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Complete List of Authors:	El Dib, Regina; Unesp – Univ Estadual Paulista, São Paulo, Brazil, Department of Anaesthesiology, Botucatu Medical School Suzumura, Erica; Hospital do Coração (HCor), São Paulo, Brazil, Research Institute Akl, Elie; American University of Beirut, Department of Internal Medicine; McMaster University, Department of Clinical Epidemiology and Biostatistics Goma, Huda; Tanta Chest Hospital, Department of Pharmacy Agarwal, Arnav; University of Toronto Faculty of Medicine, Faculty of Medicine; McMaster University, Department of Clinical Epidemiology & Biostatistics Chang, Yaping ; McMaster University, Department of Clinical Epidemiology & Biostatistics Prasad, Manya; Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Department of Community Medicine Ashoorion, Vahid; Isfahan University of Medical Sciences, Isfahan Medical Education Research Centre Heels-Ansdell, Diane; McMaster University, Department of Clinical Epidemiology & Biostatistics Maziak, Wasim; Florida International University, College of Public Health Guyatt, Gordon; McMaster University, Department of Clinical Epidemiology & Biostatistics
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Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis

Regina El Dib, PhD[1,2*]; Erica A. Suzumura, MSc[3]; Elie A. Akl, MD, MPH, PhD[4,5]; Huda Goma, BCPS[6]; Arnav Agarwal, BHSc, MD(C)[5,7]; Yaping Chang, MSc[5]; Manya Prasad, MBBS[8]; Vahid Ashoorion, MD, MSc, PhD[5,9]; Diane Heels-Ansdell, MSc[5]; Wasim Maziak MD, PhD[10]; Gordon Guyatt, MD, MSc[5,11]

1. Department of Anaesthesiology, Botucatu Medical School, Unesp – Univ Estadual Paulista, São Paulo, Brazil
2. McMaster Institute of Urology, McMaster University, Hamilton, Ontario, Canada
3. Research Institute - Hospital do Coração (HCor), São Paulo, Brazil
4. Clinical Research Institute (CRI); Center for Systematic Reviews in Health Policy and Systems Research (SPARK) and Department of Internal Medicine, American University of Beirut, Lebanon
5. Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada
6. Department of Pharmacy, Tanta Chest Hospital, Tanta, Egypt
7. Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
8. Department of Community Medicine, Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India
9. Isfahan Medical Education Research Centre, Isfahan University of Medical Sciences, Isfahan, Iran
10. Department of Epidemiology, Robert Stempel College of Public Health and Social Work, Florida International University, Miami, Florida
11. Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Corresponding author:

Regina El Dib
Assistant Professor
Department of Anaesthesiology
Distrito de Rubião Júnior, s/n
Univ Estadual Paulista, São Paulo, Brazil
Botucatu, SP 18618-970
+ 55 11 9 9999 6647
eldib@fmb.unesp.br

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ABSTRACT

Objective: A systematic review and meta-analysis to investigate the impact of ENDS and/or ENNDS versus no smoking cessation aid, or alternative smoking cessation aids, in current or former cigarette smokers on long-term tobacco use.

Data sources: Searches of MEDLINE, EMBASE, PsycInfo, CINAHL, CENTRAL and Web of Science up to December 2015.

Study selection: Randomized controlled trials (RCTs) and prospective cohort studies.

Data extraction: Three pairs of reviewers independently screened potentially eligible articles, extracted data from included studies on populations, interventions and outcomes, and assessed their risk of bias. We used the GRADE approach to rate overall certainty of the evidence by outcome.

Data synthesis: Three randomized trials including 1,007 participants and nine cohort including 13,115 participants proved eligible. Results provided by the RCTs suggest a possible increase in tobacco smoking cessation with ENDS in comparison to ENNDS (RR 2.03, 95% CI 0.94, 4.38; p = 0.07; I^2=0%, risk difference (RD) 64/1,000 over 6 to 12 months, low certainty evidence). Results from cohort studies suggested a possible reduction in quit rates with use of ENDS compared to no use of ENDS (OR 0.74, 95% CI 0.55, 1.00; p = 0.051; I^2=56%, very low certainty).

Conclusions: There is no robust evidence regarding the impact of ENDS or ENNDS on tobacco smoking cessation or reduction: data from RCTs are of low and observational studies of very low certainty.

Strengths and limitations of this study

- Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias, and data abstraction independently and in duplicate; assessment of risk of bias that included a sensitivity analysis addressing loss to follow-up; and use of the GRADE approach in rating the certainty of evidence for each outcome.
- The primary limitation of our review is the low certainty consequent on study limitations. Moreover, loss to follow-up was substantial, and, our sensitivity analysis demonstrated the vulnerability of borderline effects to missing data. The limitations of the cohort studies led us to a rating of very low certainty evidence from which no credible inferences can be drawn.
- The small number of studies made it impossible to address our subgroup hypotheses related dose-response of nicotine, more versus less frequent use of e-cigarettes, or the relative impact of newer versus older e-cigarette models.

INTRODUCTION

Tobacco smokers who quit their habit reduce their risk of developing and dying from tobacco-related diseases [1-4]. Both psychosocial [5-7] and pharmacological interventions (e.g., nicotine replacement therapy (NRT)) [5-7] increase the likelihood of quitting cigarettes. Even with these aids, however, most smokers fail to quit.

Electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) represent a potential third option for those seeking to stop smoking. ENDS are devices that deliver nicotine in an aerosolized form, while ENNDS devices ENNDS are labeled as not containing nicotine (though labeling may not always be accurate). In theory, these devices as well as the nicotine inhalers may facilitate quitting smoking to a greater degree than other nicotine based products or no intervention because they deal, at least partly, with the behavioral and sensory aspects of smoking addiction (e.g. hand mouth movement) [8]. The debate about the role of ENDS in smoking cessation however, is compounded by the lack of clear evidence about their value as a smoking cessation tool, their potential to hook tobacco- naïve youth on nicotine, as well as act as a bridge to combustible tobacco use [11, 47, 48]. While evidence about all these aspects of ENDS is accumulating, establishing their real place in smoking cessation is essential to outline the public health context of considering them as a potential harm-reduced products [49]. There are, however, other reasons for ENDS use such as for relaxation or recreation (i.e. the same reason people smoke), with the possibility that adverse health effects may be less than conventional smoking.

There are many types of ENDS. The cigalikes are the first generation of ENDS that provides an appearance of tobacco cigarettes; they are not rechargeable. The second generation of ENDS looks like a pen, allows the user to mix flavors, and may contain a prefilled or a refillable cartridge. The advanced personal vaporizers are the third generation of

ENDS that includes mechanical mods and variable voltage devices. The fourth generation contains a large, refillable cartridge and has a tank-style design.

A previous Cochrane systematic review [8] summarized results from randomized controlled trials (RCTs) and cohort studies. The authors included two RCTs and 11 cohort studies, and concluded that there was evidence to support the potential benefit of ENDS in increasing tobacco smoking cessation [8]. The certainty of evidence supporting this conclusion was, however, deemed low, primarily due to the small number of trials resulting in wide confidence intervals around effect estimates [8]. Another systematic review [9] including a total of six studies (RCTs, cohort, and cross-sectional studies) involving 7,551 participants concluded that ENDS is associated with smoking cessation and reduction; however the included studies were heterogeneous, due to different study designs and gender variation. One other review [10] comparing e-cigarettes to other nicotine replacement therapies or placebo included five studies (RCTs and controlled before-after studies) and concluded that participants using nicotine e-cigarettes were more likely to stop smoking, but but noted no statistically significance differences [10]. A more recent systematic review Kalkhoran & Glantz 2016 [11] included 20 studies (15 cohort studies, 3 cross-sectional studies, and 2 clinical trials), and found 28% lower odds rates of quitting cigarettes in those who used e-cigarettes compared with those who did not use e-cigarettes; although the methodological aspects of the observational studies was rated as unclear or high on outcome assessors, and a RCT was rated as high risk of performance and attrition bias.

Previous reviews were, however, limited in that they did not include all studies in this rapidly evolving field, and all but one did not use the GRADE approach to rating quality of evidence. We therefore conducted an updated systematic review of RCTs and cohort studies that assessed the impact of ENDS and/or ENNDS versus no smoking cessation aid or alternative smoking cessation aids on long-term tobacco use, among current or former

cigarette smokers or users of other combustible tobacco products, regardless of whether the users were using them as part of a quit attempt.

METHODS

We adhered to methods described in the Cochrane Handbook for Intervention Reviews [12]. Our reporting adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) Statements [14]. This work was commissioned by the World Health Organization.

Eligibility Criteria

- Study designs: RCTs and prospective cohort studies.
- Participants: current or former cigarette smokers or users of other combustible tobacco products (henceforth referred to as "smokers"), regardless of whether the users were using them as part of a quit attempt.
- Interventions: electronic nicotine delivery systems (ENDS) or electronic non-nicotine delivery systems (ENNDS).
- Comparators:
    - No smoking cessation aid;
    - Alternative non-electronic smoking cessation aid, including nicotine replacement therapy (NRT), behavioral and/or pharmacological cessation aids;
    - Alternative electronic smoking cessation aid (ENDS or ENNDS).
- Outcomes:
    - Tobacco smoking cessation, with preference to biochemically validated outcomes [e.g., carbon monoxide (CO)] measured at six months or longer follow-up;
    - Reduction in cigarette use of at least 50%;

- Serious (e.g., pneumonia, myocardial infarction) and non-serious (e.g., nausea, vomiting) adverse events measured at one week or longer follow-up

Data source and searches

A previous Cochrane review with similar eligibility criteria ran a comprehensive search strategy up to July 2014 [8]. Using Medical Subject Headings (MeSH) based on the terms "electronic nicotine," "smoking-cessation," "tobacco-use-disorder," "tobacco-smoking," and "quit" we replicated the search strategy of that review [8] in Medline, EMBASE, PsycInfo, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Science, and the trial registry (clinicaltrials.gov). The appendix Table 1 shows the search strategy for Ovid MEDLINE. This strategy was adapted for the other databases and run from April 1, 2014 to December 29, 2015. We did not impose any language restrictions.

In addition, we established a literature surveillance strategy based on the weekly search alerts by CDC's Smoking & Health Resource Library of published articles (http://nccd.cdc.gov/shrl/NewCitationsSearch.aspx) as well as the Gene Borio's Daily news items (www.tobacco.org). The surveillance strategy commenced from the time of running the comprehensive literature search up to the time of the submission of this manuscript.

Selection of studies

Three pairs of reviewers underwent calibration exercises and used standardized pilot tested screening forms. They worked in teams of two and independently screened all titles and abstracts identified by the literature search, obtained full-text articles of all potentially eligible studies, and evaluated them for eligibility. Reviewers resolved disagreement by discussion or, if necessary, with third party adjudication. We also considered studies reported only as conference abstracts. For each study, we cite all articles that used data from that study.

Data extraction

Reviewers underwent calibration exercises, and worked in pairs to independently extract data from included studies. They resolved disagreement by discussion or, if necessary, with third party adjudication. They abstracted the following data using a pre-tested data extraction form: study design; participants; interventions; comparators; outcome assessed; and relevant statistical data. When available, we prioritized carbon monoxide (CO) measurements as evidence of quitting. When CO measurement was unavailable, we used self-report measures of quitting.

Risk of bias assessment

Reviewers, working in pairs, independently assessed the risk of bias of included RCTs using a modified version of the Cochrane Collaboration's instrument [15] (http:/distillercer.com/resources/) [16]. That version includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the previously cited domains [16].

For cohort studies, reviewers independently assessed risk of bias with a modified version of the Ottawa-Newcastle instrument [17] that includes confidence in assessment of exposure and outcome, adjusted analysis for differences between groups in prognostic characteristics, and missing data [17]. For incomplete outcome data in individual studies (both RCTs and prospective cohort studies) we stipulated as low risk of bias for loss to follow-up of less than 10% and a difference of less than 5% in missing data between intervention/exposure and control groups.

When information regarding risk of bias or other aspects of methods or results was unavailable, we attempted to contact study authors for additional information.

Certainty of evidence

We summarized the evidence and assessed its certainty separately for bodies of evidence from RCTs and cohort studies. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate certainty of the evidence for each outcome as high, moderate, low, or very low [18]. In the GRADE approach RCTs begin as high certainty and cohort studies as low certainty. Detailed GRADE guidance was used to assess overall risk of bias [19], imprecision [20], inconsistency [21], indirectness [22] and publication bias [23], and to summarize results in an evidence profile. We planned to assess publication bias through visual inspection of funnel plots for each outcome in which we identified 10 or more eligible studies; however we were not able to because there were an insufficient number of studies to allow for this assessment. Cohort studies can be rated up for a large effect size, evidence of dose–response gradient or if all plausible confounding would reduce an apparent effect [24].

Data synthesis and statistical analysis

We analyzed all outcomes as dichotomous variables. In three-arm studies, we combined results from arms judged to be sufficiently similar (e.g. Caponnetto 2013 [25], two arms with similar ENDS regimens: 7.2 mg ENDS and, 7.2 mg ENDS plus 5.4 mg ENDS). When studies reported results for daily or intensive use of ENDS separately from non-daily or less intensive use we included only the daily/intensive use in the primary pooled analysis (e.g., Brose 2015 [26-28], we excluded patients with non-daily users; and Biener 2015 [29], we excluded patients with intermittent defined use). We conducted a sensitivity analysis in which we included all ENDS users, both daily/intensive and intermittent/less intensive use. For this analysis when necessary we assumed a correlation of 0.5 between the effects in the daily/intensive and intermittent/less intensive groups.

We synthesized the evidence separately for bodies of evidence from RCTs and cohort studies. For RCTs we calculated pooled Mantel-Haenszel risk ratios (RRs) and associated

95% CIs using random-effects models. For observational studies, we pooled adjusted odds ratios (ORs) using random effects models.

After calculating pooled relative effects, we also calculated absolute effects and 95% CI. For each outcome, we multiplied the pooled RR and its 95% CI by the median probability of that outcome. We obtained the median probability from the control groups of the available randomized trials. We planned to perform separate analyses for comparisons with interventions consisting of ENDS and/or ENNDS and each of type of control interventions with known different effects [no smoking cessation aid; alternative non-electronic smoking cessation aid including NRT; alternative electronic smoking cessation aid (ENDS or ENNDS)]. For meta-analyses we used six months data or the nearest follow-up to six months available.

For dealing with missing data, we used complete case as our primary analysis; that is, we excluded participants with missing data. If results of the primary analysis achieved or approached statistical significance, we conducted sensitivity analyses to test the robustness of those results. Specifically, we conducted a plausible worst-case sensitivity analysis in which all participants with missing data from the arm of the study with the lower quit rates were assumed to have 3 times the quit rate as those with complete data, and those with missing data from the other arm were assumed to have the same quit rate as participants with complete data [30, 31].

We assessed variability in results across studies by using the I^2 statistic and the p-value for the chi square test of heterogeneity provided by Review Manager. We used Review Manager (RevMan) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses [32].

RESULTS

Study Selection

Figure 1 presents the process of identifying eligible studies, including publications in the last systematic review [8], citations identified through search in electronic databases, and studies identified through contact with experts in the field. Based on title and abstract screening, we assessed 69 full-texts of which we included 19 publications describing three RCTs involving 1,007 participants [25, 33-39] and nine cohort studies with a total of 13,115 participants [26-29, 40-46]. The inter-observer agreement for the full-text screening was substantial (kappa 0.73).

We contacted the authors of the 12 included studies, nine of whom [26-29, 33-41, 43, 44, 46] supplied us with all requested data; authors of further three studies [25, 42, 46] did not supply the requested information (Appendix table 3).

Study Characteristics

Table 1 describes study characteristics related to design of study, setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up. Five studies [25-28, 33, 42, 46] were conducted largely in Europe, six in the US [29, 40, 41, 43-45], and one in New Zealand [34-39]. Randomized trials sample size ranged from 50 [33] to 657 [34-39], and observational studies from 100 [46] to 3,891 [26-28]. Typical participants were females in their 40s and 50s. Studies followed participants from four weeks [46] to 36 months [29].

Table 2 describes study characteristics related to population, intervention or exposure groups, comparator, and assessed outcomes. Of the three RCTs, one compared ENDS to both NRT and ENNDS [34-39], another to different concentrations of ENDS to ENNDS [25], and the third compared different types of ENDS [33]. Only the Borderud study [41] included participants who were also currently receiving other behavioral and other pharmacologic treatment. The participants from Vickerman 2013 [44] study were all enrolled in a state quitline programs that provided behavioral treatment and in some cases NRT. All nine cohort

studies [26-29, 34-46] compared ENDS to no use of ENDS [26-29, 40, 41] or tobacco cigarettes only [42]; in one [41], both exposure and non-exposure groups received behavioral and other pharmacologic treatment.

Table 3 describes the mean number of conventional cigarettes and/or other tobacco products use per day at both baseline and the end of study. The mean number at baseline ranged from 11.9 in the no ENDS group [45] to 20.6 in the ENDS group [33]. In only two studies [26-28, 45] the mean number of conventional cigarettes/other tobacco products used per day presented a reduction from the baseline to the end of study in the ENDS group compared to the no ENDS groups, mainly in the daily users [26-28]. No included study addressed users of combustible tobacco products other than cigarettes.

Appendix table 3 presents the types of e-cigarettes used in the included studies. The three RCTs [25, 33-39] evaluated only ENDS type cigalikes. 23.7% of the participants from Brose 2015 [26-28] study used tank and in the Hajek 2015 [46] study participants used either cigalike or tank. The remaining studies did not report the type of ENDS used.

Risk of Bias

Figures 2 and 3, and table 4, describe the risk of bias assessment for the RCTs. The major issue regarding risk of bias in the RCTs of ENDS versus ENNDS was the extent of missing outcome data [25, 34-39]. RCTs comparing ENDS to other nicotine replacement therapies had additional problems of concealment of randomization [33] and blinding [33-39].

Table 4. Risk of bias assessment for the randomized controlled trials

Author, year	Was the randomization sequence adequately generated?	Was allocation adequately concealed?	Was there blinding of participants?	Was there blinding of caregivers?	Was there blinding of data collectors?	Was there blinding of statistician?	Was there blinding of outcome assessors?	Was loss to follow-up (missing outcome data) infrequent?*	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?
Randomized controlled trials assessing ENDS *versus* ENNDS										
Bullen, 2013 [34-39]	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely no	Definitely yes	Definitely yes
Caponnetto, 2013 [25]	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely no	Definitely yes	Definitely yes
Randomized controlled trials assessing ENDS *versus* other quitting mechanisms										
Adriaens, 2014 [33]	Definitely yes	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no	Definitely no	Probably yes	Probably yes
Bullen, 2013 [34-39]	Definitely yes	Definitely yes	Definitely no	Definitely no	Probably yes	Probably yes	Definitely yes	Definitely no	Definitely yes	Definitely yes

*Defined as less than 10% loss to outcome data or difference between groups less than 5% and those excluded are not likely to have made a material difference in the effect observed.

ENDS: electronic nicotine delivery systems. ENNDS: electronic non-nicotine delivery systems.

All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).

Figure 4 and table 5 describe the risk of bias assessment of the cohort studies. Seven [26-29, 40-42, 44, 45] of nine cohort studies were rated as high risk of bias for limitations in matching exposed and unexposed groups or adjusting analysis for prognosis variables; confidence in the assessment of the presence or absence of prognostic factors; confidence in the assessment of outcome; and similarity of co-interventions between groups; all studies suffered from high risk of bias for missing outcome data.

Table 5. Risk of bias assessment of the cohort studies.

Author, year	Was selection of exposed and non-exposed cohorts drawn from the same population?*	Can we be confident in the assessment of exposure?**	Can we be confident that the outcome of interest was not present at start of study? ***	Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? ****	Can we be confident in the assessment of the presence or absence of prognostic factors?*****	Can we be confident in the assessment of outcome? ******	Was the follow up of cohorts adequate? *******	Were co-interventions similar between groups? ********
Al-Delaimy 2015 [40]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Biener 2015 [29]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Brose 2015 [26-28]	Definitely yes	Probably yes	Probably no	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Hajek 2015 [46]	Probably yes	Probably yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably no
Harrington 2015 [45]	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no
Manzoli 2015 [42]	Definitely yes	Probably yes	Definitely no	Definitely no	Definitely no	Probably no	Definitely no	Probably no
Borderud 2014 [41]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely yes
Prochaska 2014 [43]	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely no	Definitely yes	Probably No
Vickerman 2013 [44]	Probably yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no

* Examples of low risk of bias: Exposed and unexposed drawn from same administrative data base of patients presenting at same points of care over the same time frame.

** This means that investigators accurately assess the use of ENDS at baseline.

*** This means that smoking cessation was not present at the start of the study.

**** Examples of low risk of bias: comprehensive matching or adjustment for all plausible prognostic variables.

***** Examples of low risk of bias: Interview of all participants; self-completed survey from all participants; review of charts with reproducibility demonstrated; from data base with documentation of accuracy of abstraction of prognostic data.

****** Outcome self-reported was considered as definitely no for adequate assessment. Smoking abstinence, biochemically verified was considered as definitely yes for adequate assessment.

*******Defined as less than 10% loss to outcome data or subjects lost to follow-up unlikely to introduce bias.

******** Examples of low risk of bias: Most or all relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.

All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).

Outcomes

The mean number of conventional cigarettes/tobacco products used per day at the end of the studies ranged from 0.7 [34-39] in both ENDS and ENNDS groups to 13.9 [26-28] among non-daily users of ENDS (Table 3). The three RCTs [25, 33-39] and one cohort study [42] biochemically confirmed nicotine abstinence while the others presented only self-reported data [26-29, 40, 41, 43-45] (Table 3).

Tobacco cessation smoking

Synthesized results from randomized controlled trials

Results from two RCTs [25, 34-39] suggest a possible increase in smoking cessation with ENDS in comparison to ENNDS (RR 2.03, 95% CI 0.94, 4.38; p = 0.07; I^2=0%, risk difference (RD) 64/1,000 over 6 to 12 months, low quality evidence) (Figure 5, Table 6). A plausible worse case sensitivity analysis yielded results that were inconsistent with the primary complete case analysis and suggest no difference in the effects of ENDS in comparison to ENNDS (RR 1.16, 95% CI 0.72, 1.87; p = 0.54; I^2=0%) (Appendix Figure 1). Certainty in evidence was rated down to low because of imprecision and risk of bias, due to missing outcome data in all studies and lack of blinding of participants [34-39], caregivers, data collectors, statistician and outcome assessors in the ENDS versus other nicotine replacement therapy studies [47] (Figure 2, Tables 4 and 6).

Adriaens 2014 [33] also compared two types of ENDS and ENDS and e-liquid; results showed no difference between the ENDS groups with a very wide confidence interval (RR 1.15, 95% CI 0.28, 4.76, p = 0.84).

Table 6. *GRADE evidence profile for RCTs:* Electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) for reducing cigarette smoking.

Quality assessment						Summary of findings					Certainty in estimates
						Study event rates		Relative risk	Anticipated absolute effects over 6-12 months		OR
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	ENNDS*	ENDS	(95% CI)	ENNDS*	ENDS	Quality of evidence
Cessation/nicotine abstinence (Includes self-reported and biochemically validated by eCO)											
481 (2) 6-12 mo	Serious limitations[1]	No serious limitations	No serious limitations	Serious imprecision[2]	Undetected	7/ 112	43/ 369	**2.03** (0.94-4.38)	213 per 1000	219 more per 1000 (13 fewer to 720 more)	⊕⊕OO LOW
Self-report of reduction in cigarettes of > 50%											
481 (2)	Serious limitations[1]	Serious limitations	No serious limitations	Serious imprecision[2]	Undetected	45/ 112	184/ 369	**0.97** (0.57-1.66)	213 per 1000	7 fewer per 1000 (92 fewer to 140 more)	⊕⊕OO LOW

6-12 mo				

*The estimated risk control was taken from the median estimated control risks of the cohort studies.

[1]Two studies presented high risk of bias for missing outcome data. [3]Moreover, one was not blinded to participants and caregiver [29, 37-41] and, other [26-28] also was not blinded to data collectors, statistician and outcome assessors. While not specifically rating down for risk of bias, these additional concerns plus borderline clinically important imprecision led to downgrading of certainty in estimates for all outcomes.

[2]95% CI for absolute effects include clinically important benefit and no benefit.

Bullen 2013 [34-39] also compared ENDS and ENNDS with NRT; results showed no difference between these groups with a very wide confidence interval (RR 1.10, 95% CI 0.60, 2.03, p = 0.76) and (RR 0.67, 95% CI 0.20, 2.19, p = 0.50), respectively.

Synthesized results from cohort studies

The adjusted OR from primary meta-analysis of eight cohort studies [26-29, 40-45] comparing ENDS to no ENDS without reported concomitant interventions suggested no benefit in cessation smoking (OR 0.74, 95% CI 0.55, 1.00; p = 0.051; I^2=56%) (Figure 6). A sensitivity analysis from the eight cohort studies [26-29, 40-45] using any rather than daily use of ENDS for Brose study [26-28], both intensive (used e-cigarettes daily for at least 1 month), and intermittent use (used regularly, but not daily for more than 1 month) of ENDS for Biener study [29] and, any use versus never used for Vickerman study [44] suggested a reduction in cessation smoking rates with ENDS (adjusted OR 0.69, 95% CI 0.53, 0.91; p = 0.01; I^2=59%) (Appendix Figure 2).

Another sensitivity analysis from the same eight cohort studies [26-29, 40-45], examined whether low and high risk of bias limited to the one characteristic in which the studies differed substantially: confidence in whether the outcome was present at the beginning of the study. Although there were substantial differences in the point estimates in the low risk of bias group (adjusted OR 1.00, 95% CI 0.51, 1.94; p = 1.00; I2=67) and the high risk of bias (adjusted OR 0.62, 95% CI 0.50, 0.77; p < 0.001; I2=0%), the difference is easily explained by chance (interaction p-value was 0.19) (Appendix Figure 3).

Certainty in evidence from the observational studies was rated down from low to very low because risk of bias due to missing outcome data, imprecision in the assessment of prognostic factors and outcomes (Figure 4, Tables 5 and 7), as well as inconsistency in the results.

Table 7. *GRADE evidence profile for cohort studies:* Electronic nicotine delivery systems (ENDS) and no ENDS for reducing cigarette smoking.

Quality assessment						Summary of findings					Certainty in estimates
						Study event rates		Relative risk	Anticipated absolute effects over 6-12 months		OR
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	ENNDS*	ENDS	(95% CI)	ENNDS*	ENDS	Quality of evidence
Cessation/nicotine abstinence (Includes self-reported and biochemically validated by eCO)											
7,826 (8) 6-36 mo	Serious limitations[1]	No serious limitations	No serious limitations	Serious imprecision[2]	Undetected	1300/ 5693	336/ 2133	**0.74** (0.55-1.00)	213 per 1000	56 fewer per 1000 (96 fewer to 0 more)	⊕OOO VERY LOW

*The estimated risk control was taken from the median estimated control risks of the cohort studies.

[1]All studies were rated as high risk of bias for adjustment for prognosis variable; assessment of prognostic factors; assessment of outcomes; adequate follow-up of cohort; and similarity of co-interventions between groups.

[2]95% CI for absolute effects include clinically important benefit and no benefit.

Borderud 2014 [41] reported cessation smoking in 25 out of 58 cancer patients using ENDS plus behavioral and pharmacologic treatment versus in 158 out of 356 cancer patients who received only behavioral and pharmacologic treatment (adjusted OR 0.97, 95% CI 0.71 to 1.33).

Reduction in cigarette use of at least 50%

Synthesized results from randomized controlled trials

Two RCTs [25, 34-39] results suggested no difference between ENDS type cigalikes versus ENNDS group with regards to reduction in cigarettes but with a very wide confidence interval (RR 0.97, 95% CI 0.57, 1.66; p = 0.92; I^2=61%) (Appendix Figure 4). Certainty in evidence was rated low because of imprecision and risk of bias [25, 34-39] (Figure 2, Tables 4 and 6).

Synthesized results from cohort studies

Two studies [26-29] suggested increased reduction rates in those with greater versus lesser use of ENDS. Biener [29] reported an adjusted OR for quitting of 6.07 (95% CI 1.11, 33.2) in those with intensive use versus an OR of 0.31 (0.04, 2.80) in those with intermittent use. Brose [26-28] reported a greater likelihood of substantial reduction (but not quitting) in those with daily use of ENDS (OR 2.49, 95% CI 1.14, 5.45) but not those with intermittent use (OR 0.85 0.43 to 1.71).

Adverse effects

Synthesized results from randomized controlled trials

Bullen 2013 [34-39] study reported serious side effects in 27 out of 241 participants in the 16 mg ENDS group and 5 out of 57 for the ENNDS group followed at 6 months; results showed no difference between these groups with a very wide confidence interval (OR 1.31, 95% CI 0.48, 3.57; p = 0.59). Results suggested possible increase in side effects in the 21 mg nicotine patches group (14 of 215) in comparison to ENDS (OR 1.81, 95% CI 0.92, 3.55; p = 0.08). Serious side effects includes death (n = 1, in nicotine e-cigarettes group), life

threatening illness (n = 1, in nicotine e-cigarettes group), admission to hospital or prolongation of hospital stay (12% of all events in nicotine e-cigarettes group, 8% in patches group, and 11% in placebo e-cigarettes group), persistent or significant disability or incapacity, and other medically important events (6% of all events in nicotine e-cigarettes group, 4% in patches group, and 3% placebo e-cigarettes group).

Adriaens 2014 [33] study reported no serious adverse events in both ENDS groups as well as in the e-liquid group at eight months of follow-up; however at one week from start of intervention there were three cases of non-serious adverse events in the ENDS groups.

Caponnetto 2013 [25] mentioned that no serious adverse events occurred during the study and; authors found a significant reduction in frequency of reported symptoms compared to baseline.

