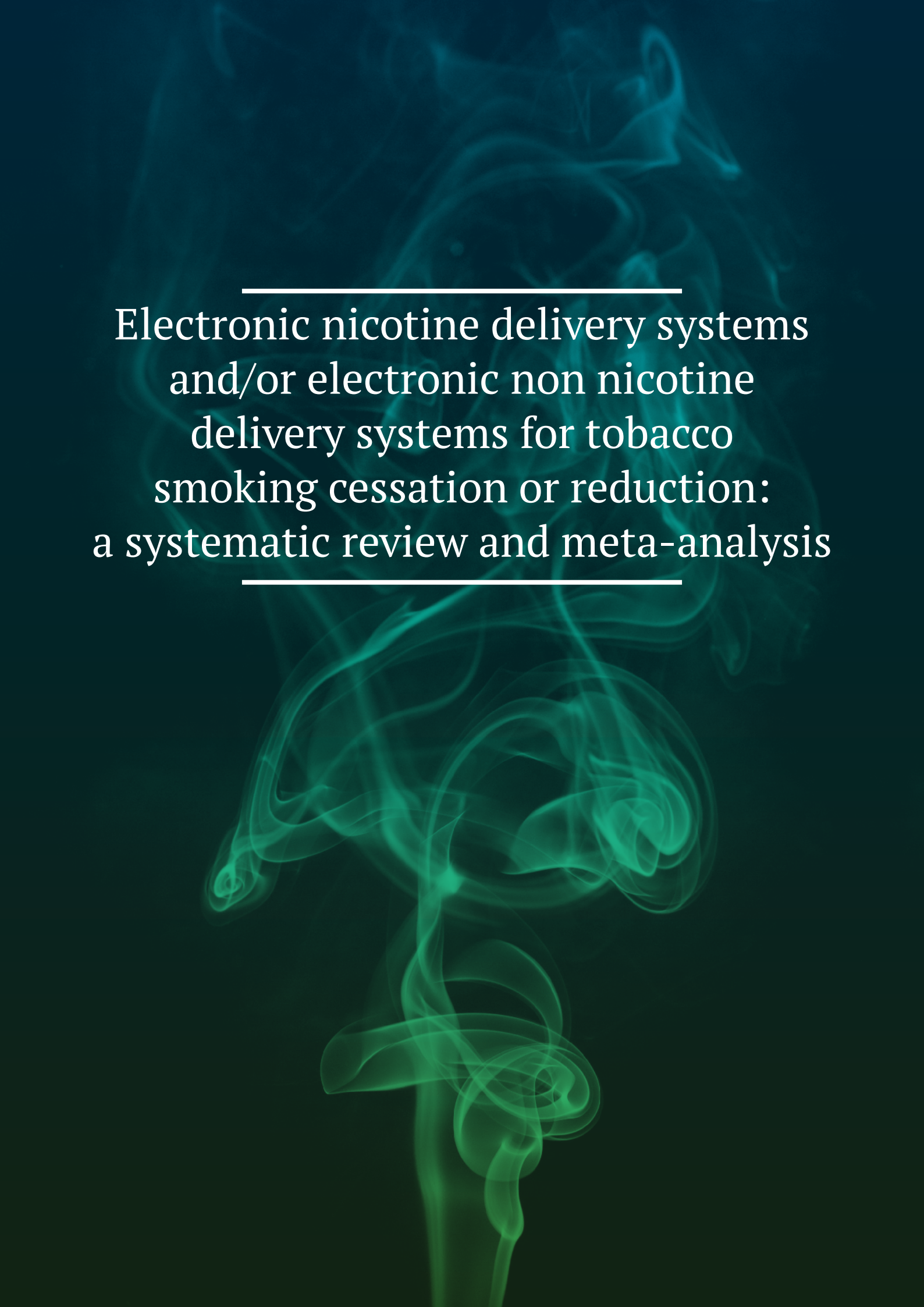
Electronic nicotine delivery systems and/or electronic non nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis



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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.

Abbreviations

CI	confidence interval
ENDS	electronic nicotine delivery system
ENNDS	electronic non-nicotine delivery system
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MeSH	Medical Subject Headings
MOOSE	meta-analysis of observational studies in epidemiology
OR	odds ratio
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCT	randomized controlled trial
RD	risk difference
RR	risk ratio

Abstract

Background: Electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS), of which electronic cigarettes are the most common type, may help tobacco smokers to reduce or end their tobacco use. The extent of potential benefits and adverse effects of ENDS and ENNDS remain uncertain.

