhofer 2015[19] assessed withdrawal with the Questionnaire on Smoking Urges (QSU), Hajek[4] used a composite urge score (frequency and strength of urge to smoke), Hatsukami 2019[20] measured the severity of withdrawal using the Minnesota Nicotine Withdrawal Scale, and Lee SM 2018[21] assessed withdrawal symptoms as part of their adverse event assessment. In light of the differences in outcome assessment measures, the data were not pooled.

In Eisenhofer 2015,[19] urges and cravings to smoke were significantly reduced in the e-cigarette group (t=3.8, p = 0.03), but not in the NRT group (t=2.1, p = 0.08).

In Hajek 2019,[4] urges for e-cigarette users decreased more than for NRT users at 1 week (MD: -0.4 (-0.6 to -0.2)) and at 4 weeks (MD: -0.3 (-0.5 to -0.1)). E-cigarette users also reported a smaller increase from baseline in irritability, restlessness, inability to concentrate, hunger, and depression. The withdrawal symptoms disappeared mostly for both groups by week 4.

In Hatsukami 2019,[20] participants in the e-cigarette group reported lower median [min/max] changes from baseline on the severity scale compared to participants in the NRT group at all measurement points, with week 1 (3.0 [-9.0/25.0] vs 3.5 [-20.0/32.0]), week 2 (1.0 [-13.0/25.0] vs 3.0 [-13.0/39.0]), and week 4 (1.0 [-17.0/30.0] vs 2.5 [-28.0/29.0]). The planned pairwise comparisons were significant with p <0.017. As well, fewer participants (5.3%) withdrew from the complete substitution e-cigarettes group than from the NRT group (15.8%) for product related reasons (disliking product or experiencing withdrawal symptoms; p value not reported).

Lee SM 2018[22] only reported on withdrawal symptoms for the NRT group, and did not report on withdrawal symptoms for the e-cigarette group.

Acceptance of therapy

Four studies reported on acceptance of therapy (Bullen 2013,[18] Hajek 2019,[4] Hatsukami 2019,[20] and Lee SM 2018[22]), and all used different scales. In light of the difference in outcome assessment measures, the data were not pooled.

In the Bullen 2013[1]study,[18] 230 out of 260 participants (88%) in the e-cigarettes group said they would recommend their allocated product to a friend at 1 month, as compared to 130 out of 232 participants (56%) in the NRT group (RR 1.58 [1.40, 1.78]). At 6 months, 205 out of 241 participants (85%) in the e-cigarettes group said they would recommend their allocated product as compared to 107 out of 215 participants (50%) in the NRT group (RR 1.71 [1.48, 1.97]).

In the Hajek 2019 study,[4] acceptance of therapy was measured with a Likert scale (1 to 5, with a higher score associated with higher acceptance). At 4 weeks post quit date, helpfulness of e-cigarettes was rated 4.3 (SD 0.9) while that of NRT was 3.7 (SD 0.9) (mean difference 0.6 (0.4, 0.7)). Taste was scored at 3.5 (SD 1.3) for the e-cigarette group and 3.1 (SD 1.5) (mean difference 0.4 (0.2,0.6)), and satisfaction was rated at 2.7 (SD 1.1) and 2.3 (SD 1.2), respectively, for the e-cigarette and NRT groups (mean difference 0.5 (0.3, 0.6)).

In the Hatsukami 2019 study[20], acceptance of therapy was defined as satisfaction with the product, psychological reward, enjoyment of sensation, aversion, and ability to reduce craving. Results are reported for the NRT group as an estimated mean difference and 95% CI in product evaluation sub-scales using the e-cigarette group as a reference. The following results are reported; satisfaction: -0.6 (-1.0, -0.1), psychological reward: -0.4 (-0.8, 0.01), enjoyment of sensation: -0.6 (-1.1, -0.1), aversion: 0.1 (-0.2, 0.4), and ability to reduce craving: -0.3 (-0.8, 0.2).

Lastly, the Lee SM 2018 trial[22] defined acceptance of therapy as satisfaction with the assigned product, measured with a Likert scale (1 to 7, with a higher score associated with higher satisfaction). Median scores and IQR are reported. Participants randomized to the e-cigarette

group reported scores of 6 [4-7], 5.5 [2.5-7], and 6 [5-7], respectively, while participants randomized to the NRT group reported scores of 5 [3-7], 5 [3-6], and 7 [6-7], respectively for the following questions. “The product is helpful for quitting smoking”, “I was satisfied with the product to help with quitting”, “I would recommend the product to someone interested in quitting smoking”.

Risk of bias across studies

The review process we used was thorough, and we took every precaution to minimize the risk of bias due to publication bias or selective reporting. We reached out to clinical experts to enquire about unpublished reports, examined protocol registries, and contacted the authors of identified protocols to request unpublished results. Given the low number of retained studies, we did not include a funnel plot.

Sensitivity, subgroup and meta-regression analyses

We performed a sensitivity analysis for the smoking cessation outcome by removing the Lee SM 2018 study[22]. While the other 4 studies aimed to assess smoking cessation in general, Lee et al were targeting a peri-operative population, who may have had different motivations to quit smoking. The pooled data, once Lee SM 2018[22] is removed, yield a RR of smoking abstinence of 1.39 [0.92, 2.11] when comparing ENDS to NRT (Figure 4a).

We had planned on undertaking multiple subgroup analyses. We were unable to perform the subgroup analyses based on age (all participants were adults), smoking intensity (no study enrolled smokers $\geq$ 25 cigarettes per day), or biochemically validated smoking cessation (all studies used biochemical validation). We also could not perform a subgroup analysis of studies with ties to industry as only Bullen 2013[18] was found to have ties to the vaping industry.

We did, however, perform the following subgroup analyses: limiting comparator to nicotine patches (Bullen 2013[18] and Lee SM 2018[21]), and including only studies assessing continuous/sustained smoking abstinence $\geq$ 6 months given that smoking cessation is defined as sustained abstinence for at least 6 months;[23] (Bullen 2013,[18] Hajek 2019,[4] Lee SH 2019[21]) (Figures 4b and 4c, respectively).

Metaregression analyses were not performed as our threshold of 10 eligible studies was not met.

DISCUSSION

In our review, there was no significant difference in smoking cessation, smoking reduction, or harms between e-cigarette and NRT users. However, we report on results from a limited number of RCTs, and the level of evidence is low. Our efficacy results are similar to those described in a 2016 Cochrane review,[5] which also showed no difference between abstinence rates between the nicotine e-cigarette group and NRT group. Their review only included one study[18] , also included in our review for this particular outcome. Similar to the evidence we are

presenting, none of the studies examined in the Cochrane review reported serious adverse events considered to be related to e-cigarette use.

Although our meta-analysis of the 5 trials that examined ***smoking cessation*** showed no significant difference between e-cigarette and nicotine replacement therapy, there was a trend towards favoring e-cigarettes. Interestingly, our sensitivity analysis limiting inclusion to studies reporting smoking cessation of 6 months or greater yielded a smaller point estimate than the one obtained from the main analysis, although still with no difference between groups. It could be hypothesized that additional benefits that may be attributed to e-cigarette early on in smoking cessation may be attenuated as time progresses. This again should be interpreted with caution given the small number of studies[4,18,20] and the very significant heterogeneity.

In all comparisons, our results need to be interpreted carefully. There was significant clinical heterogeneity between studies in terms of the population enrolled, smoking intensity at baseline, type and nicotine concentration of e-cigarettes, type and dose of NRT, as well as methodological heterogeneity in terms of study conduct, and intervention and control protocols. For instance, one of the included studies[18] used first-generation e-cigarettes, with nicotine delivery about 20% of that obtained from cigarette smoking. While e-cigarette users were couriered the supplies needed, NRT users had to redeem vouchers from community pharmacies to obtain their patches. The low nicotine content of the e-cigarettes, the extra step in obtaining NRT supplies, and the low intensity of additional co-interventions likely contributed to the low rate of smoking abstinence at 6 months in both groups, limiting the generalizability of the results. Another included study[4] allowed for multiple types and concentrations of ENDS, as well as upwards of 10 NRT products and doses, complicating the interpretation of the results. Nicotine concentrations reported in the trials ranged from 0.01 to 48 mg/mL,[4,18,20-22] making comparisons between studies difficult.

Given that the risk of bias was assessed as high in 5 of 6 included studies[4,18-21], our smoking cessation outcome results need to be interpreted with caution. In addition, it is interesting to note that all studies verified self-reported smoking cessation with an exhaled carbon monoxide test, however different cut-off values were used. Additionally, there are limitations to using carbon monoxide (CO) as a way to verify smoking cessation. CO has a relatively short half-life and is eliminated from the body within 24 hours; it can, therefore, lead to false negative results. However, this issue is somewhat mitigated by the fact that smoking cessation study participants tend to be daily smokers.

All studies included in this review examined ***smoking reduction***. There was no difference between groups in the mean reduction of cigarettes from baseline in the studies that measured that outcome, or in the proportion of participants successfully reducing their smoking consumption.

None of the included studies reported severe ***adverse events*** related to ENDS or NRT, and, for the four studies with data that could be pooled, there was no difference between groups in terms of harms related to either therapy. However, in addition to the clinical heterogeneity

mentioned above, there was significant methodological heterogeneity in how adverse events were collected. We evaluated the quality of the evidence as very low, given the high risk of bias of included studies, the significant heterogeneity, and the inability to accurately determine the number of subjects involved in this outcome, thus leading to result imprecision.

Since the included trials were powered to detect a difference in the primary outcome, it is possible that rare or unexpected harms were not detected due to a lack of power for this specific outcome. Also, it is important to acknowledge that these studies are limited by their short time-frame. Data on long-term side effects of ENDS are lacking. The recent e-cigarette, or vaping product use-associated lung injury (EVALI) epidemic, is a reminder that further research is needed before widespread recommendations can be made with regards to the use of ENDS. In addition, there are now emerging concerns that respiratory disease caused by the novel coronavirus SARS-CoV-2, the virus responsible for the COVID-19 pandemic, could be exacerbated by exposure to ENDS.[24-26]

Finally, although there seemed to be ***increased acceptance of therapy*** towards e-cigarettes in the four studies that considered it,[4,18,20,22] high risk of bias, significant heterogeneity, and the small number of studies using widely different scales leading to imprecise measures, mean that the results should be interpreted with extreme caution. In addition, given that the trials were unblinded, participants who were disappointed with their treatment allocation may have reported less acceptability than their counterparts.

Limitations at review level

We restricted our search to RCTs to try to minimize the risk of bias, however, this considerably limited the number of available studies for this review. It is surprising that, given the widespread availability of e-cigarettes and how aggressively they have been marketed as smoking cessation agents, there are so few head-to-head trials comparing ENDS and traditional NRT. While there may be some unpublished studies that our review did not capture, our literature search was thorough and included personal communications to multiple experts in the field.

Our review identified 7 ongoing trials[27-33] that potentially met our inclusion criteria, totaling over 1500 targeted participants. None of the investigators had any data ready to be shared, however it is hoped that this ongoing research can shed light on the effectiveness of ENDS as smoking cessation tools, as compared to traditional NRTs. Long-term research is also needed to investigate the long-term effects of ENDS, as well as the optimal dosing and method of delivery.

Conclusion

We found no difference in smoking cessation, harms, and smoking reduction between e-cigarette and NRT users. However, the quality of the evidence was low. Further research is needed before widespread recommendations can be made with regards to the use of ENDS. Research is also needed to investigate the long-term effects of ENDS, as well as optimal dosing.

Acknowledgements

We thank Katie O'Hearn, MSc, (Children's Hospital of Eastern Ontario Research Institute), Dr Matthew McInnes, and Dr Dean Fergusson (University of Ottawa), for methodological assistance.

Data sharing

Data collection forms and all raw data can be requested through the corresponding author.

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30. ACTRN12617001324303. Comparing electronic-cigarettes to traditional oral nicotine replacement therapy for smoking cessation among low-socioeconomic status smokers: a randomised controlled trial
31. NCT03249428. E-Cigarette Inner City NRT
32. ACTRN12619001787178. Project NEAT: nicotinE As Treatment for tobacco smoking following discharge from residential withdrawal services
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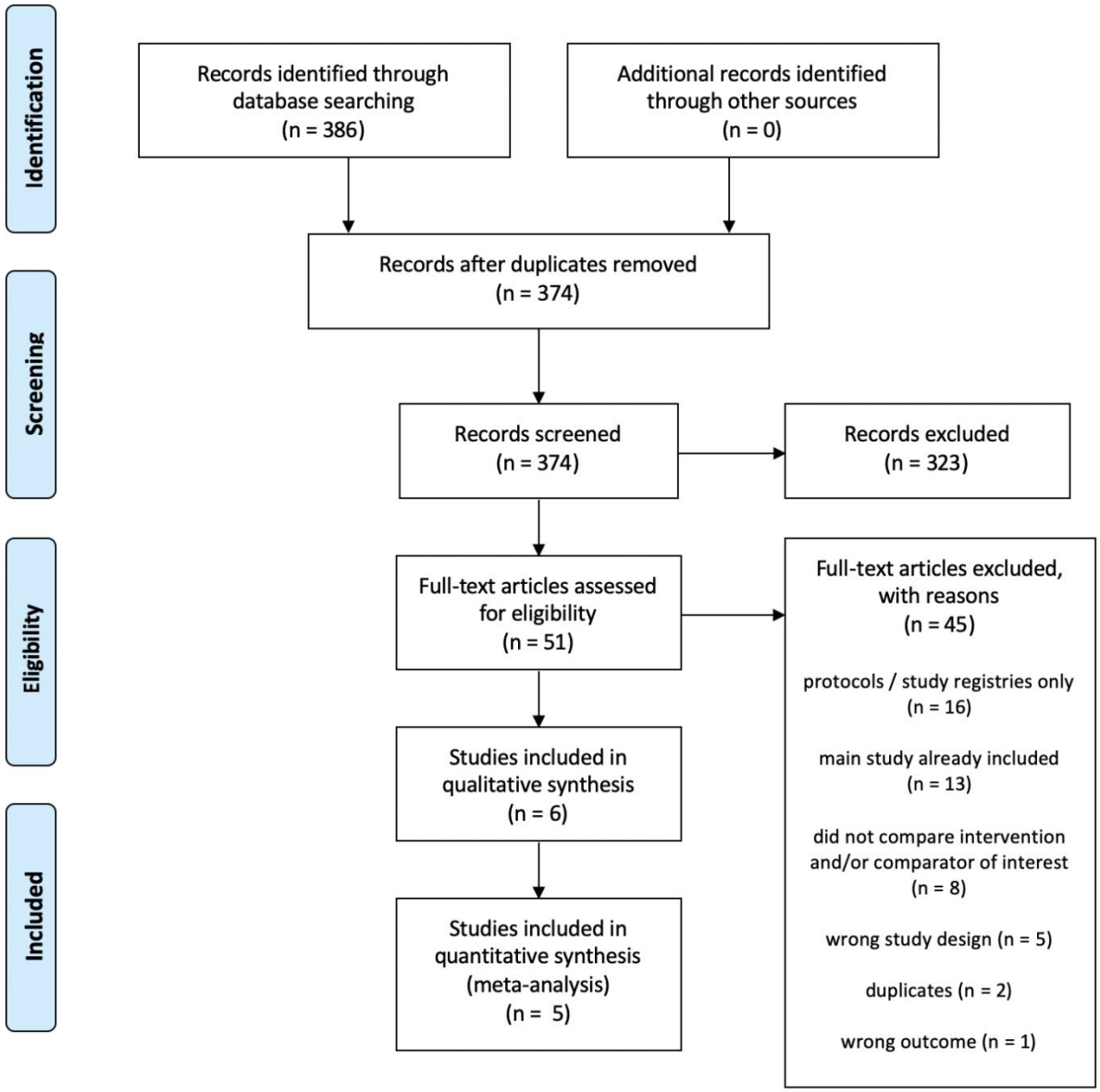
Figure 1. Study flow diagram