Synthesized results from cohort studies

Manzoli [42] reported no significant differences in self-reported serious side effects, but observed four cases of pneumonia, four COPD exacerbations, three myocardial infarctions, and one angina as possibly-related serious side effects: two among the ENDS users (both switched to tobacco smoking during follow-up); six among tobacco smokers (three quit all smoking); four among tobacco and ENDS smokers.

Hajek 2015 [46] reported one leak irritating a participant's mouth and some reports of irritation at the back of the throat and minor coughing. The remaining studies did not report adverse effects.

DISCUSSION

Main findings

Based on pooled data from two randomized trials with 481 participants, we found evidence for a possible increase in tobacco smoking cessation with ENDS in comparison to

ENNDS (Figure 5). The evidence is, however, of low certainty: the 95% confidence interval of the relative risk crossed 1.0 and a plausible worse case sensitivity analyses to assess the risks of bias associated with missing participant data yielded results that were inconsistent with the primary complete case analysis (Appendix Figure 1). Furthermore, in all these RCTs, the ENDS tested were earlier generation; it is possible that later generation of e-cigarettes would have greater benefit. There was no robust evidence of side effects associated with ENDS in the RCTs.

Cohort studies provide very low certainty evidence suggesting a possible reduction in quit rates with use of ENDS compared to no use of ENDS (Figure 7). These studies had a number of limitations: an unknown number of these participants were not using ENDS as a cessation device; some were not using ENDS during a quit attempt; many did not have immediate plans to quit smoking. In our risk of bias assessment, we judged that 7 of 9 studies did not have optimal adjustment for prognostic variables. Further, as any cohort study, the results are vulnerable to residual confounding. In particular, use of ENDS may reflect the degree of commitment to smoking cessation, and it may be the degree of commitment, rather than use of ENDS, that is responsible for the change in quit rates. For instance, the finding in two studies that daily use of ENDS, but not intermittent use, increased quit/reduction rates could be interpreted as evidence of the effectiveness of daily use. An alternative interpretation, however, is that those that used ENDS daily were more motivated to stop smoking, and the increased motivation, rather than daily use of ENDS, was responsible for their degree of success.

In terms of bias against ENDS, cohort studies sometimes enroll smokers already using ENDS and still smoking. Such individuals may cohort studies may already be failing in their attempts to stop smoking. If so, enrolling these participants will underestimate ENDS beneficial effects. Additional concerns with cohort studies include their failure to provide

optimal adjustment for prognostic variables or provide data regarding use of alternative smoking reduction aids.

One could argue that these limitations make the pooling of results we have undertaken inadvisable. On the other hand, the pooling does highlight the possibility of an adverse effect of e-cigarettes on quit rates, a possibility that until definitively refuted by randomized trials needs consideration in policy debates regarding e-cigarettes.

Strengths and limitations

Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias, and data abstraction independently and in duplicate; assessment of risk of bias that included a sensitivity analysis addressing loss to follow-up; and use of the GRADE approach in rating the certainty of evidence for each outcome.

The primary limitation of our review is the low certainty consequent on study limitations. We identified only a small number of RCTs with a modest number of participants resulting wide confidence intervals. Moreover, loss to follow-up was substantial, and, our sensitivity analysis demonstrated the vulnerability of borderline effects to missing data. The limitations of the cohort studies led us to a rating of very low certainty evidence from which no credible inferences can be drawn.

Another limitation of this review is the fact that we could not address our hypothesis about increase rates in smoking cessation in those who used e-cigarettes with higher concentrations of nicotine compared to those using less nicotine, or daily e-cigarette users compared to nondaily e-cigarette users, or those who use newer forms of ENDS compared to users of first generation devices due to lack of evidence. However, although these assumptions seems logical it should be noted that nicotine delivery from ENDS depends on

other factors such as the efficiency of the device in aerosolising the liquid and user experience, apart from the concentration of nicotine in the ENDS liquid.

Furthermore, whether or not ENDS are an effective aid in the cessation smoking may depend on whether the users were using ENDS as part of a quit attempt or not and, this may play an important role also as a possible confounder. Data is not yet available to conduct a subgroup analysis addressing this hypothesis. Subsequent trials should help provide information regarding whether their impact on cessation of smoking depends on whether users were intended to quit smoking, as well as the other unresolved issues.

Other limitations of this review were the fact of having insufficient number of included studies to allow the complete statistical analysis that we had planned. We were not able to assess publication bias because there were less than 10 eligible studies addressing the same outcome in a meta-analysis. We also planned to perform subgroup analyses according to the characteristics of:

- Participants (commitment to stopping smoking, use of e-cigarettes at baseline).
- Interventions (dose of nicotine delivered by the e-cigarette, frequency of use of the e-cigarette, type of e-cigarettes and type of e-cigarettes).
- Concomitant interventions in both e-cigarettes and control groups.

However, we also were not able to conduct these analyses because they did not meet our minimal criteria, which were at least five studies available, with at least two in each sub-group.

Relation to prior work

The previous Cochrane review [8] concluded that due to low event rates and wide confidence intervals only low certainty evidence was available from studies comparing ENDS to ENND. We excluded some studies included in that Cochrane review as they were either case series, cross-sectional or did not include one arm with ENDS/ENNDS compared

to alternative strategies. We also included one additional RCT [33], and nine new cohort studies [26-29, 40-46], not included in the Cochrane review. The rationale for including the prospective cohort studies in our review was that it was anticipated that the search would return few RCTs. The authors of the Cochrane review found that ENDS is a useful aid to stop smoking long-term compared with ENNDS.

Another review [9] including two of our three RCTs [25, 34-39], and further two case series, and two cross-sectional studies, assessed the impact of e-cigarettes in achieving smoking abstinence or reduction in cigarette consumption among current smokers who had used the devices for six months or more. The authors concluded that e-cigarette use is associated with smoking cessation; these results are similar to our meta-analysis comparing ENDS versus ENNDS (Figure 5). Khoudigian's 2016 review [10] reported a non-statistically significant trend toward smoking cessation in adults using nicotine e-cigarettes compared with other therapies or placebo. However, the review by Kalkhoran & Glatz 2016 [11] concluded that e-cigarettes are associated with significantly less quitting among smokers.

Implications

Existing smoking reduction aids such as nicotine replacement therapy are effective, but their impact is limited: the proportion of those who quit when using these aids remains small. The available evidence, of low or very low quality, provides no support for the hypothesis that, because they address not only nicotine addiction but also potentially deal with behavioural and sensory aspects of cigarette use, ENDS may be more effective than other nicotine replacement strategies. This is an important finding, and raises serious questions regarding the importance of thee behavioural and sensory aspects of cigarette use in their addictive potential. Thus, the focus of subsequent work should perhaps be on the dose and delivery of nicotine. It is possible that type of ENDS or dose of exposure may influence quit rates, and that newer models may be more effective, but there is no available data to

provide insight into these issues. This review underlines the urgent need to conduct well-designed trials in the use of ENDS.

AUTHORS' CONTRIBUTIONS

Conceiving the review: Gordon Henry Guyatt (GHG), Regina El Dib (RED), Wasim Maziak (WM), and Elie A. Akl (EAA)

Undertaking searches: Diane Heels-Ansdell (DHA)

Screening search results: RED, Erica Aranha Suzumura (EAS), Huda Goma (HG), Arnav Agarwal (AA), Yaping Chang (YC), Manya Prasad (MP), Vahid Ashoorion (VA)

Organizing retrieval of papers: EAS

Screening retrieved papers against inclusion criteria: RED, EAS, HG, AA, YC, MP and VA

Appraising quality of papers: RED, EAS, HG, AA, YC, MP and VA

Extracting data from papers: RED, EAS, HG, AA, YC, MP and VA

Writing to authors of papers for additional information: RED

Providing additional data about papers: RED

Obtaining and screening data on unpublished studies: RED and EAS

Managing data for the review: RED

Entering data into Review Manager (RevMan): RED and EAS

Analyzing RevMan statistical data: RED, EAS, GHG, WM and EAA

Interpreting data: RED, EAS, GHG, WM and EAA

Making statistical inferences: RED, EAS, GHG, WM and EAA

Writing the review: RED, GHG, WM and EAA

Taking responsibility for reading and checking the review before submission: RED, EAS, HG, AA, YC, MP, VA, EAA, WM and GHG

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AUTHORS' CONTRIBUTIONS

All authors contributed to all aspects of this study, including conducting the literature search, study design, data collection, data analysis, data interpretation, and writing of the paper.

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FIGURE LEGENDS

Figure 1. PRISMA diagram of included studies.

Figure 2. Risk of bias for RCTs comparing ENDS versus ENNDS.

Figure 3. Risk of bias for RCTs comparing ENDS versus other strategies.

Figure 4. Risk of bias for cohort studies.

Figure 5. Meta-analysis of RCTs on cessation smoking comparing ENDS versus ENND.

Figure 6. Meta-analysis of cohort studies on cessation smoking with adjusted ORs.

Appendix Figure 1. Sensitivity analysis of RCTs on cessation smoking comparing ENDS versus ENNDS.

Appendix Figure 2. Meta-analysis of cohort studies on cessation smoking with adjusted ORs using a sensitivity analyses with an assumed correlation=0.5.

Appendix Figure 3. Sensitivity analysis of cohort studies on cessation smoking comparing e-cigarettes versus no e-cigarettes.

Appendix Figure 4. Meta-analysis of RCTs on reduction.

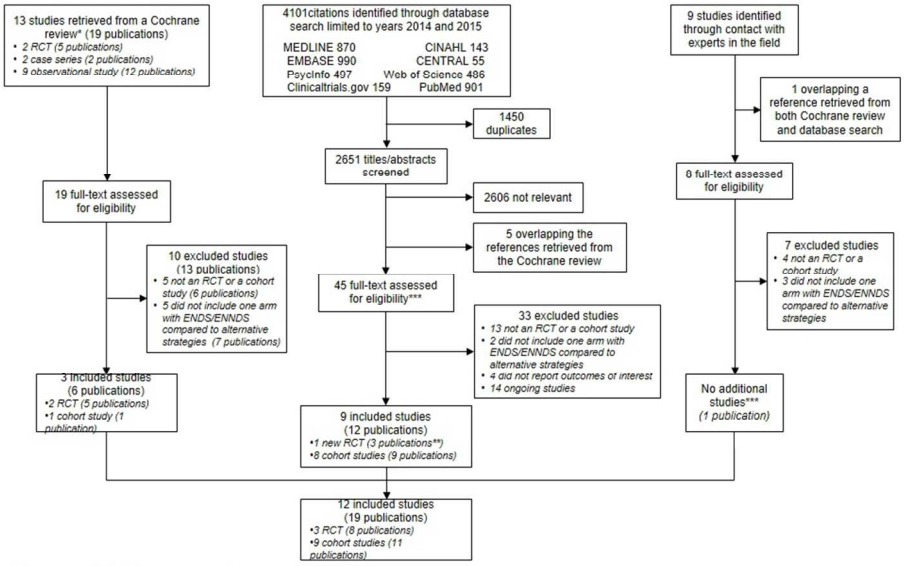

Figure 1. PRISMA diagram of included studies.
*McRobbie, 2014[8]
**Further two publications from one RCT included by the Cochrane review were identified only in our search strategy
***Further one publication from one cohort study identified by our search strategy was identified throughout the expert search

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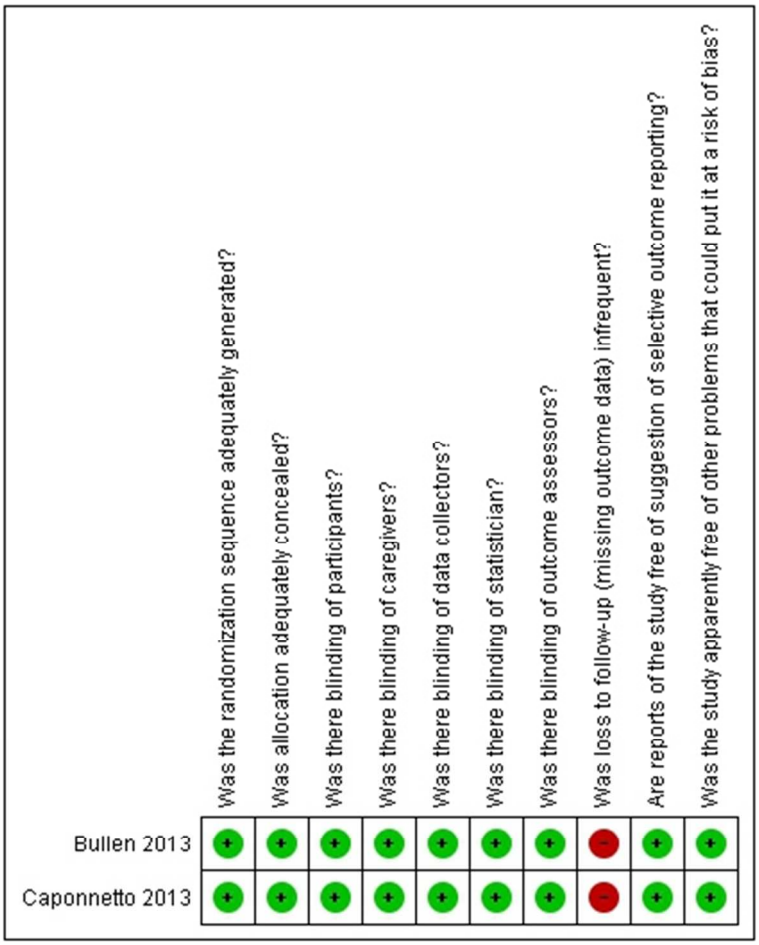

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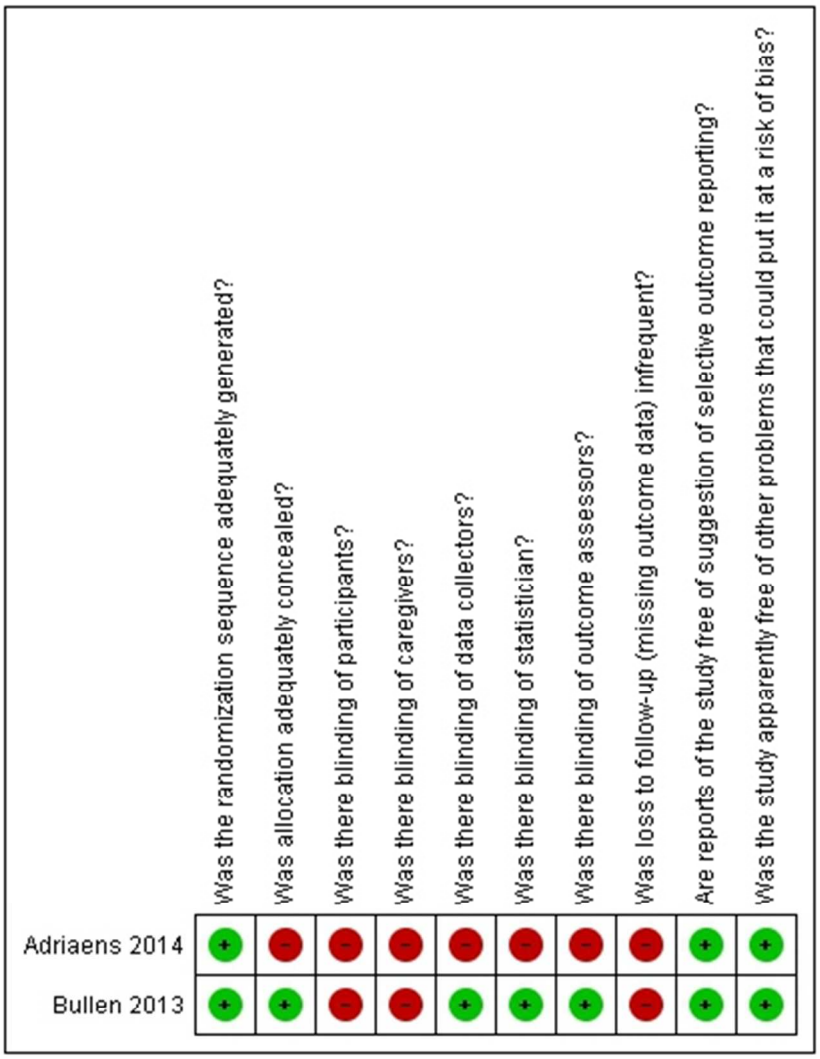

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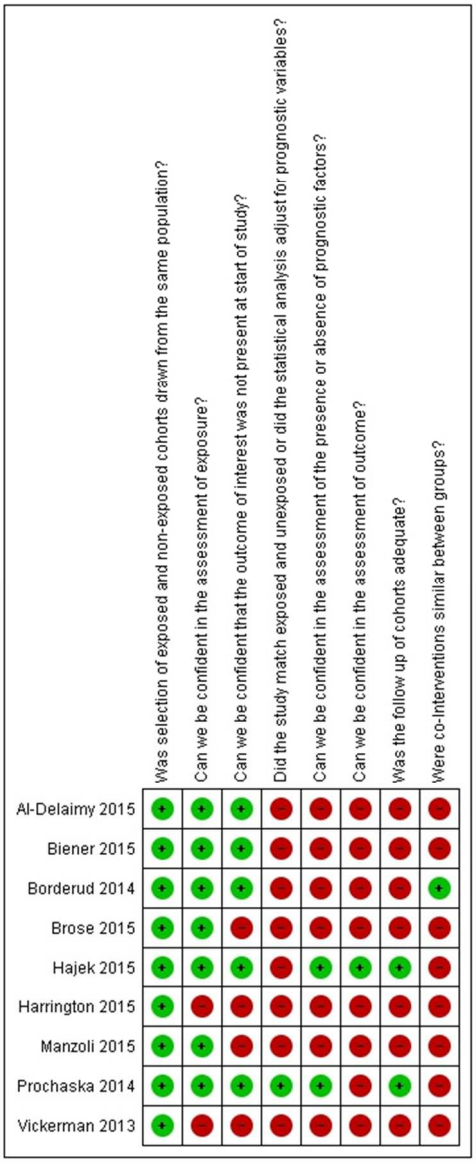

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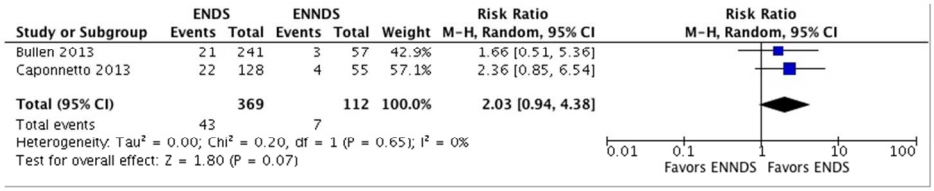

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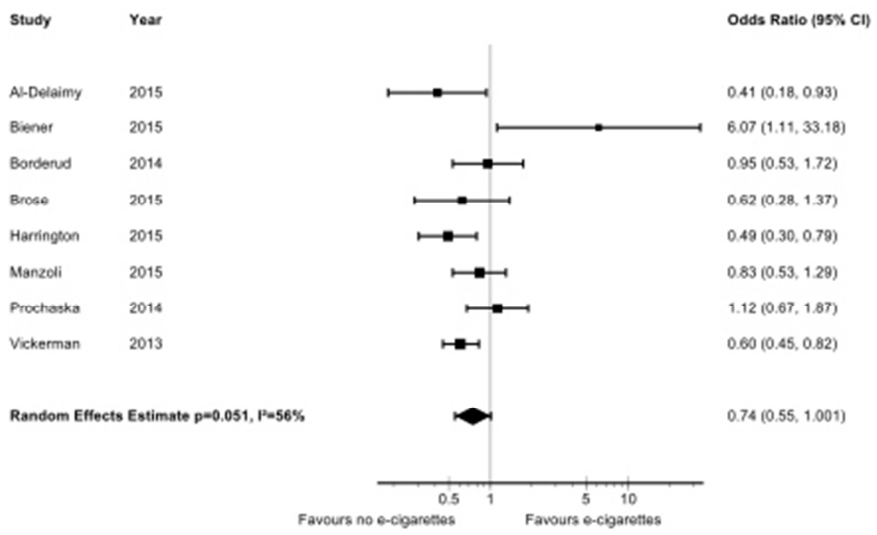


42x30mm (300 x 300 DPI)

Table 1. Study characteristics related to design of study, setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up.

Author, year	Design of study	Location	No.* participants	Mean age	No. male (%)	Inclusion criteria	Exclusion criteria	Follow-up (months)
Randomized controlled trials								
Adriaens, 2014 [33]	Parallel RCT	Leuven, Belgium	50	ENDS1: 44.7 ENDS2: 46.0 Control/ENDS**: 40.3	21 (43.7)	Being a smoker for at least three years; smoking a minimum of 10 factory-made cigarettes per day and not having the intention to quit smoking in the near future, but willing to try out a less unhealthy alternative	Self-reported diabetes; severe allergies; asthma or other respiratory diseases; psychiatric problems; dependence on chemicals other than nicotine, pregnancy; breast feeding; high blood pressure; cardiovascular disease; currently using any kind of smoking cessation therapy and prior use of an e-cigarette	8
Bullen, 2013 [34-39]	Parallel RCT	New Zealand	657	16 mg ENDS: 43.6 21 mg patches NRT: 40.4 ENNDS: 43.2	252 (38.3)	Aged 18 years or older; had smoked ten or more cigarettes per day for the past year; wanted to stop smoking; and could provide consent	Pregnant and breastfeeding women; people using cessation drugs or in an existing cessation programme; those reporting heart attack, stroke, or severe angina in the previous two weeks; and those with poorly controlled medical disorders, allergies, or other chemical dependence	6

Caponnetto, 2013 [25]	Parallel RCT	Catania, Italy	300	7.2 mg ENDS: 45.9 7.2 mg ENDS + 5.4 mg ENDS: 43.9 ENNDS: 42.2	190 (63.3)	Smoke 10 factory made cigarettes per day (cig/day) for at least the past five years; age 18–70 years; in good general health; not currently attempting to quit smoking or wishing to do so in the next 30 days; committed to follow the trial procedures	Symptomatic cardiovascular disease; symptomatic respiratory disease; regular psychotropic medication use; current or past history of alcohol abuse; use of smokeless tobacco or nicotine replacement therapy, and pregnancy or breastfeeding	12
Cohort studies								
Al-Delaimy, 2015 [40]	Cohort	California, US	628	Not reported	478 (47.8)	Residents of California; aged 18 to 59 years who had smoked at least 100 cigarettes during their lifetime and are current smokers	Participants who reported that they “might use e-cig” or changed their reporting at follow-up, as they did not represent a definitive group of users or never-users e-cig and might overlap with both	12
Biener, 2015 [29]	Cohort	Dallas and Indianapolis areas, US	1374	Not reported	383 (55.2)	Adults smokers residing in the Dallas and Indianapolis metropolitan areas, who had been interviewed by telephone and gave permission to be re-contacted	Anyone over 65 years old	36

Brose, 2015 [26-28]	Cohort	Web-based, United Kingdom	3891***	ENDS Among daily users: 45.7 Among non-daily users: 45.2 No ENDS[α]: 45.7	2,015 (49.6)	Members were invited by e-mail to participate in an online study about smoking and who answered a screening question about their past-year smoking status	Baseline pipe or cigar smokers, and follow-up pipe or cigar smokers or unsure about smoking status	12
Hajek 2015 [46]	Cohort	Europe	100	ENDS: 41.8 No ENDS: 39	57 (57)	All smokers joining the UK Stop Smoking Services in addition to the standard treatment (weekly support and stop smoking medications including NRT and varenicline).	No exclusion criteria	4 weeks[β]
Harrington 2015 [45]	Cohort	US	979	46.0****	525 (53.6)	Hospitalized cigarette smokers at a tertiary care medical center; self-identified smoker who smoked at least one puff in previous 30 days; English speaking and reading; over age 18 and; cognitively and physically able to participate in study	Pregnant	6
Manzoli, 2015 [42]	Cohort	Abruzzo and Lazio region, Italy	1355	ENDS only: 45.2 Tobacco cigarettes only: 44.2 Dual smoking: 44.3	757 (55.9)	Aged between 30 and 75 years; smoker of e-cig (inhaling at least 50 puffs per week) containing nicotine since six or more months (E-cig only group); smoker of at least one traditional cigarette per day since six or more months (traditional cigarettes only group); smoker of both electronic and traditional cigarettes (at least one per day) since six or more	Illicit drug use, breastfeeding or pregnancy, major depression or other psychiatric conditions, severe allergies, active antihypertensive medication, angina pectoris, past episodes of major cardiovascular diseases (myocardial infarction, stroke/TIA, congestive heart failure, COPD, cancer of the lung, esophagus, larynx, oral cavity, bladder, pancreas, kidney, stomach, cervix, and myeloid leukemia	12

						months (mixed Group)		
Borderud, 2014 [41]	Cohort	New York, US	1074	ENDS use+ behavioral and pharmacological treatment: 56.3 No ENDS + behavioral and pharmacological treatment: 55.6	467 (43.5)	Patients with cancer referred to a tobacco cessation program who provided data on their recent (past 30 days) e-cig use	No exclusion criteria	6 to 12
Prochaska 2014 [43]	Cohort	US	956	39.0****	478 (50.0)	Adult daily smokers (at least 5 cigarettes/day with serious mental illness at four psychiatric hospitals in the San Francisco Bay Area	Non-English speaking; medical contraindications to NRT use (pregnancy, recent myocardial infarction); and lack of capacity to consent as determined by a 3-item screener of study purpose, risks, and benefits	18
Vickerman 2013 [44]	Cohort	US	2,758[€]	Used ENDS one month or more: 48.1 Used ENDS less than one month: 45.3 No ENDS: 49.6	913 (36.9)	Participants from six state quitlines who registered for tobacco cessation services. Adult tobacco users, consented to evaluation follow-up, spoke English, provided a valid phone number, and completed at least one intervention call	No exclusion criteria	7

no.: number; e-cig: e-cigarettes; ENDS: Electronic nicotine delivery system; ENNDS: electronic non-nicotine delivery systems; RCT: randomized controlled trial; US: United States; ENDS1 and ENDS2: the e-cig groups received the e-cig and four bottles of e-liquid at session 1 (group e-cig1 received the "Joyetech eGo-C" and group e-cig2 received the "Kanger T2-CC"); at session 2, participants' empty bottles were replenished up to again four bottles and at session 3, they were allowed to keep the remaining bottles.
*Randomized or at baseline
**For the first two months control group consisted of no e-cigarettes use. After that period, the participants of control group received the e-cig and e-liquid. ENDS1 = "Joyetech eGo-C" e-cig and ENDS2 = "Kanger T2-CC" e-cig.

***The 4117 were reported in a publication that focused on baseline characteristics, not on the use of e-cigarettes and changes in smoking behavior, so the remaining 53 participants are irrelevant to this review.
****Mean age of the overall population.
[α]The comparator comprises of current non-users of e-cig, which included never-users and those who had previously tried but were not using at the moment.
[β]Hajek 2015 was the only study that entered in the review due to meet the criteria for adverse events.
[€]But only 2,476 asnwered the question “Have you ever used e-cigarettes, electronic, or vapor cigarettes?”

Table 2. Study characteristics related to population, intervention or exposure groups, comparator, and assessed outcomes.