Purpose: To perform a systematic review and meta-analysis addressing, in cigarette smokers, the effects of ENDS and/or ENNDS versus no smoking cessation aid or alternative smoking cessation aids on long-term tobacco use.

Data sources: Searches of MEDLINE, EMBASE, PsycInfo, CINAHL, CENTRAL and Web of Science up to December 2015, and review of reference lists of related published reviews and primary studies as well as a trial registry (clinicaltrials.gov).

Study selection: Randomized controlled trials (RCTs) and prospective cohort studies addressing the question of this review.

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 1007 participants and nine cohort studies 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) 64/1000 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).

Limitations: Randomized trials suffer from small total sample size, used older types of ENDS that have been replaced by possibly more effective versions, and risk of bias

from missing outcome data. Observational studies are likely to suffer from residual confounding and serious risk of bias in their conduct.

Conclusion: There is very limited 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. The available data provide little support for the use of ENDS or ENNDS as a smoking reduction strategy.

Key words: electronic cigarettes; ENDS; ENNDS; smoking cessation; GRADE; systematic review; meta-analysis.

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1. Introduction

Tobacco smokers who quit their habit reduce their risk of developing and dying from tobacco-related diseases *(1–4)*. Both psychosocial and pharmacological interventions (e.g. nicotine replacement therapy) increase the likelihood of quitting cigarettes *(5–7)*. 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 do not deliver nicotine. 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 behavioural 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, as well as their potential to hook tobacco naive youths on nicotine and to act as a bridge to combustible tobacco use *(9)*. While evidence about all these aspects of ENDS is accumulating, establishing their real place in smoking cessation is essential to define the public health context of considering them as potential harm-reducing 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 for conventional smoking.

There are many types of ENDS. The cigalikes are the first generation of ENDS and provide an appearance of tobacco cigarettes; they are not rechargeable. The second generation of ENDS looks like a pen, allows the user to mix flavours and may contain a prefilled or a refillable cartridge. The third generation of ENDS, including 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 systematic review summarized results from randomized controlled trials (RCTs) 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 including RCTs and cohort and cross-sectional studies concluded that ENDS are associated with smoking cessation and reduction *(10)*. However, another review comparing e-cigarettes to other nicotine replacement therapies or a placebo included only five studies; it concluded that participants using nicotine e-cigarettes were more likely to stop smoking, but there was no statistically significant difference *(11)*. A more recent systematic review found 28% lower odds rates of quitting cigarettes in those who used e-cigarettes compared with those who did not use e-cigarettes *(9)*.

Previous reviews were, however, limited in that they did not include all studies in this rapidly evolving field, and did not use the Grading of Recommendations Assessment, Development and Evaluation (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.

2. Methodology

2.1 Methods

The Cochrane handbook for systematic reviews of interventions *(12)* guided our choice of methods. 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)*. The results of these searches were used to prepare a report commissioned by the World Health Organization.

2.2 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, behavioural 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) 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.

2.3 Data sources 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 clinical trials registry.[1] Table A1.1 (Annex 1) shows the search strategy for Ovid MEDLINE. This strategy was adapted for the other databases and runs from 1 April 2014 to 29 December 2015. We did not impose any language restrictions.

In addition, we set up a literature surveillance strategy based on the weekly search alerts by the Centers for Disease Control and Prevention and tobacco.org's news and information page.[2] The surveillance strategy commenced from the time of running the comprehensive literature search up to the time of the submission of this manuscript.

2.4 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.

2.5 Data extraction

Reviewers underwent calibration exercises, and worked in teams of two 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 pretested data extraction form: study design; participants; interventions; comparators; outcome assessed; and relevant statistical data. When available, we prioritized carbon monoxide measurements as evidence of quitting. When carbon monoxide measurement was unavailable, we used self-report measures of quitting.

2.6 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, 16)*. That version includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors,

1 clinicaltrials.gov (U.S. National Institutes of Health).

2 http://www.tobacco.org.

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, which 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.

2.7 Certainty of evidence

We summarized the evidence and assessed its certainty separately for bodies of evidence from RCTs and cohort studies. We used the 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. 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)*.