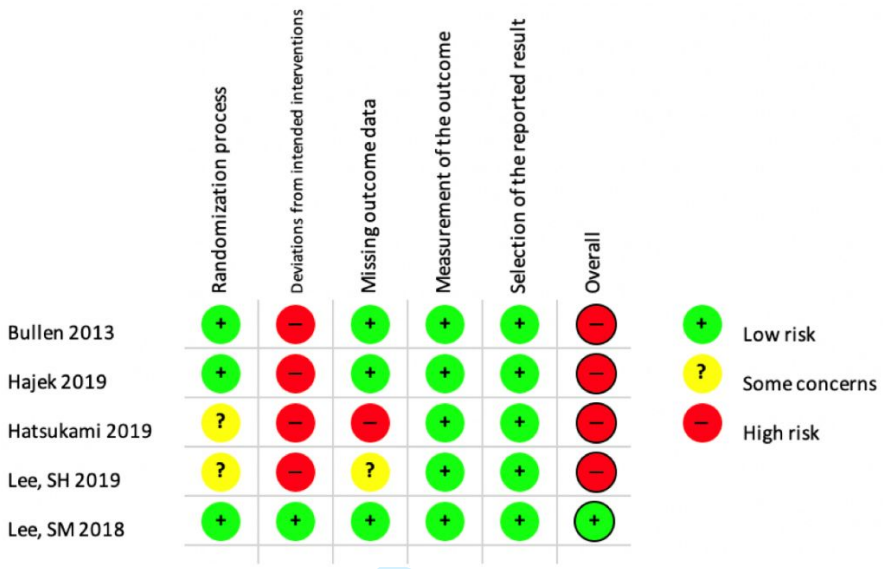


Figure 2a
Risk of bias for smoking cessation outcome

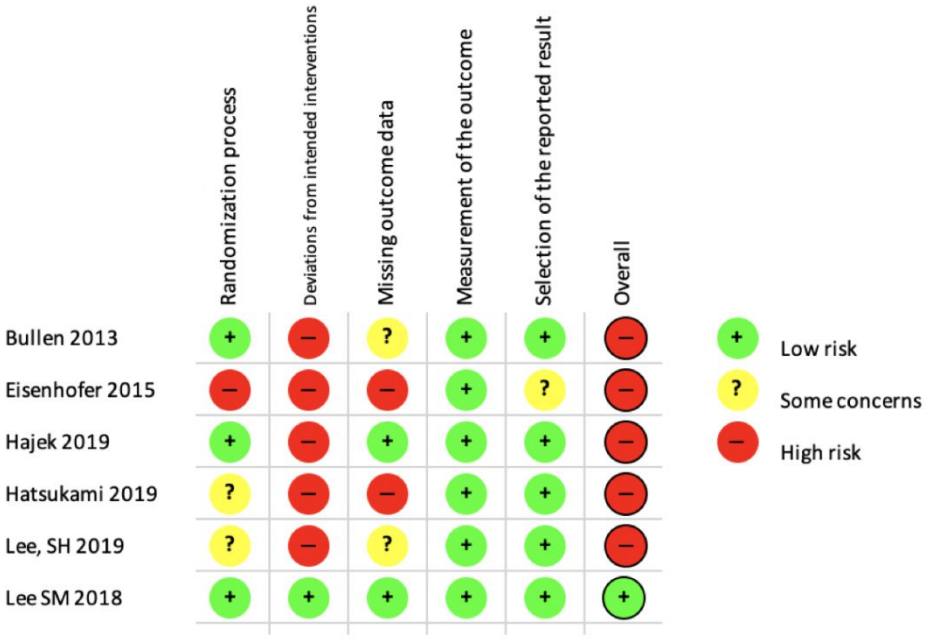


Figure 2b
Risk of bias for smoking reduction outcome

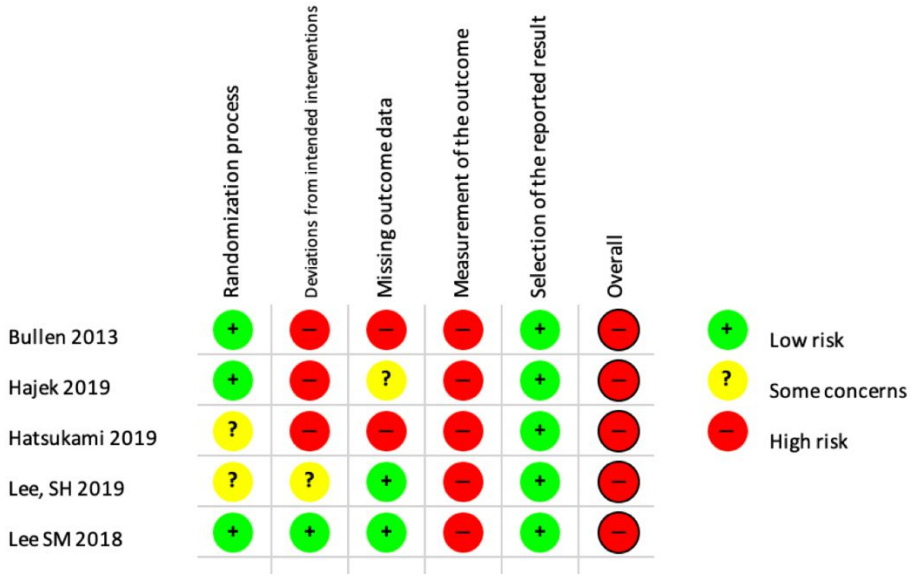


Figure 2c
Risk of bias for harms outcome

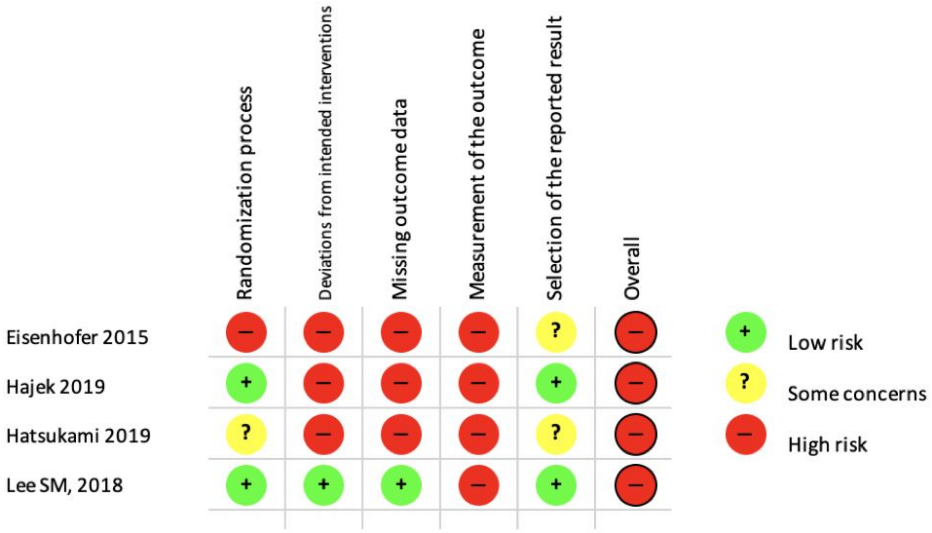


Figure 2d
Risk of bias for withdrawal symptoms outcome

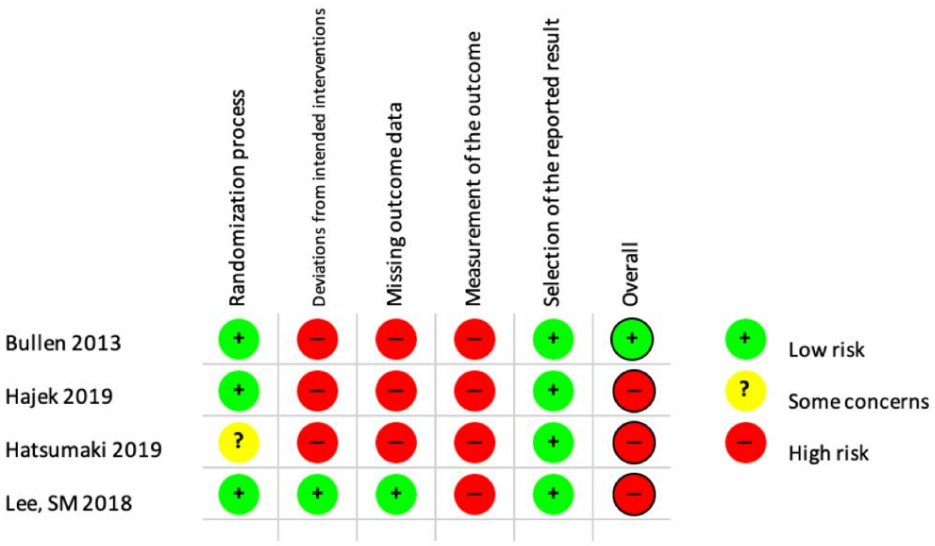


Figure 2e
Risk of bias for acceptance of therapy outcome

Study or Subgroup	ENDS Events	ENDS Total	NRT Events	NRT Total	Weight	Risk Ratio IV, Random, 95% CI
Bullen	21	289	17	295	20.5%	1.26 [0.68, 2.34]
Hajek	79	438	44	446	32.2%	1.83 [1.30, 2.58]
Hatsukami	25	76	13	76	21.5%	1.92 [1.07, 3.47]
Lee SH	16	75	21	75	22.4%	0.76 [0.43, 1.34]
Lee SM	5	20	1	10	3.4%	2.50 [0.34, 18.63]
Total (95% CI)		**898**		**902**	**100.0%**	**1.42 [0.97, 2.09]**
Total events	146		96			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 8.00$, df = 4 (P = 0.09); $I^2 = 50\%$
Test for overall effect: Z = 1.80 (P = 0.07)

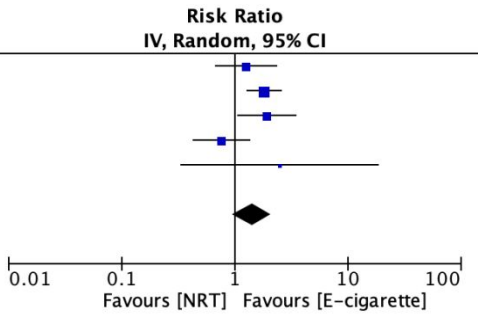


Figure 3a Smoking cessation

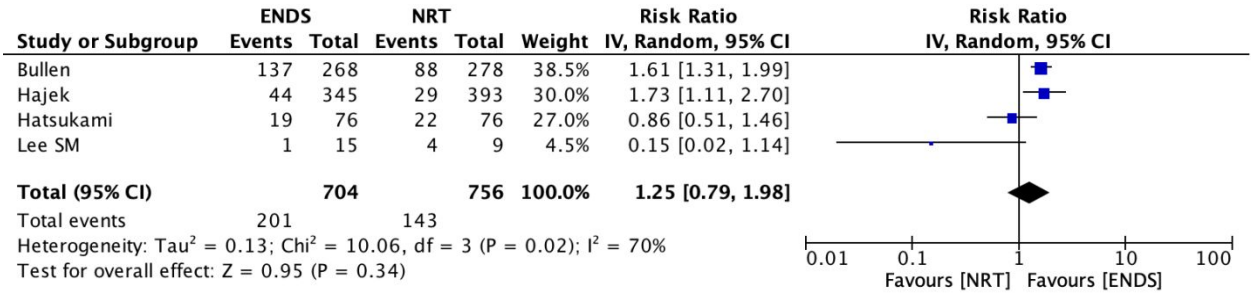


Figure 3b Proportion of participants successfully reducing smoking consumption by 50%

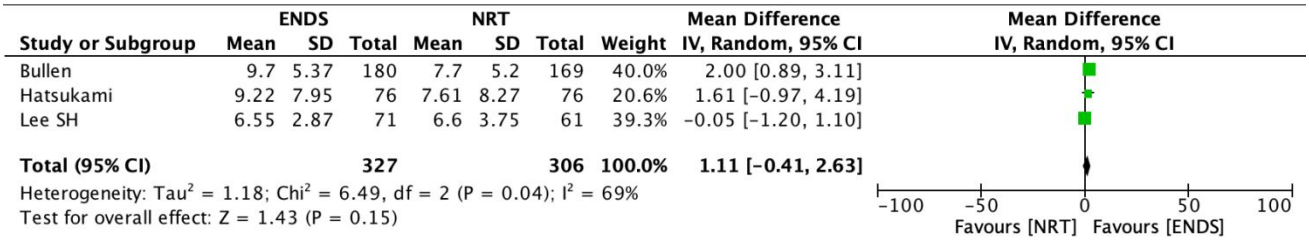


Figure 3c Mean reduction of cigarettes from baseline

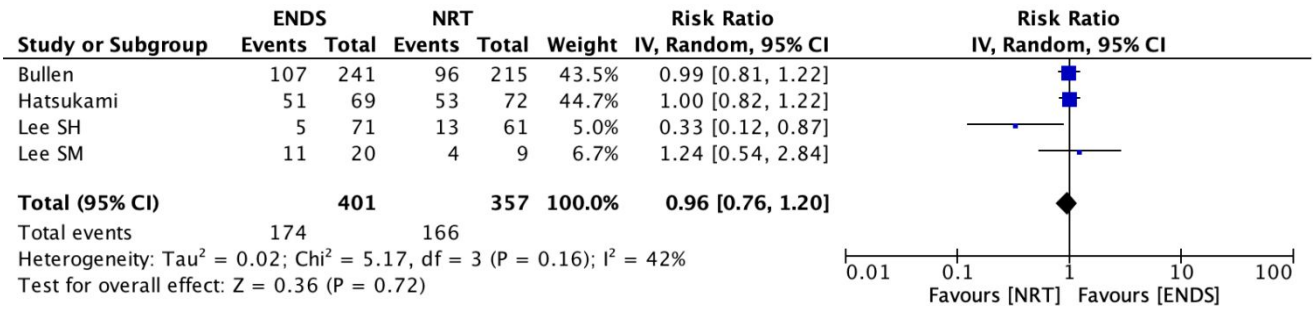


Figure 3d Proportion of participants experiencing adverse events

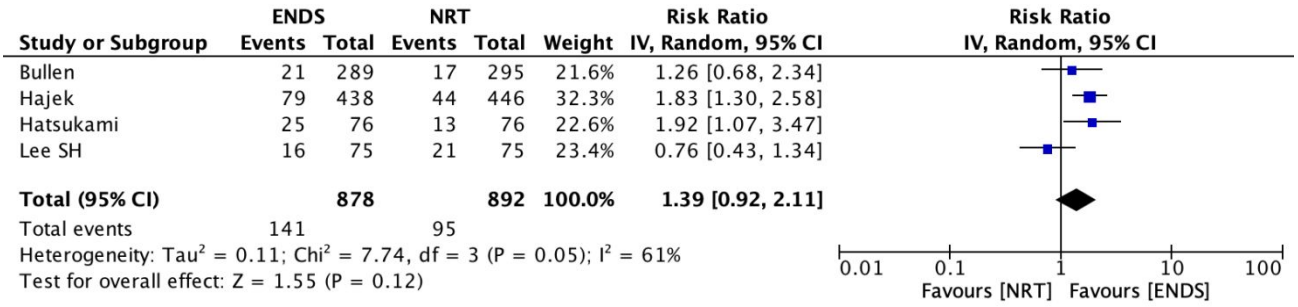


Figure 4a Sensitivity Analysis—Smoking cessation, for studies examining smoking cessation in the general population

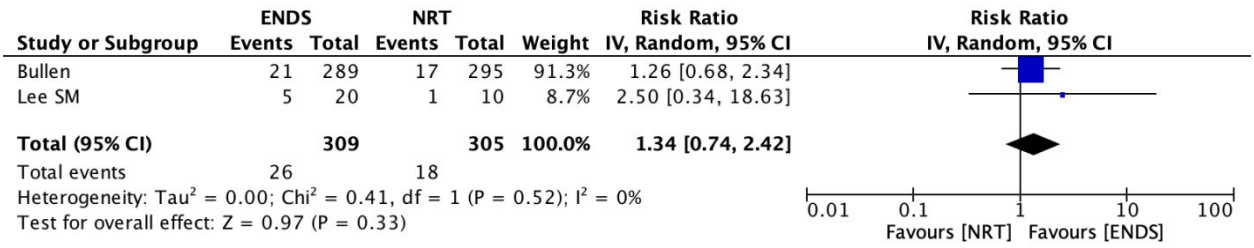


Figure 4b Subgroup Analysis—Smoking cessation, comparing e-cigarettes to nicotine patches only

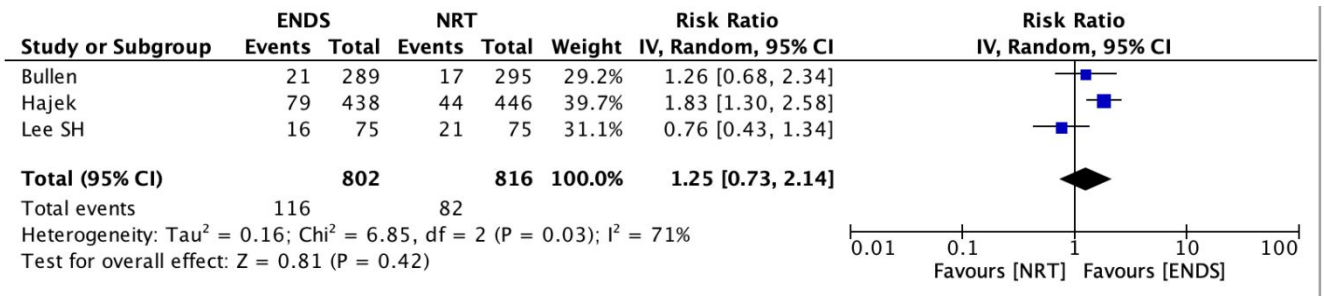


Figure 4c Subgroup Analysis— Continuous/sustained abstinence, 6 months and greater only

Supplementary Material 1
Search strategies

MEDLINE, Embase, CENTRAL

Note: Searches were conducted using an Ovid multi-database search and duplicate records were removed online giving preference to MEDLINE, then Embase, with no field preference. Lines 1-3 are optimized for MEDLINE and the main question constructs are broken out in separate lines for clarity. Lines 4-7 are optimized for Embase and lines 8-10 are optimized for CENTRAL. The next lines isolate the records to the database the search was designed for, combine those sets and then remove duplicate records and final isolate the records from each database again so each can be downloaded and imported into the citation manager using a database-specific import filter.