Author, year	Population	No.* of participants intend to quit smoking	No.* of participants in intervention or exposure groups and comparator	Description of intervention or exposure groups	Description of comparators	Measured outcomes	Definition of quitters or abstinence
Randomized controlled trials							
Adriaens, 2014 [33]	Participants unwilling to quit smoking (participants from the control group kept on smoking regular tobacco cigarettes during the first eight weeks of the study)	Yes 0 No 50	ENDS 1: 16 ENDS 2: 17 Control/ENDS: 17	ENDS ("Joyetech eGo-C") ENDS E-cigarettes ("Kanger T2-CC")	ENDS and e-liquid**	Quitting, defined as eCO of 5 ppm or smaller; questionnaire self-report of reduction in cigarettes of > 50% or complete quitting	No more cigarette smoking
Bullen, 2013 [34-39]	Had smoked ten or more cigarettes per day for the past year, interested in quitting	Yes 657 No 0	ENDS: 289 NRT: 295 ENNDS: 73	16 mg nicotine ENDS	21 mg patches NRT ENNDS	Continuous smoking abstinence, biochemically verified (eCO measurement <10 ppm); seven day point prevalence abstinence; reduction; and adverse events	Abstinence allowing ≤5 cigarettes in total, and proportion reporting no smoking of tobacco cigarettes, not a puff, in the past 7 days

Caponnetto, 2013 [25]	Smokers not intending to quit	Yes 0 No 300	ENDS 1: 100 ENDS 2: 100 ENNDS: 100	7.2 mg nicotine ENDS 7.2 mg nicotine ENDS + 5.4 mg nicotine ENDS	ENNDS	Self-report of reduction in cigarettes of > 50%; abstinence from smoking, defined as complete self-reported abstinence from tobacco smoking - not even a puff, biochemically verified (eCO measurement ≤7 ppm); and adverse events	Complete self-reported abstinence from tobacco smoking - not even a puff
Cohort studies							
Al-Delaimy, 2015 [40]	Current smokers; regardless of whether the users were using ENDS as part of a quit attempt	Yes 415 No 542	ENDS: 236[Ψ] No ENDS: 392[Ψ]	ENDS	No ENDS	Quit attempts; 20% reduction in monthly no. of cigarettes; and current abstinence from cigarette use	Duration of abstinence of one month or longer to be currently abstinent
Biener, 2015 [29]	All respondents had reported being cigarette smokers at baseline; regardless of whether the users were using ENDS as part of a quit attempt	Yes 364[β] No 331[€]	1374[$]	ENDS[£] intermittent use ENDS[£] intensive use	No ENDS (used once or twice ENDS)	Smoking cessation; and reduction in motivation to quit smoking among those who had not quit, not otherwise specified	Smoking cessation was defined as abstinence from cigarettes for at least one month

Brose, 2015 [26-28]	Current smokers; regardless of whether the users were using ENDS as part of a quit attempt	Not reported	ENDS: 1507 No ENDS: 2610	ENDS daily ENDS non-daily	No ENDS[€]	Quit attempts[ϕ]; cessation[ϖ]; and substantial reduction defined as a reduction by at least 50% from baseline CPD to follow-up CPD	Change from being a smoker at baseline to being an ex-smoker at follow-up was coded as cessation
Hajek, 2015 [46]	69% (n=69) accepted e-cigs as part of their smoking cessation treatment	Not reported	ENDS: 69 No ENDS: 31	ENDS was offered to all smokers in addition to the standard treatment (weekly support and stop smoking medications including NRT and varenicline)	No ENDS	Self-reported abstinence was biochemically validated by exhaled CO levels in end-expired breath using a cut-off point on 9ppm, adverse events	Self-reported abstinence from cigarettes at 4 weeks
Harrington, 2015 [45]	Hospitalized cigarette smokers. All were cigarette smokers initially; regardless of whether the users were using ENDS as part of a quit attempt	Yes: 220*** No: not reported	ENDS: 171 No ENDS: 759	ENDS	No ENDS	Quitting smoking based on 30-day point prevalence at 6 months	Only self-reported quitting smoking
Manzoli, 2015 [42]	Smokers of ≥1 tobacco cigarette/day (tobacco smokers), users of any type of e-cig, inhaling ≥50 puffs weekly (e-smokers), or smokers of both tobacco and e-cig (dual smokers)	Not reported	ENDS: 343 Tobacco and ENDS: 319 Tobacco only: 693	ENDS Tobacco and ENDS	Tobacco cigarettes only	Abstinence, proportion of quitters, biochemically verified (eCO measurement > 7ppm), reduce tobacco smoking, and serious adverse events	Percentage of subjects reporting sustained (30 days) smoking abstinence from tobacco smoking

Borderud, 2014 [41]	Patients who presented for cancer treatment and identified as current smokers (any tobacco use within the past 30 days); regardless of whether the users were using ENDS as part of a quit attempt	Yes 633[¥] No 42[¥]	ENDS: 285 No ENDS: 789	ENDS[£] + Evidence-based behavioral and pharmacologic treatment	No ENDS+Evidence-based behavioral and pharmacologic treatment	Smoking cessation by self-report	Patients were asked if they had smoked even a puff of a (traditional) cigarette within the last 7 days
Prochaska, 2014 [43]	Adult daily smokers with serious mental illness; regardless of whether the users were using ENDS as part of a quit attempt	At baseline, 24% intended to quit smoking in the next month	ENDS: 101 No ENDS: 855	ENDS	No ENDS	Smoking cessation by self-report and, biochemically verified (CO and cotinine)	Past 7 day tobacco abstinence
Vickerman, 2013 [44]	Adult tobacco current or past users; regardless of whether the users were using ENDS as part of a quit attempt	Not reported	ENDS: 765 No ENDS: 1,711	ENDS used for 1 month or more ENDS used for less than 1 month	No ENDS (never tried)	Tobacco abstinence	Self-reported 30-day tobacco abstinence at 7 month follow-up

no.: number; C: comparator group; CPD: cigarettes smoked per day; e-cig: e-cigarettes; ENDS: Electronic nicotine delivery system; ENNDS: electronic non-nicotine delivery systems; eCO: exhaled breath carbon monoxide; NE: non-exposure group; NRT: Nicotine replacement therapy.
*Numbers randomized or at baseline.
**For the first two months control group consisted of no e-cigarettes use. After that period, the participants of control group received the e-cig and e-liquid. ENDS1 = "Joyetech eGo-C" e-cig and ENDS2 = "Kanger T2-CC" e-cig.
***Only among those who reported any previous use of e-cigs.
[α]Information retrieved through contact with author.
[€]The comparator comprises of current non-users of e-cig, which included never-users and those who had previously tried but were not using at the moment.
[Ψ]Participants who will never use e-cig plus those who never heard of e-cig = 392; participants who have used e-cig = 236 (numbers taken from the California Smokers Cohort, a longitudinal survey).
[β]Intentions to quit smoking, those who tried e-cigarettes only once or twice are grouped with never users ("non-users/triers").
[€]Intermittent use (i.e., used regularly, but not daily for more than 1 month) plus intensive use (i.e., used e-cig daily for at least 1 month).
[$]No. of the whole sample including comparator.
[£]All ENDS.
[¥]The other participants either quit more than a month ago but less than six months, less than a month ago, or more than six months ago.
[ϕ]Smokers and recent ex-smokers were asked about the number of attempts to stop they had made in the previous year. Those reporting at least one attempt and 37 respondents who did not report an attempt but had stopped smoking be- tween baseline and follow-up were coded as having made an attempt.
[ϖ]Change from being a smoker at baseline to being an ex-smoker at follow-up was coded as cessation.

Table 3. Mean number of conventional cigarettes and/or other tobacco products use per day at both baseline and the end of study*.

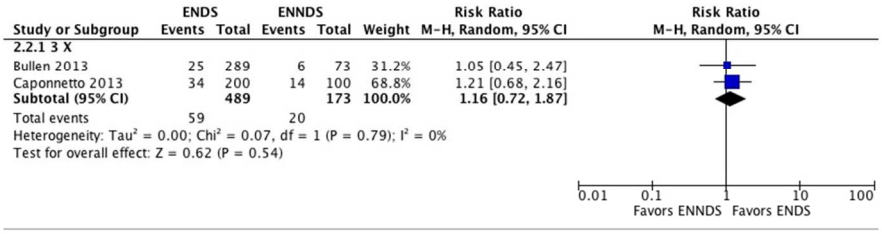
Author, year	Groups	Mean no. of conventional cigarettes/other tobacco products used per day at baseline	Mean no. of conventional cigarettes/other tobacco products used per day at the end of study	Biochemically quitters (no. of events per no. of total participants)	Self-reported quitters (no. of events per no. of total participants)
Adriaens, 2014 [33]	ENDS1	20.1	7.0[£]	3/13	4/13
	ENDS2	20.6	8.1[£]	3/12	3/12
	Control/ENDS[αφ]	16.7	7.7[£]	4/13	4/13
Bullen, 2013 [34-39]	ENDS	18.4	0.7[ϖ]	21/241	Not available
	ENNDS	17.7	0.7	3/57	Not available
	NRT	17.6	0.8[ϖ]	17/215	Not available
Caponnetto, 2013 [25]	7.2 mg ENDS	19.0 (14.0-25.0)[Ψ]	12 (5.8-20)[Ψ¢]	Combined ENDS groups: 22/128	Not available
	7.2 mg ENDS plus 5.4 mg ENDS	21.0 (15.0-26.0)[Ψ]	14 (6-20)[Ψ¢]		Not available
	ENNDS	22.0 (15.0-27.0)[Ψ]	12 (9-20)[Ψ¢]	4/55	Not available
Al-Delaimy, 2015 [40]	ENDS	14.1[Ω]	13.8[δ]	Not available	12/179
	ENNDS			Not available	32/145
Biener, 2015 [29]	ENDS intermittent use	16.7[¢]	Not available	Not available	Combined ENDS groups: 42/331
	ENDS intensive use	17.1[¢]	Not available	Not available	
	No ENDS	15.4[¢]	Not available	Not available	82/364

Table 3. (Continued)

Author, year	Group	Mean no. of conventional cigarettes/other tobacco products used per day at baseline	Mean no. of conventional cigarettes/other tobacco products used per day at the end of study	Biochemically quitters (no. of events per no. of total participants)	Self-reported quitters (no. of events per no. of total participants)
Brose, 2015 [26-28]	ENDS daily users	14.3	13.0 [θ]	Not available	7/86
	ENDS non-daily users	13.5	13.9 [θ]	Not available	25/263
	No ENDS[ς]	13.3	13.5	Not available	168/1307
Hajek, 2015 [46]	ENDS	Not available	Not available	Not applicable**	Not applicable**
	No ENDS	Not available	Not available	Not applicable**	Not applicable**
Harrington, 2015 [45]	ENDS	14.1[$]	10.3[$]	Not available	21/171
	No ENDS	11.9[$]	9.8[$]	Not available	62/464
Manzoli, 2015 [42]	ENDS only	Not available	12	Not available	Not available
	Tobacco cigarettes only	14.1	12.8	101/491	Not available
	Dual smoking	14.9	9.3	51/232	Not available
Borderud, 2014 [41]	ENDS	13.7	12.3	Not available	25/58
	No ENDS	12.4	10.1	Not available	158/356
Prochaska, 2014 [43]	ENDS	17.0	10.0	21/101	Not available
	No ENDS	17.0	10.1	162/855	Not available
Vickerman, 2013 [44]	ENDS used for 1 month or more	19.4	13.5	Not available	59/273
	ENDS used for less than 1 month	18.9	14.0	Not available	73/439
	No ENDS (never tried)	18.1	12.9	Not available	535/1711

No.: number; e-cig: eletronic cigarettes; ENDS: Electronic nicotine delivery system; ENNDS: electronic non-nicotine delivery systems; ENDS1 and ENDS 2: the e-cig groups received the e-cig and four bottles of e-liquid at session 1 (group e-cig1 received the “Joyetech eGo-C” and group e-cig2 received the “Kanger T2-CC”); at session 2; RYO: roll your own (loose tobacco) cigarettes.

*When authors provided data for different time points, we presented the data for the longest follow-up.
**Not applicable because they followed participants only for 4 weeks, but the study reported adverse events at one week or longer.
[φ]For the first two months control group consisted of no e-cigarettes use. After that period, the participants of control group received the e-cig and e-liquid. ENDS1 = “Joyetech eGo-C” e-cig and ENDS2 = “Kanger T2-CC” e-cig.
[α]Control group consisted of received the e-cig and e-liquid (six bottles) for two months at the end of session 3 (eight of the 16 participants of the control group received the “Joyetech eGo-C” and the remaining eight participants received the “Kanger T2-CC”).
[£]8 months from start of intervention.
[Ψ]Data shown as median and interquartile.
[¢]At six months after the last lab session.
[θ]No. of cigarette per week divided by 7 days.
[Ω]Of the 1,000 subjects, 993 responded to the question “How many conventional cigarettes smoked per day during the past 30 days".
[δ]Of the 1,000 subjects, 881 responded to the question “How many cigarettes smoked per day during the past 30 days".
[ϖ]For those reporting smoking at least one cigarette in past 7 days.
[¢]Number of conventional cigarettes used in the prior month at baseline.
[ς]The comparator comprises of current non-users of e-cig which included never-users and those who had previously tried but were not using at the moment.
[$]Data for baseline current e-cig users.



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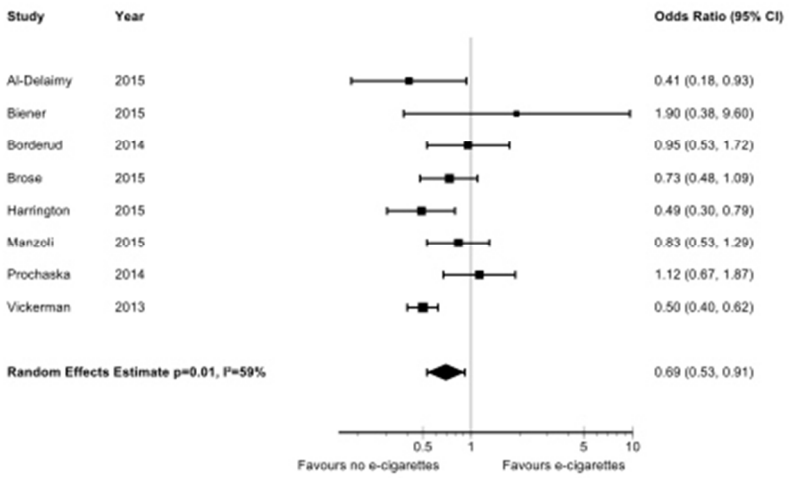

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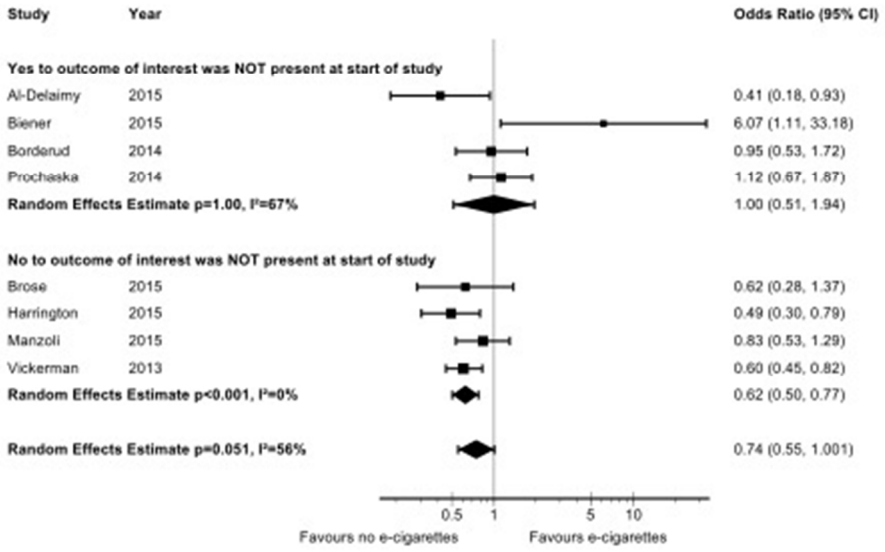

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Appendix Table 1. Search strategy

1	Electronic Cigarettes/
2	e-cig*.mp.
3	(electr* adj2 cig*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4	(electronic adj2 nicotine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5	(nicotine adj2 delivery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6	(ENDS adj3 nicotine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7	(vape or vaping).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8	or/1-7
9	"tobacco use"/ or smoking/
10	"tobacco use cessation"/ or smoking cessation/
11	Tobacco/
12	Nicotine/
13	(smok$ or cigar$ or tobacco$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14	((quit$ or stop$ or ceas$ or giv$ or prevent$) adj smok$).mp.
15	or/9-14
16	(electronic or electric or vapor or vapour).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17	15 and 16
18	8 or 17
19	Epidemiologic Studies/
20	exp Case-Control Studies/
21	exp Cohort Studies/
22	Case control.tw.
23	(cohort adj (study or studies)).tw.
24	Cohort analy$.tw.
25	(Follow up adj (study or studies)).tw.

26	(observational adj (study or studies)).tw.
27	Longitudinal.tw.
28	Retrospective.tw.
29	Cross sectional.tw.
30	Cross-sectional studies/
31	or/19-30
32	18 and 31
33	randomized controlled trial.pt.
34	controlled clinical trial.pt.
35	randomized.ab.
36	placebo.ab.
37	drug therapy.fs.
38	randomly.ab.
39	trial.ab.
40	groups.ab.
41	or/33-40
42	exp animals/ not humans.sh.
43	41 not 42
44	clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs.
45	randomized controlled trial.pt. or placebo.mp.
46	44 or 45
47	18 and 43
48	18 and 46
49	32 or 47 or 48

Appendix Table 2. Information about contact with the authors of the included studies.

Author, year	E-mail sent by the reviewers	Did the author of the study reply?	Did the author provide the requested data?
Adriaens, 2014 [33]	**Yes**	Yes	Yes
Bullen, 2013 [34-39]	**Yes**	Yes	Yes
Caponnetto, 2013 [25]	**Yes**	Yes	No (however author replied stating that will contact us later)
Al-Delaimy, 2015 [40]	**Yes**	Yes	Yes
Biener, 2015 [29]	**Yes**	Yes	Yes
Brose, 2015 [26-28]	**Yes**	Yes	Yes
Hajek, 2015 [46]	**Yes**	No	No
Harrington, 2015 [45]	**Yes**	Yes	Yes
Manzoli, 2015 [42]	**Yes**	Yes	No (however author replied stating that will contact us later)
Borderud, 2014 [41]	**Yes**	Yes	Yes
Prochaska, 2014 [43]	**Yes**	Yes	Yes
Vickerman, 2013 [44]	**Yes**	Yes	Yes

Appendix Table 3. Characteristics of e-cigarettes from the included studies.

Study	Device				Eliquid			Use	
	Type	Brand and model	Battery voltage	Metal in heating resistance	Nicotine concentration	Flavors in the eliquid	Conveyants	Puff regime during study	Amount of eliquid consumed/day
Adriaens, 2014 [33]	Cigalike (second generation ENDS devices)	Joyetech eGo-C	3.3 V, 1000 mAh lithium-ion battery	2.2-ohm atomizer head	18mg of nicotine per mL for both types	Tobacco-flavored (Dekang "Turkish Blend") for both types	Not reported	Not reported	Not reported
		Kanger T2-CC	3.7 V, 650 mAh lithium-ion battery	2.5-ohm coil					
Bullen, 2013 [34-39]	Cigalike	Elusion	Not reported	Not reported	Labelled 16mg (commissioned analyses showed 10-16mg of nicotine per mL)	Not reported	Not reported	Participants used e-cig as desired from 1 week before until 12 weeks after their chosen quit day	Not reported
Caponnetto, 2013 [25]	Cigalike	Categoria model 401	3.7 V, 90 mAh lithium-ion battery	Not reported	Cartridges of 7.2mg and 5.4mg nicotine	Cartridge without nicotine (control group): "sweet tobacco'' aroma	Solution of propylene glycol and vegetable glycerin	Not reported	Not reported
Al-Delaimy, 2015 [40]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Biener, 2015 [29]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Brose, 2015 [26-28]	76.3% used Cigalike 23.7% used Tank	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Hajek, 2015 [46]	1) Cigalike 2) Tank	1) Gamucci 2) Basic EVOD tank system, The EVOD's were later replaced with an Aspire product due to issues with leakage from the cheap EVOD model	Not reported	Not reported	1) With a choice of 1.6% or 2.2% per ml nicotine 2) 1.8% per ml nicotine e-liquid	Not reported	Not reported	Not reported	Not reported
Harrington, 2015 [45]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Manzoli, 2015 [42]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Borderud, 2014 [41]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Prochaska, 2014 [43]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Vickerman, 2013 [44]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Appendix Table 4. Characteristics of e-cigarettes from the included studies.

Study	Device				Eliquid			Use	
	Type	Brand and model	Battery voltage	Metal in heating resistance	Nicotine concentration	Flavors in the eliquid	Conveyants	Puff regime during study	Amount of eliquid consumed/day
Adriaens, 2014 [30]	Cigalike	Joyetech eGo-C	3.3 V, 1000 mAh lithium-ion battery	2.2-ohm atomizer head	18mg of nicotine per mL for both types	Tobacco-flavored (Dekang "Turkish Blend") for both types	Not reported	Not reported	Not reported
		Kanger T2-CC	3.7 V, 650 mAh lithium-ion battery	2.5-ohm coil					
Bullen, 2013 [31-36]	Cigalike	Elusion	Not reported	Not reported	Labelled 16mg (commissioned analyses showed 10-16mg of nicotine per mL)	Not reported	Not reported	Participants used e-cig as desired from 1 week before until 12 weeks after their chosen quit day	Not reported
Caponnetto, 2013 [25]	Cigalike	Categoria model 401	3.7 V, 90 mAh lithium-ion battery	Not reported	Cartridges of 7.2mg and 5.4mg nicotine	Cartridge without nicotine (control group): "sweet tobacco" aroma	Solution of propylene glycol and vegetable glycerin	Not reported	Not reported
Al-Delaimy, 2015 [37]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Biener, 2015 [38]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Brose, 2015 [40-42]	76.3% used Cigalike 23.7% used Tank	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Hajek, 2015 [47]	1) Cigalike 2) Tank	1) Gamucci 2) Basic EVOD tank system, The EVOD's were later replaced with an Aspire product due to issues with leakage from the cheap EVOD model	Not reported	Not reported	1) With a choice of 1.6% or 2.2% per ml nicotine 2) 1.8% per ml nicotine e-liquid	Not reported	Not reported	Not reported	Not reported
Harrington, 2015 [46]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Manzoli, 2015 [43]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Borderud, 2014 [39]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Prochaska, 2014 [43]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Vickerman, 2013 [45]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
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.	4,5
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.	4,5
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.	Appendix Table 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.	4,5
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.	6,7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7,8,9
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.	9

PRISMA 2009 Checklist

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).	7,8,9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
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.	10
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.	10,11
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).	11
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.	12-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-15
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).	15, 16
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).	16,17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
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.	18

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Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis

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Complete List of Authors:	El Dib, Regina; Unesp – Univ Estadual Paulista, São Paulo, Brazil, Department of Anaesthesiology, Botucatu Medical School Suzumura, Erica; Hospital do Coração (HCor), São Paulo, Brazil, Research Institute Akl, Elie; American University of Beirut, Department of Internal Medicine; McMaster University, Department of Clinical Epidemiology and Biostatistics Goma, Huda; Tanta Chest Hospital, Department of Pharmacy Agarwal, Arnav; University of Toronto Faculty of Medicine, Faculty of Medicine; McMaster University, Department of Clinical Epidemiology & Biostatistics Chang, Yaping ; McMaster University, Department of Clinical Epidemiology & Biostatistics Prasad, Manya; Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Department of Community Medicine Ashoorion, Vahid; Isfahan University of Medical Sciences, Isfahan Medical Education Research Centre Heels-Ansdell, Diane; McMaster University, Department of Clinical Epidemiology & Biostatistics Maziak, Wasim; Florida International University, College of Public Health Guyatt, Gordon; McMaster University, Department of Clinical Epidemiology & Biostatistics
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Keywords:	electronic cigarettes, ENDS, smoking cessation, GRADE, systematic review

Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis

Regina El Dib, PhD[1,2*]; Erica A. Suzumura, MSc[3]; Elie A. Akl, MD, MPH, PhD[4,5]; Huda Goma, BCPS[6]; Arnav Agarwal, BHSc, MD(C)[5,7]; Yaping Chang, MSc[5]; Manya Prasad, MBBS[8]; Vahid Ashoorion, MD, MSc, PhD[5,9]; Diane Heels-Ansdell, MSc[5]; Wasim Maziak MD, PhD[10]; Gordon Guyatt, MD, MSc[5,11]

1. Department of Anaesthesiology, Botucatu Medical School, Unesp – Univ Estadual Paulista, São Paulo, Brazil
2. McMaster Institute of Urology, McMaster University, Hamilton, Ontario, Canada
3. Research Institute - Hospital do Coração (HCor), São Paulo, Brazil
4. Clinical Research Institute (CRI); Center for Systematic Reviews in Health Policy and Systems Research (SPARK) and Department of Internal Medicine, American University of Beirut, Lebanon
5. Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada
6. Department of Pharmacy, Tanta Chest Hospital, Tanta, Egypt
7. Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
8. Department of Community Medicine, Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India
9. Isfahan Medical Education Research Centre, Isfahan University of Medical Sciences, Isfahan, Iran
10. Department of Epidemiology, Robert Stempel College of Public Health and Social Work, Florida International University, Miami, Florida
11. Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Corresponding author:

Regina El Dib
Assistant Professor
Department of Anaesthesiology
Distrito de Rubião Júnior, s/n
Univ Estadual Paulista, São Paulo, Brazil
Botucatu, SP 18618-970
+ 55 11 9 9999 6647
eldib@fmb.unesp.br

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Key words: electronic cigarettes; ENDS; smoking cessation; GRADE; systematic review.

Word count: 4,546

ABSTRACT

Objective: A systematic review and meta-analysis to investigate the impact of electronic nicotine delivery systems (ENDS) and/or electronic non-nicotine delivery systems (ENNDS) versus no smoking cessation aid, or alternative smoking cessation aids, in cigarette smokers on long-term tobacco use.

Data sources: Searches of MEDLINE, EMBASE, PsycInfo, CINAHL, CENTRAL and Web of Science up to December 2015.

Study selection: Randomized controlled trials (RCTs) and prospective cohort studies.

Data extraction: Three pairs of reviewers independently screened potentially eligible articles, extracted data from included studies on populations, interventions and outcomes, and assessed their risk of bias. We used the GRADE approach to rate overall certainty of the evidence by outcome.

Data synthesis: Three randomized trials including 1,007 participants and nine cohort including 13,115 participants proved eligible. Results provided by the RCTs suggest a possible increase in tobacco smoking cessation with ENDS in comparison to ENNDS (RR 2.03, 95% CI 0.94, 4.38; p = 0.07; I^2=0%, risk difference (RD) 64/1,000 over 6 to 12 months, low certainty evidence). Results from cohort studies suggested a possible reduction in quit rates with use of ENDS compared to no use of ENDS (OR 0.74, 95% CI 0.55, 1.00; p = 0.051; I^2=56%, very low certainty).

Conclusions: There is very limited evidence regarding the impact of ENDS or ENNDS on tobacco smoking cessation or reduction: data from RCTs are of low certainty and observational studies of very low certainty.

Strengths and limitations of this study

- Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias, and data abstraction independently and in duplicate; assessment of risk of bias that included a sensitivity analysis addressing loss to follow-up; and use of the GRADE approach in rating the certainty of evidence for each outcome.
- The primary limitation of our review is the low certainty consequent on study limitations. Moreover, loss to follow-up was substantial, and, our sensitivity analysis demonstrated the vulnerability of borderline effects to missing data. The limitations of the cohort studies led us to a rating of very low certainty evidence from which no credible inferences can be drawn.
- The small number of studies made it impossible to address our subgroup hypotheses related dose-response of nicotine, more versus less frequent use of e-cigarettes, or the relative impact of newer versus older e-cigarette models.

INTRODUCTION

Tobacco smokers who quit their habit reduce their risk of developing and dying from tobacco-related diseases [1-4]. Both psychosocial [5-7] and pharmacological interventions (e.g., nicotine replacement therapy (NRT)) [5-7] increase the likelihood of quitting cigarettes. Even with these aids, however, most smokers fail to quit.

Electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) represent a potential third option for those seeking to stop smoking. ENDS are devices that deliver nicotine in an aerosolized form, while ENNDS devices are labeled as not containing nicotine (though labeling may not always be accurate). In theory, these devices as well as the nicotine inhalers may facilitate quitting smoking to a greater degree than other nicotine based products or no intervention because they deal, at least partly, with the behavioral and sensory aspects of smoking addiction (e.g. hand mouth movement) [8]. The debate about the role of ENDS in smoking cessation however, is compounded by the lack of clear evidence about their value as a smoking cessation tool, their potential to hook tobacco- naïve youth on nicotine, as well as act as a bridge to combustible tobacco use [11]. While evidence about all these aspects of ENDS is accumulating, establishing their real place in smoking cessation is essential to outline the public health context of considering them as a potential harm-reduced products. There are, however, other reasons for ENDS use such as for relaxation or recreation (i.e. the same reason people smoke), with the possibility that adverse health effects may be less than conventional smoking.

There are many types of ENDS. The cigalikes are the first generation of ENDS that provides an appearance of tobacco cigarettes; they are not rechargeable. The second generation of ENDS looks like a pen, allows the user to mix flavors, and may contain a prefilled or a refillable cartridge. The third generation of ENDS includes variable wattage

devices are used only with refillable tank systems. The fourth generation contains a large, refillable cartridge and has a tank-style design.

A previous Cochrane systematic review [8] summarized results from randomized controlled trials (RCTs) and cohort studies. The authors included two RCTs and 11 cohort studies, and concluded that there was evidence to support the potential benefit of ENDS in increasing tobacco smoking cessation [8]. The certainty of evidence supporting this conclusion was, however, deemed low, primarily due to the small number of trials resulting in wide confidence intervals around effect estimates [8]. Another systematic review [9] including a total of six studies (RCTs, cohort, and cross-sectional studies) involving 7,551 participants concluded that ENDS is associated with smoking cessation and reduction; however the included studies were heterogeneous, due to different study designs and gender variation. One other review [10] comparing e-cigarettes to other nicotine replacement therapies or placebo included five studies (RCTs and controlled before-after studies) and concluded that participants using nicotine e-cigarettes were more likely to stop smoking, but but noted no statistically significance differences [10]. A more recent systematic review Kalkhoran & Glantz 2016 [11] included 20 studies (15 cohort studies, 3 cross-sectional studies, and 2 clinical trials), and found 28% lower odds rates of quitting cigarettes in those who used e-cigarettes compared with those who did not use e-cigarettes; however the methodological aspects of the observational studies was rated as unclear or high on outcome assessors, and a RCT was rated as high risk of performance and attrition bias.

Previous reviews were, however, limited in that they did not include all studies in this rapidly evolving field, and all but one did not use the GRADE approach to rating quality of evidence. We therefore conducted an updated systematic review of RCTs and cohort studies that assessed the impact of ENDS and/or ENNDS versus no smoking cessation aid or

alternative smoking cessation aids on long-term tobacco use, among cigarette smokers, regardless of whether the users were using them as part of a quit attempt.

METHODS

We adhered to methods described in the Cochrane Handbook for Intervention Reviews [12]. Our reporting adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) Statements [14]. This work was commissioned by the World Health Organization.

Eligibility Criteria

- Study designs: RCTs and prospective cohort studies.
- Participants: cigarette smokers, regardless of whether the users were using them as part of a quit attempt.
- Interventions: ENDS or ENNDS.
- Comparators:
    - No smoking cessation aid;
    - Alternative non-electronic smoking cessation aid, including nicotine replacement therapy (NRT), behavioral and/or pharmacological cessation aids (e.g., bupropion and varenicline);
    - Alternative electronic smoking cessation aid (ENDS or ENNDS).
- Outcomes:
    - Tobacco smoking cessation, with preference to biochemically validated outcomes [e.g., carbon monoxide (CO)] measured at six months or longer follow-up;
    - Reduction in cigarette use of at least 50%;

- Serious (e.g., pneumonia, myocardial infarction) and non-serious (e.g., nausea, vomiting) adverse events measured at one week or longer follow-up

Data source and searches

A previous Cochrane review with similar eligibility criteria ran a comprehensive search strategy up to July 2014 [8]. Using Medical Subject Headings (MeSH) based on the terms "electronic nicotine," "smoking-cessation," "tobacco-use-disorder," "tobacco-smoking," and "quit" we replicated the search strategy of that review [8] in Medline, EMBASE, PsycInfo, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Science, and the trial registry (clinicaltrials.gov). The appendix Table 1 shows the search strategy for Ovid MEDLINE. This strategy was adapted for the other databases and run from April 1, 2014 to December 29, 2015. We did not impose any language restrictions.