2.8 Data synthesis and statistical analysis

We analysed all outcomes as dichotomous variables. In three-arm studies, we combined results from arms judged to be sufficiently similar (e.g. Caponnetto et al. *(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., for the Brose study, 2015 *(26–28)*, we excluded patients with non-daily users; and for the Biener study, 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 user groups. 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% confidence intervals (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 type of control intervention with known different effects (no smoking cessation aid; alternative non-electronic smoking cessation aid; 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 cases 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, and for the outcomes of smoking cessation and change in cigarette consumption, 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 *(27, 28)*.

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 *(29)*.

2.9 Subgroup analyses

We planned possible subgroup analyses according to the characteristics of:

- **Participants** (commitment to stopping smoking, use of e-cigarettes at baseline). We postulated larger effects when participants were committed to stopping smoking (i.e., users were using ENDS as part of a quit attempt) than when they were not, and smaller effects in smokers using e-cigarettes at baseline.

- **Interventions** (dose of nicotine delivered by the e-cigarette, frequency of use of the ecigarette and type of e-cigarette). We postulated that smoking cessation would be increased in those who used e-cigarettes with higher concentrations of nicotine compared to those using less nicotine, that daily e-cigarette users would have increased smoking cessation compared to non-daily e-cigarette users, and that those who use newer forms of ENDS (e.g. second, third or fourth generation) would have increased smoking cessation compared to users of first generation devices.

- **Concomitant interventions in both e-cigarettes and control groups**. We postulated larger effects with no concomitant interventions.

We planned to conduct subgroup analyses only when five or more studies were available, with at least two in each subgroup.

3. Results

3.1 Study selection

Figure 1 presents the process of identifying eligible studies, including publications in the last systematic review *(8)*, citations identified through searches 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 1007 participants *(25, 30–36)* and nine cohort studies with a total of 13 115 participants *(37–47)*. The interobserver agreement for the full text screening was substantial (kappa 0.73).