1. Electronic Nicotine Delivery Systems/ or (e cig* or electr* cigar* or electronic nicotine).mp. or (vape or vaper or vapers or vaping or non-combustible nicotine-containing product).ti,ab,kf.
2. exp "Tobacco Use Cessation Devices"/ or NRT.ti,ab,kf. or (nicotine adj2 (patch* or gum or nasal spray or mouth spray or mouth strips or lozenge* or tablet* or microtab* or sublingual or replac*)).mp. or (nicotine adj3 therapy).mp.
3. (1 and 2 and ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.)) not exp animals/ not humans.sh.
4. Electronic Cigarette/ or (e cig* or electr* cigar* or electronic nicotine).mp. or (vape or vaper or vapers or vaping or non-combustible nicotine-containing product).ti,ab,kw.
5. Nicotine Replacement Therapy/ or NRT.ti,ab,kw. or (nicotine adj2 (patch* or gum or nasal spray or mouth spray or mouth strips or lozenge* or tablet* or microtab* or sublingual or replac*)).mp. or (nicotine adj3 therapy).mp.
6. 4 and 5 and (Crossover-Procedure/ or Double-Blind Procedure/ or Randomized Controlled Trial/ or Single-Blind Procedure/ or (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).ti,ab,kw.)
7. limit 6 to embase
8. (e cig* or electr* cigar* or electronic nicotine).mp. or (vape or vaper or vapers or vaping or non-combustible nicotine-containing product).ti,ab,kw.
9. NRT.ti,ab,kw. or (nicotine adj2 (patch* or gum or nasal spray or mouth spray or mouth strips or lozenge* or tablet* or microtab* or sublingual or replac*)).mp. or (nicotine adj3 therapy).mp.
10. 8 and 9
11. 3 use medall
12. 7 use emczd
13. 10 use cctr
14. 11 or 12 or 13
15. remove duplicates from 14
16. 15 use medall
17. 15 use emczd
18. 15 use cctr

ClinicalTrials.gov
(electronic cigarette OR vape OR vaping OR electronic nicotine) AND (nicotine replacement OR NRT OR patch OR gum OR nasal spray OR mouth spray OR mouth strips OR lozenge OR tablet OR microtab OR microtablet OR sublingual) | Interventional Studies
91 records retrieved

WHO ICTRP
electronic cigarette OR vape or vaping OR electronic nicotine
153 records retrieved with 20 remaining after records with a TrialID starting with NCT were removed prior to screening

Note: As the ICTRP registry has limited search capabilities[35], only terms related to the intervention were used and protocols with a NCT number were removed from the retrieval, as those protocols would also be included in ClinicalTrials.gov.

Supplementary Material 2
Abstracted data

The abstracted data included the following:

1- *study characteristics*:
author names, year of publication, ties with tobacco industry, funding of study, country of study, study setting, study design, number of participating sites, recruitment procedures, enrolment dates, length of study period, random sequence generation, allocation sequence concealment, blinding, methods for preventing and controlling confounding, selection bias, information bias and missing bias, unit of analysis, covariates inclusion, funding, financial and conflict of interest disclosure including ties with industry, inclusion and exclusion criteria, sample size, number of participants that were analyzed, number of participants lost to follow up for each outcome and for the whole study, number of participants at study onset and randomized to each group, and type of analysis (intention to treat vs per protocol)

2- *participant characteristics:*
age, gender, comorbidities, ethnicities, socio-economic status, income, education, cigarettes smoked per day, Fagerström test for cigarette dependence

3- *intervention characteristics:*
type, model, brand and generation of ENDS, type and flavor of e-liquid, nicotine content, intervention protocol, length of time ENDS were provided free of charge, frequency of use, duration of intervention, integrity of intervention, description of co-interventions

4- *comparator characteristics:*
type of nicotine replacement therapy used, dose, frequency of use, nicotine content, control protocol, frequency of use, length of time supplies were provided free of charge, combination of products, frequency of use duration of control, integrity of control, description of co-interventions

5- *outcomes:*
smoking cessation, method of assessment for smoking cessation used (self-report vs biochemical), smoking abstinence definition, longest time point of smoking cessation, harms assessment, methods of harms assessment, definition of harms, withdrawal symptoms, method of assessment for withdrawal symptoms, reduction in cigarettes smoked, method of assessment of reduction in cigarettes smoked, number of quit attempts, method of quit attempt measurement, acceptance of ENDS/NRT, method of acceptance assessment, method of aggregation used for each outcome, timing of measurement for each outcome, summary data for each outcome, method of aggregation used for each outcome.

Supplementary Material 3
Detailed description of the included studies

Supplementary Table 1a. Characteristics of randomized controlled trials measuring smoking cessation at 6 months or later Characteristics of randomized controlled trials measuring smoking cessation at 6 months or later

Bullen, 2013	
Methods	**Design**: 3 parallel groups RCT **Recruitment:** Participants were recruited via community newspapers, inviting people to call the study centre for eligibility pre-screening **Setting**: one single center in Auckland Australia **Inclusion criteria:** 18 years of age or older, smoked 10 or more cigarettes per day for the past year, and wanted to quit smoking. **Exclusion criteria:** Pregnant or breastfeeding women, people using smoking cessation drugs, those reporting heart attack, stroke, severe angina in the previous 2 weeks, and people with poorly controlled medical disorders allergies, or other chemical dependence were excluded
Participants	**Total N:** 657 smokers were included in this study, but we only extracted 584 participants for our review (2 of the 3 groups) as the e-cigarette placebo group did not fit our eligibility criteria. Most participants were women (62%), of a mean age > 40. Approximately one third were of Maori descent, and a little over half had completed grade 12 or above education level. The average daily number of cigarettes smoked at study onset was around 18, and mean Fagerström test result (0 to 10 scale) for cigarette dependence was > 5.
Interventions	**Randomization:** 4:4:1 ratio to nicotine e-cigarettes, nicotine patches and placebo e-cigarette group **Nicotine e-cigarette group** Participants were couriered a first-generation e-cigarette, spare battery and charger, as well as cartridges containing 10 to 16mg of nicotine per mL (although labelled to contain 16 mg), plus simple instructions to use the e-cigarettes as desired from 1 week before until 12 weeks after their chosen quit day. Participants received on average around 20% of the nicotine obtained from cigarette smoking. **Nicotine patch group** Participants were sent exchange cards in the mail redeemable for nicotine patches 21 mg from community pharmacies, with instructions to use the patches daily, from 1 week before until 12 weeks after their chosen quit day. Vouchers were also supplied to participants to cover dispensing costs. **Both groups**

	Participants in all groups were also referred to telephone-based behavioural support
Outcomes	Continuous abstinence at 6 months after quit day, defined as self-reported abstinence over the whole follow-up period allowing for 5 or less cigarettes in total, was self-reported, and verified with exhaled breath carbon monoxide of <10 ppm. Harms were both clinically assessed and self-reported, throughout the study period. Withdrawal symptoms were assessed at 1, 3, and 6 months. Reduction in daily cigarettes smoked was measured at 6 months, and acceptance of therapy was measured at 1 and 6 months.
Notes	Some of this study's authors reported ties to e-cigarette manufacturers, and smoking cessation drug companies
Hajek, 2019	
Methods	**Design:** 2 parallel groups RCT **Recruitment:** Participants were recruited through stop smoking services, which included trial information in their advertising. Participants were also recruited through social media, and leaflets advertising the trial were delivered to local households. **Setting:** 3 sites in the United Kingdom **Inclusion criteria**: Adults, with no strong preference towards e-cigarette or NRT, who were not using either type of product at the time of study enrolment **Exclusion criteria:** Pregnant women or breastfeeding women
Participants	**Total N:** 884 participants were included in this study Median age for both groups was 41, and women comprised 48% of participants. Most participants were White British, and the majority had post-secondary education. Median daily number of cigarettes smoked at study onset was 15, and mean Fagerström test result for cigarette dependence was 4.5 in the e-cigarette group and 4.6 in the NRT group.
Interventions	**Randomization:** nicotine-containing e-cigarettes of varying doses, and any choice of a list of NRT, in a 1:1 ratio **E-cigarette group** Participants were provided with a starter pack called One Kit, which included an atomizer, a battery, and one 30 mL bottle of Tobacco Royale flavor e-liquid. Participants were asked to purchase their future e-liquid online or from local vape shops and to buy a different e-cigarette device if the one supplied did not meet their needs. They were encouraged to experiment with e-liquids of different strengths and flavors. Those who were unable to obtain their own supply were provided with one further 10-ml bottle, but this was not offered proactively. Participants received oral and written information on how to operate the e-cigarette.

	NRT group Participants were informed about the range of nicotine-replacement products (patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs) and selected their preferred product. Use of combinations was encouraged, typically the patch and a faster-acting oral product. Participants were also free to switch products.ps **Both groups** Participants in both groups were offered multisession behavioral support as per UK stop smoking service practice, involving weekly one on one session with local clinicians. Participants were also asked to sign a commitment to not use the unassigned treatment for 4 weeks
Outcomes	Continuous abstinence at 52 weeks after quit day, defined as self-reported abstinence over the whole follow-up period allowing for 5 or less cigarettes in total, was self-reported, and verified with exhaled breath carbon monoxide of <8 ppm. Harms were self-reported throughout the study period. Withdrawal symptoms were assessed at 1 and 4 weeks in abstainers. Reduction in daily cigarettes smoked was also measured at 52 weeks, as well as acceptance of e-cigarettes and NRT
Notes	Some of this study's authors reported ties to smoking cessation drug companies.
Lee SH, 2019	
Methods	**Design:** 2 parallel groups RCT **Recruitment:** Participants were recruited from a motor company in the Republic of Korea. **Setting:** One site in Cheonan, Republic of Korea **Inclusion criteria:** Participants were adults 18 years and above, male, who smoked at least 10 cigarettes per day in the preceding year, and who were motivated to stop smoking entirely or to reduce their cigarette consumption **Exclusion criteria:** Participants were excluded if they had a past medical history of serious clinical diseases or had attempted to stop smoking in the last 12 months by using other NRT.
Participants	**Total N:** 150 participants were included in the study Mean age was 42 years and all participants were men. Almost 40% had post-secondary education. Median daily number of cigarettes smoked at study onset was 1 pack per day, and mean Fagerström test result for cigarette dependence was 4.
Interventions	**Randomization:** nicotine-containing e-cigarettes, and nicotine gum in a 1:1 ratio **E-cigarette group**

	Participants received a 24-week supply of e-cigarettes eGo-C Ovale, Janty-Korea Co., Janty-Asia Co., Seoul, Republic of Korea, nicotine 0.01 mg/mL. **Nicotine gum group** Participants received a 24-week supply of nicotine gum Nicoman, Daewoog Pharmaceutical, Seongnam, Republic of Korea, 2 mg/tablet **Both groups** Participants in both groups were offered 55-minute education sessions on smoking cessation aids
Outcomes	Continuous abstinence was defined as abstinence from smoking from 9 to 24 weeks, validated with end-expiratory carbon monoxide (<10 ppm) and a negative urine cotinine result. Harms were self-reported throughout the study period. Reduction in daily cigarettes smoked was also measured at 24 weeks.
Notes	None of the study authors were found to have ties to industry.
Lee SM, 2018	
Methods	**Design:** 2 parallel groups RCT **Recruitment**: Participants were recruited from an anesthesia preoperative clinic for elective surgery. **Setting:** San Francisco Veterans' Affairs Medical Center, affiliated with the University of California in San Francisco United States of America **Inclusion criteria:** Participants were eligible if they presented to the clinic 3 or more days prior to elective surgery, smoked more than two cigarettes per day, and had smoked at least once in the last 7 days **Exclusion criteria**: Participants were excluded if they exclusively used other forms of tobacco (e.g. pipe tobacco) or marijuana only, were pregnant or breastfeeding, had an unstable condition, were using smoking cessation therapy at the time of study enrolment or were in another smoking cessation trial, or currently used e-cigarettes daily.
Participants	**Total N:** 30 participants were included in this study Most participants were men (90%) in their 50's. Some had comorbidities including diabetes, hypertension, heart disease, and chronic obstructive pulmonary disease. Most were Caucasians. The average daily number of cigarettes smoked at study onset was 15.3 in the e-cigarette group, and 10.8 in the NRT group, and the mean Fagerström test result for cigarette dependence was 3.7 in the e-cigarette group and 2.5 in the NRT group.
Interventions	**Randomization:** e-cigarettes and nicotine patches in a 2:1 ratio **E-cigarette group** Participants received a 6-week supply of NJOY e-cigarettes (Scottsdale, AZ, USA), a disposable first-generation e-cigarette that is available in shops and online. They were issued a number of e-cigarettes corresponding to

	the reported baseline cigarettes smoked per day, calculated assuming one NJOY e-cigarette was equivalent to 10 cigarettes. Participants were instructed to smoke bold (4.5%) e-cigarettes ad libitum for 3 weeks, then the Gold (2.4%) e-cigarettes ad libitum for 2 weeks, and then the Study (0%) e-cigarettes ad libitum for the final week. **Nicotine patch group** Participants randomized to the nicotine patches group were given a 6-week supply of Nicoderm CQ patches (5 weeks) and placebo patches (1 week) appropriate to baseline nicotine consumption. Those smoking an average of ten or more cigarettes per day were given a 21 mg/day patch for 3 weeks, a 14 mg/day patch for 1 week, a 7 mg/day patch for 1 week, and a 0 mg/day patch for 1 week. Participants who reported smoking an average of fewer than 10 cigarettes per day at baseline were given a 14 mg/day patch for 3 weeks, a 7 mg/day patch for 2 weeks, and a 0 mg/day patch for 1 week. **Both groups** Participants in both groups were given referral California Smokers' Helpline and were asked to refrain from the use of cigarettes during the study period.
Outcomes	Smoking cessation at 6 months was self-reported through 7-day point-prevalence abstinence and verified with exhaled breath carbon monoxide of <10 ppm. Harms and withdrawal symptoms were systematically collected at 8 weeks. Reduction in daily cigarettes smoked was also measured at 6 months, as well as acceptance of e-cigarettes and NRT.
Notes	None of the study authors were found to have ties to industry.

Supplementary Table 1b. Characteristics of randomized controlled trial measuring smoking cessation earlier than 6 months

Hatsukami, 2019	
Methods	**Design:** 4 parallel groups RCT **Recruitment:** Participants were culled from two sets of studies, one of which also included two groups randomized to snus (spitless smokeless tobacco); one was complete substitution with snus, and the other was ad libitum use. Due to recruitment challenges, the two snus groups were dropped midway through the study, resulting in four experimental groups: ad libitum use of e-cigarettes (participants may smoke as many cigarettes as they like), complete substitution with e-cigarettes (aiming for smoking

	cessation), complete substitution with NRT, continued smoking with usual brand of cigarettes. Participants were recruited through various media outlets across three institutions. The advertisements stated that a study was recruiting smokers who were interested in trying a product that may reduce exposure to harmful tobacco smoke. **Settings:** 3 sites, University of Minnesota, Twin Cities (lead site); The Ohio State University, Columbus, OH; Roswell Park Cancer Center, Buffalo, NY United States of America **Inclusion criteria:** Participants were adults at least 18 years of age, smoked at least 5 cigarettes per day with a breath carbon monoxide test of at least 10 ppm or a NicAlert test = level 6, and in stable physical and mental health. **Exclusion criteria:** Participants were excluded if they had a serious quit attempt in the past 3 months, recent (<3 months) alcohol or drug abuse problems, regular use of other nicotine or tobacco products, were planning to quit smoking in the next 3 months, suffered from chronic conditions affecting results of biomarker analyses, were currently using NRT or other cessation medication, or if they were pregnant or planning to become pregnant, or breastfeeding
Participants	**Total N:** 264 participants were included in the study, but data for this review were only extracted from the complete substitution with e-cigarette group, and complete substitution with NRT group (152 participants), as the other two groups did not fit our eligibility criteria. Median age was 47 years, and women comprised 49% of participants. Most participants were White, and the majority had post-secondary education. The median daily number of cigarettes smoked at study onset was 15, and median Fagerström test result for cigarette dependence was 3.
Interventions	**Randomization:** e-cigarettes and nicotine gum or lozenges **E-cigarette group** Participants randomized to this group used Vuse Solo, manufactured by RJ Reynolds Inc as the primary e-cigarette. Early in the study, Blu e-cigarettes (cartridge-based system) and Fin (prefilled tanks system) were used, but Vuse attained the highest market share early on so the study switched exclusively to Vuse. E-cigarettes with a 4.8% nicotine concentration were provided to participants free of charge for 8 weeks, as well as 7 cartridges weekly, with the option of returning to the clinic to obtain additional cartridges if needed. Tobacco, menthol, mint, and berry flavors were available. **NRT group**

	Participants could choose between mint, cinnamon or fruit-flavored nicotine gum or nicotine lozenge, at a dose of 4 mg. If adverse effects were recorded, the dose was decreased to 2 mg. **Both groups** After randomization, participants were asked to complete daily diaries via interactive voice recording to chart the number of cigarettes smoked daily, as well as document assigned product use for the duration of the trial. Participants received a monetary bonus if they complied with the protocol; this included keeping an accurate record of product use, completing the daily diaries, and returning unused products. They also got a bonus payment if they had a carbon monoxide level $\leq$ 4 ppm at each visit. Participants also received a brief counseling session on how to avoid smoking.
Outcomes	Smoking cessation was determined by 7-day point prevalence at 8 weeks, mainly through biochemical verification but also by self-report Reduction in daily cigarettes smoked was also measured at 8 weeks, as well as acceptance of e-cigarettes and NRT. Harms were assessed systematically at 20 weeks, 12 weeks after the end of the study period. Withdrawal symptoms were assessed at weeks 1, 2, 4, 6, and 8.
Notes	One of the study authors is a member of the FDA Tobacco Products Scientific Advisory Committee and another one has served as an expert witness in tobacco company litigation.