In addition, we established a literature surveillance strategy based on the weekly search alerts by CDC's Smoking & Health Resource Library of published articles (http://nccd.cdc.gov/shrl/NewCitationsSearch.aspx) as well as the Gene Borio's Daily news items (www.tobacco.org). The surveillance strategy commenced from the time of running the comprehensive literature search up to the time of the submission of this manuscript.

Selection of studies

Three pairs of reviewers underwent calibration exercises and used standardized pilot tested screening forms. They worked in teams of two and independently screened all titles and abstracts identified by the literature search, obtained full-text articles of all potentially eligible studies, and evaluated them for eligibility. Reviewers resolved disagreement by discussion or, if necessary, with third party adjudication. We also considered studies reported only as conference abstracts. For each study, we cite all articles that used data from that study.

Data extraction

Reviewers underwent calibration exercises, and worked in pairs to independently extract data from included studies. They resolved disagreement by discussion or, if necessary, with third party adjudication. They abstracted the following data using a pre-tested data extraction form: study design; participants; interventions; comparators; outcome assessed; and relevant statistical data. When available, we prioritized carbon monoxide (CO) measurements as evidence of quitting. When CO measurement was unavailable, we used self-report measures of quitting.

Risk of bias assessment

Reviewers, working in pairs, independently assessed the risk of bias of included RCTs using a modified version of the Cochrane Collaboration's instrument [15] (http:/distillercer.com/resources/) [16]. That version includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the previously cited domains [16].

For cohort studies, reviewers independently assessed risk of bias with a modified version of the Ottawa-Newcastle instrument [17] that includes confidence in assessment of exposure and outcome, adjusted analysis for differences between groups in prognostic characteristics, and missing data [17]. For incomplete outcome data in individual studies (both RCTs and prospective cohort studies) we stipulated as low risk of bias for loss to follow-up of less than 10% and a difference of less than 5% in missing data between intervention/exposure and control groups.

When information regarding risk of bias or other aspects of methods or results was unavailable, we attempted to contact study authors for additional information.

Certainty of evidence

We summarized the evidence and assessed its certainty separately for bodies of evidence from RCTs and cohort studies. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate certainty of the evidence for each outcome as high, moderate, low, or very low [18]. In the GRADE approach RCTs begin as high certainty and cohort studies as low certainty. Detailed GRADE guidance was used to assess overall risk of bias [19], imprecision [20], inconsistency [21], indirectness [22] and publication bias [23], and to summarize results in an evidence profile. We planned to assess publication bias through visual inspection of funnel plots for each outcome in which we identified 10 or more eligible studies; however we were not able to because there were an insufficient number of studies to allow for this assessment. Cohort studies can be rated up for a large effect size, evidence of dose–response gradient or if all plausible confounding would reduce an apparent effect [24].

Data synthesis and statistical analysis

We analyzed all outcomes as dichotomous variables. In three-arm studies, we combined results from arms judged to be sufficiently similar (e.g. Caponnetto 2013 [25], two arms with similar ENDS regimens: 7.2 mg ENDS and, 7.2 mg ENDS plus 5.4 mg ENDS). When studies reported results for daily or intensive use of ENDS separately from non-daily or less intensive use we included only the daily/intensive use in the primary pooled analysis (e.g., Brose 2015 [26-28], we excluded patients with non-daily users; and Biener 2015 [29], we excluded patients with intermittent defined use). We conducted a sensitivity analysis in which we included all ENDS users, both daily/intensive and intermittent/less intensive use. For this analysis when necessary we assumed a correlation of 0.5 between the effects in the daily/intensive and intermittent/less intensive groups.

We synthesized the evidence separately for bodies of evidence from RCTs and cohort studies. For RCTs we calculated pooled Mantel-Haenszel risk ratios (RRs) and associated

95% CIs using random-effects models. For observational studies, we pooled adjusted odds ratios (ORs) using random effects models.

After calculating pooled relative effects, we also calculated absolute effects and 95% CI. For each outcome, we multiplied the pooled RR and its 95% CI by the median probability of that outcome. We obtained the median probability from the control groups of the available randomized trials. We planned to perform separate analyses for comparisons with interventions consisting of ENDS and/or ENNDS and each of type of control interventions with known different effects [no smoking cessation aid; alternative non-electronic smoking cessation aid including NRT; alternative electronic smoking cessation aid (ENDS or ENNDS)]. For meta-analyses we used six months data or the nearest follow-up to six months available.

For dealing with missing data, we used complete case as our primary analysis; that is, we excluded participants with missing data. If results of the primary analysis achieved or approached statistical significance, we conducted sensitivity analyses to test the robustness of those results. Specifically, we conducted a plausible worst-case sensitivity analysis in which all participants with missing data from the arm of the study with the lower quit rates were assumed to have 3 times the quit rate as those with complete data, and those with missing data from the other arm were assumed to have the same quit rate as participants with complete data [30, 31].

We assessed variability in results across studies by using the I^2 statistic and the p-value for the chi square test of heterogeneity provided by Review Manager. We used Review Manager (RevMan) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses [32].

RESULTS

Study Selection

Figure 1 presents the process of identifying eligible studies, including publications in the last systematic review [8], citations identified through search in electronic databases, and studies identified through contact with experts in the field. Based on title and abstract screening, we assessed 69 full-texts of which we included 19 publications describing three RCTs involving 1,007 participants [25, 33-39] and nine cohort studies with a total of 13,115 participants [26-29, 40-46]. The inter-observer agreement for the full-text screening was substantial (kappa 0.73).

We contacted the authors of the 12 included studies, nine of whom [26-29, 33-41, 43, 44, 46] supplied us with all requested data; authors of further three studies [25, 42, 46] did not supply the requested information (Appendix table 2).

Study Characteristics

Table 1 describes study characteristics related to design of study, setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up. Five studies [25-28, 33, 42, 46] were conducted largely in Europe, six in the US [29, 40, 41, 43-45], and one in New Zealand [34-39]. Randomized trials sample size ranged from 50 [33] to 657 [34-39], and observational studies from 100 [46] to 3,891 [26-28]. Typical participants were females in their 40s and 50s. Studies followed participants from four weeks [46] to 36 months [29].

Table 1. Study characteristics related to design of study, setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up.

Author, year	Design of study	Location	No.* participants	Mean age	No. male (%)	Inclusion criteria	Exclusion criteria	Follow-up (months)
Randomized controlled trials								
Adriaens, 2014 [33]	Parallel RCT	Leuven, Belgium	50	ENDS1: 44.7 ENDS2: 46.0 Control/ENDS**: 40.3	21 (43.7)	Being a smoker for at least three years; smoking a minimum of 10 factory-made cigarettes per day and not having the intention to quit smoking in the near future, but willing to try out a less unhealthy alternative	Self-reported diabetes; severe allergies; asthma or other respiratory diseases; psychiatric problems; dependence on chemicals other than nicotine, pregnancy; breast feeding; high blood pressure; cardiovascular disease; currently using any kind of smoking cessation therapy and prior use of an e-cigarette	8
Bullen, 2013 [34-39]	Parallel RCT	New Zealand	657	16 mg ENDS: 43.6 21 mg patches NRT: 40.4 ENNDS: 43.2	252 (38.3)	Aged 18 years or older; had smoked ten or more cigarettes per day for the past year; wanted to stop smoking; and could provide consent	Pregnant and breastfeeding women; people using cessation drugs or in an existing cessation programme; those reporting heart attack, stroke, or severe angina in the previous two weeks; and those with poorly controlled medical disorders, allergies, or other chemical dependence	6

								13
Caponnetto, 2013 [25]	Parallel RCT	Catania, Italy	300	7.2 mg ENDS: 45.9 7.2 mg ENDS + 5.4 mg ENDS: 43.9 ENNDS: 42.2	190 (63.3)	Smoke 10 factory made cigarettes per day (cig/day) for at least the past five years; age 18–70 years; in good general health; not currently attempting to quit smoking or wishing to do so in the next 30 days; committed to follow the trial procedures	Symptomatic cardiovascular disease; symptomatic respiratory disease; regular psychotropic medication use; current or past history of alcohol abuse; use of smokeless tobacco or nicotine replacement therapy, and pregnancy or breastfeeding	12
Cohort studies								
Al-Delaimy, 2015 [40]	Cohort	California, US	628	Not reported	478 (47.8)	Residents of California; aged 18 to 59 years who had smoked at least 100 cigarettes during their lifetime and are current smokers	Participants who reported that they “might use e-cig” or changed their reporting at follow-up, as they did not represent a definitive group of users or never-users e-cig and might overlap with both	12
Biener, 2015 [29]	Cohort	Dallas and Indianapolis areas, US	1374	Not reported	383 (55.2)	Adults smokers residing in the Dallas and Indianapolis metropolitan areas, who had been interviewed by telephone and gave permission to be re-contacted	Anyone over 65 years old	36

Brose, 2015 [26-28]	Cohort	Web-based, United Kingdom	3891***	ENDS Among daily users: 45.7 Among non-daily users: 45.2 No ENDS[α]: 45.7	2,015 (49.6)	Members were invited by e-mail to participate in an online study about smoking and who answered a screening question about their past-year smoking status	Baseline pipe or cigar smokers, and follow-up pipe or cigar smokers or unsure about smoking status	12
Hajek 2015 [46]	Cohort	Europe	100	ENDS: 41.8 No ENDS: 39	57 (57)	All smokers joining the UK Stop Smoking Services in addition to the standard treatment (weekly support and stop smoking medications including NRT and varenicline).	No exclusion criteria	4 weeks[β]
Harrington 2015 [45]	Cohort	US	979	46.0****	525 (53.6)	Hospitalized cigarette smokers at a tertiary care medical center; self-identified smoker who smoked at least one puff in previous 30 days; English speaking and reading; over age 18 and; cognitively and physically able to participate in study	Pregnant	6
Manzoli, 2015 [42]	Cohort	Abruzzo and Lazio region, Italy	1355	ENDS only: 45.2 Tobacco cigarettes only: 44.2 Dual smoking: 44.3	757 (55.9)	Aged between 30 and 75 years; smoker of e-cig (inhaling at least 50 puffs per week) containing nicotine since six or more months (E-cig only group); smoker of at least one traditional cigarette per day since six or more months (traditional cigarettes only group); smoker of both electronic and traditional cigarettes (at least one per	Illicit drug use, breastfeeding or pregnancy, major depression or other psychiatric conditions, severe allergies, active antihypertensive medication, angina pectoris, past episodes of major cardiovascular diseases (myocardial infarction, stroke/TIA, congestive heart failure, COPD, cancer of the lung, esophagus, larynx, oral cavity, bladder, pancreas, kidney, stomach, cervix, and myeloid leukemia	12

15

						day) since six or more months (mixed Group)		
Borderud, 2014 [41]	Cohort	New York, US	1074	ENDS use+ behavioral and pharmacological treatment: 56.3 No ENDS + behavioral and pharmacological treatment: 55.6	467 (43.5)	Patients with cancer referred to a tobacco cessation program who provided data on their recent (past 30 days) e-cig use	No exclusion criteria	6 to 12
Prochaska 2014 [43]	Cohort	US	956	39.0****	478 (50.0)	Adult daily smokers (at least 5 cigarettes/day with serious mental illness at four psychiatric hospitals in the San Francisco Bay Area	Non-English speaking; medical contraindications to NRT use (pregnancy, recent myocardial infarction); and lack of capacity to consent as determined by a 3-item screener of study purpose, risks, and benefits	18
Vickerman 2013 [44]	Cohort	US	2,758[€]	Used ENDS one month or more: 48.1 Used ENDS less than one month: 45.3 No ENDS: 49.6	913 (36.9)	Participants from six state quitlines who registered for tobacco cessation services. Adult tobacco users, consented to evaluation follow-up, spoke English, provided a valid phone number, and completed at least one intervention call	No exclusion criteria	7

no.: number; e-cig: e-cigarettes; ENDS: Electronic nicotine delivery system; ENNDS: electronic non-nicotine delivery systems; RCT: randomized controlled trial; US: United States; ENDS1 and ENDS2: the e-cig groups received the e-cig and four bottles of e-liquid at session 1 (group e-cig1 received the "Joyetech eGo-C" and group e-cig2 received the "Kanger T2-CC"); at session 2, participants' empty bottles were replenished up to again four bottles and at session 3, they were allowed to keep the remaining bottles.

*Randomized or at baseline

**For the first two months control group consisted of no e-cigarettes use. After that period, the participants of control group received the e-cig and e-liquid. ENDS1 = “Joyetech eGo-C” e-cig and ENDS2 = “Kanger T2-CC” e-cig.

***The 4117 were reported in a publication that focused on baseline characteristics, not on the use of e-cigarettes and changes in smoking behavior, so the remaining 53 participants are irrelevant to this review.

****Mean age of the overall population.

[α]The comparator comprises of current non-users of e-cig, which included never-users and those who had previously tried but were not using at the moment.

[β]Hajek 2015 was the only study that entered in the review due to meet the criteria for adverse events.

[€]But only 2,476 asnwered the question “Have you ever used e-cigarettes, electronic, or vapor cigarettes?”

Table 2 describes study characteristics related to population, intervention or exposure groups, comparator, and assessed outcomes. Of the three RCTs, one compared ENDS to both NRT and ENNDS [34-39], another to different concentrations of ENDS to ENNDS [25], and the third compared different types of ENDS [33]. Only the Borderud study [41] included participants who were also currently receiving other behavioral and other pharmacologic treatment. The participants from Vickerman 2013 [44] study were all enrolled in a state quitline programs that provided behavioral treatment and in some cases NRT. All nine cohort studies [26-29, 34-46] compared ENDS to no use of ENDS [26-29, 40, 41] or tobacco cigarettes only [42]; in one [41], both exposure and non-exposure groups received behavioral and other pharmacologic treatment.

Table 2. Study characteristics related to population, intervention or exposure groups, comparator, and assessed outcomes.

Author, year	Population	No.* of participants intend to quit smoking	No.* of participants in intervention or exposure groups and comparator	Description of intervention or exposure groups	Description of comparators	Measured outcomes	Definition of quitters or abstinence
Randomized controlled trials							
Adriaens, 2014 [33]	Participants unwilling to quit smoking (participants from the control group kept on smoking regular tobacco cigarettes during the first eight weeks of the study)	Yes 0 No 50	ENDS 1: 16 ENDS 2: 17 Control/ENDS: 17	ENDS ("Joyetech eGo-C") ENDS E-cigarettes ("Kanger T2-CC")	ENDS and e-liquid**	Quitting, defined as eCO of 5 ppm or smaller; questionnaire self-report of reduction in cigarettes of > 50% or complete quitting	No more cigarette smoking
Bullen, 2013 [34-39]	Had smoked ten or more cigarettes per day for the past year, interested in quitting	Yes 657 No 0	ENDS: 289 NRT: 295 ENNDS: 73	16 mg nicotine ENDS	21 mg patches NRT ENNDS	Continuous smoking abstinence, biochemically verified (eCO measurement <10 ppm); seven day point prevalence abstinence; reduction; and adverse events	Abstinence allowing ≤5 cigarettes in total, and proportion reporting no smoking of tobacco cigarettes, not a puff, in the past 7 days

Caponnetto, 2013 [25]	Smokers not intending to quit	Yes 0 No 300	ENDS 1: 100 ENDS 2: 100 ENNDS: 100	7.2 mg nicotine ENDS 7.2 mg nicotine ENDS + 5.4 mg nicotine ENDS	ENNDS	Self-report of reduction in cigarettes of > 50%; abstinence from smoking, defined as complete self-reported abstinence from tobacco smoking - not even a puff, biochemically verified (eCO measurement ≤7 ppm); and adverse events	Complete self-reported abstinence from tobacco smoking - not even a puff
Cohort studies							
Al-Delaimy, 2015 [40]	Current smokers; regardless of whether the users were using ENDS as part of a quit attempt	Yes 415 No 542	ENDS: 236[Ψ] No ENDS: 392[Ψ]	ENDS	No ENDS	Quit attempts; 20% reduction in monthly no. of cigarettes; and current abstinence from cigarette use	Duration of abstinence of one month or longer to be currently abstinent
Biener, 2015 [29]	All respondents had reported being cigarette smokers at baseline; regardless of whether the users were using ENDS as part of a quit attempt	Yes 364[β] No 331[€]	1374[$]	ENDS[£] intermittent use ENDS[£] intensive use	No ENDS (used once or twice ENDS)	Smoking cessation; and reduction in motivation to quit smoking among those who had not quit, not otherwise specified	Smoking cessation was defined as abstinence from cigarettes for at least one month

Brose, 2015 [26-28]	Current smokers; regardless of whether the users were using ENDS as part of a quit attempt	Not reported	ENDS: 1507 No ENDS: 2610	ENDS daily ENDS non-daily	No ENDS[€]	Quit attempts[ϕ]; cessation[ϖ]; and substantial reduction defined as a reduction by at least 50% from baseline CPD to follow-up CPD	Change from being a smoker at baseline to being an ex-smoker at follow-up was coded as cessation
Hajek, 2015 [46]	69% (n=69) accepted e-cigs as part of their smoking cessation treatment	Not reported	ENDS: 69 No ENDS: 31	ENDS was offered to all smokers in addition to the standard treatment (weekly support and stop smoking medications including NRT and varenicline)	No ENDS	Self-reported abstinence was biochemically validated by exhaled CO levels in end-expired breath using a cut-off point on 9ppm, adverse events	Self-reported abstinence from cigarettes at 4 weeks
Harrington, 2015 [45]	Hospitalized cigarette smokers. All were cigarette smokers initially; regardless of whether the users were using ENDS as part of a quit attempt	Yes: 220*** No: not reported	ENDS: 171 No ENDS: 759	ENDS	No ENDS	Quitting smoking based on 30-day point prevalence at 6 months	Only self-reported quitting smoking
Manzoli, 2015 [42]	Smokers of ≥1 tobacco cigarette/day (tobacco smokers), users of any type of e-cig, inhaling ≥50 puffs weekly (e-smokers), or smokers of both tobacco and e-cig (dual smokers)	Not reported	ENDS: 343 Tobacco and ENDS: 319 Tobacco only: 693	ENDS Tobacco and ENDS	Tobacco cigarettes only	Abstinence, proportion of quitters, biochemically verified (eCO measurement > 7ppm), reduce tobacco smoking, and serious adverse events	Percentage of subjects reporting sustained (30 days) smoking abstinence from tobacco smoking

Borderud, 2014 [41]	Patients who presented for cancer treatment and identified as current smokers (any tobacco use within the past 30 days); regardless of whether the users were using ENDS as part of a quit attempt	Yes 633[¥] No 42[¥]	ENDS: 285 No ENDS: 789	ENDS[£] + Evidence-based behavioral and pharmacologic treatment	No ENDS+Evidence-based behavioral and pharmacologic treatment	Smoking cessation by self-report	Patients were asked if they had smoked even a puff of a (traditional) cigarette within the last 7 days
Prochaska, 2014 [43]	Adult daily smokers with serious mental illness; regardless of whether the users were using ENDS as part of a quit attempt	At baseline, 24% intended to quit smoking in the next month	ENDS: 101 No ENDS: 855	ENDS	No ENDS	Smoking cessation by self-report and, biochemically verified (CO and cotinine)	Past 7 day tobacco abstinence
Vickerman, 2013 [44]	Adult tobacco current or past users; regardless of whether the users were using ENDS as part of a quit attempt	Not reported	ENDS: 765 No ENDS: 1,711	ENDS used for 1 month or more ENDS used for less than 1 month	No ENDS (never tried)	Tobacco abstinence	Self-reported 30-day tobacco abstinence at 7 month follow-up

no.: number; C: comparator group; CPD: cigarettes smoked per day; e-cig: e-cigarettes; ENDS: Electronic nicotine delivery system; ENNDS: electronic non-nicotine delivery systems; eCO: exhaled breath carbon monoxide; NE: non-exposure group; NRT: Nicotine replacement therapy.

*Numbers randomized or at baseline.

**For the first two months control group consisted of no e-cigarettes use. After that period, the participants of control group received the e-cig and e-liquid. ENDS1 = “Joyetech eGo-C” e-cig and ENDS2 = “Kanger T2-CC” e-cig.

***Only among those who reported any previous use of e-cigs.

[α]Information retrieved through contact with author.

[€]The comparator comprises of current non-users of e-cig, which included never-users and those who had previously tried but were not using at the moment.

[Ψ]Participants who will never use e-cig plus those who never heard of e-cig = 392; participants who have used e-cig = 236 (numbers taken from the California Smokers Cohort, a longitudinal survey).

[β]Intentions to quit smoking, those who tried e-cigarettes only once or twice are grouped with never users ("non-users/triers").

[€]Intermittent use (i.e., used regularly, but not daily for more than 1 month) plus intensive use (i.e., used e-cig daily for at least 1 month).

[$]No. of the whole sample including comparator.

[£]All ENDS.

[¥]The other participants either quit more than a month ago but less than six months, less than a month ago, or more than six months ago.

[ϕ]Smokers and recent ex-smokers were asked about the number of attempts to stop they had made in the previous year. Those reporting at least one attempt and 37 respondents who did not report an attempt but had stopped smoking be- tween baseline and follow-up were coded as having made an attempt.

[ϖ]Change from being a smoker at baseline to being an ex-smoker at follow-up was coded as cessation.

Table 3 describes the mean number of conventional cigarettes used per day at both baseline and the end of study. The mean number at baseline ranged from 11.9 in the no ENDS group [45] to 20.6 in the ENDS group [33]. In only two studies [26-28, 45] the mean number of conventional cigarettes used per day presented a reduction from the baseline to the end of study in the ENDS group compared to the no ENDS groups, mainly in the daily users [26-28]. No included study addressed users of combustible tobacco products other than cigarettes.

Table 3. Mean number of conventional cigarettes used per day at both baseline and the end of study*.

Author, year	Groups	Mean no. of conventional cigarettes used per day at baseline	Mean no. of conventional cigarettes used per day at the end of study	Biochemically quitters (no. of events per no. of total participants)	Self-reported quitters (no. of events per no. of total participants)
Adriaens, 2014 [33]	ENDS1	20.1	7.0[£]	3/13	4/13
	ENDS2	20.6	8.1[£]	3/12	3/12
	Control/ENDS[αφ]	16.7	7.7[£]	4/13	4/13
Bullen, 2013 [34-39]	ENDS	18.4	0.7[ϖ]	21/241	Not available
	ENNDS	17.7	0.7	3/57	Not available
	NRT	17.6	0.8[ϖ]	17/215	Not available
Caponnetto, 2013 [25]	7.2 mg ENDS	19.0 (14.0-25.0)[Ψ]	12 (5.8-20)[Ψ¢]	Combined ENDS groups: 22/128	Not available
	7.2 mg ENDS plus 5.4 mg ENDS	21.0 (15.0-26.0)[Ψ]	14 (6-20)[Ψ¢]		Not available
	ENNDS	22.0 (15.0-27.0)[Ψ]	12 (9-20)[Ψ¢]	4/55	Not available
Al-Delaimy, 2015 [40]	ENDS	14.1[Ω]	13.8[δ]	Not available	12/179
	ENNDS			Not available	32/145
Biener, 2015 [29]	ENDS intermittent use	16.7[ę]	Not available	Not available	Combined ENDS groups: 42/331
	ENDS intensive use	17.1[ę]	Not available	Not available	
	No ENDS	15.4[ę]	Not available	Not available	82/364

Table 3. (Continued)

Author, year	Group	Mean no. of conventional cigarettes used per day at baseline	Mean no. of conventional cigarettes used per day at the end of study	Biochemically quitters (no. of events per no. of total participants)	Self-reported quitters (no. of events per no. of total participants)
Brose, 2015 [26-28]	ENDS daily users	14.3	13.0 [θ]	Not available	7/86
	ENDS non-daily users	13.5	13.9 [θ]	Not available	25/263
	No ENDS[ς]	13.3	13.5	Not available	168/1307
Hajek, 2015 [46]	ENDS	Not available	Not available	Not applicable**	Not applicable**
	No ENDS	Not available	Not available	Not applicable**	Not applicable**
Harrington, 2015 [45]	ENDS	14.1[$]	10.3[$]	Not available	21/171
	No ENDS	11.9[$]	9.8[$]	Not available	62/464
Manzoli, 2015 [42]	ENDS only	Not available	12	Not available	Not available
	Tobacco cigarettes only	14.1	12.8	101/491	Not available
	Dual smoking	14.9	9.3	51/232	Not available
Borderud, 2014 [41]	ENDS	13.7	12.3	Not available	25/58
	No ENDS	12.4	10.1	Not available	158/356
Prochaska, 2014 [43]	ENDS	17.0	10.0	21/101	Not available
	No ENDS	17.0	10.1	162/855	Not available
Vickerman, 2013 [44]	ENDS used for 1 month or more	19.4	13.5	Not available	59/273
	ENDS used for less than 1 month	18.9	14.0	Not available	73/439
	No ENDS (never tried)	18.1	12.9	Not available	535/1711

No.: number; e-cig: eletronic cigarettes; ENDS: Electronic nicotine delivery system; ENNDS: electronic non-nicotine delivery systems; ENDS1 and ENDS 2: the e-cig groups received the e-cig and four bottles of e-liquid at session 1 (group e-cig1 received the “Joyetech eGo-C” and group e-cig2 received the “Kanger T2-CC”); at session 2; RYO: roll your own (loose tobacco) cigarettes.

*When authors provided data for different time points, we presented the data for the longest follow-up.

**Not applicable because they followed participants only for 4 weeks, but the study reported adverse events at one week or longer.

[φ]For the first two months control group consisted of no e-cigarettes use. After that period, the participants of control group received the e-cig and e-liquid. ENDS1 = “Joyetech eGo-C” e-cig and ENDS2 = “Kanger T2-CC” e-cig.

[α]Control group consisted of received the e-cig and e-liquid (six bottles) for two months at the end of session 3 (eight of the 16 participants of the control group received the “Joyetech eGo-C” and the remaining eight participants received the “Kanger T2-CC”).

[£]8 months from start of intervention.

[Ψ]Data shown as median and interquartile.

[ɸ]At six months after the last lab session.

[θ]No. of cigarette per week divided by 7 days.

[Ω]Of the 1,000 subjects, 993 responded to the question “How many conventional cigarettes smoked per day during the past 30 days".

[δ]Of the 1,000 subjects, 881 responded to the question “How many cigarettes smoked per day during the past 30 days".

[ϖ]For those reporting smoking at least one cigarette in past 7 days.

[¢]Number of conventional cigarettes used in the prior month at baseline.

[ς]The comparator comprises of current non-users of e-cig which included never-users and those who had previously tried but were not using at the moment.

[$]Data for baseline current e-cig users.

Appendix table 3 presents the types of e-cigarettes used in the included studies. The three RCTs [25, 33-39] evaluated only ENDS type cigalikes. 23.7% of the participants from Brose 2015 [26-28] study used tank and in the Hajek 2015 [46] study participants used either cigalike or tank. The remaining studies did not report the type of ENDS used.

Risk of Bias

Figures 2 and 3, and table 4, describe the risk of bias assessment for the RCTs. The major issue regarding risk of bias in the RCTs of ENDS versus ENNDS was the extent of missing outcome data [25, 34-39]. RCTs comparing ENDS to other nicotine replacement therapies had additional problems of concealment of randomization [33] and blinding [33-39].

Table 4. Risk of bias assessment for the randomized controlled trials

Author, year	Was the randomization sequence adequately generated?	Was allocation adequately concealed?	Was there blinding of participants?	Was there blinding of caregivers?	Was there blinding of data collectors?	Was there blinding of statistician?	Was there blinding of outcome assessors?	Was loss to follow-up (missing outcome data) infrequent?*	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?
Randomized controlled trials assessing ENDS *versus* ENNDS										
Bullen, 2013 [34-39]	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely no	Definitely yes	Definitely yes
Caponnetto, 2013 [25]	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely no	Definitely yes	Definitely yes
Randomized controlled trials assessing ENDS *versus* other quitting mechanisms										
Adriaens, 2014 [33]	Definitely yes	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no	Definitely no	Probably yes	Probably yes
Bullen, 2013 [34-39]	Definitely yes	Definitely yes	Definitely no	Definitely no	Probably yes	Probably yes	Definitely yes	Definitely no	Definitely yes	Definitely yes

*Defined as less than 10% loss to outcome data or difference between groups less than 5% and those excluded are not likely to have made a material difference in the effect observed.

ENDS: electronic nicotine delivery systems. ENNDS: electronic non-nicotine delivery systems.

All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).

Figure 4 and table 5 describe the risk of bias assessment of the cohort studies. Seven [26-29, 40-42, 44, 45] of nine cohort studies were rated as high risk of bias for limitations in matching exposed and unexposed groups or adjusting analysis for prognosis variables; confidence in the assessment of the presence or absence of prognostic factors; confidence in the assessment of outcome; and similarity of co-interventions between groups; all studies suffered from high risk of bias for missing outcome data.

Table 5. Risk of bias assessment of the cohort studies.

Author, year	Was selection of exposed and non-exposed cohorts drawn from the same population?*	Can we be confident in the assessment of exposure?**	Can we be confident that the outcome of interest was not present at start of study? ***	Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? ****	Can we be confident in the assessment of the presence or absence of prognostic factors?*****	Can we be confident in the assessment of outcome? ******	Was the follow up of cohorts adequate? *******	Were co-interventions similar between groups? ********
Al-Delaimy 2015 [40]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Biener 2015 [29]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Brose 2015 [26-28]	Definitely yes	Probably yes	Probably no	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Hajek 2015 [46]	Probably yes	Probably yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably no
Harrington 2015 [45]	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no
Manzoli 2015 [42]	Definitely yes	Probably yes	Definitely no	Definitely no	Definitely no	Probably no	Definitely no	Probably no
Borderud 2014 [41]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely yes
Prochaska 2014 [43]	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely no	Definitely yes	Probably No
Vickerman 2013 [44]	Probably yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no

* Examples of low risk of bias: Exposed and unexposed drawn from same administrative data base of patients presenting at same points of care over the same time frame.