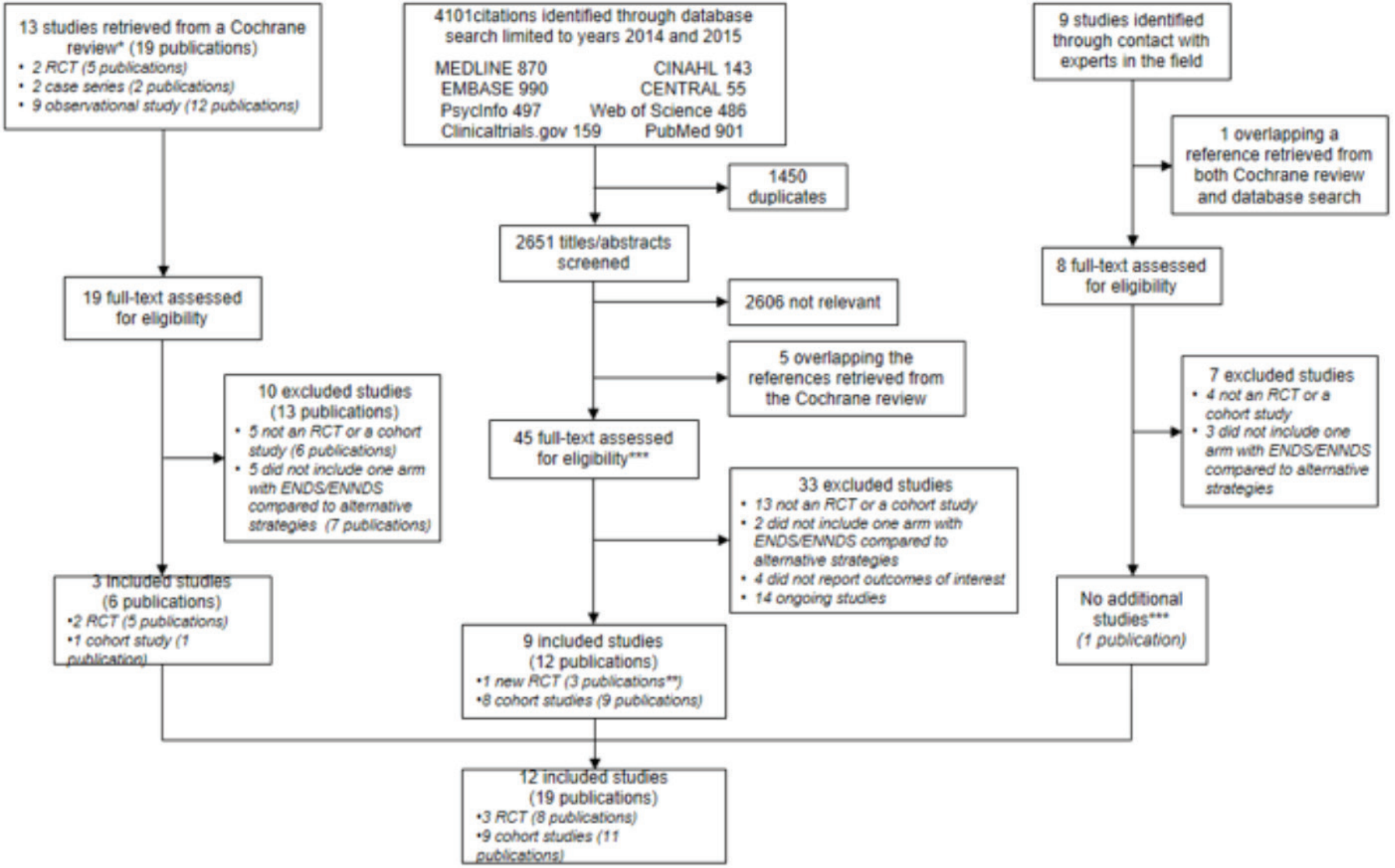


Figure 1. PRISMA diagram of included studies.

*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

We identified 14 studies through the trial registry as potential future studies (Annex 1, Table A1.2). We contacted the authors of the 12 included studies, nine of whom *(30–42, 44–46)* supplied us with all requested data; authors of a further three studies *(25, 43, 47)* did not supply the requested information (Annex 1, Table A1.3).

3.2 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, 30, 40–43, 47)* were conducted largely in Europe, six in the United States of America *(37–39, 44–46)*, and one in New Zealand *(31–36)*. The sample size for randomized trials ranged from 50 *(30)* to 657 *(31–36)*, and observational studies from 100 *(47)* to 3891 *(40–42)*. Typical participants were females aged 40–59 years. Studies followed participants for periods in the range four weeks *(47)* to 36 months *(38)*.

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[a]	Mean age	No. male (%)	Inclusion criteria	Exclusion criteria	Follow-up (months)
Randomized controlled trials								
Adriaens, 2014 *(30)*	Parallel RCT	Leuven, Belgium	50	ENDS1: 44.7[b] ENDS2: 46.0 ENDS and e-liquid[c]: 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; breastfeeding; high blood pressure; cardiovascular disease; currently using any kind of smoking cessation therapy and prior use of an e-cigarette	8
Bullen, 2013 *(31–36)*	Parallel RCT	New Zealand	657	16 mg ENDS: 43.6 21 mg patches Nicotine replacement therapy: 40.4 ENNDS: 43.2	252 (38.3)	Aged 18 years or older; had smoked 10 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

Author, year	Design of study	Location	No. participants[a]	Mean age	No. male (%)	Inclusion criteria	Exclusion criteria	Follow-up (months)
Cohort studies								
Al-Delaimy, 2015 *(37)*	Cohort	California, U.S.	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-cigarette" or changed their reporting at follow-up, as they did not represent a definitive group of users or never-users and might overlap with both	12
Biener, 2015 *(38)*	Cohort	Dallas and Indianapolis areas, U.S.	1 374	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 recontacted	Anyone over 65 years old	36
Brose, 2015 *(40–42)*	Cohort	Web-based, United Kingdom	3 891[d]	ENDS Among daily users: 45.7 Among non-daily users: 45.2 No ENDS[e]: 45.7	2,015 (49.6)	Members were invited by email 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 *(47)*	Cohort	Europe	100	ENDS: 41.8 No ENDS: 39	57 (57)	All smokers joining the U.K. Stop Smoking Services in addition to the standard treatment (weekly support and stop smoking medications, including nicotine replacement therapy and varenicline)	No exclusion criteria	4 weeks[g]
Harrington, 2015 *(46)*	Cohort	U.S.	979	46.0[f]	525 (53.6)	Hospitalized cigarette smokers at a tertiary care medical centre; self-identified smoker who	Pregnant	6