Supplementary Table 1c. Characteristics of randomized controlled trial measuring other outcomes

Eisenhofer, 2015	
Methods	**Design:** 2 parallel groups RCT **Recruitment:** Not specified **Setting:** Not specified **Inclusion criteria:** Veterans who met criteria for tobacco disorder as per the DSM **Exclusion criteria:** Not specified
Participants	**Total N:** 11 participants were included Mean age was 52, and 82% were males. The vast majority of participants were African American. The average daily number of cigarettes smoked at study onset was 26.5, and the mean Fagerström test result for cigarette dependence was 7.5.
Intervention	**Randomization:** e-cigarettes and nicotine patches **E-cigarette group**

	Participants received nicotine-containing e-cigarettes with 16 mg of nicotine per cartridge **NRT group** Participants received nicotine patch 16 mg daily **Both groups** All participants were instructed to smoke ad libitum during week 1, and to smoke as little as possible during week 3.
Outcomes	Reduction in cigarettes smoked per day was self-reported at 3 weeks and compared to week 1. Withdrawal symptoms were compared between week 1 and week 3.
Notes	This study was available as an abstract only therefore limited details are available.

Supplementary Material 4
Details on Risk of Bias Assessment for each outcome of interest

Supplementary Table 2. Detailed description of concerns for each domain marked identified as "some concerns" or "high risk" on Risk of Bias Assessment

Smoking cessation outcome					
	Randomization Process	**Deviations from intended intervention**	**Missing of outcome data**	**Measurement of the outcome**	**Selection of the reported result**
Bullen 2013	Low risk	Adherence higher in the ENDS group compared to NRT group at all timepoints. At 6 months, 29% of ENDS group vs 8% of NRT group still using assigned treatment.	Low risk	Low risk	Low risk
Hajek 2019	Low risk	At 52 weeks among participants with 1-year abstinence, 80% were using e-cigarettes in the ENDS group vs 9% in the NRT group. Also, 6% of participants in the ENDS group reported using non-allocated NRT for at least five consecutive days in the past six months compared to 22% in the NRT group that reported using non-allocated product	Low risk	Low risk	Low risk
Hatsukami 2019	No information provided with regards to randomization process and allocation concealment. However, there were no	The NRT group had the highest dropout rates compared to the other groups in the study. At 8 weeks, 24% dropped out in the ENDS group compared to 30% in the NRT group.	Large number of dropouts; participants who did not stop smoking could be less motivated to continue with study follow up	Low risk	Low risk

	significant baseline differences between groups				
Lee, SH 2019	The use of constant block sizes of 2 makes it easy to determine order of randomization.	No participants discontinued the intervention. However, 4 and 14 participants in the ENDS and NRT group dropped out before treatment, respectively.	Although data was missing for 12% of randomized individuals, all dropouts occurred prior to the start of treatment. Missingness in this case less likely to be due to the value of the outcome as it happened prior to onset of therapy	Low risk	Low risk
Lee, SM 2018	Low risk	Low risk	Low risk	Low risk	Low risk
Smoking reduction outcome					
Bullen 2013	Low risk	Refer to smoking cessation outcome	Sensitivity analyses conducted for the smoking cessation outcome were not performed for the smoking reduction outcome	Low risk	Low risk
Eisenhofer 2015	Not enough information available in abstract	Not enough information available in abstract	Not enough information available in abstract	Low risk	Not enough information available in abstract
Hajek 2019	Low risk	Refer to smoking cessation outcome	Low risk	Low risk	Low risk
Hatsukami 2019	Refer to smoking cessation outcome	Refer to smoking cessation outcome	Refer to smoking cessation outcome	Low risk	Low risk
Lee, SH 2019	Refer to smoking cessation outcome	Refer to smoking cessation outcome	Refer to smoking cessation outcome	Low risk	Low risk
Lee, SM 2018	Low risk	Low risk	Low risk	Low risk	Low risk
Harms outcome					

Bullen 2013	Low risk	Differences in treatment adherence could potentially lead to discrepancies in harm reporting	No information on the proportion of participants on whom adverse events were collected; it is likely that people who experienced more severe side effects did not continue with study follow-up activities	high likelihood that participants who were unhappy with their treatment allocation would report side effects more often than their counterparts.	Low risk
Hajek 2019	Low risk	Differences in treatment adherence could potentially lead to discrepancies in harm reporting	The authors reported harm data based on number of participants at randomization, however significant dropout seen at 4-week follow up, raising concerns that adverse event data not collected on all participants	High likelihood that participants who were unhappy with their treatment allocation would report side effects more often than their counterparts	Low risk
Hatsukami 2019	Refer to smoking cessation outcome	Differences in treatment adherence could potentially lead to discrepancies in harm reporting	No information on the proportion of participants on whom adverse events were collected; it is likely that people who experienced more severe side effects did not continue with study follow-up activities	High likelihood that participants who were unhappy with their treatment allocation would report side effects more often than their counterparts	Low risk
Lee, SH 2019	Refer to smoking cessation outcome	Differences in treatment adherence could potentially lead to discrepancies in harm reporting however non-adherence happened prior to onset of treatment, therefore less likely to have an impact	Low risk	High likelihood that participants who were unhappy with their treatment allocation would report side effects more often than their counterparts	Low risk
Lee, SM 2018	Low risk	Low risk	Low risk	High likelihood that participants who were unhappy with their	Low risk

				treatment allocation would report side effects more often than their counterparts	
Withdrawal symptoms outcome					
Eisenhofer 2015	Not enough information available in abstract	Not enough information available in abstract	Not enough information available in abstract	Not enough information available in abstract	Not enough information available in abstract
Hajek 2019	Low risk	Differences in treatment adherence could potentially lead to discrepancies in withdrawal symptoms reporting	Outcome not available for all randomized participants; likely that people who experienced more nicotine withdrawal symptoms did not continue with study follow-up activities	Given that the withdrawal measurements were self-reported, there is a high likelihood that participants who were unhappy with treatment allocation reported more withdrawal symptoms than their counterparts	Low risk
Hatsukami 2019	Refer to smoking cessation outcome	Differences in treatment adherence could potentially lead to discrepancies in withdrawal symptoms reporting	Outcome not available for all randomized participants; likely that people who experienced more nicotine withdrawal symptoms did not continue with study follow-up activities	Given that the withdrawal measurements were self-reported, there is a high likelihood that participants who were unhappy with treatment allocation reported more withdrawal symptoms than their counterparts	No information on how withdrawal symptom assessment was performed
Lee, SM 2018	Low risk	Low risk	Low risk	Given that the withdrawal measurements were self-reported, there is a high likelihood that participants who were	Low risk

				unhappy with treatment allocation reported more withdrawal symptoms than their counterparts	
Acceptance of therapy outcome					
Bullen 2013	Low risk	Differences in treatment adherence could potentially lead to discrepancies in acceptance of therapy outcome	Participants unhappy with their assigned therapy likely did not continue with study follow-up activities	Highly subjective outcome, inability to blind participants to assigned therapy	Low risk
Hajek 2019	Low risk	Differences in treatment adherence could potentially lead to discrepancies in acceptance of therapy outcome	Participants unhappy with their assigned therapy likely did not continue with study follow-up activities	Highly subjective outcome, inability to blind participants to assigned therapy	Low risk
Hatsukami 2019	Not enough information available in abstract	Differences in treatment adherence could potentially lead to discrepancies in acceptance of therapy outcome	Participants unhappy with their assigned therapy likely did not continue with study follow-up activities	Highly subjective outcome, inability to blind participants to assigned therapy	Low risk
Lee, SM 2018	Low risk	Low risk	Low risk	Highly subjective outcome, inability to blind participants to assigned therapy	Low risk

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	0
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5,6, Supp material 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, Supp material 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,8, Supp material 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Figures 2a,b,c,d,e
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-13, Figures 3a,b,c,d,
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12, Figures 3a,b,c,d
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13, Figures 4a,b,c
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-15

PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	0

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Smoking cessation in individuals who use vaping as compared to traditional nicotine replacement therapies; a systematic review and meta-analysis

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Smoking cessation in individuals who use vaping as compared to traditional nicotine replacement therapies; a systematic review and meta-analysis

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Contributors statements:
Dr Pound conceptualized and designed the study, carried out the analyses, interpreted the data, drafted the initial manuscript, reviewed, and revised the manuscript.
Mrs Zhang participated in the conceptualization and design of the study, carried out the analyses, interpreted the data, participated in drafting the initial manuscript, reviewed and revised the manuscript.
Ms Kodua participated in the conceptualization and design of the study, and reviewed the manuscript.
Dr Sampson participated in the design of the study, developed the search strategies, reviewed, and revised the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives: Despite the aggressive marketing of electronic nicotine device systems (ENDS) as smoking cessation tools, the evidence of their effectiveness is mixed. We conducted a systematic review of randomized controlled trials to determine the effect of ENDS on cigarette smoking cessation, as compared to other types of nicotine replacement therapies (NRT).

Design: Systematic review and meta-analysis using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Data sources: MEDLINE, Embase, the CENTRAL Trials Registry of the Cochrane Collaboration using the Ovid interface, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform trials registries were searched through June 17th 2020.

Eligibility criteria for studies: Randomized controlled trials in which any type of ENDS was compared to any type of NRT, in traditional cigarette users.

Data extraction and synthesis: The primary outcome was smoking cessation, defined as abstinence from traditional cigarette smoking for any time period, as reported in each included study, regardless of whether abstinence is self-reported or biochemically validated. Secondary outcomes included smoking reduction, harms, withdrawal, and acceptance of therapy. A random-effect model was used, and data were pooled in meta-analyses where appropriate.

Results: Six studies were retained from 270. Most outcomes were judged to be at high risk of bias. The overall quality of evidence was graded as 'low' or 'very low'. Pooled results showed no difference in smoking cessation (RR 1.42 [0.97, 2.09]), proportion of participants reducing smoking consumption (RR 1.25 [0.79, 1.98]), mean reduction in cigarettes smoked per day (MD 1.11 [-0.41, 2.63]), or harms (RR 0.96 [0.76, 1.20]), between groups.

Conclusion: We found no difference in smoking cessation, harms, and smoking reduction between e-cigarette and NRT users. However, the quality of the evidence was low. Further research is needed before widespread recommendations are made with regards to the use of ENDS.

Systematic review registration number: protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO) on February 27th, 2020. Registration number pending.

Strengths and limitations of this study

- This study provides up to date meta-analyses of direct comparisons of vaping with nicotine replacement therapy for smoking cessation, studied through randomized controlled trials.
- We examined harms associated with vaping, which are becoming increasingly concerning.

- This study makes extensive efforts to obtain unreported data from investigators.
- Careful consideration is given to the potential impact of risk of bias and methodological heterogeneity.
- As we included only RCTs, many studies that used weaker study designs were ineligible for this review.

Abstract word count: 298 words
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INTRODUCTION

Background

Despite a significant lack of rigorous pharmacological testing, the use of electronic nicotine device systems (ENDS), otherwise known as vaping devices, has been aggressively marketed as an effective method to quit smoking. In Canada, 32% of current and former smokers report having used ENDS as a smoking cessation aid.[1] In addition to delivering nicotine to the user, ENDS are thought to replace some of the habitual behaviours and sensations associated with smoking, such as the action of bringing a cigarette to the mouth. By doing so, ENDS may provide coping mechanisms that other traditional nicotine replacement therapies (NRT) do not offer, and therefore may help with the behavioural component of smoking reduction and cessation.[2] While vaping is believed to be less harmful than cigarette smoking, a large number of emerging reports on the health impacts of vaping are worrisome. In addition, the evidence on the effectiveness of ENDS as a smoking cessation aid is mixed.

In 2016, a meta-analysis of 20 studies found that people using ENDS had a 28% reduction in the odds of stopping cigarette smoking as compared to those not using ENDS.[3] However, in a 2019 recent randomized controlled trial (RCT), individuals randomized to nicotine-containing e-cigarettes were more likely to abstain from smoking at one year compared to individuals randomized to nicotine patches (18% compared to 9.9%, RR 1.83; 95% CI 1.30 to 2.58).[4] A Cochrane review[5] found that nicotine-containing e-cigarettes were more effective than non-nicotine containing e-cigarettes for smoking cessation, but was not able to compare ENDS products to traditional NRT.

Little information is known about the long-term health impacts of ENDS. Reports of acute toxicity have recently captured the public's attention. In late 2019 and early 2020, "e-cigarette, or vaping, product use-associated lung injury" (EVALI) caused 2807 illnesses and 68 deaths in the US,[6] and 19 cases in Canada.[7] Other short-term adverse events reported with the use of ENDS include cardiovascular changes such as increased heart rate and blood pressure, cough, wheeze,[8] and mucus production.[9] Burn injuries have also been reported, as well as fatalities from drinking or injecting the e-liquid.[8]

There is no long-term data available on the relationship between ENDS and oral, respiratory, and cardiovascular health, as well as cancer. There is however available data linking the chemicals present in e-liquids with cellular DNA damage and carcinogenicity.[9,10] There is some evidence that the use of ENDS is associated with asthma exacerbations.[11] No human long-term data exist on the use of ENDS in pregnancy and their impact on the developing fetus.

Given the large number of smokers using ENDS as a potential smoking cessation tool, there is a need to review and synthesize the evidence of trials examining a head to head comparison of ENDS versus traditional NRT for smoking cessation.

Objective

The objective of this review is to systematically review the evidence found in RCTs to determine the effect of electronic nicotine delivery systems (ENDS) on cigarette smoking cessation in smokers, as compared to other types of nicotine replacement therapies (NRT).

METHODS

Protocol and registration

The protocol for this systematic review was submitted to International Prospective Register of Systematic Reviews (PROSPERO) on February 27th, 2020 (registration pending) and uploaded as a preprint on Open Science Framework (OSF) Preprints on May 12th 2020.[12]

Patient and public involvement

No patient involved

Criteria for study inclusion

Study Characteristics:

RCTs in which ENDS were compared to non-electronic NRT in smokers were included. We restricted our inclusion to RCTs to minimize the risk of bias. No language limits were imposed. No date limits were imposed either, although we did not anticipate studies published prior to 2003, since this is when the first e-cigarette was invented.[13] There was no geographical restriction of studies.

Study Population:

All traditional cigarette users were included, regardless of age, amount of traditional cigarette use, and motivation to quit.

Intervention of interest:

The intervention of interest comprised all types, models, and brands of ENDS.

Comparators:

All included studies compared ENDS with non-electronic NRT. NRT comprised, but were not limited to, nicotine patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strips, microtabs, and combination of products.

Outcome measures:

The primary outcome measure is traditional cigarette smoking cessation defined as abstinence from traditional cigarette smoking for any time period, as reported in each included study, regardless of whether abstinence is self-reported or biochemically validated.
Secondary outcomes include reduction in the number of traditional cigarettes smoked in any given time period, adverse events, withdrawal symptoms, and participants' acceptance of therapy. We had planned on collecting quit attempts information but none of the studies reported on this outcome.

Settings:

All health care and community settings were included.

Study Identification

The following databases were searched through June 17th 2020: MEDLINE (1946 to June 2020), Embase (1947 to June 2020) and the CENTRAL Trials Registry of the Cochrane Collaboration (May 2020 Issue) using the Ovid interface. The MEDLINE search was limited using the Cochrane Highly Sensitive Search Strategy and the Embase search was limited using the recommended limit for controlled trials.[14] Searches were developed by a librarian experienced in systematic reviews, using a method designed to optimize term selection.[15] ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) trials registries were searched for registered intervention studies, regardless of their completion status. Electronic search strategies are presented in Supplementary Material 1. The reference lists of included studies and any applicable review studies were searched.

Authors of protocols identified through registries were contacted electronically, to request data for the review. In addition, clinical experts in the field of vaping and smoking cessation were contacted to enquire about any unpublished research fulfilling our inclusion criteria.

Selection of Studies

Records retrieved by the electronic search were downloaded and imported into a Reference Manager database for duplicate removal, and then uploaded to Covidence. Throughout the review, newly identified records were integrated into the set for screening.

Each title and abstract was independently screened by two review authors (from CP, JZ, and ATK) against the eligibility criteria.[14] Full text of all studies deemed potentially eligible was obtained and reviewed independently by two of the same review authors to determine eligibility. For screening, data extraction, and risk of bias assessment, disagreements were resolved by discussion, and with a third reviewer when needed.

Data extraction and management

For studies that fulfilled the inclusion criteria, two reviewers (CP, JZ) extracted the data into an electronic data collection form, which was piloted by both reviewers (Supplementary Material 2). The data collection was revised, based on feedback from the reviewers. Study authors were contacted electronically to obtain relevant but unavailable data.

Risk of bias assessment for included studies

Two reviewers (CP, JZ) independently conducted the risk of bias assessment for each study at the outcome level using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[16]

Measures of treatment effect

Dichotomous data was analyzed by calculating the prevalence rate ratio, using the longest follow-up time reported, as well as the 95% confidence interval. The prevalence rate ratio (RR) for smoking cessation was calculated as such:

$$RR = \frac{N\ of\ subjects\ abstaining\ from\ smoking\ in\ intervention \Big/ N\ of\ subjects\ in\ intervention}{N\ of\ subjects\ abstaining\ from\ smoking\ in\ control \Big/ N\ of\ subjects\ in\ control}$$

Continuous data for the secondary outcomes were analyzed through mean differences between groups as the same scales were used. In the case of studies with multiple arms, we only extracted data for the groups relevant to this review.