** This means that investigators accurately assess the use of ENDS at baseline.

*** This means that smoking cessation was not present at the start of the study.

**** Examples of low risk of bias: comprehensive matching or adjustment for all plausible prognostic variables.

***** Examples of low risk of bias: Interview of all participants; self-completed survey from all participants; review of charts with reproducibility demonstrated; from data base with documentation of accuracy of abstraction of prognostic data.

****** Outcome self-reported was considered as definitely no for adequate assessment. Smoking abstinence, biochemically verified was considered as definitely yes for adequate assessment.

*******Defined as less than 10% loss to outcome data or subjects lost to follow-up unlikely to introduce bias.

******** Examples of low risk of bias: Most or all relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.

All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).

Outcomes

The mean number of conventional cigarettes/tobacco products used per day at the end of the studies ranged from 0.7 [34-39] in both ENDS and ENNDS groups to 13.9 [26-28] among non-daily users of ENDS (Table 3). The three RCTs [25, 33-39] and one cohort study [42] biochemically confirmed nicotine abstinence while the others presented only self-reported data [26-29, 40, 41, 43-45] (Table 3).

Tobacco cessation smoking

Synthesized results from randomized controlled trials

Results from two RCTs [25, 34-39] suggest a possible increase in smoking cessation with ENDS in comparison to ENNDS (RR 2.03, 95% CI 0.94, 4.38; p = 0.07; I^2=0%, risk difference (RD) 64/1,000 over 6 to 12 months, low quality evidence) (Figure 5, Table 6). A plausible worse case sensitivity analysis yielded results that were inconsistent with the primary complete case analysis and fail to show a difference in the effects of ENDS in comparison to ENNDS (RR 1.16, 95% CI 0.72, 1.87; p = 0.54; I^2=0%) (Appendix Figure 1). Certainty in evidence was rated down to low because of imprecision and risk of bias, due to missing outcome data in all studies and lack of blinding of participants [34-39], caregivers, data collectors, statistician and outcome assessors in the ENDS versus other nicotine replacement therapy studies (Figure 2, Tables 4 and 6).

Adriaens 2014 [33] also compared two types of ENDS and ENDS and e-liquid; results failed to show a difference between the ENDS groups with a very wide confidence interval (RR 1.15, 95% CI 0.28, 4.76, p = 0.84).

Table 6. *GRADE evidence profile for RCTs:* Electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) for reducing cigarette smoking.

Quality assessment						Summary of findings					Certainty in estimates
						Study event rates		Relative risk	Anticipated absolute effects over 6-12 months		OR
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	ENNDS*	ENDS	(95% CI)	ENNDS*	ENDS	Quality of evidence
Cessation/nicotine abstinence (Includes self-reported and biochemically validated by eCO)											
481 (2) 6-12 mo	Serious limitations[1]	No serious limitations	No serious limitations	Serious imprecision[2]	Undetected	7/ 112	43/ 369	**2.03** (0.94-4.38)	213 per 1000	219 more per 1000 (13 fewer to 720 more)	⊕⊕OO LOW
Self-report of reduction in cigarettes of > 50%											
481 (2)	Serious limitations[1]	Serious limitations	No serious limitations	Serious imprecision[2]	Undetected	45/ 112	184/ 369	**0.97** (0.57-1.66)	213 per 1000	7 fewer per 1000 (92 fewer to 140 more)	⊕⊕OO LOW

6-12 mo				

*The estimated risk control was taken from the median estimated control risks of the cohort studies.

[1]Two studies presented high risk of bias for missing outcome data. [3]Moreover, one was not blinded to participants and caregiver [29, 37-41] and, other [26-28] also was not blinded to data collectors, statistician and outcome assessors. While not specifically rating down for risk of bias, these additional concerns plus borderline clinically important imprecision led to downgrading of certainty in estimates for all outcomes.

[2]95% CI for absolute effects include clinically important benefit and no benefit.

Bullen 2013 [34-39] also compared ENDS and ENNDS with NRT; results failed to show a difference between these groups with a very wide confidence interval (RR 1.10, 95% CI 0.60, 2.03, p = 0.76) and (RR 0.67, 95% CI 0.20, 2.19, p = 0.50), respectively.

Synthesized results from cohort studies

The adjusted OR from primary meta-analysis of eight cohort studies [26-29, 40-45] comparing ENDS to no ENDS without reported concomitant interventions failed to show a benefit in cessation smoking (OR 0.74, 95% CI 0.55, 1.00; p = 0.051; I^2=56%) (Figure 6). A sensitivity analysis from the eight cohort studies [26-29, 40-45] using any rather than daily use of ENDS for Brose study [26-28], both intensive (used e-cigarettes daily for at least 1 month), and intermittent use (used regularly, but not daily for more than 1 month) of ENDS for Biener study [29] and, any use versus never used for Vickerman study [44] suggested a reduction in cessation smoking rates with ENDS (adjusted OR 0.69, 95% CI 0.53, 0.91; p = 0.01; I^2=59%) (Appendix Figure 2).

Another sensitivity analysis from the same eight cohort studies [26-29, 40-45], examined whether low and high risk of bias limited to the one characteristic in which the studies differed substantially: confidence in whether the outcome was present at the beginning of the study. Although there were substantial differences in the point estimates in the low risk of bias group (adjusted OR 1.00, 95% CI 0.51, 1.94; p = 1.00; I2=67%) and the high risk of bias (adjusted OR 0.62, 95% CI 0.50, 0.77; p < 0.001; I2=0%), the difference is easily explained by chance (interaction p-value was 0.19) (Appendix Figure 3).

A second sensitivity analysis from the same eight cohort studies [26-29, 40-45], examined whether low and high risk of bias limited to "two or fewer domains rated as low risk of bias" versus "three or more domains rated as low risk of bias" differed substantially. There were substantial differences in the point estimates between the "two or fewer domains rated as low risk of bias" group (adjusted OR 0.61, 95% CI 0.49, 0.75; p < 0.001 ; I2=0%)

and the "three or more domains rated as low risk of bias" (adjusted OR 1.26, 95% CI 0.68, 2.33; p=0.46; I2=51%), with an interaction p-value of 0.03 (Appendix Figure 4).

Certainty in evidence from the observational studies was rated down from low to very low because risk of bias due to missing outcome data, imprecision in the assessment of prognostic factors and outcomes (Figure 4, Tables 5 and 7), as well as inconsistency in the results.

Table 7. *GRADE evidence profile for cohort studies:* Electronic nicotine delivery systems (ENDS) and no ENDS for reducing cigarette smoking.

Quality assessment						Summary of findings					Certainty in estimates
						Study event rates		Relative risk	Anticipated absolute effects over 6-12 months		OR
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	ENNDS*	ENDS	(95% CI)	ENNDS*	ENDS	Quality of evidence
Cessation/nicotine abstinence (Includes self-reported and biochemically validated by eCO)											
7,826 (8) 6-36 mo	Serious limitations[1]	No serious limitations	No serious limitations	Serious imprecision[2]	Undetected	1300/ 5693	336/ 2133	**0.74** (0.55-1.00)	213 per 1000	56 fewer per 1000 (96 fewer to 0 more)	⊕OOO VERY LOW

*The estimated risk control was taken from the median estimated control risks of the cohort studies.

[1]All studies were rated as high risk of bias for adjustment for prognosis variable; assessment of prognostic factors; assessment of outcomes; adequate follow-up of cohort; and similarity of co-interventions between groups.

[2]95% CI for absolute effects include clinically important benefit and no benefit.

Borderud 2014 [41] reported cessation smoking in 25 out of 58 cancer patients using ENDS plus behavioral and pharmacologic treatment versus in 158 out of 356 cancer patients who received only behavioral and pharmacologic treatment (adjusted OR 0.97, 95% CI 0.71 to 1.33).

Reduction in cigarette use of at least 50%

Synthesized results from randomized controlled trials

Two RCTs [25, 34-39] results failed to show a difference between ENDS type cigalikes versus ENNDS group with regards to reduction in cigarettes but with a very wide confidence interval (RR 0.97, 95% CI 0.57, 1.66; p = 0.92; I^2=61%) (Appendix Figure 5). Certainty in evidence was rated low because of imprecision and risk of bias [25, 34-39] (Figure 2, Tables 4 and 6).

Synthesized results from cohort studies

Two studies [26-29] suggested increased reduction rates in those with greater versus lesser use of ENDS. Biener [29] reported an adjusted OR for quitting of 6.07 (95% CI 1.11, 33.2) in those with intensive use versus an OR of 0.31 (0.04, 2.80) in those with intermittent use. Brose [26-28] reported a greater likelihood of substantial reduction (but not quitting) in those with daily use of ENDS (OR 2.49, 95% CI 1.14, 5.45) but not those with intermittent use (OR 0.85 0.43 to 1.71).

Adverse effects

Synthesized results from randomized controlled trials

Bullen 2013 [34-39] study reported serious side effects in 27 out of 241 participants in the 16 mg ENDS group and 5 out of 57 for the ENNDS group followed at 6 months; results failed to show a difference between these groups with a very wide confidence interval (OR 1.31, 95% CI 0.48, 3.57; p = 0.59). Results suggested possible increase in side effects in the 21 mg nicotine patches group (14 of 215) in comparison to ENDS (OR 1.81, 95% CI 0.92, 3.55; p = 0.08). Serious side effects includes death (n = 1, in nicotine e-cigarettes group), life

threatening illness (n = 1, in nicotine e-cigarettes group), admission to hospital or prolongation of hospital stay (12% of all events in nicotine e-cigarettes group, 8% in patches group, and 11% in placebo e-cigarettes group), persistent or significant disability or incapacity, and other medically important events (6% of all events in nicotine e-cigarettes group, 4% in patches group, and 3% placebo e-cigarettes group).

Adriaens 2014 [33] study reported no serious adverse events in both ENDS groups as well as in the e-liquid group at eight months of follow-up; however at one week from start of intervention there were three cases of non-serious adverse events in the ENDS groups.

Caponnetto 2013 [25] mentioned that no serious adverse events occurred during the study and; authors found a significant reduction in frequency of reported symptoms compared to baseline.

Synthesized results from cohort studies

Manzoli [42] reported no significant differences in self-reported serious side effects, but observed four cases of pneumonia, four COPD exacerbations, three myocardial infarctions, and one angina as possibly-related serious side effects: two among the ENDS users (both switched to tobacco smoking during follow-up); six among tobacco smokers (three quit all smoking); four among tobacco and ENDS smokers.

Hajek 2015 [46] reported one leak irritating a participant's mouth and some reports of irritation at the back of the throat and minor coughing. The remaining studies did not report adverse effects.

DISCUSSION

Main findings

Based on pooled data from two randomized trials with 481 participants, we found evidence for a possible increase in tobacco smoking cessation with ENDS in comparison to ENNDS (Figure 5). The evidence is, however, of low certainty: the 95% confidence interval

of the relative risk crossed 1.0 and a plausible worse case sensitivity analyses to assess the risks of bias associated with missing participant data yielded results that were inconsistent with the primary complete case analysis (Appendix Figure 1). Furthermore, in all these RCTs, the ENDS tested were earlier generation; it is possible that later generation of e-cigarettes would have greater benefit. There was no robust evidence of side effects associated with ENDS in the RCTs.

Cohort studies provide very low certainty evidence suggesting a possible reduction in quit rates with use of ENDS compared to no use of ENDS (Figure 7). These studies had a number of limitations: an unknown number of these participants were not using ENDS as a cessation device; some were not using ENDS during a quit attempt; many did not have immediate plans to quit smoking. In our risk of bias assessment, we judged that 7 of 9 studies did not have optimal adjustment for prognostic variables. Further, as any cohort study, the results are vulnerable to residual confounding. In particular, use of ENDS may reflect the degree of commitment to smoking cessation, and it may be the degree of commitment, rather than use of ENDS, that is responsible for the change in quit rates. For instance, the finding in two studies that daily use of ENDS, but not intermittent use, increased quit/reduction rates could be interpreted as evidence of the effectiveness of daily use. An alternative interpretation, however, is that those that used ENDS daily were more motivated to stop smoking, and the increased motivation, rather than daily use of ENDS, was responsible for their degree of success.

In terms of bias against ENDS, cohort studies sometimes enroll smokers already using ENDS and still smoking. Such individuals may cohort studies may already be failing in their attempts to stop smoking. If so, enrolling these participants will underestimate ENDS beneficial effects. Additional concerns with cohort studies include their failure to provide

optimal adjustment for prognostic variables or provide data regarding use of alternative smoking reduction aids.

Strengths and limitations

Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias, and data abstraction independently and in duplicate; assessment of risk of bias that included a sensitivity analysis addressing loss to follow-up; and use of the GRADE approach in rating the certainty of evidence for each outcome.

The primary limitation of our review is the low certainty consequent on study limitations. We identified only a small number of RCTs with a modest number of participants resulting wide confidence intervals. Moreover, loss to follow-up was substantial, and, our sensitivity analysis demonstrated the vulnerability of borderline effects to missing data. The limitations of the cohort studies led us to a rating of very low certainty evidence from which no credible inferences can be drawn.

Another limitation of this review is the fact that we could not address our hypothesis about increase rates in smoking cessation in those who used e-cigarettes with higher concentrations of nicotine compared to those using less nicotine, or daily e-cigarette users compared to nondaily e-cigarette users, or those who use newer forms of ENDS compared to users of first generation devices due to lack of evidence. However, although these assumptions seems logical, nicotine delivery from ENDS depends on other factors such as the efficiency of the device in aerosolising the liquid and user experience, apart from the concentration of nicotine in the ENDS liquid.

Furthermore, whether or not ENDS are an effective aid in the cessation smoking may depend on whether the users were using ENDS as part of a quit attempt or not and, this may play an important role also as a possible confounder. Data is not yet available to conduct a subgroup analysis addressing this hypothesis. Subsequent trials should help provide

information regarding whether their impact on cessation of smoking depends on whether users were intended to quit smoking, as well as the other unresolved issues.

Other limitations of this review were the fact of having insufficient number of included studies to allow the complete statistical analysis that we had planned. We were not able to assess publication bias because there were less than 10 eligible studies addressing the same outcome in a meta-analysis. We also planned to perform subgroup analyses according to the characteristics of:

- Participants (commitment to stopping smoking, use of e-cigarettes at baseline).
- Interventions (dose of nicotine delivered by the e-cigarette, frequency of use of the e-cigarette, type of e-cigarettes and type of e-cigarettes).
- Concomitant interventions in both e-cigarettes and control groups.

However, we also were not able to conduct these analyses because they did not meet our minimal criteria, which were at least five studies available, with at least two in each sub-group. A final statistical limitation is that we calculated differences from 6 to 12 months of follow-up. Absolute differences may differ across this time frame and constitute a source of variability. Moreover, there are three schools of thought with respect to use of fixed and random effect models: those who prefer always to use fixed effects, those who prefer (almost) always random effects, and those who would choose fixed and random depending on the degree of heterogeneity. Each argument has its proponents within the statistical community. The argument in favor of the second rather than the third is a) there is always some heterogeneity, so any threshold of switching models is arbitrary and b) when there is little heterogeneity, fixed and random yield similar or identical results, so one might as well commit oneself to random from the start. We find these two arguments compelling; thus, our choice.

Finally, another limitation of the observational studies in this review is the potential for selection bias as the populations compared differ in terms of intention to quit. Furthermore, in all these RCTs, the ENDS tested were earlier generation; it is possible that later generation of e-cigarettes would have greater benefit.

Although this review presents several limitations, the issue is whether one should dismiss these results entirely, or consider them bearing in mind the limitations. The latter represent our view of the matter.

Relation to prior work

The previous Cochrane review [8] concluded that due to low event rates and wide confidence intervals only low certainty evidence was available from studies comparing ENDS to ENND. We excluded some studies included in that Cochrane review as they were either case series, cross-sectional or did not include one arm with ENDS/ENNDS compared to alternative strategies. We also included one additional RCT [33], and nine new cohort studies [26-29, 40-46], not included in the Cochrane review. The rationale for including the prospective cohort studies in our review was that it was anticipated that the search would return few RCTs. The authors of the Cochrane review found that ENDS is a useful aid to stop smoking long-term compared with ENNDS.

Another review [9] including two of our three RCTs [25, 34-39], and further two case series, and two cross-sectional studies, assessed the impact of e-cigarettes in achieving smoking abstinence or reduction in cigarette consumption among current smokers who had used the devices for six months or more. The authors concluded that e-cigarette use is associated with smoking cessation; these results are similar to our meta-analysis comparing ENDS versus ENNDS (Figure 5). Khoudigian's 2016 review [10] reported a non-statistically significant trend toward smoking cessation in adults using nicotine e-cigarettes compared

with other therapies or placebo. However, the review by Kalkhoran & Glatz 2016 [11] concluded that e-cigarettes are associated with significantly less quitting among smokers.

Implications

Existing smoking reduction aids such as nicotine replacement therapy are effective, but their impact is limited: the proportion of those who quit when using these aids remains small. The available evidence, of low or very low quality, provides no support for the hypothesis that, because they address not only nicotine addiction but also potentially deal with behavioural and sensory aspects of cigarette use, ENDS may be more effective than other nicotine replacement strategies. This is an important finding, and raises serious questions regarding the importance of thee behavioural and sensory aspects of cigarette use in their addictive potential. Thus, the focus of subsequent work should perhaps be on the dose and delivery of nicotine. It is possible that type of ENDS or dose of exposure may influence quit rates, and that newer models may be more effective, but there is insufficient data to provide insight into these issues. This review underlines the urgent need to conduct well-designed trials in the use of ENDS.

AUTHORS' CONTRIBUTIONS

Conceiving the review: Gordon Henry Guyatt (GHG), Regina El Dib (RED), Wasim Maziak (WM), and Elie A. Akl (EAA)

Undertaking searches: Diane Heels-Ansdell (DHA)

Screening search results: RED, Erica Aranha Suzumura (EAS), Huda Goma (HG), Arnav Agarwal (AA), Yaping Chang (YC), Manya Prasad (MP), Vahid Ashoorion (VA)

Organizing retrieval of papers: EAS

Screening retrieved papers against inclusion criteria: RED, EAS, HG, AA, YC, MP and VA

Appraising quality of papers: RED, EAS, HG, AA, YC, MP and VA

Extracting data from papers: RED, EAS, HG, AA, YC, MP and VA

Writing to authors of papers for additional information: RED

Providing additional data about papers: RED

Obtaining and screening data on unpublished studies: RED and EAS

Managing data for the review: RED

Entering data into Review Manager (RevMan): RED and EAS

Analyzing RevMan statistical data: RED, EAS, GHG, WM and EAA

Interpreting data: RED, EAS, GHG, WM and EAA

Making statistical inferences: RED, EAS, GHG, WM and EAA

Writing the review: RED, GHG, WM and EAA

Taking responsibility for reading and checking the review before submission: RED, EAS, HG, AA, YC, MP, VA, EAA, WM and GHG

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AUTHORS' CONTRIBUTIONS

All authors contributed to all aspects of this study, including conducting the literature search, study design, data collection, data analysis, data interpretation, and writing of the paper.

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FIGURE LEGENDS

Figure 1. PRISMA diagram of included studies.

Figure 2. Risk of bias for RCTs comparing ENDS versus ENNDS.

Figure 3. Risk of bias for RCTs comparing ENDS versus other strategies.

Figure 4. Risk of bias for cohort studies.

Figure 5. Meta-analysis of RCTs on cessation smoking comparing ENDS versus ENND.

Figure 6. Meta-analysis of cohort studies on cessation smoking with adjusted ORs.

Appendix Figure 1. Sensitivity analysis of RCTs on cessation smoking comparing ENDS versus ENNDS.

Appendix Figure 2. Meta-analysis of cohort studies on cessation smoking with adjusted ORs using a sensitivity analyses with an assumed correlation=0.5.

Appendix Figure 3. Sensitivity analysis of cohort studies on cessation smoking comparing e-cigarettes versus no e-cigarettes.

Appendix Figure 4. Sensitivity analysis of cohort studies on cessation smoking comparing e-cigarettes versus no e-cigarettes.

Appendix Figure 5. Meta-analysis of RCTs on reduction.

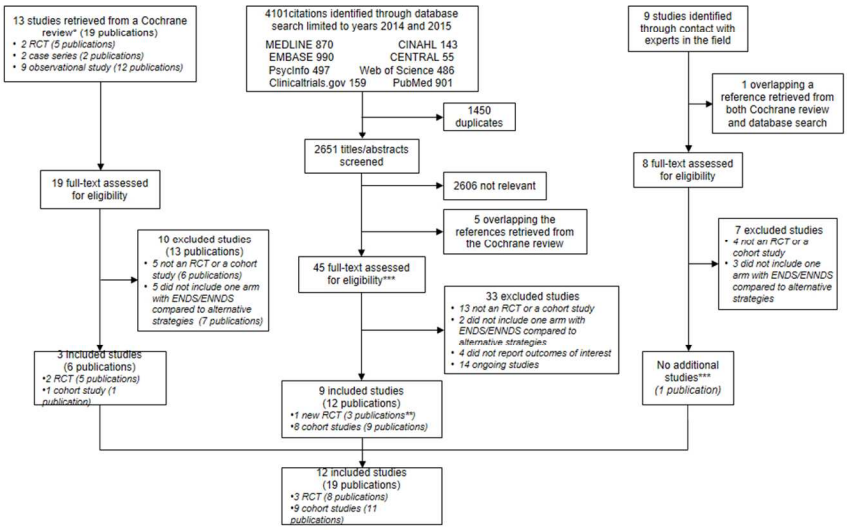
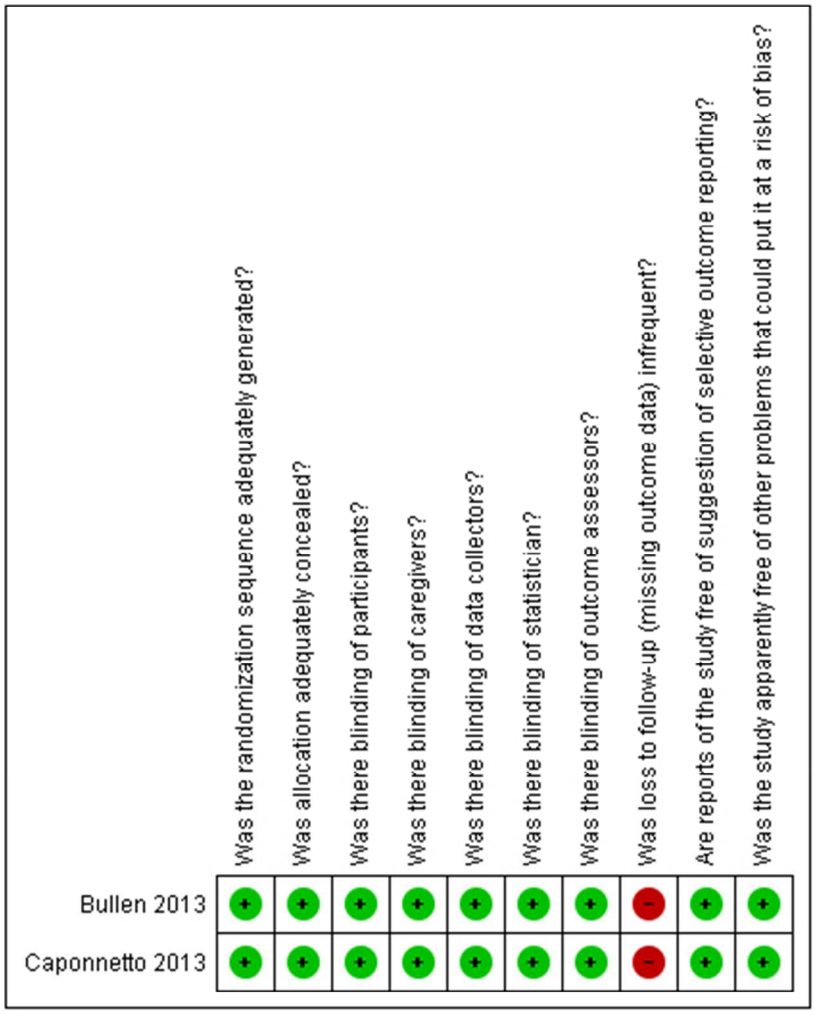


Figure 1. PRISMA diagram of included studies.

*McRobbie, 2014[8]
**Further two publications from one RCT included by the Cochrane review were identified only in our search strategy
***Further one publication from one cohort study identified by our search strategy was identified throughout the expert search

95x69mm (300 x 300 DPI)



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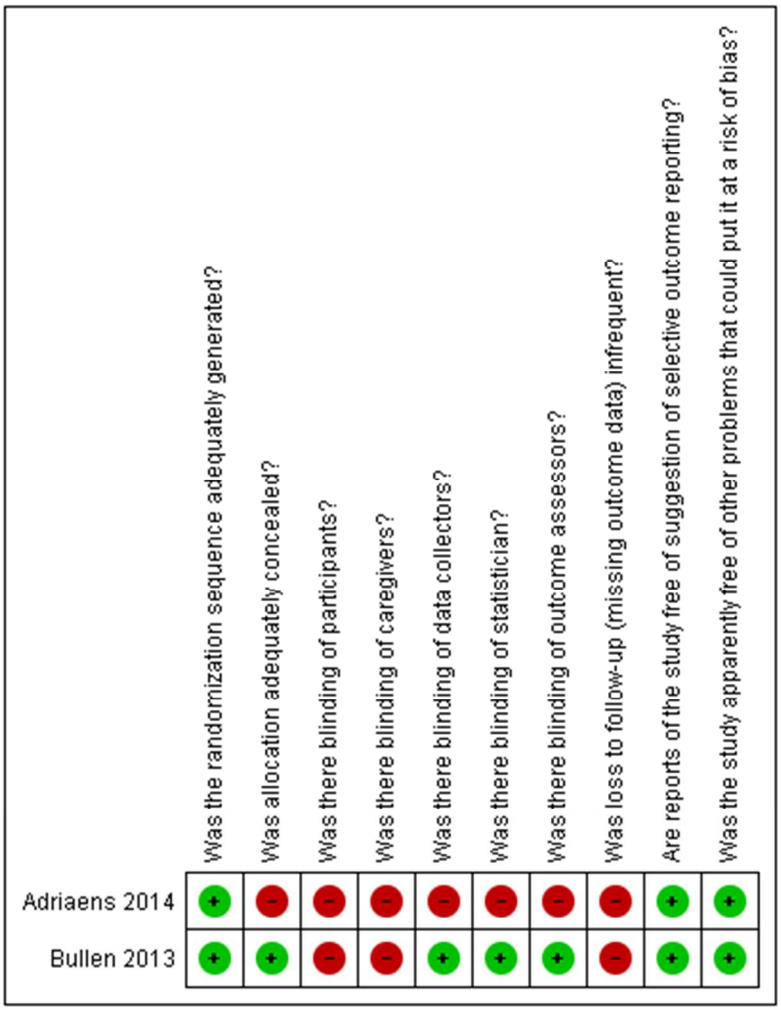

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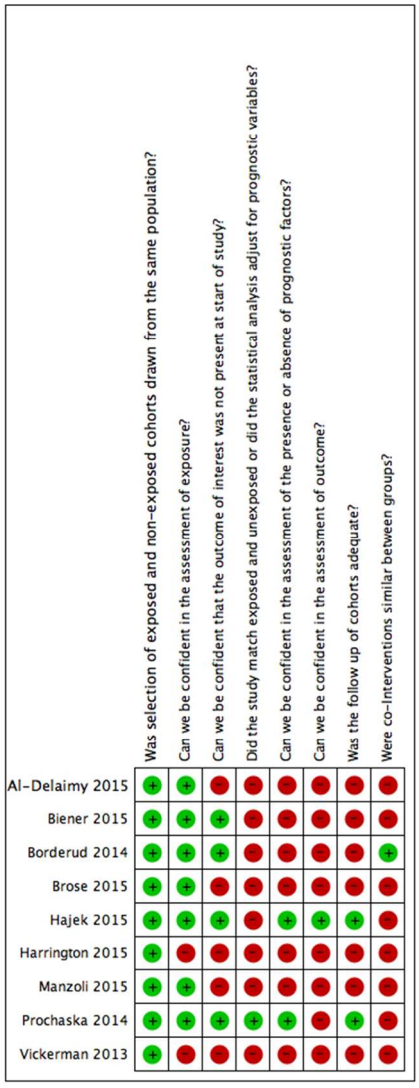

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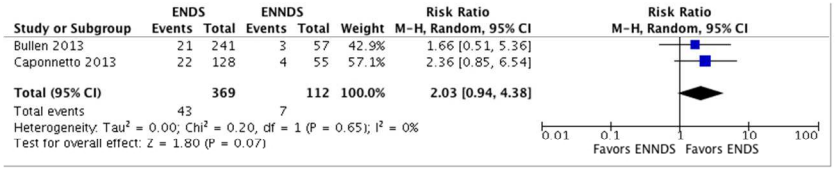

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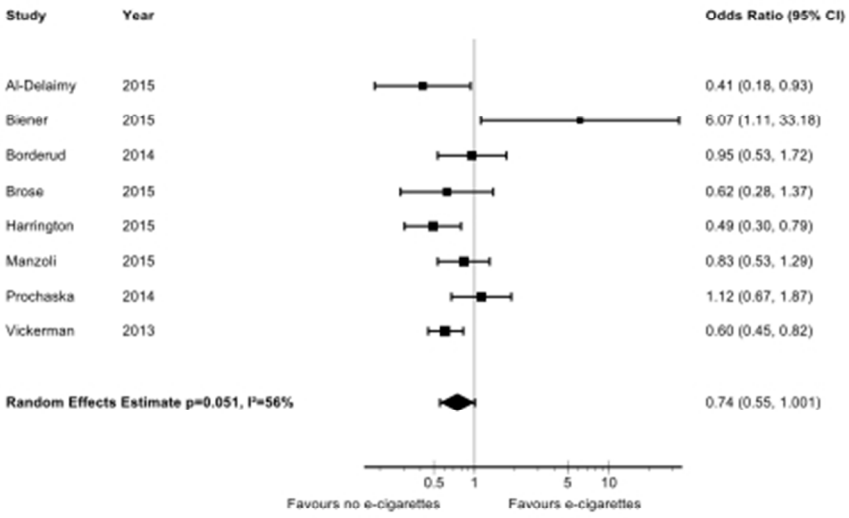


43x30mm (300 x 300 DPI)

Appendix Table 1. Search strategy

1	Electronic Cigarettes/
2	e-cig*.mp.
3	(electr* adj2 cig*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4	(electronic adj2 nicotine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5	(nicotine adj2 delivery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6	(ENDS adj3 nicotine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7	(vape or vaping).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8	or/1-7
9	"tobacco use"/ or smoking/
10	"tobacco use cessation"/ or smoking cessation/
11	Tobacco/
12	Nicotine/
13	(smok$ or cigar$ or tobacco$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14	((quit$ or stop$ or ceas$ or giv$ or prevent$) adj smok$).mp.
15	or/9-14
16	(electronic or electric or vapor or vapour).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17	15 and 16
18	8 or 17
19	Epidemiologic Studies/
20	exp Case-Control Studies/
21	exp Cohort Studies/
22	Case control.tw.
23	(cohort adj (study or studies)).tw.
24	Cohort analy$.tw.
25	(Follow up adj (study or studies)).tw.