Author, year	Design of study	Location	No. participants[a]	Mean age	No. male (%)	Inclusion criteria	Exclusion criteria	Follow-up (months)
						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		
Manzoli, 2015 *(43)*	Cohort	Abruzzo and Lazio region, Italy	1 355	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-cigarette (inhaling at least 50 puffs per week) containing nicotine since six or more months (e-cigarette 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 months (mixed group)	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, oesophagus, larynx, oral cavity, bladder, pancreas, kidney, stomach, cervix, and myeloid leukaemia	12
Borderud, 2014 *(39)*	Cohort	New York, U.S.	1 074	ENDS use+ behavioural and pharmacological treatment: 56.3 No ENDS + behavioural and pharmacological treatment: 55.6	467 (43.5)	Patients with cancer referred to a tobacco cessation programme who provided data on their recent (past 30 days) e-cigarette use	No exclusion criteria	6 to 12
Prochaska, 2014 *(44)*	Cohort	U.S.	956	39.0[f]	478 (50.0)	Adult daily smokers (at least five cigarettes/day with serious mental illness	Non-English speaking; medical contraindications to nicotine replacement therapy use (pregnancy, recent myocardial infarction); and lack of	18

Author, year	Design of study	Location	No. participants[a]	Mean age	No. male (%)	Inclusion criteria	Exclusion criteria	Follow-up (months)
						at four psychiatric hospitals in the San Francisco Bay Area	capacity to consent as determined by a three-item screener of study purpose, risks, and benefits	
Vickerman, 2013 *(45)*	Cohort	U.S.	2 758[h]	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

[a] Randomized or at baseline

[b] ENDS1 and ENDS2: the e-cigarette groups received the e-cigarette 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.

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

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

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

[f] Mean age of the overall population.

[g] Hajek, 2015 *(47)* was the only study that entered in the review due to meet the criteria for adverse events.

[h] But only 2476 answered 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 nicotine replacement therapy and ENNDS *(31–36)*, another compared different concentrations of ENDS to ENNDS *(25)*, and the third compared different types of ENDS *(30)*. The three RCTs *(25, 30–36)* evaluated only ENDS-type cigalikes. All nine cohort studies *(37–47)* compared ENDS to no use of ENDS *(37–42, 44–47)* or tobacco cigarettes only *(43)*; in one study *(39)*, both exposure and non-exposure groups received behavioural and other pharmacologic treatment.

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

Author, year	Population	No.[a] of participants intend to quit smoking	No.[a] 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 *(30)*	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 48	ENDS 1: 16 ENDS 2: 17 ENDS and e-liquid: 17	ENDS ("Joyetech eGo-C") ENDS E-cigarettes ("Kanger T2-CC")	ENDS and e-liquid[b]	Quitting, defined as exhaled breath carbon monoxide (eCO) of 5 ppm or smaller; questionnaire self-report of reduction in cigarettes of > 50% or complete quitting	No more cigarette smoking
Bullen, 2013 *(31–36)*	Had smoked 10 or more cigarettes per day for the past year, interested in quitting	Yes 657 No 0	ENDS: 289 Nicotine replacement therapy: 295 ENNDS: 73	16 mg nicotine ENDS	21 mg patches nicotine replacement therapy 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 seven 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 *(37)*	Current smokers; regardless of whether the users were using ENDS as part of a quit attempt	Yes 415 No 542	ENDS: 236[c] No ENDS: 392[c]	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