Data synthesis

We provide a synthesis of the included studies (Table 1). Where appropriate, data have been pooled for meta-analyses, and random effects were used for all analyses in RevMan.[14] The inverse-variance random-effects and the mean difference approach (using standard deviations and sample sizes) were used for dichotomous and continuous outcomes, respectively, to assign the weight given to each study. Participants with missing data were considered as still smoking.[5] The proportion of adverse events reported was based on the number of people available for outcome assessment. For the reduction of the number of cigarettes smoked, missing values were assumed to be zero.

Assessment of heterogeneity

A p value of 0.10 for the chi-squared test (Cochrane Q) and an I^2 value of >50% were used as indicators of substantial heterogeneity. This however needs to be interpreted with caution given the small number of studies available for the meta-analysis. Clinical and methodological diversity was also explored.

We planned to assess reporting/publication bias using funnel plots of effect estimate against standard error, and testing for funnel plot asymmetry, however, the number of included studies was too low (<10).

We also planned on conducting a number of sensitivity analyses to determine the robustness of the results of the meta-analyses; subgroup analyses to investigate potentially modifying factors such as age and smoking intensity; as well as meta-regression to study the impact of covariates such as motivation to quit smoking, provision of training, and other factors,[17] but minimum data thresholds were not met.

We present a 'Summary of Findings' table (Table 2) for all outcomes. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias)[14] to assess the quality of evidence for each outcome and to draw conclusions about the robustness of evidence within this review.

RESULTS

Our initial bibliographic search yielded 270 records, and after screening and full-text review, we retained 6 RCTs. An updated search conducted in June 2020 yielded an additional 116 records (for a total of 386 records), none of which were included after screening (Figure 1).

We identified six RCTs (Bullen 2013,[18] Eisenhofer 2015,[19] Hajek 2019,[4] Hatsukami 2019,[20] Lee SH 2019,[21] Lee SM 2018[22]). Of these, five contributed data to our primary outcome of smoking cessation.[4,18,20-22] Four studies[4,18,21,22] examined cessation at 6 months or longer, while one[20] examined short term cessation (< 6 months). Table 1 includes the salient features of the included studies. A more detailed description of included studies can be found in Supplementary Material 3.

Table 1. Characteristics of included studies

Characteristics of RCTs measuring smoking cessation at 6 months or later							
Author and year of publication	**Design**	**Country**	**Number of participants**	**Main eligibility criteria**	**Intervention**	**Comparator**	**Main outcome of interest**
Bullen, 2013[17]	3-group, parallel, single center	Australia	657 total, 584 included in this review (2 of 3 groups)	≥ 18 years, smoked ≥ 10 cigarettes per day in the past year, motivated to quit	First-generation e-cigarette x 12 weeks	Nicotine patch x 12 weeks	Continuous abstinence 6 months after quit day
Hajek 2019[4]	2-group, parallel, multi-centre	United Kingdom	884	Adults with no strong preference towards e-cigarette or NRT	Any type of e-cigarette	Any nicotine-replacement therapy	Continuous abstinence 52 weeks after quit day
Lee SH, 2019[20]	2-group, parallel, single center	Republic of Korea	150	≥ 18 years, smoked ≥ 10 cigarettes per day in the past year, motivated to quit	e-cigarette x 24 weeks	Nicotine gum x 24 weeks	Continuous abstinence 24 weeks after quit day
Lee SM, 2018[21]	2 group, parallel, single center	USA	30	Adults, smoked ≥ 2 cigarettes per day in the past year, smoked at least once in last 7 days	e-cigarette x 6 weeks	Nicotine patch x 5 weeks, then placebo patch x 1 week	7-day point prevalence abstinence at 6 months
Characteristics of RCT measuring smoking cessation earlier than 6 months							

Hatsukami, 2019[19]	4 group, parallel, multi-center	USA	264 total, 152 included in this review (2 of 4 groups)	≥ 18 years, smoked ≥ 5 cigarettes per day	e-cigarettes	Nicotine gum or nicotine lozenge	7-day point prevalence abstinence at 8 months
Characteristics of RCT measuring other outcomes							
Eisenhofer, 2015[18]	2-group, parallel, single center	USA	11	Veterans who met criteria for tobacco disorder	e-cigarettes x 3 weeks	Nicotine patch x 3 weeks	Reduction in number of cigarettes smoked per day at 3 weeks

Risk of bias in included studies

We assessed risk of bias for each included study. A detailed report of the risk of bias assessment can be found in Supplementary Material 4.

Figure 2 illustrates the risk of bias for each outcome.

Effect of Interventions

Smoking cessation

Five of the six studies reported on smoking cessation.[4,18,20-22] When comparing e-cigarettes to NRT in the context of smoking cessation, there was no significant difference between groups in verified self-reported continuous abstinence at 6 months (21/289 vs 17/295, RR 1.26 [0.68, 2.34], p=0.46) in the Bullen 2013[18] study, and in continuous abstinence from 9 to 24 weeks (16/75 vs 21/75, RR 0.76 [0.43, 1.34], p = 0.344) in the Lee SH 2019[21] study. In addition, the Lee SM 2018[22] study showed no difference between groups for the 7-day point prevalence abstinence at 6 months in the context of perioperative smoking cessation (5/20 vs 1/10, RR 2.50 [0.34, 18.63], p = 0.63).

In the Hajek 2019[4] study, self-reported, verified continuous abstinence at 1 year was found to be higher in the e-cigarette group (79/438 vs 44/446, RR 1.83 [1.30, 2.58], P<0.001), and smoking cessation assessed by 7-day point prevalence at 8 weeks in the Hatsukami 2019[20] trial was also higher in the e-cigarette group (25/76 vs 13/76, RR 1.92 [1.07, 4.37], p = 0.039).

We combined data from all 5 studies comparing smoking cessation between e-cigarettes and NRT and obtained a pooled RR of 1.42 [0.97, 2.09] (Figure 3).

Smoking reduction

All six studies[4,18-22] assessed smoking reduction. Bullen 2013,[18], Eisenhofer,[19] Hajek 2019,[4] and Lee SM 2018[22] reported the proportion of participants reducing smoking by at least 50%. While Lee SH 2019[21] also reported on this outcome, the size of the reduction was not specified. Bullen 2013[18] and Lee SH 2019[21] reported an absolute reduction, and Hatsukami 2019[20] reported a relative reduction in cigarettes per day from baseline.

In the Bullen 2013 study,[18] mean cigarette consumption at 6 months decreased by 9.7 (SE 0.4) in the e-cigarette group, and by 7.7 (SE 0.4) in the NRT group. Mean difference between groups was 1.9 (SE 0.6) (p = 0.002). After excluding people who successfully quit smoking, the RR of decreasing cigarette smoking by at least 50% when comparing the e-cigarette to the NRT groups was 1.61 [1.31, 1.99].

Eisenhofer 2015[19] compared week 3 to week 1, and showed that both e-cigarettes (t = 5.3, p = 0.013) and NRT (t = 3.4, p = 0.015) significantly reduced (~50%) self-reports of cigarettes smoked in the previous 24 hours. This was confirmed by significant reductions of breath CO levels in both groups No additional information could be obtained from the abstract and none of the authors could be reached.

In the Hajek 2019[4] study, 44 of 345 participants in the e-cigarette group, and 29 of 393 participants in the NRT group experienced a carbon monoxide-validated reduction in smoking of $\geq$ 50% in participants without abstinence between weeks 26 and 52, yielding a relative risk of smoking reduction of 1.73 (1.11-2.70).

Hatsukami 2019[20] defined smoking reduction by the estimated ratio of cigarettes smoked at 8 weeks as compared to baseline, with a result of 0.25 (0.17, 0.37) in the e-cigarette group, and 0.29 (0.21, 0.39) in the NRT group (p = 0.185). Additional data obtained from the author showed that 19 participants in the e-cigarette group and 22 participants in the NRT group reduced smoking consumption by 50% (RR 0.86 [0.51, 1.46]) at 8 weeks, and that mean cigarette consumption decreased by 9.22 (SD 7.95) in the e-cigarette group, and by 7.61 (SD 8.27) in the NRT group. The mean difference between groups was 1.61 [-0.97, 4.19] .

In the Lee SH 2019[21] study, mean cigarette consumption decreased at 24 weeks by 6.5 +/- 2.87 (SD) in the e-cigarette group, and by 6.60 +/- 3.75 (SD) in the NRT group (p = 0.974). In addition, 31 out of 75 participants (41.3%) in the e-cigarette group and 19 out of 75 participants (25.3%) in the NRT group reduced their daily cigarette consumption (p = 0.038), but no information on size of smoking reduction is provided. After excluding abstainers, a RR of 1.49 [0.97, 2.31] was obtained for decrease in daily cigarette consumption.

Lastly, in the Lee SM 2018,[22] 1 participant in the END group and 4 participants in the NRT group reduced their cigarette consumption by at least half, resulting in a RR 0.15 [0.02, 1.14].

We combined data from the Bullen 2013,[18] Hajek 2019,[4] Hatsukami 2019[20] and Lee SM 2018[22] studies comparing smoking reduction of at least 50% between e-cigarettes and NRT, as they used similar measures. Pooled results comparing the difference in smoking reduction between the e-cigarette and the NRT groups produced a RR of 1.25, with the line of equivalence falling within the confidence interval [0.79, 1.98] (Figure 3).

We also combined data from the Bullen 2013,[18], Hatsukami 2019,[20] and Lee SH 2019[21] comparing mean reduction of cigarettes per day from baseline for ENDs and NRT. Meta-analysis

yielded a MD of 1.11, with the line of equivalence falling within the confidence interval [-0.41, 2.63] (Figure 3).

Harms

Five studies reported on harms (Bullen 2013,[18] Hajek 2019,[4] Hatsukami 2019,[20] Lee SH 2019,[21] Lee SM 2018[21]). None of the included studies reported serious adverse events (SAEs) related to e-cigarettes or NRT.

In the Bullen 2013[18] study, 107 participants in the e-cigarette group reported 137 adverse events, while 96 participants in the NRT group (patches) reported 119 events, and, using the number of participants available for analysis at 6 months, there was no difference in the incidence of adverse events between groups (RR 0.99, [0.81, 1,22]). No difference between groups was also observed in the Hatsukami 2019[20] study, where additional data provided by the author showed that 51 of 69 participants in the e-cigarette group and 53 of 72 participants in the NRT group reported adverse events (1.00 [0.82, 1.22]), and in the Lee SM 2018[22] study, where no significant difference in the incidence of adverse events between groups was seen at 8 weeks (RR 1.24 [0.54, 2.84]).

Hajek 2019[4] defined adverse events of interest as nausea, sleep disturbances, and throat and mouth irritation. There were 27 SAEs in the e-cigarette group and 22 in the NRT group, none felt to be related to the intervention or control products. Based on the number of participants available at the 12 month follow-up, e-cigarettes were found to be less likely associated with nausea (RR 0.78 [0.66, 0.92]) and sleep disturbances (RR 0.88 [0.83, 0.95]), but more likely associated with throat/mouth irritation (RR 1.24 [1.13, 1.37]). These numbers however should be interpreted with caution as it was not possible to determine with certainty the denominator from the data.

In the Lee SH 2019 study, [21] 5 participants in the e-cigarette group and 13 participants in the nicotine gum group reported adverse events. There were no SAEs. Based on the number of participants who completed the study, e-cigarettes were less likely to be associated with adverse events (RR 0.13 [0.12, 0.87]).

We combined data from the Bullen 2013,[18] Hatsukami 2019,[20] Lee SH 2019,[21] Lee SM 2018[22] studies comparing harms between e-cigarettes and NRT. Hajek 2019[4] was excluded as they did not clearly report the number of participants that experienced any adverse events and reported only on specific adverse events. Pooled results comparing ENDS to NRT yielded a RR of 0.96 [0.76, 1.20] (Figure 3).

Withdrawal symptoms

Four studies reported on the results of withdrawal symptoms (Eisenhofer 2015,[19] Hajek 2019,[4] Hatsukami 2019,[20] and Lee SM 2018[22]) and all used different scales. Eisenhofer 2015[19] assessed withdrawal with the Questionnaire on Smoking Urges (QSU), Hajek[4] used a composite urge score (frequency and strength of urge to smoke), Hatsukami 2019[20] measured the severity of withdrawal using the Minnesota Nicotine Withdrawal Scale, and Lee SM 2018[21] assessed withdrawal symptoms as part of their adverse event assessment. In light of the differences in outcome assessment measures, the data were not pooled.

In Eisenhofer 2015,[19] urges and cravings to smoke were significantly reduced in the e-cigarette group (t=3.8, p = 0.03), but not in the NRT group (t=2.1, p = 0.08).

In Hajek 2019,[4] urges for e-cigarette users decreased more than for NRT users at 1 week (MD: -0.4 (-0.6 to -0.2)) and at 4 weeks (MD: -0.3 (-0.5 to -0.1)). E-cigarette users also reported a smaller increase from baseline in irritability, restlessness, inability to concentrate, hunger, and depression. The withdrawal symptoms disappeared mostly for both groups by week 4.

In Hatsukami 2019,[20] participants in the e-cigarette group reported lower median [min/max] changes from baseline on the severity scale compared to participants in the NRT group at all measurement points, with week 1 (3.0 [-9.0/25.0] vs 3.5 [-20.0/32.0]), week 2 (1.0 [-13.0/25.0] vs 3.0 [-13.0/39.0]), and week 4 (1.0 [-17.0/30.0] vs 2.5 [-28.0/29.0]). The planned pairwise comparisons were significant with p <0.017. As well, fewer participants (5.3%) withdrew from the complete substitution e-cigarettes group than from the NRT group (15.8%) for product related reasons (disliking product or experiencing withdrawal symptoms; p value not reported).

Lee SM 2018[22] only reported on withdrawal symptoms for the NRT group, and did not report on withdrawal symptoms for the e-cigarette group.

Acceptance of therapy

Four studies reported on acceptance of therapy (Bullen 2013,[18] Hajek 2019,[4] Hatsukami 2019,[20] and Lee SM 2018[22]), and all used different scales. In light of the difference in outcome assessment measures, the data were not pooled.

In the Bullen 2013[1]study,[18] 230 out of 260 participants (88%) in the e-cigarettes group said they would recommend their allocated product to a friend at 1 month, as compared to 130 out of 232 participants (56%) in the NRT group (RR 1.58 [1.40, 1.78]). At 6 months, 205 out of 241 participants (85%) in the e-cigarettes group said they would recommend their allocated product as compared to 107 out of 215 participants (50%) in the NRT group (RR 1.71 [1.48, 1.97]).

In the Hajek 2019 study,[4] acceptance of therapy was measured with a Likert scale (1 to 5, with a higher score associated with higher acceptance). At 4 weeks post quit date, helpfulness of e-cigarettes was rated 4.3 (SD 0.9) while that of NRT was 3.7 (SD 0.9) (mean difference 0.6 (0.4, 0.7)). Taste was scored at 3.5 (SD 1.3) for the e-cigarette group and 3.1 (SD 1.5) (mean difference 0.4 (0.2,0.6)), and satisfaction was rated at 2.7 (SD 1.1) and 2.3 (SD 1.2), respectively, for the e-cigarette and NRT groups (mean difference 0.5 (0.3, 0.6)).

In the Hatsukami 2019 study[20], acceptance of therapy was defined as satisfaction with the product, psychological reward, enjoyment of sensation, aversion, and ability to reduce craving. Results are reported for the NRT group as an estimated mean difference and 95% CI in product evaluation sub-scales using the e-cigarette group as a reference. The following results are reported; satisfaction: -0.6 (-1.0, -0.1), psychological reward: -0.4 (-0.8, 0.01), enjoyment of sensation: -0.6 (-1.1, -0.1), aversion: 0.1 (-0.2, 0.4), and ability to reduce craving: -0.3 (-0.8, 0.2).

Lastly, the Lee SM 2018 trial[22] defined acceptance of therapy as satisfaction with the assigned product, measured with a Likert scale (1 to 7, with a higher score associated with higher satisfaction). Median scores and IQR are reported. Participants randomized to the e-cigarette group reported scores of 6 [4-7], 5.5 [2.5-7], and 6 [5-7], respectively, while participants randomized to the NRT group reported scores of 5 [3-7], 5 [3-6], and 7 [6-7], respectively for the following questions. “The product is helpful for quitting smoking”, “I was satisfied with the product to help with quitting”, “I would recommend the product to someone interested in quitting smoking”.

Risk of bias across studies

The review process we used was thorough, and we took every precaution to minimize the risk of bias due to publication bias or selective reporting. We reached out to clinical experts to enquire about unpublished reports, examined protocol registries, and contacted the authors of identified protocols to request unpublished results. Given the low number of retained studies, we did not include a funnel plot.

Sensitivity, subgroup and meta-regression analyses

We performed a sensitivity analysis for the smoking cessation outcome by removing the Lee SM 2018 study[22]. While the other 4 studies aimed to assess smoking cessation in general, Lee et al were targeting a peri-operative population, who may have had different motivations to quit smoking. The pooled data, once Lee SM 2018[22] is removed, yield a RR of smoking abstinence of 1.39 [0.92, 2.11] when comparing ENDS to NRT (Figure 4).