26	(observational adj (study or studies)).tw.
27	Longitudinal.tw.
28	Retrospective.tw.
29	Cross sectional.tw.
30	Cross-sectional studies/
31	or/19-30
32	18 and 31
33	randomized controlled trial.pt.
34	controlled clinical trial.pt.
35	randomized.ab.
36	placebo.ab.
37	drug therapy.fs.
38	randomly.ab.
39	trial.ab.
40	groups.ab.
41	or/33-40
42	exp animals/ not humans.sh.
43	41 not 42
44	clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs.
45	randomized controlled trial.pt. or placebo.mp.
46	44 or 45
47	18 and 43
48	18 and 46
49	32 or 47 or 48

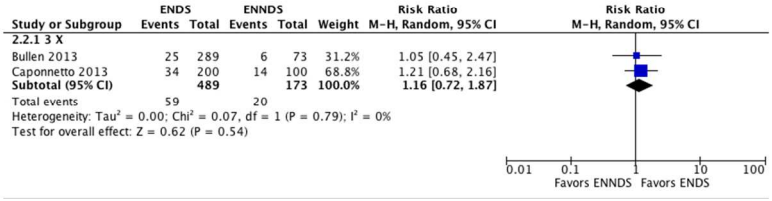
Appendix Table 2. Information about contact with the authors of the included studies.

Author, year	E-mail sent by the reviewers	Did the author of the study reply?	Did the author provide the requested data?
Adriaens, 2014 [33]	**Yes**	Yes	Yes
Bullen, 2013 [34-39]	**Yes**	Yes	Yes
Caponnetto, 2013 [25]	**Yes**	Yes	No (however author replied stating that will contact us later)
Al-Delaimy, 2015 [40]	**Yes**	Yes	Yes
Biener, 2015 [29]	**Yes**	Yes	Yes
Brose, 2015 [26-28]	**Yes**	Yes	Yes
Hajek, 2015 [46]	**Yes**	No	No
Harrington, 2015 [45]	**Yes**	Yes	Yes
Manzoli, 2015 [42]	**Yes**	Yes	No (however author replied stating that will contact us later)
Borderud, 2014 [41]	**Yes**	Yes	Yes
Prochaska, 2014 [43]	**Yes**	Yes	Yes
Vickerman, 2013 [44]	**Yes**	Yes	Yes

Appendix Table 3. Characteristics of e-cigarettes from the included studies.

Study	Device				Eliquid			Use	
	Type	Brand and model	Battery voltage	Metal in heating resistance	Nicotine concentration	Flavors in the eliquid	Conveyants	Puff regime during study	Amount eliquid consumed
Adriaens, 2014 [33]	Not a cigalike (tank-type atomizer) (second generation ENDS devices)	Joyetech eGo-C Kanger T2-CC	3.3 V, 1000 mAh lithium-ion battery 3.7 V, 650 mAh lithium-ion battery	2.2-ohm atomizer head 2.5-ohm coil	18mg of nicotine per mL for both types	Tobacco-flavored (Dekang "Turkish Blend") for both types	Not reported	Not reported	Not repor
Bullen, 2013 [34-39]	Cigalike	Elusion	Not reported	Not reported	Labelled 16mg (commissioned analyses showed 10-16mg of nicotine per mL)	Not reported	Not reported	Participants used e-cig as desired from 1 week before until 12 weeks after their chosen quit day	Not repor
Caponnetto, 2013 [25]	Cigalike	Categoria model 401	3.7 V, 90 mAh lithium-ion battery	Not reported	Cartridges of 7.2mg and 5.4mg nicotine	Cartridge without nicotine (control group): "sweet tobacco'' aroma	Solution of propylene glycol and vegetable glycerin	Not reported	Not repor
Al-Delaimy, 2015 [40]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Biener, 2015 [29]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Brose, 2015 [26-28]	76.3% used Cigalike 23.7% used Tank	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor

Hajek, 2015 [46]	1) Cigalike 2) Tank	1) Gamucci 2) Basic EVOD tank system, The EVOD's were later replaced with an Aspire product due to issues with leakage from the cheap EVOD model	Not reported	Not reported	1) With a choice of 1.6% or 2.2% per ml nicotine 2) 1.8% per ml nicotine e-liquid	Not reported	Not reported	Not reported	Not repor
Harrington, 2015 [45]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Manzoli, 2015 [42]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Borderud, 2014 [41]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Prochaska, 2014 [43]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Vickerman, 2013 [44]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor



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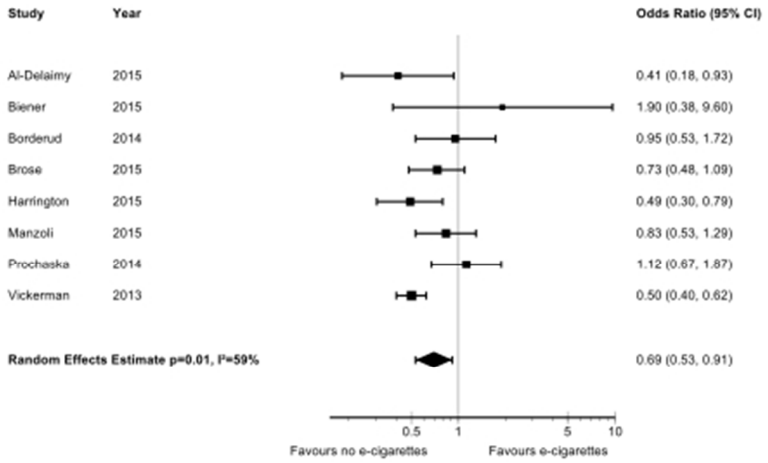

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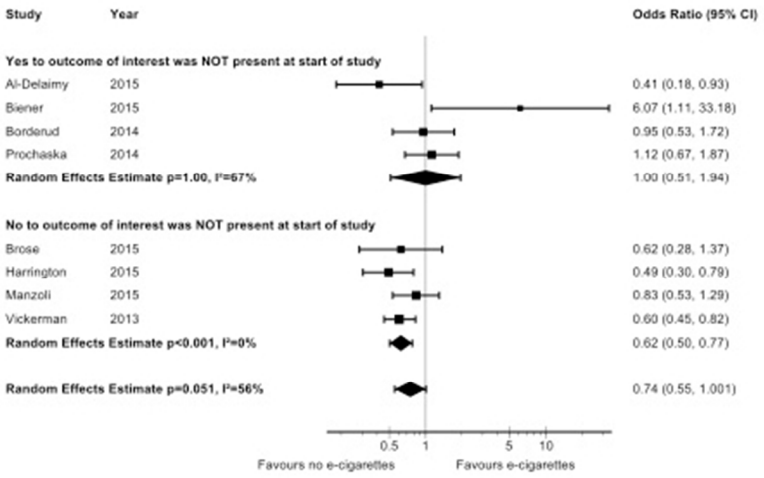

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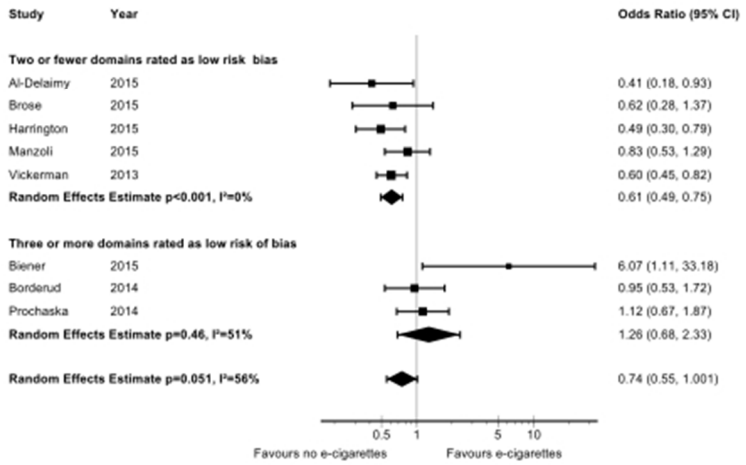

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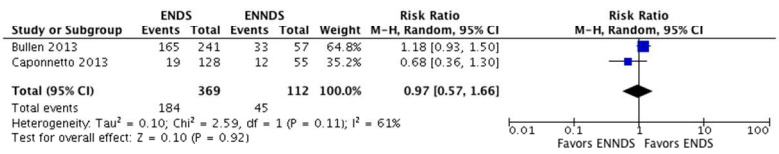

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
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.	4,5
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.	4,5
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.	Appendix Table 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.	4,5
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.	6,7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7,8,9
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.	9

PRISMA 2009 Checklist

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).	7,8,9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
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.	10
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.	10,11
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).	11
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.	12-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-15
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).	15, 16
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).	16,17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
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.	18

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(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis

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Complete List of Authors:	El Dib, Regina; Unesp – Univ Estadual Paulista, São Paulo, Brazil, Department of Anaesthesiology, Botucatu Medical School Suzumura, Erica; Hospital do Coração (HCor), São Paulo, Brazil, Research Institute Akl, Elie; American University of Beirut, Department of Internal Medicine; McMaster University, Department of Clinical Epidemiology and Biostatistics Goma, Huda; Tanta Chest Hospital, Department of Pharmacy Agarwal, Arnav; University of Toronto Faculty of Medicine, Faculty of Medicine; McMaster University, Department of Clinical Epidemiology & Biostatistics Chang, Yaping ; McMaster University, Department of Clinical Epidemiology & Biostatistics Prasad, Manya; Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Department of Community Medicine Ashoorion, Vahid; Isfahan University of Medical Sciences, Isfahan Medical Education Research Centre Heels-Ansdell, Diane; McMaster University, Department of Clinical Epidemiology & Biostatistics Maziak, Wasim; Florida International University, College of Public Health Guyatt, Gordon; McMaster University, Department of Clinical Epidemiology & Biostatistics
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Evidence based practice, Smoking and tobacco
Keywords:	electronic cigarettes, ENDS, smoking cessation, GRADE, systematic review

Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis

Regina El Dib, PhD[1,2*]; Erica A. Suzumura, MSc[3]; Elie A. Akl, MD, MPH, PhD[4,5]; Huda Goma, BCPS[6]; Arnav Agarwal, BHSc, MD(C)[5,7]; Yaping Chang, MSc[5]; Manya Prasad, MBBS[8]; Vahid Ashoorion, MD, MSc, PhD[5,9]; Diane Heels-Ansdell, MSc[5]; Wasim Maziak MD, PhD[10]; Gordon Guyatt, MD, MSc[5,11]

1. Department of Anaesthesiology, Botucatu Medical School, Unesp – Univ Estadual Paulista, São Paulo, Brazil
2. McMaster Institute of Urology, McMaster University, Hamilton, Ontario, Canada
3. Research Institute - Hospital do Coração (HCor), São Paulo, Brazil
4. Clinical Research Institute (CRI); Center for Systematic Reviews in Health Policy and Systems Research (SPARK) and Department of Internal Medicine, American University of Beirut, Lebanon
5. Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada
6. Department of Pharmacy, Tanta Chest Hospital, Tanta, Egypt
7. Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
8. Department of Community Medicine, Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India
9. Isfahan Medical Education Research Centre, Isfahan University of Medical Sciences, Isfahan, Iran
10. Department of Epidemiology, Robert Stempel College of Public Health and Social Work, Florida International University, Miami, Florida
11. Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Corresponding author:

Regina El Dib
Assistant Professor
Department of Anaesthesiology
Distrito de Rubião Júnior, s/n
Univ Estadual Paulista, São Paulo, Brazil
Botucatu, SP 18618-970
+ 55 11 9 9999 6647
eldib@fmb.unesp.br

Data sharing statement: No additional data available.

Key words: electronic cigarettes; ENDS; smoking cessation; GRADE; systematic review.

Word count: 4,546

ABSTRACT

Objective: A systematic review and meta-analysis to investigate the impact of electronic nicotine delivery systems (ENDS) and/or electronic non-nicotine delivery systems (ENNDS) versus no smoking cessation aid, or alternative smoking cessation aids, in cigarette smokers on long-term tobacco use.

Data sources: Searches of MEDLINE, EMBASE, PsycInfo, CINAHL, CENTRAL and Web of Science up to December 2015.

Study selection: Randomized controlled trials (RCTs) and prospective cohort studies.

Data extraction: Three pairs of reviewers independently screened potentially eligible articles, extracted data from included studies on populations, interventions and outcomes, and assessed their risk of bias. We used the GRADE approach to rate overall certainty of the evidence by outcome.

Data synthesis: Three randomized trials including 1,007 participants and nine cohort including 13,115 participants proved eligible. Results provided by only two RCTs suggest a possible increase in tobacco smoking cessation with ENDS in comparison to ENNDS (RR 2.03, 95% CI 0.94, 4.38; p = 0.07; I^2=0%, risk difference (RD) 64/1,000 over 6 to 12 months, low certainty evidence). Results from cohort studies suggested a possible reduction in quit rates with use of ENDS compared to no use of ENDS (OR 0.74, 95% CI 0.55, 1.00; p = 0.051; I^2=56%, very low certainty).

Conclusions: There is very limited evidence regarding the impact of ENDS or ENNDS on tobacco smoking cessation, reduction or adverse effects: data from RCTs are of low certainty and observational studies of very low certainty. The limitations of the cohort studies led us to a rating of very low certainty evidence from which no credible inferences can be drawn. Lack of usefulness with regard to address the question of e- cigarettes' efficacy on smoking

reduction and cessation was largely due to poor reporting. This review underlines the need to conduct well-designed trials measuring biochemically validated outcomes and adverse effects.

Strengths and limitations of this study

- Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias, and data abstraction independently and in duplicate; assessment of risk of bias that included a sensitivity analysis addressing loss to follow-up; and use of the GRADE approach in rating the certainty of evidence for each outcome.
- The primary limitation of our review is the low certainty consequent on study limitations. Moreover, loss to follow-up was substantial, and, our sensitivity analysis demonstrated the vulnerability of borderline effects to missing data. The limitations of the cohort studies led us to a rating of very low certainty evidence from which no credible inferences can be drawn.
- The small number of studies made it impossible to address our subgroup hypotheses related dose-response of nicotine, more versus less frequent use of e-cigarettes, or the relative impact of newer versus older e-cigarette models.

INTRODUCTION

Tobacco smokers who quit their habit reduce their risk of developing and dying from tobacco-related diseases [1-4]. Both psychosocial [5-7] and pharmacological interventions (e.g., nicotine replacement therapy (NRT)) [5-7] increase the likelihood of quitting cigarettes. Even with these aids, however, most smokers fail to quit.

Electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) represent a potential third option for those seeking to stop smoking. ENDS are devices that deliver nicotine in an aerosolized form, while ENNDS devices are labeled as not containing nicotine (though labeling may not always be accurate). In theory, these devices as well as the nicotine inhalers may facilitate quitting smoking to a greater degree than other nicotine based products or no intervention because they deal, at least partly, with the behavioral and sensory aspects of smoking addiction (e.g. hand mouth movement) [8]. The debate about the role of ENDS in smoking cessation however, is compounded by the lack of clear evidence about their value as a smoking cessation tool, their potential to hook tobacco- naïve youth on nicotine, as well as act as a bridge to combustible tobacco use [11]. While evidence about all these aspects of ENDS is accumulating, establishing their real place in smoking cessation is essential to outline the public health context of considering them as a potential harm-reduced products. There are, however, other reasons for ENDS use such as for relaxation or recreation (i.e. the same reason people smoke), with the possibility that adverse health effects may be less than conventional smoking.

There are many types of ENDS. The cigalikes are the first generation of ENDS that provides an appearance of tobacco cigarettes; they are not rechargeable. The second generation of ENDS looks like a pen, allows the user to mix flavors, and may contain a prefilled or a refillable cartridge. The third generation of ENDS includes variable wattage

devices are used only with refillable tank systems. The fourth generation contains a large, refillable cartridge and has a tank-style design.

A previous Cochrane systematic review [8] summarized results from randomized controlled trials (RCTs) and cohort studies. The authors included two RCTs and 11 cohort studies, and concluded that there was evidence to support the potential benefit of ENDS in increasing tobacco smoking cessation [8]. The certainty of evidence supporting this conclusion was, however, deemed low, primarily due to the small number of trials resulting in wide confidence intervals around effect estimates [8]. Another systematic review [9] including a total of six studies (RCTs, cohort, and cross-sectional studies) involving 7,551 participants concluded that ENDS is associated with smoking cessation and reduction; however the included studies were heterogeneous, due to different study designs and gender variation. One other review [10] comparing e-cigarettes to other nicotine replacement therapies or placebo included five studies (RCTs and controlled before-after studies) and concluded that participants using nicotine e-cigarettes were more likely to stop smoking, but but noted no statistically significance differences [10]. A more recent systematic review Kalkhoran & Glantz 2016 [11] included 20 studies (15 cohort studies, 3 cross-sectional studies, and 2 clinical trials), and found 28% lower odds rates of quitting cigarettes in those who used e-cigarettes compared with those who did not use e-cigarettes; however the methodological aspects of the observational studies was rated as unclear or high on outcome assessors, and a RCT was rated as high risk of performance and attrition bias.

Previous reviews were, however, limited in that they did not include all studies in this rapidly evolving field, and all but one did not use the GRADE approach to rating quality of evidence. We therefore conducted an updated systematic review of RCTs and cohort studies that assessed the impact of ENDS and/or ENNDS versus no smoking cessation aid or

alternative smoking cessation aids on long-term tobacco use, among cigarette smokers, regardless of whether the users were using them as part of a quit attempt.

METHODS

We adhered to methods described in the Cochrane Handbook for Intervention Reviews [12]. Our reporting adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) Statements [14]. This work was commissioned by the World Health Organization.

Eligibility Criteria

- Study designs: RCTs and prospective cohort studies.
- Participants: cigarette smokers, regardless of whether the users were using them as part of a quit attempt.
- Interventions: ENDS or ENNDS.
- Comparators:
    - No smoking cessation aid;
    - Alternative non-electronic smoking cessation aid, including nicotine replacement therapy (NRT), behavioral and/or pharmacological cessation aids (e.g., bupropion and varenicline);
    - Alternative electronic smoking cessation aid (ENDS or ENNDS).
- Outcomes:
    - Tobacco smoking cessation, with preference to biochemically validated outcomes [e.g., carbon monoxide (CO)] measured at six months or longer follow-up;
    - Reduction in cigarette use of at least 50%;

- Serious (e.g., pneumonia, myocardial infarction) and non-serious (e.g., nausea, vomiting) adverse events measured at one week or longer follow-up

Data source and searches

A previous Cochrane review with similar eligibility criteria ran a comprehensive search strategy up to July 2014 [8]. Using Medical Subject Headings (MeSH) based on the terms "electronic nicotine," "smoking-cessation," "tobacco-use-disorder," "tobacco-smoking," and "quit" we replicated the search strategy of that review [8] in Medline, EMBASE, PsycInfo, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Science, and the trial registry (clinicaltrials.gov). The appendix Table 1 shows the search strategy for Ovid MEDLINE. This strategy was adapted for the other databases and run from April 1, 2014 to December 29, 2015. We did not impose any language restrictions.

In addition, we established a literature surveillance strategy based on the weekly search alerts by CDC's Smoking & Health Resource Library of published articles (http://nccd.cdc.gov/shrl/NewCitationsSearch.aspx) as well as the Gene Borio's Daily news items (www.tobacco.org). The surveillance strategy commenced from the time of running the comprehensive literature search up to the time of the submission of this manuscript.

Selection of studies

Three pairs of reviewers underwent calibration exercises and used standardized pilot tested screening forms. They worked in teams of two and independently screened all titles and abstracts identified by the literature search, obtained full-text articles of all potentially eligible studies, and evaluated them for eligibility. Reviewers resolved disagreement by discussion or, if necessary, with third party adjudication. We also considered studies reported only as conference abstracts. For each study, we cite all articles that used data from that study.

Data extraction

Reviewers underwent calibration exercises, and worked in pairs to independently extract data from included studies. They resolved disagreement by discussion or, if necessary, with third party adjudication. They abstracted the following data using a pre-tested data extraction form: study design; participants; interventions; comparators; outcome assessed; and relevant statistical data. When available, we prioritized carbon monoxide (CO) measurements as evidence of quitting. When CO measurement was unavailable, we used self-report measures of quitting.

Risk of bias assessment

Reviewers, working in pairs, independently assessed the risk of bias of included RCTs using a modified version of the Cochrane Collaboration's instrument [15] (http:/distillercer.com/resources/) [16]. That version includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the previously cited domains [16].

For cohort studies, reviewers independently assessed risk of bias with a modified version of the Ottawa-Newcastle instrument [17] that includes confidence in assessment of exposure and outcome, adjusted analysis for differences between groups in prognostic characteristics, and missing data [17]. For incomplete outcome data in individual studies (both RCTs and prospective cohort studies) we stipulated as low risk of bias for loss to follow-up of less than 10% and a difference of less than 5% in missing data between intervention/exposure and control groups.

When information regarding risk of bias or other aspects of methods or results was unavailable, we attempted to contact study authors for additional information.

Certainty of evidence

We summarized the evidence and assessed its certainty separately for bodies of evidence from RCTs and cohort studies. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate certainty of the evidence for each outcome as high, moderate, low, or very low [18]. In the GRADE approach RCTs begin as high certainty and cohort studies as low certainty. Detailed GRADE guidance was used to assess overall risk of bias [19], imprecision [20], inconsistency [21], indirectness [22] and publication bias [23], and to summarize results in an evidence profile. We planned to assess publication bias through visual inspection of funnel plots for each outcome in which we identified 10 or more eligible studies; however we were not able to because there were an insufficient number of studies to allow for this assessment. Cohort studies can be rated up for a large effect size, evidence of dose–response gradient or if all plausible confounding would reduce an apparent effect [24].

Data synthesis and statistical analysis

We analyzed all outcomes as dichotomous variables. In three-arm studies, we combined results from arms judged to be sufficiently similar (e.g. Caponnetto 2013 [25], two arms with similar ENDS regimens: 7.2 mg ENDS and, 7.2 mg ENDS plus 5.4 mg ENDS). When studies reported results for daily or intensive use of ENDS separately from non-daily or less intensive use we included only the daily/intensive use in the primary pooled analysis (e.g., Brose 2015 [26-28], we excluded patients with non-daily users; and Biener 2015 [29], we excluded patients with intermittent defined use). We conducted a sensitivity analysis in which we included all ENDS users, both daily/intensive and intermittent/less intensive use. For this analysis when necessary we assumed a correlation of 0.5 between the effects in the daily/intensive and intermittent/less intensive groups.

We synthesized the evidence separately for bodies of evidence from RCTs and cohort studies. For RCTs we calculated pooled Mantel-Haenszel risk ratios (RRs) and associated

95% CIs using random-effects models. For observational studies, we pooled adjusted odds ratios (ORs) using random effects models.

After calculating pooled relative effects, we also calculated absolute effects and 95% CI. For each outcome, we multiplied the pooled RR and its 95% CI by the median probability of that outcome. We obtained the median probability from the control groups of the available randomized trials. We planned to perform separate analyses for comparisons with interventions consisting of ENDS and/or ENNDS and each of type of control interventions with known different effects [no smoking cessation aid; alternative non-electronic smoking cessation aid including NRT; alternative electronic smoking cessation aid (ENDS or ENNDS)]. For meta-analyses we used six months data or the nearest follow-up to six months available.

For dealing with missing data, we used complete case as our primary analysis; that is, we excluded participants with missing data. If results of the primary analysis achieved or approached statistical significance, we conducted sensitivity analyses to test the robustness of those results. Specifically, we conducted a plausible worst-case sensitivity analysis in which all participants with missing data from the arm of the study with the lower quit rates were assumed to have 3 times the quit rate as those with complete data, and those with missing data from the other arm were assumed to have the same quit rate as participants with complete data [30, 31].

We assessed variability in results across studies by using the I^2 statistic and the p-value for the chi square test of heterogeneity provided by Review Manager. We used Review Manager (RevMan) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses [32].

RESULTS

Study Selection

Figure 1 presents the process of identifying eligible studies, including publications in the last systematic review [8], citations identified through search in electronic databases, and studies identified through contact with experts in the field. Based on title and abstract screening, we assessed 69 full-texts of which we included 19 publications describing three RCTs involving 1,007 participants [25, 33-39] and nine cohort studies with a total of 13,115 participants [26-29, 40-46]. The inter-observer agreement for the full-text screening was substantial (kappa 0.73).

We contacted the authors of the 12 included studies, nine of whom [26-29, 33-41, 43, 44, 46] supplied us with all requested data; authors of further three studies [25, 42, 46] did not supply the requested information (Appendix table 3).

Study Characteristics

Table 1 describes study characteristics related to design of study, setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up. Five studies [25-28, 33, 42, 46] were conducted largely in Europe, six in the US [29, 40, 41, 43-45], and one in New Zealand [34-39]. Randomized trials sample size ranged from 50 [33] to 657 [34-39], and observational studies from 100 [46] to 3,891 [26-28]. Typical participants were females in their 40s and 50s. Studies followed participants from four weeks [46] to 36 months [29].

Table 1. Study characteristics related to design of study, setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up.

Author, year	Design of study	Location	No.* participants	Mean age	Inclusion criteria	Exclusion criteria	Follow-up (months)
RCT							
Adriaens, 2014 [33]	Parallel RCT	Leuven, Belgium	T: NT:	T: 34.5 NT: 23.9	Being a smoker for at least three years; smoking a minimum of 10 factory-made cigarettes per day and not having the intention to quit smoking in the near future, but willing to try out a less unhealthy alternative	Self-reported diabetes; severe allergies; asthma or other respiratory diseases; psychiatric problems; dependence on chemicals other than nicotine, pregnancy; breast feeding; high blood pressure; cardiovascular disease; currently using any kind of smoking cessation therapy and prior use of an e-cigarette	NR
Bullen, 2013 [34-39]	Parallel RCT	New Zealand	657	16 mg ENDS: 43.6 21 mg patches NRT: 40.4 ENNDS: 43.2	Aged 18 years or older; had smoked ten or more cigarettes per day for the past year; wanted to stop smoking; and could provide consent	Pregnant and breastfeeding women; people using cessation drugs or in an existing cessation programme; those reporting heart attack, stroke, or severe angina in the previous two weeks; and those with poorly controlled medical disorders, allergies, or other chemical dependence	6

13

Caponnetto, 2013 [25]	Parallel RCT	Catania, Italy	300	7.2 mg ENDS: 45.9 7.2 mg ENDS + 5.4 mg ENDS: 43.9 ENNDS: 42.2	Smoke 10 factory made cigarettes per day (cig/day) for at least the past five years; age 18–70 years; in good general health; not currently attempting to quit smoking or wishing to do so in the next 30 days; committed to follow the trial procedures	Symptomatic cardiovascular disease; symptomatic respiratory disease; regular psychotropic medication use; current or past history of alcohol abuse; use of smokeless tobacco or nicotine replacement therapy, and pregnancy or breastfeeding	12
CCT							
Al-Delaimy, 2015 [40]	Cohort	California, US	628	Not reported	Residents of California; aged 18 to 59 years who had smoked at least 100 cigarettes during their lifetime and are current smokers	Participants who reported that they “might use e-cig” or changed their reporting at follow-up, as they did not represent a definitive group of users or never-users e-cig and might overlap with both	12
Biener, 2015 [29]	Cohort	Dallas and Indianapolis areas, US	1374	Not reported	Adults smokers residing in the Dallas and Indianapolis metropolitan areas, who had been interviewed by telephone and gave permission to be re-contacted	Anyone over 65 years old	36

no.: number; e-cig: e-cigarettes; ENDS: Electronic nicotine delivery system; ENNDS: electronic non-nicotine delivery systems; RCT: randomized controlled trial; US: United States; ENDS1 and ENDS2: the e-cig groups received the e-cig and four bottles of e-liquid at session 1 (group e-cig1 received the "Joyetech eGo-C" and group e-cig2 received the "Kanger T2-CC"); at session 2, participants' empty bottles were replenished up to again four bottles and at session 3, they were allowed to keep the remaining bottles.

*Randomized or at baseline

**For the first two months control group consisted of no e-cigarettes use. After that period, the participants of control group received the e-cig and e-liquid. ENDS1 = "Joyetech eGo-C" e-cig and ENDS2 = "Kanger T2-CC" e-cig.

***The 4117 were reported in a publication that focused on baseline characteristics, not on the use of e-cigarettes and changes in smoking behavior, so the remaining 53 participants are irrelevant to this review.

****Mean age of the overall population.

[α]The comparator comprises of current non-users of e-cig, which included never-users and those who had previously tried but were not using at the moment.

[β]Hajek 2015 was the only study that entered in the review due to meet the criteria for adverse events.

[€]But only 2,476 asnwered the question "Have you ever used e-cigarettes, electronic, or vapor cigarettes?"

Table 2 describes study characteristics related to population, intervention or exposure groups, comparator, and assessed outcomes. Of the three RCTs, one compared ENDS to both NRT and ENNDS [34-39], another to different concentrations of ENDS to ENNDS [25], and the third compared different types of ENDS [33]. Only the Borderud study [41] included participants who were also currently receiving other behavioral and other pharmacologic treatment. The participants from Vickerman 2013 [44] study were all enrolled in a state quitline programs that provided behavioral treatment and in some cases NRT. All nine cohort studies [26-29, 34-46] compared ENDS to no use of ENDS [26-29, 40, 41] or tobacco cigarettes only [42]; in one [41], both exposure and non-exposure groups received behavioral and other pharmacologic treatment.

Table 2. Study characteristics related to population, intervention or exposure groups, comparator, and assessed outcomes.

Author, year	Population	No.* of participants intend to quit smoking	No.* of participants in intervention or exposure groups and comparator	Description of intervention or exposure groups	Description of comparators	Measured outcomes	Definition of quitters or abstinence
Randomized controlled trials							
Adriaens, 2014 [33]	Participants unwilling to quit smoking (participants from the control group kept on smoking regular tobacco cigarettes during the first eight weeks of the study)	Yes 0 No 50	ENDS 1: 16 ENDS 2: 17 Control/ENDS: 17	ENDS ("Joyetech eGo-C") ENDS E-cigarettes ("Kanger T2-CC")	ENDS and e-liquid**	Quitting, defined as eCO of 5 ppm or smaller; questionnaire self-report of reduction in cigarettes of > 50% or complete quitting	No more cigarette smoking
Bullen, 2013 [34-39]	Had smoked ten or more cigarettes per day for the past year, interested in quitting	Yes 657 No 0	ENDS: 289 NRT: 295 ENNDS: 73	16 mg nicotine ENDS	21 mg patches NRT ENNDS	Continuous smoking abstinence, biochemically verified (eCO measurement <10 ppm); seven day point prevalence abstinence; reduction; and adverse events	Abstinence allowing ≤5 cigarettes in total, and proportion reporting no smoking of tobacco cigarettes, not a puff, in the past 7 days

Caponnetto, 2013 [25]	Smokers not intending to quit	Yes 0 No 300	ENDS 1: 100 ENDS 2: 100 ENNDS: 100	7.2 mg nicotine ENDS 7.2 mg nicotine ENDS + 5.4 mg nicotine ENDS	ENNDS	Self-report of reduction in cigarettes of > 50%; abstinence from smoking, defined as complete self-reported abstinence from tobacco smoking - not even a puff, biochemically verified (eCO measurement ≤7 ppm); and adverse events	Complete self-reported abstinence from tobacco smoking - not even a puff
Cohort studies							
Al-Delaimy, 2015 [40]	Current smokers; regardless of whether the users were using ENDS as part of a quit attempt	Yes 415 No 542	ENDS: 236[Ψ] No ENDS: 392[Ψ]	ENDS	No ENDS	Quit attempts; 20% reduction in monthly no. of cigarettes; and current abstinence from cigarette use	Duration of abstinence of one month or longer to be currently abstinent
Biener, 2015 [29]	All respondents had reported being cigarette smokers at baseline; regardless of whether the users were using ENDS as part of a quit attempt	Yes 364[β] No 331[€]	1374[$]	ENDS[£] intermittent use ENDS[£] intensive use	No ENDS (used once or twice ENDS)	Smoking cessation; and reduction in motivation to quit smoking among those who had not quit, not otherwise specified	Smoking cessation was defined as abstinence from cigarettes for at least one month

Brose, 2015 [26-28]	Current smokers; regardless of whether the users were using ENDS as part of a quit attempt	Not reported	ENDS: 1507 No ENDS: 2610	ENDS daily ENDS non-daily	No ENDS[€]	Quit attempts[ϕ]; cessation[ϖ]; and substantial reduction defined as a reduction by at least 50% from baseline CPD to follow-up CPD	Change from being a smoker at baseline to being an ex-smoker at follow-up was coded as cessation
Hajek, 2015 [46]	69% (n=69) accepted e-cigs as part of their smoking cessation treatment	Not reported	ENDS: 69 No ENDS: 31	ENDS was offered to all smokers in addition to the standard treatment (weekly support and stop smoking medications including NRT and varenicline)	No ENDS	Self-reported abstinence was biochemically validated by exhaled CO levels in end-expired breath using a cut-off point on 9ppm, adverse events	Self-reported abstinence from cigarettes at 4 weeks
Harrington, 2015 [45]	Hospitalized cigarette smokers. All were cigarette smokers initially; regardless of whether the users were using ENDS as part of a quit attempt	Yes: 220*** No: not reported	ENDS: 171 No ENDS: 759	ENDS	No ENDS	Quitting smoking based on 30-day point prevalence at 6 months	Only self-reported quitting smoking
Manzoli, 2015 [42]	Smokers of ≥1 tobacco cigarette/day (tobacco smokers), users of any type of e-cig, inhaling ≥50 puffs weekly (e-smokers), or smokers of both tobacco and e-cig (dual smokers)	Not reported	ENDS: 343 Tobacco and ENDS: 319 Tobacco only: 693	ENDS Tobacco and ENDS	Tobacco cigarettes only	Abstinence, proportion of quitters, biochemically verified (eCO measurement > 7ppm), reduce tobacco smoking, and serious adverse events	Percentage of subjects reporting sustained (30 days) smoking abstinence from tobacco smoking

Borderud, 2014 [41]	Patients who presented for cancer treatment and identified as current smokers (any tobacco use within the past 30 days); regardless of whether the users were using ENDS as part of a quit attempt	Yes 633[¥] No 42[¥]	ENDS: 285 No ENDS: 789	ENDS[£] + Evidence-based behavioral and pharmacologic treatment	No ENDS+Evidence-based behavioral and pharmacologic treatment	Smoking cessation by self-report	Patients were asked if they had smoked even a puff of a (traditional) cigarette within the last 7 days
Prochaska, 2014 [43]	Adult daily smokers with serious mental illness; regardless of whether the users were using ENDS as part of a quit attempt	At baseline, 24% intended to quit smoking in the next month	ENDS: 101 No ENDS: 855	ENDS	No ENDS	Smoking cessation by self-report and, biochemically verified (CO and cotinine)	Past 7 day tobacco abstinence
Vickerman, 2013 [44]	Adult tobacco current or past users; regardless of whether the users were using ENDS as part of a quit attempt	Not reported	ENDS: 765 No ENDS: 1,711	ENDS used for 1 month or more ENDS used for less than 1 month	No ENDS (never tried)	Tobacco abstinence	Self-reported 30-day tobacco abstinence at 7 month follow-up

no.: number; C: comparator group; CPD: cigarettes smoked per day; e-cig: e-cigarettes; ENDS: Electronic nicotine delivery system; ENNDS: electronic non-nicotine delivery systems; eCO: exhaled breath carbon monoxide; NE: non-exposure group; NRT: Nicotine replacement therapy.

*Numbers randomized or at baseline.

**For the first two months control group consisted of no e-cigarettes use. After that period, the participants of control group received the e-cig and e-liquid. ENDS1 = “Joyetech eGo-C” e-cig and ENDS2 = “Kanger T2-CC” e-cig.

***Only among those who reported any previous use of e-cigs.

[α]Information retrieved through contact with author.

[€]The comparator comprises of current non-users of e-cig, which included never-users and those who had previously tried but were not using at the moment.

[Ψ]Participants who will never use e-cig plus those who never heard of e-cig = 392; participants who have used e-cig = 236 (numbers taken from the California Smokers Cohort, a longitudinal survey).

[β]Intentions to quit smoking, those who tried e-cigarettes only once or twice are grouped with never users ("non-users/triers").

[€]Intermittent use (i.e., used regularly, but not daily for more than 1 month) plus intensive use (i.e., used e-cig daily for at least 1 month).

[$]No. of the whole sample including comparator.

[£]All ENDS.

[¥]The other participants either quit more than a month ago but less than six months, less than a month ago, or more than six months ago.

[ϕ]Smokers and recent ex-smokers were asked about the number of attempts to stop they had made in the previous year. Those reporting at least one attempt and 37 respondents who did not report an attempt but had stopped smoking be- tween baseline and follow-up were coded as having made an attempt.

[ϖ]Change from being a smoker at baseline to being an ex-smoker at follow-up was coded as cessation.

Table 3 describes the mean number of conventional cigarettes used per day at both baseline and the end of study. The mean number at baseline ranged from 11.9 in the no ENDS group [45] to 20.6 in the ENDS group [33]. In only two studies [26-28, 45] the mean number of conventional cigarettes used per day presented a reduction from the baseline to the end of study in the ENDS group compared to the no ENDS groups, mainly in the daily users [26-28]. No included study addressed users of combustible tobacco products other than cigarettes.

Table 3. Mean number of conventional cigarettes used per day at both baseline and the end of study*.

Author, year	Groups	Mean no. of conventional cigarettes used per day at baseline	Mean no. of conventional cigarettes used per day at the end of study	Biochemically quitters (no. of events per no. of total participants)	Self-reported quitters (no. of events per no. of total participants)
Adriaens, 2014 [33]	ENDS1	20.1	7.0[£]	3/13	4/13
	ENDS2	20.6	8.1[£]	3/12	3/12
	Control/ENDS[αφ]	16.7	7.7[£]	4/13	4/13
Bullen, 2013 [34-39]	ENDS	18.4	0.7[ϖ]	21/241	Not available
	ENNDS	17.7	0.7	3/57	Not available
	NRT	17.6	0.8[ϖ]	17/215	Not available
Caponnetto, 2013 [25]	7.2 mg ENDS	19.0 (14.0-25.0)[Ψ]	12 (5.8-20)[Ψ¢]	Combined ENDS groups: 22/128	Not available
	7.2 mg ENDS plus 5.4 mg ENDS	21.0 (15.0-26.0)[Ψ]	14 (6-20)[Ψ¢]		Not available
	ENNDS	22.0 (15.0-27.0)[Ψ]	12 (9-20)[Ψ¢]	4/55	Not available
Al-Delaimy, 2015 [40]	ENDS	14.1[Ω]	13.8[δ]	Not available	12/179
	ENNDS			Not available	32/145
Biener, 2015 [29]	ENDS intermittent use	16.7[ę]	Not available	Not available	Combined ENDS groups: 42/331
	ENDS intensive use	17.1[ę]	Not available	Not available	
	No ENDS	15.4[ę]	Not available	Not available	82/364

Table 3. (Continued)

Author, year	Group	Mean no. of conventional cigarettes used per day at baseline	Mean no. of conventional cigarettes used per day at the end of study	Biochemically quitters (no. of events per no. of total participants)	Self-reported quitters (no. of events per no. of total participants)
Brose, 2015 [26-28]	ENDS daily users	14.3	13.0 [θ]	Not available	7/86
	ENDS non-daily users	13.5	13.9 [θ]	Not available	25/263
	No ENDS[ς]	13.3	13.5	Not available	168/1307
Hajek, 2015 [46]	ENDS	Not available	Not available	Not applicable**	Not applicable**
	No ENDS	Not available	Not available	Not applicable**	Not applicable**
Harrington, 2015 [45]	ENDS	14.1[$]	10.3[$]	Not available	21/171
	No ENDS	11.9[$]	9.8[$]	Not available	62/464
Manzoli, 2015 [42]	ENDS only	Not available	12	Not available	Not available
	Tobacco cigarettes only	14.1	12.8	101/491	Not available
	Dual smoking	14.9	9.3	51/232	Not available
Borderud, 2014 [41]	ENDS	13.7	12.3	Not available	25/58
	No ENDS	12.4	10.1	Not available	158/356
Prochaska, 2014 [43]	ENDS	17.0	10.0	21/101	Not available
	No ENDS	17.0	10.1	162/855	Not available
Vickerman, 2013 [44]	ENDS used for 1 month or more	19.4	13.5	Not available	59/273
	ENDS used for less than 1 month	18.9	14.0	Not available	73/439
	No ENDS (never tried)	18.1	12.9	Not available	535/1711

No.: number; e-cig: eletronic cigarettes; ENDS: Electronic nicotine delivery system; ENNDS: electronic non-nicotine delivery systems; ENDS1 and ENDS 2: the e-cig groups received the e-cig and four bottles of e-liquid at session 1 (group e-cig1 received the “Joyetech eGo-C” and group e-cig2 received the “Kanger T2-CC”); at session 2; RYO: roll your own (loose tobacco) cigarettes.

*When authors provided data for different time points, we presented the data for the longest follow-up.

**Not applicable because they followed participants only for 4 weeks, but the study reported adverse events at one week or longer.

[φ]For the first two months control group consisted of no e-cigarettes use. After that period, the participants of control group received the e-cig and e-liquid. ENDS1 = “Joyetech eGo-C” e-cig and ENDS2 = “Kanger T2-CC” e-cig.

[α]Control group consisted of received the e-cig and e-liquid (six bottles) for two months at the end of session 3 (eight of the 16 participants of the control group received the “Joyetech eGo-C” and the remaining eight participants received the “Kanger T2-CC”).

[£]8 months from start of intervention.

[Ψ]Data shown as median and interquartile.

[ɸ]At six months after the last lab session.

[θ]No. of cigarette per week divided by 7 days.

[Ω]Of the 1,000 subjects, 993 responded to the question “How many conventional cigarettes smoked per day during the past 30 days".

[δ]Of the 1,000 subjects, 881 responded to the question “How many cigarettes smoked per day during the past 30 days".

[ϖ]For those reporting smoking at least one cigarette in past 7 days.

[¢]Number of conventional cigarettes used in the prior month at baseline.

[ς]The comparator comprises of current non-users of e-cig which included never-users and those who had previously tried but were not using at the moment.

[$]Data for baseline current e-cig users.

Appendix table 3 presents the types of e-cigarettes used in the included studies. The three RCTs [25, 33-39] evaluated only ENDS type cigalikes. 23.7% of the participants from Brose 2015 [26-28] study used tank and in the Hajek 2015 [46] study participants used either cigalike or tank. The remaining studies did not report the type of ENDS used.

Risk of Bias

Figures 2 and 3, and table 4, describe the risk of bias assessment for the RCTs. The major issue regarding risk of bias in the RCTs of ENDS versus ENNDS was the extent of missing outcome data [25, 34-39]. RCTs comparing ENDS to other nicotine replacement therapies had additional problems of concealment of randomization [33] and blinding [33-39].

Table 4. Risk of bias assessment for the randomized controlled trials

Author, year	Was the randomization sequence adequately generated?	Was allocation adequately concealed?	Was there blinding of participants?	Was there blinding of caregivers?	Was there blinding of data collectors?	Was there blinding of statistician?	Was there blinding of outcome assessors?	Was loss to follow-up (missing outcome data) infrequent?*	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?
Randomized controlled trials assessing ENDS *versus* ENNDS										
Bullen, 2013 [34-39]	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely no	Definitely yes	Definitely yes
Caponnetto, 2013 [25]	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely no	Definitely yes	Definitely yes
Randomized controlled trials assessing ENDS *versus* other quitting mechanisms										
Adriaens, 2014 [33]	Definitely yes	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no	Definitely no	Probably yes	Probably yes
Bullen, 2013 [34-39]	Definitely yes	Definitely yes	Definitely no	Definitely no	Probably yes	Probably yes	Definitely yes	Definitely no	Definitely yes	Definitely yes

*Defined as less than 10% loss to outcome data or difference between groups less than 5% and those excluded are not likely to have made a material difference in the effect observed.

ENDS: electronic nicotine delivery systems. ENNDS: electronic non-nicotine delivery systems.

All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).

Figure 4 and table 5 describe the risk of bias assessment of the cohort studies. Seven [26-29, 40-42, 44, 45] of nine cohort studies were rated as high risk of bias for limitations in matching exposed and unexposed groups or adjusting analysis for prognosis variables; confidence in the assessment of the presence or absence of prognostic factors; confidence in the assessment of outcome; and similarity of co-interventions between groups; all studies suffered from high risk of bias for missing outcome data.

Table 5. Risk of bias assessment of the cohort studies.

Author, year	Was selection of exposed and non-exposed cohorts drawn from the same population?*	Can we be confident in the assessment of exposure?**	Can we be confident that the outcome of interest was not present at start of study? ***	Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? ****	Can we be confident in the assessment of the presence or absence of prognostic factors?*****	Can we be confident in the assessment of outcome? ******	Was the follow up of cohorts adequate? *******	Were co-interventions similar between groups? ********
Al-Delaimy 2015 [40]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Biener 2015 [29]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Brose 2015 [26-28]	Definitely yes	Probably yes	Probably no	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Hajek 2015 [46]	Probably yes	Probably yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably no
Harrington 2015 [45]	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no
Manzoli 2015 [42]	Definitely yes	Probably yes	Definitely no	Definitely no	Definitely no	Probably no	Definitely no	Probably no
Borderud 2014 [41]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely yes
Prochaska 2014 [43]	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely no	Definitely yes	Probably No
Vickerman 2013 [44]	Probably yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no

* Examples of low risk of bias: Exposed and unexposed drawn from same administrative data base of patients presenting at same points of care over the same time frame.

** This means that investigators accurately assess the use of ENDS at baseline.

*** This means that smoking cessation was not present at the start of the study.

**** Examples of low risk of bias: comprehensive matching or adjustment for all plausible prognostic variables.

***** Examples of low risk of bias: Interview of all participants; self-completed survey from all participants; review of charts with reproducibility demonstrated; from data base with documentation of accuracy of abstraction of prognostic data.

****** Outcome self-reported was considered as definitely no for adequate assessment. Smoking abstinence, biochemically verified was considered as definitely yes for adequate assessment.

*******Defined as less than 10% loss to outcome data or subjects lost to follow-up unlikely to introduce bias.

******** Examples of low risk of bias: Most or all relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.

All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).

Outcomes

The mean number of conventional cigarettes/tobacco products used per day at the end of the studies ranged from 0.7 [34-39] in both ENDS and ENNDS groups to 13.9 [26-28] among non-daily users of ENDS (Table 3). The three RCTs [25, 33-39] and one cohort study [42] biochemically confirmed nicotine abstinence while the others presented only self-reported data [26-29, 40, 41, 43-45] (Table 3).

Tobacco cessation smoking

Synthesized results from randomized controlled trials

Results from two RCTs [25, 34-39] suggest a possible increase in smoking cessation with ENDS in comparison to ENNDS (RR 2.03, 95% CI 0.94, 4.38; p = 0.07; I^2=0%, risk difference (RD) 64/1,000 over 6 to 12 months, low quality evidence) (Figure 5, Table 6). A plausible worse case sensitivity analysis yielded results that were inconsistent with the primary complete case analysis and fail to show a difference in the effects of ENDS in comparison to ENNDS (RR 1.16, 95% CI 0.72, 1.87; p = 0.54; I^2=0%) (Appendix Figure 1). Certainty in evidence was rated down to low because of imprecision and risk of bias, due to missing outcome data in all studies and lack of blinding of participants [34-39], caregivers, data collectors, statistician and outcome assessors in the ENDS versus other nicotine replacement therapy studies (Figure 2, Tables 4 and 6).

Adriaens 2014 [33] also compared two types of ENDS and ENDS and e-liquid; results failed to show a difference between the ENDS groups with a very wide confidence interval (RR 1.15, 95% CI 0.28, 4.76, p = 0.84).

Table 6. *GRADE evidence profile for RCTs:* Electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) for reducing cigarette smoking.

Quality assessment						Summary of findings					Certainty in estimates
						Study event rates		Relative risk	Anticipated absolute effects over 6-12 months		OR
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	ENNDS*	ENDS	(95% CI)	ENNDS*	ENDS	Quality of evidence
Cessation/nicotine abstinence (Includes self-reported and biochemically validated by eCO)											
481 (2) 6-12 mo	Serious limitations[1]	No serious limitations	No serious limitations	Serious imprecision[2]	Undetected	7/ 112	43/ 369	**2.03** (0.94-4.38)	213 per 1000	219 more per 1000 (13 fewer to 720 more)	⊕⊕OO LOW
Self-report of reduction in cigarettes of > 50%											
481 (2)	Serious limitations[1]	Serious limitations	No serious limitations	Serious imprecision[2]	Undetected	45/ 112	184/ 369	**0.97** (0.57-1.66)	213 per 1000	7 fewer per 1000 (92 fewer to 140 more)	⊕⊕OO LOW

6-12 mo				

*The estimated risk control was taken from the median estimated control risks of the cohort studies.

[1]Two studies presented high risk of bias for missing outcome data. [3]Moreover, one was not blinded to participants and caregiver [29, 37-41] and, other [26-28] also was not blinded to data collectors, statistician and outcome assessors. While not specifically rating down for risk of bias, these additional concerns plus borderline clinically important imprecision led to downgrading of certainty in estimates for all outcomes.

[2]95% CI for absolute effects include clinically important benefit and no benefit.

Bullen 2013 [34-39] also compared ENDS and ENNDS with NRT; results failed to show a difference between these groups with a very wide confidence interval (RR 1.10, 95% CI 0.60, 2.03, p = 0.76) and (RR 0.67, 95% CI 0.20, 2.19, p = 0.50), respectively.

Synthesized results from cohort studies

The adjusted OR from primary meta-analysis of eight cohort studies [26-29, 40-45] comparing ENDS to no ENDS without reported concomitant interventions failed to show a benefit in cessation smoking (OR 0.74, 95% CI 0.55, 1.00; p = 0.051; I^2=56%) (Figure 6). A sensitivity analysis from the eight cohort studies [26-29, 40-45] using any rather than daily use of ENDS for Brose study [26-28], both intensive (used e-cigarettes daily for at least 1 month), and intermittent use (used regularly, but not daily for more than 1 month) of ENDS for Biener study [29] and, any use versus never used for Vickerman study [44] suggested a reduction in cessation smoking rates with ENDS (adjusted OR 0.69, 95% CI 0.53, 0.91; p = 0.01; I^2=59%) (Appendix Figure 2).

Another sensitivity analysis from the same eight cohort studies [26-29, 40-45], examined whether low and high risk of bias limited to the one characteristic in which the studies differed substantially: confidence in whether the outcome was present at the beginning of the study. Although there were substantial differences in the point estimates in the low risk of bias group (adjusted OR 1.00, 95% CI 0.51, 1.94; p = 1.00; I2=67%) and the high risk of bias (adjusted OR 0.62, 95% CI 0.50, 0.77; p < 0.001; I2=0%), the difference is easily explained by chance (interaction p-value was 0.19) (Appendix Figure 3).

A second sensitivity analysis from the same eight cohort studies [26-29, 40-45], examined whether low and high risk of bias limited to "two or fewer domains rated as low risk of bias" versus "three or more domains rated as low risk of bias" differed substantially. There were substantial differences in the point estimates between the "two or fewer domains rated as low risk of bias" group (adjusted OR 0.61, 95% CI 0.49, 0.75; p < 0.001 ; I2=0%)

and the "three or more domains rated as low risk of bias" (adjusted OR 1.26, 95% CI 0.68, 2.33; p=0.46; I2=51%), with an interaction p-value of 0.03 (Appendix Figure 4).

Certainty in evidence from the observational studies was rated down from low to very low because risk of bias due to missing outcome data, imprecision in the assessment of prognostic factors and outcomes (Figure 4, Tables 5 and 7), as well as inconsistency in the results.

Table 7. *GRADE evidence profile for cohort studies:* Electronic nicotine delivery systems (ENDS) and no ENDS for reducing cigarette smoking.

Quality assessment						Summary of findings					Certainty in estimates
						Study event rates		Relative risk	Anticipated absolute effects over 6-12 months		OR
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	ENNDS*	ENDS	(95% CI)	ENNDS*	ENDS	Quality of evidence
Cessation/nicotine abstinence (Includes self-reported and biochemically validated by eCO)											
7,826 (8) 6-36 mo	Serious limitations[1]	No serious limitations	No serious limitations	Serious imprecision[2]	Undetected	1300/ 5693	336/ 2133	**0.74** (0.55-1.00)	213 per 1000	56 fewer per 1000 (96 fewer to 0 more)	⊕OOO VERY LOW

*The estimated risk control was taken from the median estimated control risks of the cohort studies.

[1]All studies were rated as high risk of bias for adjustment for prognosis variable; assessment of prognostic factors; assessment of outcomes; adequate follow-up of cohort; and similarity of co-interventions between groups.

[2]95% CI for absolute effects include clinically important benefit and no benefit.

Borderud 2014 [41] reported cessation smoking in 25 out of 58 cancer patients using ENDS plus behavioral and pharmacologic treatment versus in 158 out of 356 cancer patients who received only behavioral and pharmacologic treatment (adjusted OR 0.97, 95% CI 0.71 to 1.33).

Reduction in cigarette use of at least 50%

Synthesized results from randomized controlled trials

Two RCTs [25, 34-39] results failed to show a difference between ENDS type cigalikes versus ENNDS group with regards to reduction in cigarettes but with a very wide confidence interval (RR 0.97, 95% CI 0.57, 1.66; p = 0.92; I^2=61%) (Appendix Figure 5). Certainty in evidence was rated low because of imprecision and risk of bias [25, 34-39] (Figure 2, Tables 4 and 6).

Synthesized results from cohort studies

Two studies [26-29] suggested increased reduction rates in those with greater versus lesser use of ENDS. Biener [29] reported an adjusted OR for quitting of 6.07 (95% CI 1.11, 33.2) in those with intensive use versus an OR of 0.31 (0.04, 2.80) in those with intermittent use. Brose [26-28] reported a greater likelihood of substantial reduction (but not quitting) in those with daily use of ENDS (OR 2.49, 95% CI 1.14, 5.45) but not those with intermittent use (OR 0.85 0.43 to 1.71).

Adverse effects

Synthesized results from randomized controlled trials

Bullen 2013 [34-39] study reported serious side effects in 27 out of 241 participants in the 16 mg ENDS group and 5 out of 57 for the ENNDS group followed at 6 months; results failed to show a difference between these groups with a very wide confidence interval (OR 1.31, 95% CI 0.48, 3.57; p = 0.59). Results suggested possible increase in side effects in the 21 mg nicotine patches group (14 of 215) in comparison to ENDS (OR 1.81, 95% CI 0.92, 3.55; p = 0.08). Serious side effects includes death (n = 1, in nicotine e-cigarettes group), life

threatening illness (n = 1, in nicotine e-cigarettes group), admission to hospital or prolongation of hospital stay (12% of all events in nicotine e-cigarettes group, 8% in patches group, and 11% in placebo e-cigarettes group), persistent or significant disability or incapacity, and other medically important events (6% of all events in nicotine e-cigarettes group, 4% in patches group, and 3% placebo e-cigarettes group).

Adriaens 2014 [33] study reported no serious adverse events in both ENDS groups as well as in the e-liquid group at eight months of follow-up; however at one week from start of intervention there were three cases of non-serious adverse events in the ENDS groups.

Caponnetto 2013 [25] mentioned that no serious adverse events occurred during the study and; authors found a significant reduction in frequency of reported symptoms compared to baseline.

Synthesized results from cohort studies

Manzoli [42] reported no significant differences in self-reported serious side effects, but observed four cases of pneumonia, four COPD exacerbations, three myocardial infarctions, and one angina as possibly-related serious side effects: two among the ENDS users (both switched to tobacco smoking during follow-up); six among tobacco smokers (three quit all smoking); four among tobacco and ENDS smokers.

Hajek 2015 [46] reported one leak irritating a participant's mouth and some reports of irritation at the back of the throat and minor coughing. The remaining studies did not report adverse effects.

DISCUSSION

Main findings

Based on pooled data from two randomized trials with 481 participants, we found evidence for a possible increase in tobacco smoking cessation with ENDS in comparison to ENNDS (Figure 5). The evidence is, however, of low certainty: the 95% confidence interval

of the relative risk crossed 1.0 and a plausible worse case sensitivity analyses to assess the risks of bias associated with missing participant data yielded results that were inconsistent with the primary complete case analysis (Appendix Figure 1). Furthermore, in all these RCTs, the ENDS tested were earlier generation; it is unknown whether providing later generation of e-cigarettes or a realistic scenario of allowing users to choose e-cigarettes based on self-preference would have greater benefit. There was no robust evidence of side effects associated with ENDS in the RCTs.

Cohort studies provide very low certainty evidence suggesting a possible reduction in quit rates with use of ENDS compared to no use of ENDS (Figure 6). These studies had a number of limitations: an unknown number of these participants were not using ENDS as a cessation device; some were not using ENDS during a quit attempt; many did not have immediate plans to quit smoking; and some may have already failed attempts to stop smoking. In our risk of bias assessment, we judged that 7 of 9 studies did not have optimal adjustment for prognostic variables. Further, as any cohort study, the results are vulnerable to residual confounding. In particular, use of ENDS may reflect the degree of commitment to smoking cessation, and it may be the degree of commitment, rather than use of ENDS, that is responsible for the change in quit rates. For instance, the finding in two studies that daily use of ENDS, but not intermittent use, increased quit/reduction rates could be interpreted as evidence of the effectiveness of daily use. An alternative interpretation, however, is that those that used ENDS daily were more motivated to stop smoking, and the increased motivation, rather than daily use of ENDS, was responsible for their degree of success. It is worth to mention that motivation to quit smoking is a major determinant of success regardless of the aid used.

In terms of bias against ENDS, cohort studies sometimes enroll smokers already using ENDS and still smoking. Such individuals may already be failing in their attempts to stop

smoking. If so, enrolling these participants will underestimate ENDS beneficial effects. Additional concerns with cohort studies include their failure to provide optimal adjustment for prognostic variables or provide data regarding use of alternative smoking reduction aids.

Strengths and limitations

Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias, and data abstraction independently and in duplicate; assessment of risk of bias that included a sensitivity analysis addressing loss to follow-up; and use of the GRADE approach in rating the certainty of evidence for each outcome.