We had planned on undertaking multiple subgroup analyses. We were unable to perform the subgroup analyses based on age (all participants were adults), smoking intensity (no study enrolled smokers $\geq$ 25 cigarettes per day), or biochemically validated smoking cessation (all studies used biochemical validation). We also could not perform a subgroup analysis of studies with ties to industry as only Bullen 2013[18] was found to have ties to the vaping industry.

We did, however, perform the following subgroup analyses: limiting comparator to nicotine patches (Bullen 2013[18] and Lee SM 2018[21]), and including only studies assessing continuous/sustained smoking abstinence $\geq$ 6 months given that smoking cessation is defined as sustained abstinence for at least 6 months;[23] (Bullen 2013,[18] Hajek 2019,[4] Lee SH 2019[21]) (Figure 4).

Metaregression analyses were not performed as our threshold of 10 eligible studies was not met.

DISCUSSION

In our review, there was no significant difference in smoking cessation, smoking reduction, or harms between e-cigarette and NRT users. However, we report on results from a limited number of RCTs, and the level of evidence is low. Our efficacy results are similar to those described in a 2016 Cochrane review,[5] which also showed no difference between abstinence rates between the nicotine e-cigarette group and NRT group. Their review only included one

study[18] , also included in our review for this particular outcome. Similar to the evidence we are presenting, none of the studies examined in the Cochrane review reported serious adverse events considered to be related to e-cigarette use.

Although our meta-analysis of the 5 trials that examined ***smoking cessation*** showed no significant difference between e-cigarette and nicotine replacement therapy, there was a trend towards favoring e-cigarettes. Interestingly, our sensitivity analysis limiting inclusion to studies reporting smoking cessation of 6 months or greater yielded a smaller point estimate than the one obtained from the main analysis, although still with no difference between groups. It could be hypothesized that additional benefits that may be attributed to e-cigarette early on in smoking cessation may be attenuated as time progresses. This again should be interpreted with caution given the small number of studies[4,18,20] and the very significant heterogeneity.

In all comparisons, our results need to be interpreted carefully. There was significant clinical heterogeneity between studies in terms of the population enrolled, smoking intensity at baseline, type and nicotine concentration of e-cigarettes, type and dose of NRT, as well as methodological heterogeneity in terms of study conduct, and intervention and control protocols. For instance, one of the included studies[18] used first-generation e-cigarettes, with nicotine delivery about 20% of that obtained from cigarette smoking. While e-cigarette users were couriered the supplies needed, NRT users had to redeem vouchers from community pharmacies to obtain their patches. The low nicotine content of the e-cigarettes, the extra step in obtaining NRT supplies, and the low intensity of additional co-interventions likely contributed to the low rate of smoking abstinence at 6 months in both groups, limiting the generalizability of the results. Another included study[4] allowed for multiple types and concentrations of ENDS, as well as upwards of 10 NRT products and doses, complicating the interpretation of the results. Nicotine concentrations reported in the trials ranged from 0.01 to 48 mg/mL,[4,18,20-22] making comparisons between studies difficult.

Given that the risk of bias was assessed as high in 5 of 6 included studies[4,18-21], our smoking cessation outcome results need to be interpreted with caution. In addition, it is interesting to note that all studies verified self-reported smoking cessation with an exhaled carbon monoxide test, however different cut-off values were used. Additionally, there are limitations to using carbon monoxide (CO) as a way to verify smoking cessation. CO has a relatively short half-life and is eliminated from the body within 24 hours; it can, therefore, lead to false negative results. However, this issue is somewhat mitigated by the fact that smoking cessation study participants tend to be daily smokers.

All studies included in this review examined ***smoking reduction***. There was no difference between groups in the mean reduction of cigarettes from baseline in the studies that measured that outcome, or in the proportion of participants successfully reducing their smoking consumption.

None of the included studies reported severe ***adverse events*** related to ENDS or NRT, and, for the four studies with data that could be pooled, there was no difference between groups in

terms of harms related to either therapy. However, in addition to the clinical heterogeneity mentioned above, there was significant methodological heterogeneity in how adverse events were collected. We evaluated the quality of the evidence as very low, given the high risk of bias of included studies, the significant heterogeneity, and the inability to accurately determine the number of subjects involved in this outcome, thus leading to result imprecision.

Since the included trials were powered to detect a difference in the primary outcome, it is possible that rare or unexpected harms were not detected due to a lack of power for this specific outcome. Also, it is important to acknowledge that these studies are limited by their short time-frame. Data on long-term side effects of ENDS are lacking. The recent e-cigarette, or vaping product use-associated lung injury (EVALI) epidemic, is a reminder that further research is needed before widespread recommendations can be made with regards to the use of ENDS. In addition, there are now emerging concerns that respiratory disease caused by the novel coronavirus SARS-CoV-2, the virus responsible for the COVID-19 pandemic, could be exacerbated by exposure to ENDS.[24-26]

Finally, although there seemed to be ***increased acceptance of therapy*** towards e-cigarettes in the four studies that considered it,[4,18,20,22] high risk of bias, significant heterogeneity, and the small number of studies using widely different scales leading to imprecise measures, mean that the results should be interpreted with extreme caution. In addition, given that the trials were unblinded, participants who were disappointed with their treatment allocation may have reported less acceptability than their counterparts.

Limitations at review level

We restricted our search to RCTs to try to minimize the risk of bias, however, this considerably limited the number of available studies for this review. It is surprising that, given the widespread availability of e-cigarettes and how aggressively they have been marketed as smoking cessation agents, there are so few head-to-head trials comparing ENDS and traditional NRT. While there may be some unpublished studies that our review did not capture, our literature search was thorough and included personal communications to multiple experts in the field.

Our review identified 7 ongoing trials[27-33] that potentially met our inclusion criteria, totaling over 1500 targeted participants. None of the investigators had any data ready to be shared, however it is hoped that this ongoing research can shed light on the effectiveness of ENDS as smoking cessation tools, as compared to traditional NRTs. Long-term research is also needed to investigate the long-term effects of ENDS, as well as the optimal dosing and method of delivery.

Conclusion

We found no difference in smoking cessation, harms, and smoking reduction between e-cigarette and NRT users. However, the quality of the evidence was low. Further research is needed before widespread recommendations can be made with regards to the use of ENDS. Research is also needed to investigate the long-term effects of ENDS, as well as optimal dosing.

Table 2- Summary of Findings Table

Nicotine-containing Electronic cigarettes (ENDS) vs Nicotine Replacement Therapies (NRT) for smoking cessation

Population: Current smokers at enrolment into trials

Intervention: Nicotine-containing e-cigarettes

Comparison: Nicotine-replacement therapies

Outcomes ENDS as compared to NRT	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Cessation	RR 1.42 [0.97, 2.09]	1800 (5 studies)	⨁⨁ OO[1,2] low	
Smoking reduction				
Proportion of people decreasing cigarette consumption by 50%	RR 1.25 [0.79, 1.98]	1460 (4 studies)	⨁⨁ OO[1,2] low	
Mean decrease in cigarettes per day	MD 1.11 [-0.41, 2.63]	633 (3 studies)	⨁⨁ OO[1,2] low	
Adverse events (AEs)	RR 0.96 [0.76, 1.20]	758 (4 studies)	⨁ OOO[1,2,3] Very low	No severe adverse events related to investigated products were reported
Withdrawal symptoms	Summary data not available	4 studies	⨁ OOO[1,2,3] Very low	Withdrawal measures included Minnesota Nicotine Withdrawal Scale, QSU scores, frequency of urge and strength of urge score, and pre-specified symptoms of depressed mood, irritability, restlessness, and hunger

Acceptance of therapy	Summary data not available	4 studies	⨁ OOO[1,2,3] Very low	Acceptance defined as wanting to recommend product to friends, helpfulness, taste, satisfaction, psychological reward, enjoyment of sensation, aversion, and ability to reduce craving depending on study

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level because of risk of bias
[2]Downgraded one level because of heterogeneity
[3]Downgraded one level because of imprecision of results

Data availability

Data collection forms and all raw data can be requested through the corresponding author

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Figure captions

Figure 1: Study Flow Diagram
Figure 2: Risk of bias for each outcome
Figure 3: Pooled results per outcome
Figure 4: Sensitivity and Subgroup Analyses

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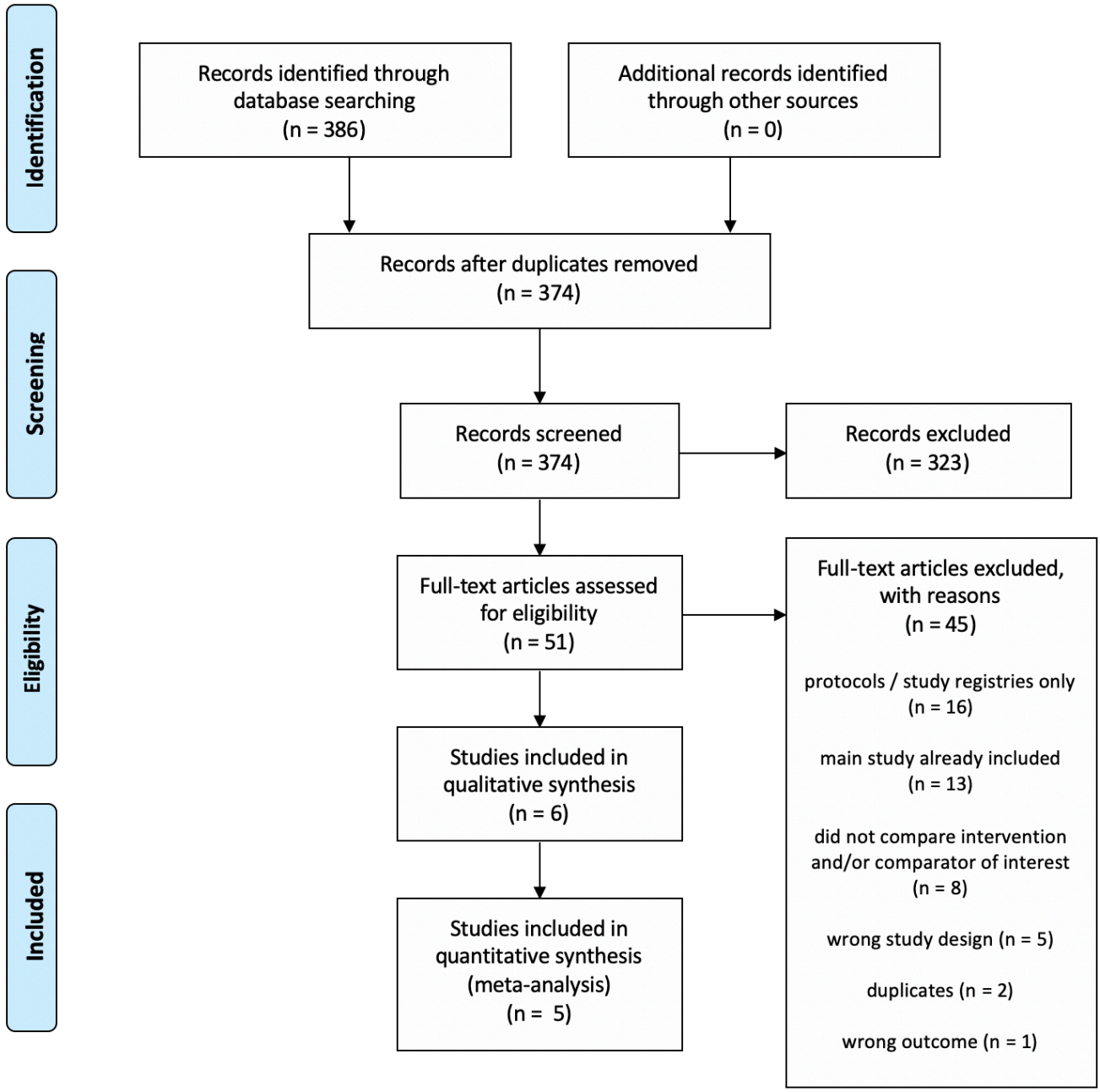
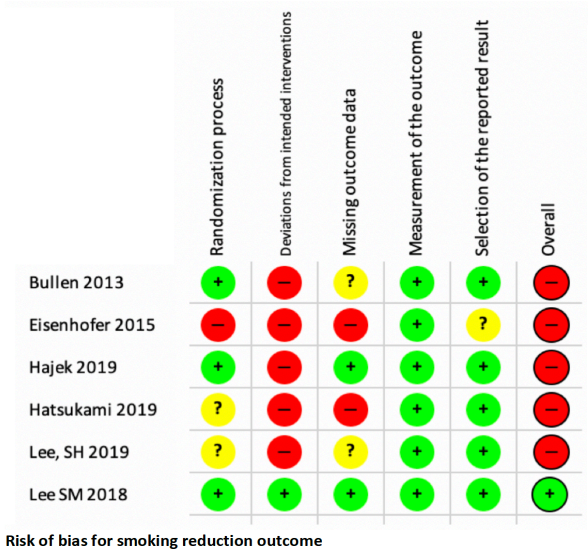
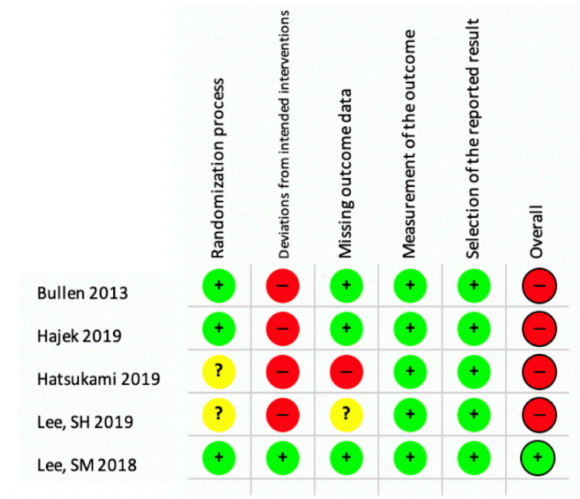


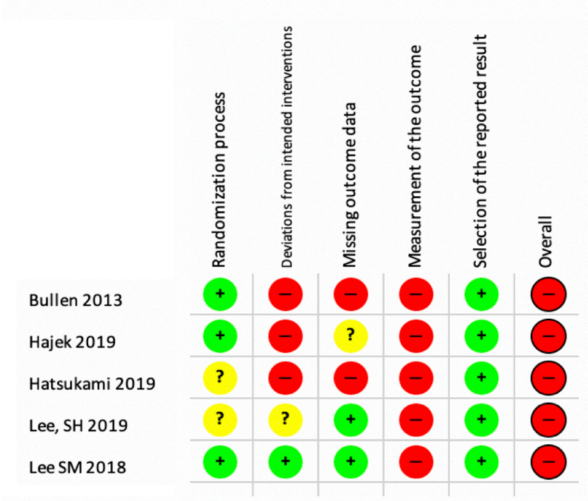
Figure 1. Study flow diagram



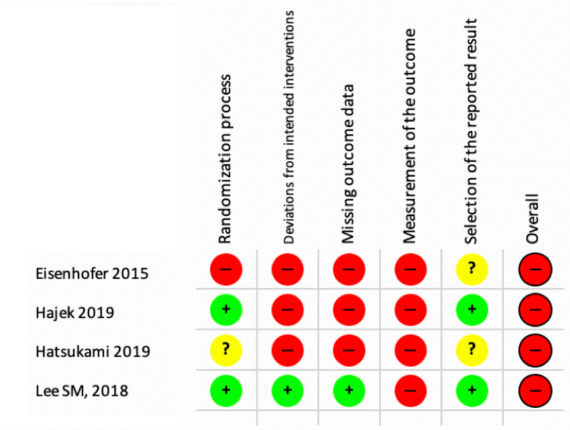
Risk of bias for smoking reduction outcome



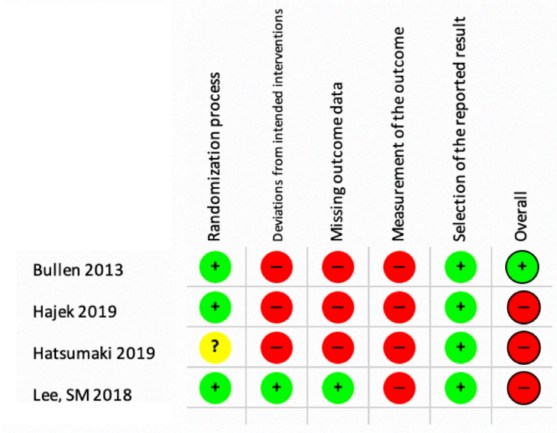
Risk of bias for smoking cessation outcome



Risk of bias for harms outcome



Risk of bias for withdrawal symptoms outcome



Risk of bias for acceptance of therapy outcome

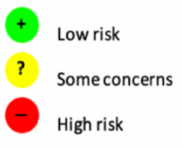
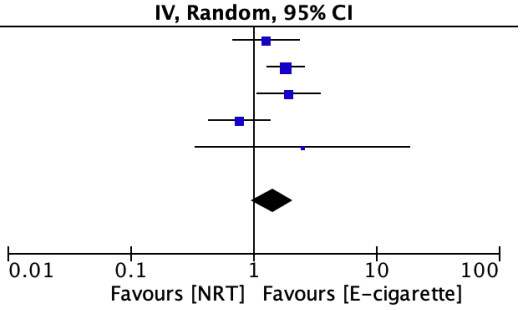