The primary limitation of our review is the low certainty consequent on study limitations. We identified only a small number of RCTs with a modest number of participants resulting wide confidence intervals. Moreover, loss to follow-up was substantial, and, our sensitivity analysis demonstrated the vulnerability of borderline effects to missing data. The limitations of the cohort studies led us to a rating of very low certainty evidence from which no credible inferences can be drawn.

Another limitation of this review is the fact that we could not address our hypothesis about increase rates in smoking cessation in those who used e-cigarettes with higher concentrations of nicotine compared to those using less nicotine, or daily e-cigarette users compared to nondaily e-cigarette users, or those who use newer forms of ENDS compared to users of first generation devices due to lack of evidence. However, although these assumptions seems logical, nicotine delivery from ENDS depends on other factors such as the efficiency of the device in aerosolising the liquid and user experience, apart from the concentration of nicotine in the ENDS liquid.

Furthermore, whether or not ENDS are an effective aid in the cessation smoking may depend on whether the users were using ENDS as part of a quit attempt or not and, this may play an important role also as a possible confounder. Data is not yet available to conduct a

subgroup analysis addressing this hypothesis. Subsequent trials should help provide information regarding whether their impact on cessation of smoking depends on whether users were intended to quit smoking, as well as the other unresolved issues.

Other limitations of this review were the fact of having insufficient number of included studies to allow the complete statistical analysis that we had planned. We were not able to assess publication bias because there were less than 10 eligible studies addressing the same outcome in a meta-analysis. We also planned to perform subgroup analyses according to the characteristics of:

- Participants (commitment to stopping smoking, use of e-cigarettes at baseline).
- Interventions (dose of nicotine delivered by the e-cigarette, frequency of use of the e-cigarette, type of e-cigarettes and type of e-cigarettes).
- Concomitant interventions in both e-cigarettes and control groups.

However, we also were not able to conduct these analyses because they did not meet our minimal criteria, which were at least five studies available, with at least two in each sub-group. A final statistical limitation is that we calculated differences from 6 to 12 months of follow-up. Absolute differences may differ across this time frame and constitute a source of variability. Moreover, there are three schools of thought with respect to use of fixed and random effect models: those who prefer always to use fixed effects, those who prefer (almost) always random effects, and those who would choose fixed and random depending on the degree of heterogeneity. Each argument has its proponents within the statistical community. The argument in favor of the second rather than the third is a) there is always some heterogeneity, so any threshold of switching models is arbitrary and b) when there is little heterogeneity, fixed and random yield similar or identical results, so one might as well commit oneself to random from the start. We find these two arguments compelling; thus, our choice.

Finally, another limitation of the observational studies in this review is the potential for selection bias as the populations compared differ in terms of intention to quit. Furthermore, in all these RCTs, the ENDS tested were earlier generation; it is possible that later generation of e-cigarettes would have greater benefit.

Although this review presents several limitations, the issue is whether one should dismiss these results entirely, or consider them bearing in mind the limitations. The latter represent our view of the matter.

Relation to prior work

The previous Cochrane review [8] concluded that due to low event rates and wide confidence intervals only low certainty evidence was available from studies comparing ENDS to ENND. We excluded some studies included in that Cochrane review as they were either case series, cross-sectional or did not include one arm with ENDS/ENNDS compared to alternative strategies. We also included one additional RCT [33], and nine new cohort studies [26-29, 40-46], not included in the Cochrane review. The rationale for including the prospective cohort studies in our review was that it was anticipated that the search would return few RCTs. The authors of the Cochrane review found that ENDS is a useful aid to stop smoking long-term compared with ENNDS.

Another review [9] including two of our three RCTs [25, 34-39], and further two case series, and two cross-sectional studies, assessed the impact of e-cigarettes in achieving smoking abstinence or reduction in cigarette consumption among current smokers who had used the devices for six months or more. The authors concluded that e-cigarette use is associated with smoking cessation; these results are similar to our meta-analysis comparing ENDS versus ENNDS (Figure 5). Khoudigian's 2016 review [10] reported a non-statistically significant trend toward smoking cessation in adults using nicotine e-cigarettes compared

with other therapies or placebo. However, the review by Kalkhoran & Glatz 2016 [11] concluded that e-cigarettes are associated with significantly less quitting among smokers.

Implications

Existing smoking reduction aids such as nicotine replacement therapy are effective, but their impact is limited: the proportion of those who quit when using these aids remains small. The available evidence, of low or very low quality, can neither verify nor exclude the hypothesis that, because they address not only nicotine addiction but also potentially deal with behavioural and sensory aspects of cigarette use, ENDS may be more effective than other nicotine replacement strategies. This is an important finding, and raises questions regarding the how effective it may be addressing the behavioural and sensory aspects of cigarette use in their addictive potential. Thus, the focus of subsequent work should perhaps be on the dose and delivery of nicotine, though teasing out the nicotine effects from sensory aspects is likely to be challenging. It is possible that type of ENDS or dose of exposure may influence quit rates, and that newer models may be more effective, but there is insufficient data to provide insight into these issues. Lack of usefulness with regard to address the question of e- cigarettes' efficacy on smoking reduction and cessation was largely due to poor reporting.

Therefore, due to the limitations of the studies included in this analysis it is impossible to make strong inferences regarding whether e-cigarette use promotes, has no effect or hinders smoking cessation.This review underlines the need to conduct well-designed trials in this field measuring biochemically validated outcomes and adverse effects.

AUTHORS' CONTRIBUTIONS

Conceiving the review: Gordon Henry Guyatt (GHG), Regina El Dib (RED), Wasim Maziak (WM), and Elie A. Akl (EAA)

Undertaking searches: Diane Heels-Ansdell (DHA)

Screening search results: RED, Erica Aranha Suzumura (EAS), Huda Goma (HG), Arnav Agarwal (AA), Yaping Chang (YC), Manya Prasad (MP), Vahid Ashoorion (VA)

Organizing retrieval of papers: EAS

Screening retrieved papers against inclusion criteria: RED, EAS, HG, AA, YC, MP and VA

Appraising quality of papers: RED, EAS, HG, AA, YC, MP and VA

Extracting data from papers: RED, EAS, HG, AA, YC, MP and VA

Writing to authors of papers for additional information: RED

Providing additional data about papers: RED

Obtaining and screening data on unpublished studies: RED and EAS

Managing data for the review: RED

Entering data into Review Manager (RevMan): RED and EAS

Analyzing RevMan statistical data: RED, EAS, GHG, WM and EAA

Interpreting data: RED, EAS, GHG, WM and EAA

Making statistical inferences: RED, EAS, GHG, WM and EAA

Writing the review: RED, GHG, WM and EAA

Taking responsibility for reading and checking the review before submission: RED, EAS, HG, AA, YC, MP, VA, EAA, WM and GHG

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AUTHORS' CONTRIBUTIONS

All authors contributed to all aspects of this study, including conducting the literature search, study design, data collection, data analysis, data interpretation, and writing of the paper.

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FIGURE LEGENDS

Figure 1. PRISMA diagram of included studies.

Figure 2. Risk of bias for RCTs comparing ENDS versus ENNDS.

Figure 3. Risk of bias for RCTs comparing ENDS versus other strategies.

Figure 4. Risk of bias for cohort studies.

Figure 5. Meta-analysis of RCTs on cessation smoking comparing ENDS versus ENND.

Figure 6. Meta-analysis of cohort studies on cessation smoking with adjusted ORs.

Appendix Figure 1. Sensitivity analysis of RCTs on cessation smoking comparing ENDS versus ENNDS.

Appendix Figure 2. Meta-analysis of cohort studies on cessation smoking with adjusted ORs using a sensitivity analyses with an assumed correlation=0.5.

Appendix Figure 3. Sensitivity analysis of cohort studies on cessation smoking comparing e-cigarettes versus no e-cigarettes.

Appendix Figure 4. Sensitivity analysis of cohort studies on cessation smoking comparing e-cigarettes versus no e-cigarettes.

Appendix Figure 5. Meta-analysis of RCTs on reduction.

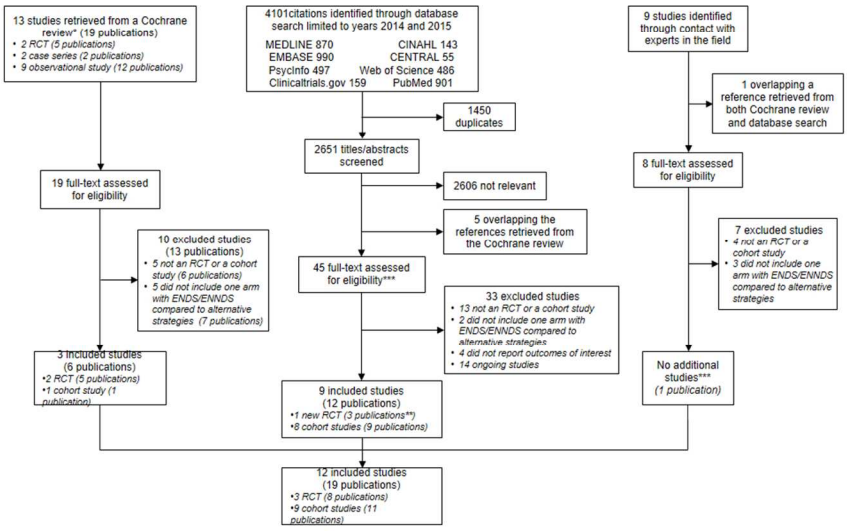
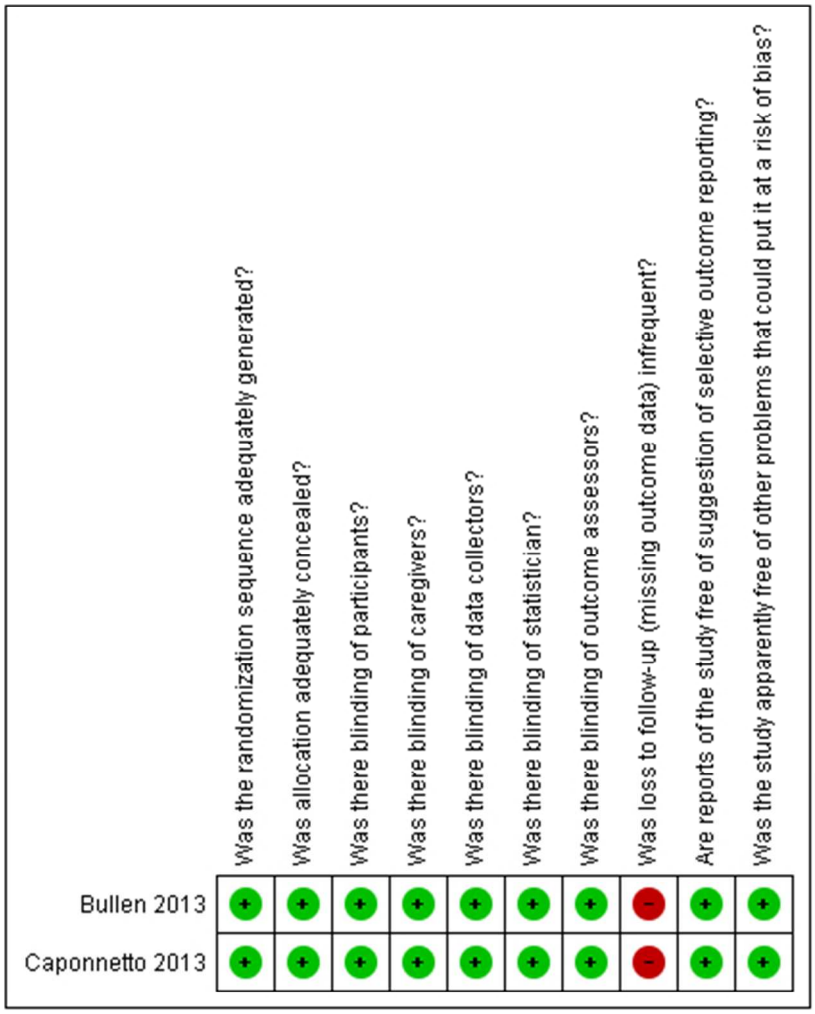


Figure 1. PRISMA diagram of included studies.

*McRobbie, 2014[8]
**Further two publications from one RCT included by the Cochrane review were identified only in our search strategy
***Further one publication from one cohort study identified by our search strategy was identified throughout the expert search

95x69mm (300 x 300 DPI)



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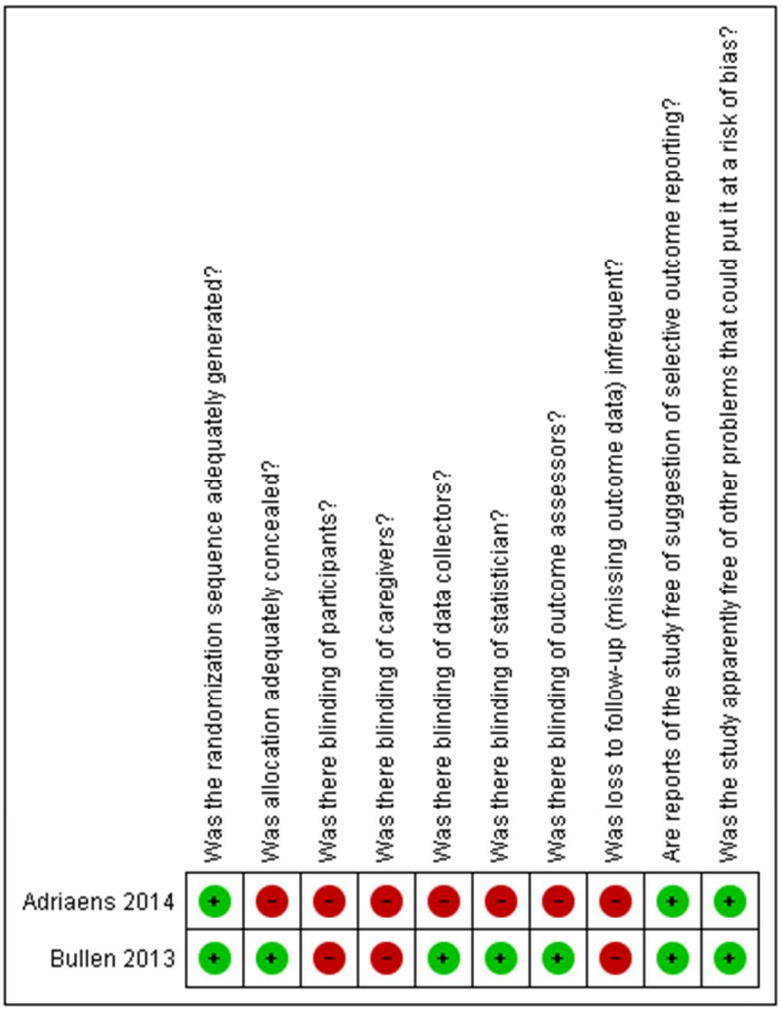


40x53mm (300 x 300 DPI)

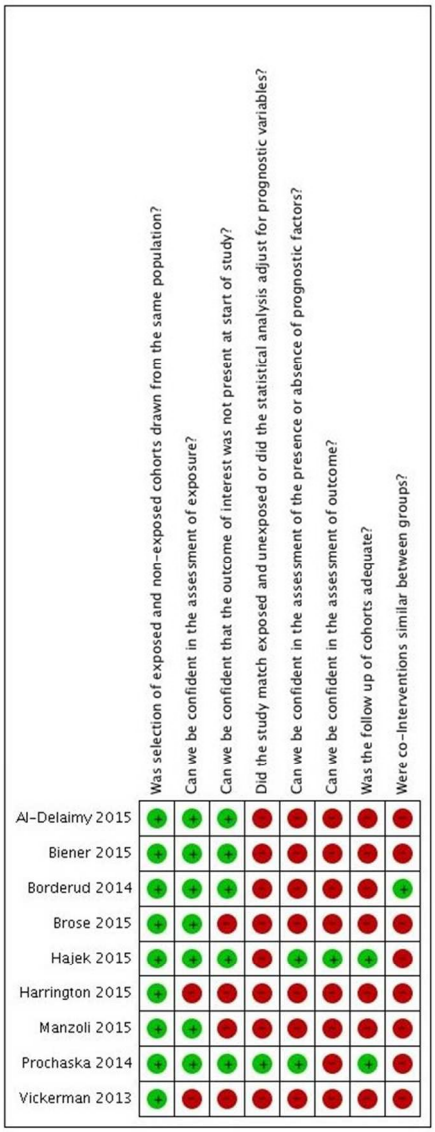
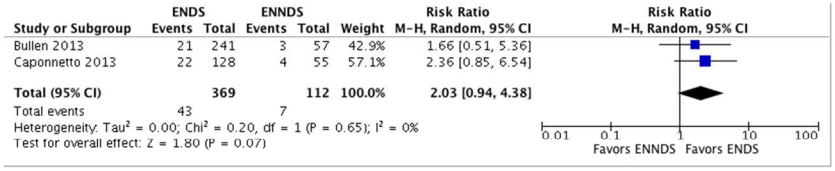
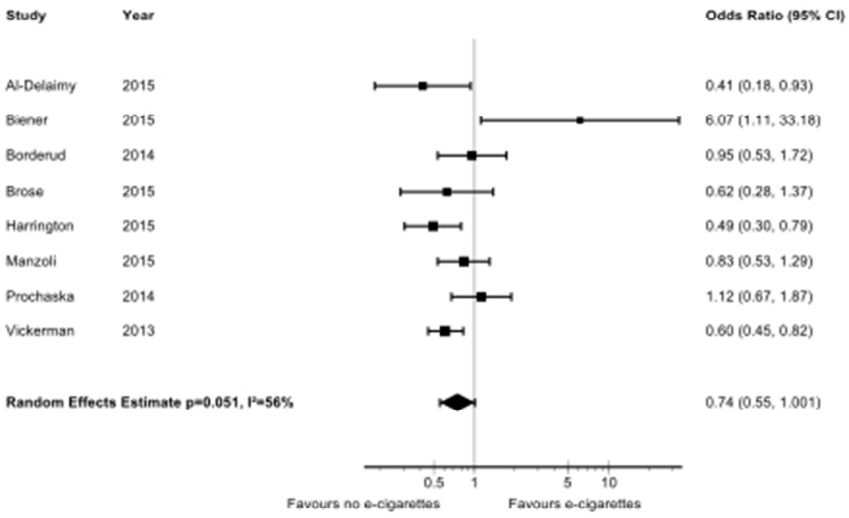


Figure 4. Risk of bias cohort studies

112x271mm (96 x 96 DPI)



83x25mm (300 x 300 DPI)



43x30mm (300 x 300 DPI)

Appendix Table 1. Search strategy

1	Electronic Cigarettes/
2	e-cig*.mp.
3	(electr* adj2 cig*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4	(electronic adj2 nicotine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5	(nicotine adj2 delivery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6	(ENDS adj3 nicotine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7	(vape or vaping).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8	or/1-7
9	"tobacco use"/ or smoking/
10	"tobacco use cessation"/ or smoking cessation/
11	Tobacco/
12	Nicotine/
13	(smok$ or cigar$ or tobacco$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14	((quit$ or stop$ or ceas$ or giv$ or prevent$) adj smok$).mp.
15	or/9-14
16	(electronic or electric or vapor or vapour).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17	15 and 16
18	8 or 17
19	Epidemiologic Studies/
20	exp Case-Control Studies/
21	exp Cohort Studies/
22	Case control.tw.
23	(cohort adj (study or studies)).tw.
24	Cohort analy$.tw.
25	(Follow up adj (study or studies)).tw.

26	(observational adj (study or studies)).tw.
27	Longitudinal.tw.
28	Retrospective.tw.
29	Cross sectional.tw.
30	Cross-sectional studies/
31	or/19-30
32	18 and 31
33	randomized controlled trial.pt.
34	controlled clinical trial.pt.
35	randomized.ab.
36	placebo.ab.
37	drug therapy.fs.
38	randomly.ab.
39	trial.ab.
40	groups.ab.
41	or/33-40
42	exp animals/ not humans.sh.
43	41 not 42
44	clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs.
45	randomized controlled trial.pt. or placebo.mp.
46	44 or 45
47	18 and 43
48	18 and 46
49	32 or 47 or 48

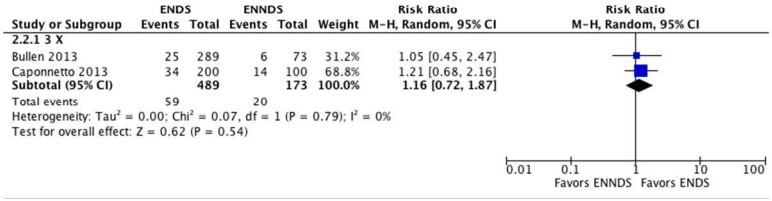
Appendix Table 2. Information about contact with the authors of the included studies.

Author, year	E-mail sent by the reviewers	Did the author of the study reply?	Did the author provide the requested data?
Adriaens, 2014 [33]	**Yes**	Yes	Yes
Bullen, 2013 [34-39]	**Yes**	Yes	Yes
Caponnetto, 2013 [25]	**Yes**	Yes	No (however author replied stating that will contact us later)
Al-Delaimy, 2015 [40]	**Yes**	Yes	Yes
Biener, 2015 [29]	**Yes**	Yes	Yes
Brose, 2015 [26-28]	**Yes**	Yes	Yes
Hajek, 2015 [46]	**Yes**	No	No
Harrington, 2015 [45]	**Yes**	Yes	Yes
Manzoli, 2015 [42]	**Yes**	Yes	No (however author replied stating that will contact us later)
Borderud, 2014 [41]	**Yes**	Yes	Yes
Prochaska, 2014 [43]	**Yes**	Yes	Yes
Vickerman, 2013 [44]	**Yes**	Yes	Yes

Appendix Table 3. Characteristics of e-cigarettes from the included studies.

Study	Device				Eliquid			Use	
	Type	Brand and model	Battery voltage	Metal in heating resistance	Nicotine concentration	Flavors in the eliquid	Conveyants	Puff regime during study	Amount eliquid consumed
Adriaens, 2014 [33]	Not a cigalike (tank-type atomizer) (second generation ENDS devices)	Joyetech eGo-C Kanger T2-CC	3.3 V, 1000 mAh lithium-ion battery 3.7 V, 650 mAh lithium-ion battery	2.2-ohm atomizer head 2.5-ohm coil	18mg of nicotine per mL for both types	Tobacco-flavored (Dekang "Turkish Blend") for both types	Not reported	Not reported	Not repor
Bullen, 2013 [34-39]	Cigalike	Elusion	Not reported	Not reported	Labelled 16mg (commissioned analyses showed 10-16mg of nicotine per mL)	Not reported	Not reported	Participants used e-cig as desired from 1 week before until 12 weeks after their chosen quit day	Not repor
Caponnetto, 2013 [25]	Cigalike	Categoria model 401	3.7 V, 90 mAh lithium-ion battery	Not reported	Cartridges of 7.2mg and 5.4mg nicotine	Cartridge without nicotine (control group): "sweet tobacco'' aroma	Solution of propylene glycol and vegetable glycerin	Not reported	Not repor
Al-Delaimy, 2015 [40]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Biener, 2015 [29]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Brose, 2015 [26-28]	76.3% used Cigalike 23.7% used Tank	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor

Hajek, 2015 [46]	1) Cigalike 2) Tank	1) Gamucci 2) Basic EVOD tank system, The EVOD's were later replaced with an Aspire product due to issues with leakage from the cheap EVOD model	Not reported	Not reported	1) With a choice of 1.6% or 2.2% per ml nicotine 2) 1.8% per ml nicotine e-liquid	Not reported	Not reported	Not reported	Not repor
Harrington, 2015 [45]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Manzoli, 2015 [42]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Borderud, 2014 [41]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Prochaska, 2014 [43]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor
Vickerman, 2013 [44]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not repor



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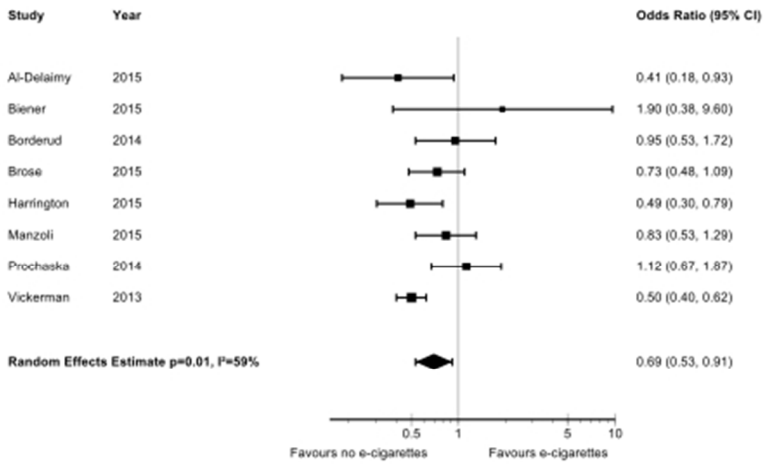

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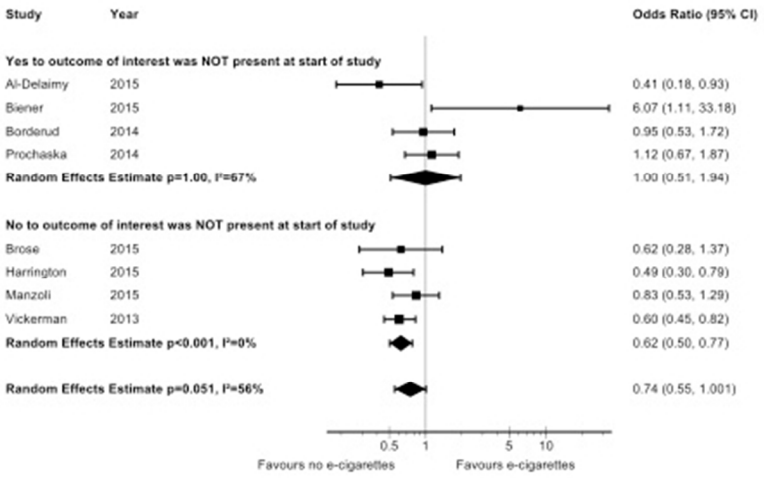

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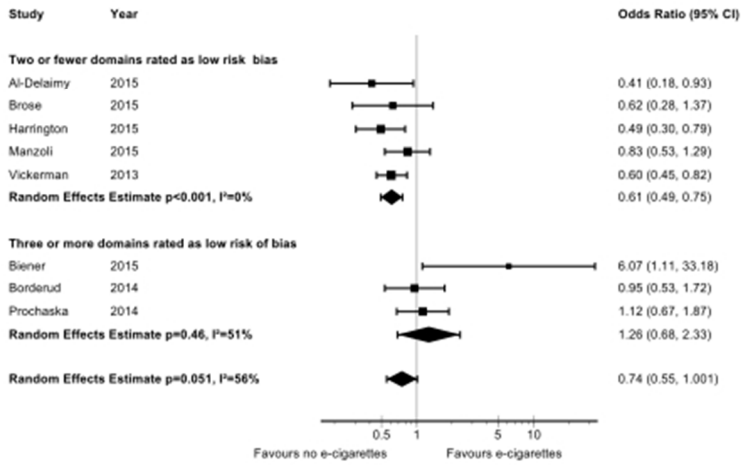

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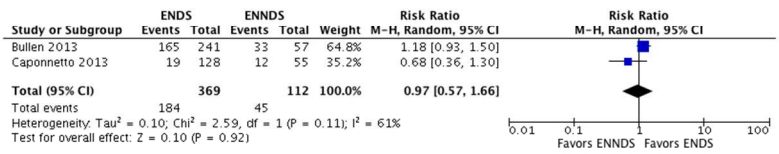

88x28mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
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.	4,5
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.	4,5
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.	Appendix Table 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.	4,5
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.	6,7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7,8,9
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.	9

PRISMA 2009 Checklist

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).	7,8,9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
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.	10
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.	10,11
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).	11
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.	12-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-15
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).	15, 16
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).	16,17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
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.	18

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(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Correction: *electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis*

El Dib R, Suzumura EA, Akl EA, *et al*. Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. *BMJ Open* 2017;7:e012680. doi: 10.1136/bmjopen-2016-012680.

The folllowing amendments were considered to the original version of this article.

The following paragraph was added in the 'Strengths and limitations' subheading under 'DISCUSSION' section: 'We usually conduct worst-case sensitivity analysis when there are significant results. However, because we noticed a possible increase in smoking cessation with ENDS (Figure 5) for cessation smoking, we have decided to conduct a worst-case sensitivity analysis to test the robustness of our findings.'

In Table 6,

- The first row should be read as 'Tobacco smoking cessation' instead of 'Mortality' and 'Reduction in cigarette use of at least 50%' instead of 'Renal insufficiency'. Also, Tobacco smoking cessation refers to OR.
- The header of eighth column should read as 'Relative risk and odds ratio (95% CI)' instead of 'Relative risk (95% CI)'.

In table 7, subheading of the seventh column should read 'Odds ratio (95% CI)' instead of 'Relative risk (95% CI)'.

The following footnote is added in both tables 6 and 7:
CI: confidence interval.

In the 'Data synthesis and statistical analysis' section under 'METHODS', the below statement has been added in the 3nd paragraph:

After calculating pooled relative effects, we also calculated absolute effects and 95% CI. For each outcome, we multiplied the pooled RR and its 95% CI by the median probability of that outcome. We obtained the median probability from the control groups of the available randomised trials. **When it is not possible, we obtained the median probability from the cohort studies**. We planned to perform separate analyses for comparisons with interventions consisting of ENDS and/or ENNDS and each type of control interventions with known different effects (no smoking cessation aid; alternative non-electronic smoking cessation aid including NRT and alternative electronic smoking cessation aid (ENDS or ENNDS)). For meta-analyses, we used 6 months data or the nearest follow-up to 6 months available.

The below statement has been added in the Acknowledgements section:

We would also like to thank Dr Aravind Gandhi Periyasamy for bringing these mistakes to our attention in order to issue an erratum rectifying.

BMJ Open 2020;**10**:e012680corr1. doi:10.1136/bmjopen-2016-012680corr1