Figure 2. Risk of bias for each outcome

Study or Subgroup	ENDS Events	ENDS Total	NRT Events	NRT Total	Weight	Risk Ratio IV, Random, 95% CI
Bullen	21	289	17	295	20.5%	1.26 [0.68, 2.34]
Hajek	79	438	44	446	32.2%	1.83 [1.30, 2.58]
Hatsukami	25	76	13	76	21.5%	1.92 [1.07, 3.47]
Lee SH	16	75	21	75	22.4%	0.76 [0.43, 1.34]
Lee SM	5	20	1	10	3.4%	2.50 [0.34, 18.63]
Total (95% CI)		**898**		**902**	**100.0%**	**1.42 [0.97, 2.09]**
Total events	146		96			

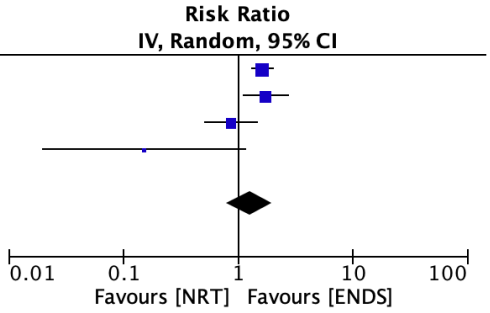
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 8.00$, df = 4 (P = 0.09); $I^2 = 50\%$
Test for overall effect: Z = 1.80 (P = 0.07)



Smoking cessation outcome

Study or Subgroup	ENDS Events	ENDS Total	NRT Events	NRT Total	Weight	Risk Ratio IV, Random, 95% CI
Bullen	137	268	88	278	38.5%	1.61 [1.31, 1.99]
Hajek	44	345	29	393	30.0%	1.73 [1.11, 2.70]
Hatsukami	19	76	22	76	27.0%	0.86 [0.51, 1.46]
Lee SM	1	15	4	9	4.5%	0.15 [0.02, 1.14]
Total (95% CI)		**704**		**756**	**100.0%**	**1.25 [0.79, 1.98]**
Total events	201		143			

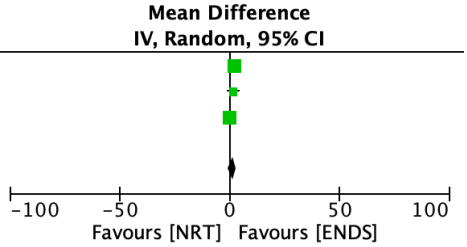
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 10.06$, df = 3 (P = 0.02); $I^2 = 70\%$
Test for overall effect: Z = 0.95 (P = 0.34)



Proportion of participants successfully reducing smoking consumption by 50%

Study or Subgroup	ENDS Mean	ENDS SD	ENDS Total	NRT Mean	NRT SD	NRT Total	Weight	Mean Difference IV, Random, 95% CI
Bullen	9.7	5.37	180	7.7	5.2	169	40.0%	2.00 [0.89, 3.11]
Hatsukami	9.22	7.95	76	7.61	8.27	76	20.6%	1.61 [−0.97, 4.19]
Lee SH	6.55	2.87	71	6.6	3.75	61	39.3%	−0.05 [−1.20, 1.10]
Total (95% CI)			**327**			**306**	**100.0%**	**1.11 [−0.41, 2.63]**

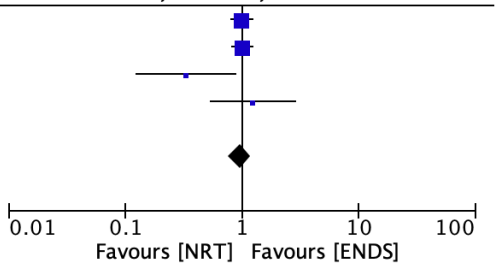
Heterogeneity: $Tau^2 = 1.18$; $Chi^2 = 6.49$, df = 2 (P = 0.04); $I^2 = 69\%$
Test for overall effect: Z = 1.43 (P = 0.15)



Mean reduction of cigarettes from baseline

Study or Subgroup	ENDS Events	ENDS Total	NRT Events	NRT Total	Weight	Risk Ratio IV, Random, 95% CI
Bullen	107	241	96	215	43.5%	0.99 [0.81, 1.22]
Hatsukami	51	69	53	72	44.7%	1.00 [0.82, 1.22]
Lee SH	5	71	13	61	5.0%	0.33 [0.12, 0.87]
Lee SM	11	20	4	9	6.7%	1.24 [0.54, 2.84]
Total (95% CI)		**401**		**357**	**100.0%**	**0.96 [0.76, 1.20]**
Total events	174		166			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.17$, df = 3 (P = 0.16); $I^2 = 42\%$
Test for overall effect: Z = 0.36 (P = 0.72)

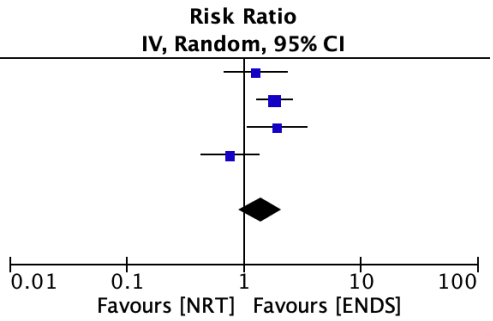


Proportion of participants experiencing adverse events

Figure 3. Pooled results per outcome

Study or Subgroup	ENDS Events	ENDS Total	NRT Events	NRT Total	Weight	Risk Ratio IV, Random, 95% CI
Bullen	21	289	17	295	21.6%	1.26 [0.68, 2.34]
Hajek	79	438	44	446	32.3%	1.83 [1.30, 2.58]
Hatsukami	25	76	13	76	22.6%	1.92 [1.07, 3.47]
Lee SH	16	75	21	75	23.4%	0.76 [0.43, 1.34]
Total (95% CI)		**878**		**892**	**100.0%**	**1.39 [0.92, 2.11]**
Total events	141		95			

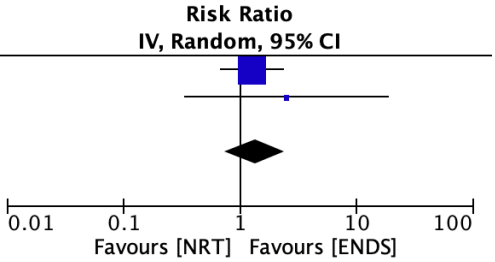
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 7.74$, df = 3 (P = 0.05); $I^2 = 61\%$
Test for overall effect: Z = 1.55 (P = 0.12)



Sensitivity Analysis—Smoking cessation, for studies examining smoking cessation in the general population

Study or Subgroup	ENDS Events	ENDS Total	NRT Events	NRT Total	Weight	Risk Ratio IV, Random, 95% CI
Bullen	21	289	17	295	91.3%	1.26 [0.68, 2.34]
Lee SM	5	20	1	10	8.7%	2.50 [0.34, 18.63]
Total (95% CI)		**309**		**305**	**100.0%**	**1.34 [0.74, 2.42]**
Total events	26		18			

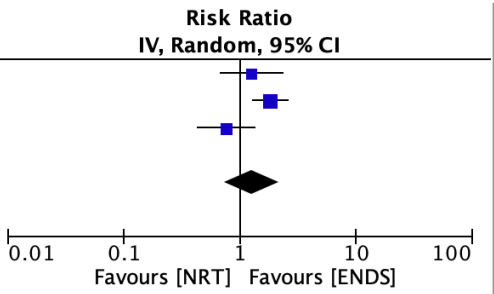
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$, df = 1 (P = 0.52); $I^2 = 0\%$
Test for overall effect: Z = 0.97 (P = 0.33)



Subgroup Analysis—Smoking cessation, comparing e-cigarettes to nicotine patches only

Study or Subgroup	ENDS Events	ENDS Total	NRT Events	NRT Total	Weight	Risk Ratio IV, Random, 95% CI
Bullen	21	289	17	295	29.2%	1.26 [0.68, 2.34]
Hajek	79	438	44	446	39.7%	1.83 [1.30, 2.58]
Lee SH	16	75	21	75	31.1%	0.76 [0.43, 1.34]
Total (95% CI)		**802**		**816**	**100.0%**	**1.25 [0.73, 2.14]**
Total events	116		82			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 6.85$, df = 2 (P = 0.03); $I^2 = 71\%$
Test for overall effect: Z = 0.81 (P = 0.42)



Subgroup Analysis— Continuous/sustained abstinence, 6 months and greater only

Figure 4. Subgroup and Sensitivity Analyses

Supplementary Material 1
Search strategies

MEDLINE, Embase, CENTRAL

Note: Searches were conducted using an Ovid multi-database search and duplicate records were removed online giving preference to MEDLINE, then Embase, with no field preference. Lines 1-3 are optimized for MEDLINE and the main question constructs are broken out in separate lines for clarity. Lines 4-7 are optimized for Embase and lines 8-10 are optimized for CENTRAL. The next lines isolate the records to the database the search was designed for, combine those sets and then remove duplicate records and final isolate the records from each database again so each can be downloaded and imported into the citation manager using a database-specific import filter.

1. Electronic Nicotine Delivery Systems/ or (e cig* or electr* cigar* or electronic nicotine).mp. or (vape or vaper or vapers or vaping or non-combustible nicotine-containing product).ti,ab,kf.
2. exp "Tobacco Use Cessation Devices"/ or NRT.ti,ab,kf. or (nicotine adj2 (patch* or gum or nasal spray or mouth spray or mouth strips or lozenge* or tablet* or microtab* or sublingual or replac*)).mp. or (nicotine adj3 therapy).mp.
3. (1 and 2 and ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.)) not exp animals/ not humans.sh.
4. Electronic Cigarette/ or (e cig* or electr* cigar* or electronic nicotine).mp. or (vape or vaper or vapers or vaping or non-combustible nicotine-containing product).ti,ab,kw.
5. Nicotine Replacement Therapy/ or NRT.ti,ab,kw. or (nicotine adj2 (patch* or gum or nasal spray or mouth spray or mouth strips or lozenge* or tablet* or microtab* or sublingual or replac*)).mp. or (nicotine adj3 therapy).mp.
6. 4 and 5 and (Crossover-Procedure/ or Double-Blind Procedure/ or Randomized Controlled Trial/ or Single-Blind Procedure/ or (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).ti,ab,kw.)
7. limit 6 to embase
8. (e cig* or electr* cigar* or electronic nicotine).mp. or (vape or vaper or vapers or vaping or non-combustible nicotine-containing product).ti,ab,kw.
9. NRT.ti,ab,kw. or (nicotine adj2 (patch* or gum or nasal spray or mouth spray or mouth strips or lozenge* or tablet* or microtab* or sublingual or replac*)).mp. or (nicotine adj3 therapy).mp.
10. 8 and 9
11. 3 use medall
12. 7 use emczd
13. 10 use cctr
14. 11 or 12 or 13
15. remove duplicates from 14
16. 15 use medall
17. 15 use emczd
18. 15 use cctr

ClinicalTrials.gov
(electronic cigarette OR vape OR vaping OR electronic nicotine) AND (nicotine replacement OR NRT OR patch OR gum OR nasal spray OR mouth spray OR mouth strips OR lozenge OR tablet OR microtab OR microtablet OR sublingual) | Interventional Studies
91 records retrieved

WHO ICTRP
electronic cigarette OR vape or vaping OR electronic nicotine
153 records retrieved with 20 remaining after records with a TrialID starting with NCT were removed prior to screening

Note: As the ICTRP registry has limited search capabilities[35], only terms related to the intervention were used and protocols with a NCT number were removed from the retrieval, as those protocols would also be included in ClinicalTrials.gov.

Supplementary Material 2
Abstracted data

The abstracted data included the following:

1- *study characteristics*:
author names, year of publication, ties with tobacco industry, funding of study, country of study, study setting, study design, number of participating sites, recruitment procedures, enrolment dates, length of study period, random sequence generation, allocation sequence concealment, blinding, methods for preventing and controlling confounding, selection bias, information bias and missing bias, unit of analysis, covariates inclusion, funding, financial and conflict of interest disclosure including ties with industry, inclusion and exclusion criteria, sample size, number of participants that were analyzed, number of participants lost to follow up for each outcome and for the whole study, number of participants at study onset and randomized to each group, and type of analysis (intention to treat vs per protocol)

2- *participant characteristics:*
age, gender, comorbidities, ethnicities, socio-economic status, income, education, cigarettes smoked per day, Fagerström test for cigarette dependence

3- *intervention characteristics:*
type, model, brand and generation of ENDS, type and flavor of e-liquid, nicotine content, intervention protocol, length of time ENDS were provided free of charge, frequency of use, duration of intervention, integrity of intervention, description of co-interventions

4- *comparator characteristics:*
type of nicotine replacement therapy used, dose, frequency of use, nicotine content, control protocol, frequency of use, length of time supplies were provided free of charge, combination of products, frequency of use duration of control, integrity of control, description of co-interventions

5- *outcomes:*
smoking cessation, method of assessment for smoking cessation used (self-report vs biochemical), smoking abstinence definition, longest time point of smoking cessation, harms assessment, methods of harms assessment, definition of harms, withdrawal symptoms, method of assessment for withdrawal symptoms, reduction in cigarettes smoked, method of assessment of reduction in cigarettes smoked, number of quit attempts, method of quit attempt measurement, acceptance of ENDS/NRT, method of acceptance assessment, method of aggregation used for each outcome, timing of measurement for each outcome, summary data for each outcome, method of aggregation used for each outcome.

Supplementary Material 3
Detailed description of the included studies

Supplementary Table 1a. Characteristics of randomized controlled trials measuring smoking cessation at 6 months or later Characteristics of randomized controlled trials measuring smoking cessation at 6 months or later

Bullen, 2013	
Methods	**Design**: 3 parallel groups RCT **Recruitment:** Participants were recruited via community newspapers, inviting people to call the study centre for eligibility pre-screening **Setting**: one single center in Auckland Australia **Inclusion criteria:** 18 years of age or older, smoked 10 or more cigarettes per day for the past year, and wanted to quit smoking. **Exclusion criteria:** Pregnant or breastfeeding women, people using smoking cessation drugs, those reporting heart attack, stroke, severe angina in the previous 2 weeks, and people with poorly controlled medical disorders allergies, or other chemical dependence were excluded
Participants	**Total N:** 657 smokers were included in this study, but we only extracted 584 participants for our review (2 of the 3 groups) as the e-cigarette placebo group did not fit our eligibility criteria. Most participants were women (62%), of a mean age > 40. Approximately one third were of Maori descent, and a little over half had completed grade 12 or above education level. The average daily number of cigarettes smoked at study onset was around 18, and mean Fagerström test result (0 to 10 scale) for cigarette dependence was > 5.
Interventions	**Randomization:** 4:4:1 ratio to nicotine e-cigarettes, nicotine patches and placebo e-cigarette group **Nicotine e-cigarette group** Participants were couriered a first-generation e-cigarette, spare battery and charger, as well as cartridges containing 10 to 16mg of nicotine per mL (although labelled to contain 16 mg), plus simple instructions to use the e-cigarettes as desired from 1 week before until 12 weeks after their chosen quit day. Participants received on average around 20% of the nicotine obtained from cigarette smoking. **Nicotine patch group** Participants were sent exchange cards in the mail redeemable for nicotine patches 21 mg from community pharmacies, with instructions to use the patches daily, from 1 week before until 12 weeks after their chosen quit day. Vouchers were also supplied to participants to cover dispensing costs. **Both groups**

	Participants in all groups were also referred to telephone-based behavioural support
Outcomes	Continuous abstinence at 6 months after quit day, defined as self-reported abstinence over the whole follow-up period allowing for 5 or less cigarettes in total, was self-reported, and verified with exhaled breath carbon monoxide of <10 ppm. Harms were both clinically assessed and self-reported, throughout the study period. Withdrawal symptoms were assessed at 1, 3, and 6 months. Reduction in daily cigarettes smoked was measured at 6 months, and acceptance of therapy was measured at 1 and 6 months.
Notes	Some of this study's authors reported ties to e-cigarette manufacturers, and smoking cessation drug companies
Hajek, 2019	
Methods	**Design:** 2 parallel groups RCT **Recruitment:** Participants were recruited through stop smoking services, which included trial information in their advertising. Participants were also recruited through social media, and leaflets advertising the trial were delivered to local households. **Setting:** 3 sites in the United Kingdom **Inclusion criteria**: Adults, with no strong preference towards e-cigarette or NRT, who were not using either type of product at the time of study enrolment **Exclusion criteria:** Pregnant women or breastfeeding women
Participants	**Total N:** 884 participants were included in this study Median age for both groups was 41, and women comprised 48% of participants. Most participants were White British, and the majority had post-secondary education. Median daily number of cigarettes smoked at study onset was 15, and mean Fagerström test result for cigarette dependence was 4.5 in the e-cigarette group and 4.6 in the NRT group.
Interventions	**Randomization:** nicotine-containing e-cigarettes of varying doses, and any choice of a list of NRT, in a 1:1 ratio **E-cigarette group** Participants were provided with a starter pack called One Kit, which included an atomizer, a battery, and one 30 mL bottle of Tobacco Royale flavor e-liquid. Participants were asked to purchase their future e-liquid online or from local vape shops and to buy a different e-cigarette device if the one supplied did not meet their needs. They were encouraged to experiment with e-liquids of different strengths and flavors. Those who were unable to obtain their own supply were provided with one further 10-ml bottle, but this was not offered proactively. Participants received oral and written information on how to operate the e-cigarette.

	NRT group Participants were informed about the range of nicotine-replacement products (patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs) and selected their preferred product. Use of combinations was encouraged, typically the patch and a faster-acting oral product. Participants were also free to switch products.ps **Both groups** Participants in both groups were offered multisession behavioral support as per UK stop smoking service practice, involving weekly one on one session with local clinicians. Participants were also asked to sign a commitment to not use the unassigned treatment for 4 weeks
Outcomes	Continuous abstinence at 52 weeks after quit day, defined as self-reported abstinence over the whole follow-up period allowing for 5 or less cigarettes in total, was self-reported, and verified with exhaled breath carbon monoxide of <8 ppm. Harms were self-reported throughout the study period. Withdrawal symptoms were assessed at 1 and 4 weeks in abstainers. Reduction in daily cigarettes smoked was also measured at 52 weeks, as well as acceptance of e-cigarettes and NRT
Notes	Some of this study's authors reported ties to smoking cessation drug companies.
Lee SH, 2019	
Methods	**Design:** 2 parallel groups RCT **Recruitment:** Participants were recruited from a motor company in the Republic of Korea. **Setting:** One site in Cheonan, Republic of Korea **Inclusion criteria:** Participants were adults 18 years and above, male, who smoked at least 10 cigarettes per day in the preceding year, and who were motivated to stop smoking entirely or to reduce their cigarette consumption **Exclusion criteria:** Participants were excluded if they had a past medical history of serious clinical diseases or had attempted to stop smoking in the last 12 months by using other NRT.
Participants	**Total N:** 150 participants were included in the study Mean age was 42 years and all participants were men. Almost 40% had post-secondary education. Median daily number of cigarettes smoked at study onset was 1 pack per day, and mean Fagerström test result for cigarette dependence was 4.
Interventions	**Randomization:** nicotine-containing e-cigarettes, and nicotine gum in a 1:1 ratio **E-cigarette group**

	Participants received a 24-week supply of e-cigarettes eGo-C Ovale, Janty-Korea Co., Janty-Asia Co., Seoul, Republic of Korea, nicotine 0.01 mg/mL. **Nicotine gum group** Participants received a 24-week supply of nicotine gum Nicoman, Daewoog Pharmaceutical, Seongnam, Republic of Korea, 2 mg/tablet **Both groups** Participants in both groups were offered 55-minute education sessions on smoking cessation aids
Outcomes	Continuous abstinence was defined as abstinence from smoking from 9 to 24 weeks, validated with end-expiratory carbon monoxide (<10 ppm) and a negative urine cotinine result. Harms were self-reported throughout the study period. Reduction in daily cigarettes smoked was also measured at 24 weeks.
Notes	None of the study authors were found to have ties to industry.
Lee SM, 2018	
Methods	**Design:** 2 parallel groups RCT **Recruitment**: Participants were recruited from an anesthesia preoperative clinic for elective surgery. **Setting:** San Francisco Veterans' Affairs Medical Center, affiliated with the University of California in San Francisco United States of America **Inclusion criteria:** Participants were eligible if they presented to the clinic 3 or more days prior to elective surgery, smoked more than two cigarettes per day, and had smoked at least once in the last 7 days **Exclusion criteria**: Participants were excluded if they exclusively used other forms of tobacco (e.g. pipe tobacco) or marijuana only, were pregnant or breastfeeding, had an unstable condition, were using smoking cessation therapy at the time of study enrolment or were in another smoking cessation trial, or currently used e-cigarettes daily.
Participants	**Total N:** 30 participants were included in this study Most participants were men (90%) in their 50's. Some had comorbidities including diabetes, hypertension, heart disease, and chronic obstructive pulmonary disease. Most were Caucasians. The average daily number of cigarettes smoked at study onset was 15.3 in the e-cigarette group, and 10.8 in the NRT group, and the mean Fagerström test result for cigarette dependence was 3.7 in the e-cigarette group and 2.5 in the NRT group.
Interventions	**Randomization:** e-cigarettes and nicotine patches in a 2:1 ratio **E-cigarette group** Participants received a 6-week supply of NJOY e-cigarettes (Scottsdale, AZ, USA), a disposable first-generation e-cigarette that is available in shops and online. They were issued a number of e-cigarettes corresponding to

	the reported baseline cigarettes smoked per day, calculated assuming one NJOY e-cigarette was equivalent to 10 cigarettes. Participants were instructed to smoke bold (4.5%) e-cigarettes ad libitum for 3 weeks, then the Gold (2.4%) e-cigarettes ad libitum for 2 weeks, and then the Study (0%) e-cigarettes ad libitum for the final week. **Nicotine patch group** Participants randomized to the nicotine patches group were given a 6-week supply of Nicoderm CQ patches (5 weeks) and placebo patches (1 week) appropriate to baseline nicotine consumption. Those smoking an average of ten or more cigarettes per day were given a 21 mg/day patch for 3 weeks, a 14 mg/day patch for 1 week, a 7 mg/day patch for 1 week, and a 0 mg/day patch for 1 week. Participants who reported smoking an average of fewer than 10 cigarettes per day at baseline were given a 14 mg/day patch for 3 weeks, a 7 mg/day patch for 2 weeks, and a 0 mg/day patch for 1 week. **Both groups** Participants in both groups were given referral California Smokers' Helpline and were asked to refrain from the use of cigarettes during the study period.
Outcomes	Smoking cessation at 6 months was self-reported through 7-day point-prevalence abstinence and verified with exhaled breath carbon monoxide of <10 ppm. Harms and withdrawal symptoms were systematically collected at 8 weeks. Reduction in daily cigarettes smoked was also measured at 6 months, as well as acceptance of e-cigarettes and NRT.
Notes	None of the study authors were found to have ties to industry.

Supplementary Table 1b. Characteristics of randomized controlled trial measuring smoking cessation earlier than 6 months

Hatsukami, 2019	
Methods	**Design:** 4 parallel groups RCT **Recruitment:** Participants were culled from two sets of studies, one of which also included two groups randomized to snus (spitless smokeless tobacco); one was complete substitution with snus, and the other was ad libitum use. Due to recruitment challenges, the two snus groups were dropped midway through the study, resulting in four experimental groups: ad libitum use of e-cigarettes (participants may smoke as many cigarettes as they like), complete substitution with e-cigarettes (aiming for smoking

	cessation), complete substitution with NRT, continued smoking with usual brand of cigarettes. Participants were recruited through various media outlets across three institutions. The advertisements stated that a study was recruiting smokers who were interested in trying a product that may reduce exposure to harmful tobacco smoke. **Settings:** 3 sites, University of Minnesota, Twin Cities (lead site); The Ohio State University, Columbus, OH; Roswell Park Cancer Center, Buffalo, NY United States of America **Inclusion criteria:** Participants were adults at least 18 years of age, smoked at least 5 cigarettes per day with a breath carbon monoxide test of at least 10 ppm or a NicAlert test = level 6, and in stable physical and mental health. **Exclusion criteria:** Participants were excluded if they had a serious quit attempt in the past 3 months, recent (<3 months) alcohol or drug abuse problems, regular use of other nicotine or tobacco products, were planning to quit smoking in the next 3 months, suffered from chronic conditions affecting results of biomarker analyses, were currently using NRT or other cessation medication, or if they were pregnant or planning to become pregnant, or breastfeeding
Participants	**Total N:** 264 participants were included in the study, but data for this review were only extracted from the complete substitution with e-cigarette group, and complete substitution with NRT group (152 participants), as the other two groups did not fit our eligibility criteria. Median age was 47 years, and women comprised 49% of participants. Most participants were White, and the majority had post-secondary education. The median daily number of cigarettes smoked at study onset was 15, and median Fagerström test result for cigarette dependence was 3.
Interventions	**Randomization:** e-cigarettes and nicotine gum or lozenges **E-cigarette group** Participants randomized to this group used Vuse Solo, manufactured by RJ Reynolds Inc as the primary e-cigarette. Early in the study, Blu e-cigarettes (cartridge-based system) and Fin (prefilled tanks system) were used, but Vuse attained the highest market share early on so the study switched exclusively to Vuse. E-cigarettes with a 4.8% nicotine concentration were provided to participants free of charge for 8 weeks, as well as 7 cartridges weekly, with the option of returning to the clinic to obtain additional cartridges if needed. Tobacco, menthol, mint, and berry flavors were available. **NRT group**

	Participants could choose between mint, cinnamon or fruit-flavored nicotine gum or nicotine lozenge, at a dose of 4 mg. If adverse effects were recorded, the dose was decreased to 2 mg. **Both groups** After randomization, participants were asked to complete daily diaries via interactive voice recording to chart the number of cigarettes smoked daily, as well as document assigned product use for the duration of the trial. Participants received a monetary bonus if they complied with the protocol; this included keeping an accurate record of product use, completing the daily diaries, and returning unused products. They also got a bonus payment if they had a carbon monoxide level $\leq$ 4 ppm at each visit. Participants also received a brief counseling session on how to avoid smoking.
Outcomes	Smoking cessation was determined by 7-day point prevalence at 8 weeks, mainly through biochemical verification but also by self-report Reduction in daily cigarettes smoked was also measured at 8 weeks, as well as acceptance of e-cigarettes and NRT. Harms were assessed systematically at 20 weeks, 12 weeks after the end of the study period. Withdrawal symptoms were assessed at weeks 1, 2, 4, 6, and 8.
Notes	One of the study authors is a member of the FDA Tobacco Products Scientific Advisory Committee and another one has served as an expert witness in tobacco company litigation.

Supplementary Table 1c. Characteristics of randomized controlled trial measuring other outcomes

Eisenhofer, 2015	
Methods	**Design:** 2 parallel groups RCT **Recruitment:** Not specified **Setting:** Not specified **Inclusion criteria:** Veterans who met criteria for tobacco disorder as per the DSM **Exclusion criteria:** Not specified
Participants	**Total N:** 11 participants were included Mean age was 52, and 82% were males. The vast majority of participants were African American. The average daily number of cigarettes smoked at study onset was 26.5, and the mean Fagerström test result for cigarette dependence was 7.5.
Intervention	**Randomization:** e-cigarettes and nicotine patches **E-cigarette group**

	Participants received nicotine-containing e-cigarettes with 16 mg of nicotine per cartridge **NRT group** Participants received nicotine patch 16 mg daily **Both groups** All participants were instructed to smoke ad libitum during week 1, and to smoke as little as possible during week 3.
Outcomes	Reduction in cigarettes smoked per day was self-reported at 3 weeks and compared to week 1. Withdrawal symptoms were compared between week 1 and week 3.
Notes	This study was available as an abstract only therefore limited details are available.

Supplementary Material 4
Details on Risk of Bias Assessment for each outcome of interest

Supplementary Table 2. Detailed description of concerns for each domain marked identified as "some concerns" or "high risk" on Risk of Bias Assessment

Smoking cessation outcome					
	Randomization Process	**Deviations from intended intervention**	**Missing of outcome data**	**Measurement of the outcome**	**Selection of the reported result**
Bullen 2013	Low risk	Adherence higher in the ENDS group compared to NRT group at all timepoints. At 6 months, 29% of ENDS group vs 8% of NRT group still using assigned treatment.	Low risk	Low risk	Low risk
Hajek 2019	Low risk	At 52 weeks among participants with 1-year abstinence, 80% were using e-cigarettes in the ENDS group vs 9% in the NRT group. Also, 6% of participants in the ENDS group reported using non-allocated NRT for at least five consecutive days in the past six months compared to 22% in the NRT group that reported using non-allocated product	Low risk	Low risk	Low risk
Hatsukami 2019	No information provided with regards to randomization process and allocation concealment. However, there were no	The NRT group had the highest dropout rates compared to the other groups in the study. At 8 weeks, 24% dropped out in the ENDS group compared to 30% in the NRT group.	Large number of dropouts; participants who did not stop smoking could be less motivated to continue with study follow up	Low risk	Low risk

	significant baseline differences between groups				
Lee, SH 2019	The use of constant block sizes of 2 makes it easy to determine order of randomization.	No participants discontinued the intervention. However, 4 and 14 participants in the ENDS and NRT group dropped out before treatment, respectively.	Although data was missing for 12% of randomized individuals, all dropouts occurred prior to the start of treatment. Missingness in this case less likely to be due to the value of the outcome as it happened prior to onset of therapy	Low risk	Low risk
Lee, SM 2018	Low risk	Low risk	Low risk	Low risk	Low risk
Smoking reduction outcome					
Bullen 2013	Low risk	Refer to smoking cessation outcome	Sensitivity analyses conducted for the smoking cessation outcome were not performed for the smoking reduction outcome	Low risk	Low risk
Eisenhofer 2015	Not enough information available in abstract	Not enough information available in abstract	Not enough information available in abstract	Low risk	Not enough information available in abstract
Hajek 2019	Low risk	Refer to smoking cessation outcome	Low risk	Low risk	Low risk
Hatsukami 2019	Refer to smoking cessation outcome	Refer to smoking cessation outcome	Refer to smoking cessation outcome	Low risk	Low risk
Lee, SH 2019	Refer to smoking cessation outcome	Refer to smoking cessation outcome	Refer to smoking cessation outcome	Low risk	Low risk
Lee, SM 2018	Low risk	Low risk	Low risk	Low risk	Low risk
Harms outcome					

Bullen 2013	Low risk	Differences in treatment adherence could potentially lead to discrepancies in harm reporting	No information on the proportion of participants on whom adverse events were collected; it is likely that people who experienced more severe side effects did not continue with study follow-up activities	high likelihood that participants who were unhappy with their treatment allocation would report side effects more often than their counterparts.	Low risk
Hajek 2019	Low risk	Differences in treatment adherence could potentially lead to discrepancies in harm reporting	The authors reported harm data based on number of participants at randomization, however significant dropout seen at 4-week follow up, raising concerns that adverse event data not collected on all participants	High likelihood that participants who were unhappy with their treatment allocation would report side effects more often than their counterparts	Low risk
Hatsukami 2019	Refer to smoking cessation outcome	Differences in treatment adherence could potentially lead to discrepancies in harm reporting	No information on the proportion of participants on whom adverse events were collected; it is likely that people who experienced more severe side effects did not continue with study follow-up activities	High likelihood that participants who were unhappy with their treatment allocation would report side effects more often than their counterparts	Low risk
Lee, SH 2019	Refer to smoking cessation outcome	Differences in treatment adherence could potentially lead to discrepancies in harm reporting however non-adherence happened prior to onset of treatment, therefore less likely to have an impact	Low risk	High likelihood that participants who were unhappy with their treatment allocation would report side effects more often than their counterparts	Low risk
Lee, SM 2018	Low risk	Low risk	Low risk	High likelihood that participants who were unhappy with their	Low risk

				treatment allocation would report side effects more often than their counterparts	
Withdrawal symptoms outcome					
Eisenhofer 2015	Not enough information available in abstract	Not enough information available in abstract	Not enough information available in abstract	Not enough information available in abstract	Not enough information available in abstract
Hajek 2019	Low risk	Differences in treatment adherence could potentially lead to discrepancies in withdrawal symptoms reporting	Outcome not available for all randomized participants; likely that people who experienced more nicotine withdrawal symptoms did not continue with study follow-up activities	Given that the withdrawal measurements were self-reported, there is a high likelihood that participants who were unhappy with treatment allocation reported more withdrawal symptoms than their counterparts	Low risk
Hatsukami 2019	Refer to smoking cessation outcome	Differences in treatment adherence could potentially lead to discrepancies in withdrawal symptoms reporting	Outcome not available for all randomized participants; likely that people who experienced more nicotine withdrawal symptoms did not continue with study follow-up activities	Given that the withdrawal measurements were self-reported, there is a high likelihood that participants who were unhappy with treatment allocation reported more withdrawal symptoms than their counterparts	No information on how withdrawal symptom assessment was performed
Lee, SM 2018	Low risk	Low risk	Low risk	Given that the withdrawal measurements were self-reported, there is a high likelihood that participants who were	Low risk

				unhappy with treatment allocation reported more withdrawal symptoms than their counterparts	
Acceptance of therapy outcome					
Bullen 2013	Low risk	Differences in treatment adherence could potentially lead to discrepancies in acceptance of therapy outcome	Participants unhappy with their assigned therapy likely did not continue with study follow-up activities	Highly subjective outcome, inability to blind participants to assigned therapy	Low risk
Hajek 2019	Low risk	Differences in treatment adherence could potentially lead to discrepancies in acceptance of therapy outcome	Participants unhappy with their assigned therapy likely did not continue with study follow-up activities	Highly subjective outcome, inability to blind participants to assigned therapy	Low risk
Hatsukami 2019	Not enough information available in abstract	Differences in treatment adherence could potentially lead to discrepancies in acceptance of therapy outcome	Participants unhappy with their assigned therapy likely did not continue with study follow-up activities	Highly subjective outcome, inability to blind participants to assigned therapy	Low risk
Lee, SM 2018	Low risk	Low risk	Low risk	Highly subjective outcome, inability to blind participants to assigned therapy	Low risk

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	0
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5,6, Supp material 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, Supp material 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,8, Supp material 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Figures 2a,b,c,d,e
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-13, Figures 3a,b,c,d,
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12, Figures 3a,b,c,d
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13, Figures 4a,b,c
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-15

PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	0

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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