Author, year	Population	No.[a] of participants intend to quit smoking	No.[a] 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
Biener, 2015 *(38)*	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[d] No 331[e]	1 374[f]	ENDS[g] intermittent use ENDS[g] 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 *(40–42)*	Current smokers; regardless of whether the users were using ENDS as part of a quit attempt	Not reported	ENDS: 1 507 No ENDS: 2 610	ENDS daily ENDS non-daily	No ENDS[e]	Quit attempts[h]; cessation[i]; and substantial reduction defined as a reduction by at least 50% from baseline cigarettes smoked per day to follow-up cigarettes smoked per day	Change from being a smoker at baseline to being an ex-smoker at follow-up was coded as cessation
Hajek, 2015 *(47)*	69% (n=69) accepted e-cigarettes 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 nicotine replacement therapy and varenicline)	No ENDS	Self-reported abstinence was biochemically validated by exhaled CO levels in end-expired breath using a cut-off point on 9 ppm, adverse events	Self-reported abstinence from cigarettes at four weeks
Harrington, 2015 *(46)*	Hospitalized cigarette smokers. All were cigarette smokers initially; regardless of whether the users were using ENDS as part of a quit attempt	Yes: 220[j] No: not reported	ENDS: 171 No ENDS: 759	ENDS	No ENDS	Quitting smoking based on 30-day point prevalence at six months	Only self-reported quitting smoking
Manzoli, 2015 *(43)*	Smokers of ≥ 1 tobacco cigarette/day (tobacco smokers), users of any type of e-cigarette,	Not reported	ENDS: 343 Tobacco and ENDS: 319	ENDS Tobacco and ENDS	Tobacco cigarettes only	Abstinence, proportion of quitters, biochemically verified (eCO measurement > 7ppm), reduce tobacco	Percentage of subjects reporting sustained (30 days) abstinence from

Author, year	Population	No.[a] of participants intend to quit smoking	No.[a] 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
	inhaling ≥ 50 puffs weekly (e-smokers), or smokers of both tobacco and e-cigarette (dual smokers)		Tobacco only: 693			smoking, and serious adverse events	tobacco smoking
Borderud, 2014 *(39)*	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[k] No 42[k]	ENDS: 285 No ENDS: 789	ENDS[l] + evidence-based behavioural and pharmacologic treatment	No ENDS + evidence-based behavioural 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 seven days
Prochaska, 2014 *(44)*	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 seven days tobacco abstinence
Vickerman, 2013 *(45)*	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 seven months follow-up

[a] Numbers randomized or at baseline.

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

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

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

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

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

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

[h] 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 between baseline and follow-up were coded as having made an attempt.

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

[j] Only among those who reported any previous use of e-cigarettes.

[k] 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.

[l] All ENDS.

[α] Information retrieved through contact with author.

Table 3 describes the mean number of conventional cigarettes and/or other tobacco products 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 *(46)* to 20.6 in the ENDS group *(30)*.

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[a]	Mean no. of conventional cigarettes/other tobacco products used per day at the end of study[a]	Biochemically quitters (no. of events per no. of total participants)	Self-reported quitters (no. of events per no. of total participants)
Adriaens, 2014 *(30)*	ENDS1[b]	20.1	7.0[c]	3/13	4/13
	ENDS2[b]	20.6	8.1[c]	3/12	3/12
	ENDS and e-liquid[d,e]	16.7	7.7[c]	4/13	4/13
Bullen, 2013 *(31–36)*	ENDS	18.4	0.7[f]	21/241	Not available
	ENNDS	17.7	0.7	3/57	Not available
	Nicotine replacement therapy	17.6	0.8[f]	17/215	Not available
Caponnetto, 2013 *(25)*	7.2 mg ENDS	19.0 (14.0–25.0)[g]	12 (5.8–20)[g,h]	Combined ENDS groups: 22/128	Not available
	7.2 mg ENDS plus 5.4 mg ENDS	21.0 (15.0–26.0)[g]	14 (6–20)[g,h]		Not available
	ENNDS	22.0 (15.0-27.0)[g]	12 (9-20)[g,h]	4/55	Not available
Al-Delaimy, 2015 *(37)*	ENDS	14.1[i]	13.8[j]	Not available	12/179
	ENNDS			Not available	32/145
Biener, 2015 *(38)*	ENDS intermittent use	16.7[k]	Not available	Not available	Combined ENDS groups: 42/331
	ENDS intensive use	17.1[k]	Not available	Not available	
	No ENDS	15.4[k]	Not available	Not available	82/364
Brose, 2015	ENDS daily users	14.3	13.0[m]	Not available	7/86

(40–42)	ENDS non-daily users	13.5	13.9[m]	Not available	25/263
	No ENDS[l]	13.3	13.5	Not available	168/1307
Hajek, 2015 *(47)*	ENDS	Not available	Not available	Not applicable[n]	Not applicable[n]
	No ENDS	Not available	Not available	Not applicable[n]	Not applicable[n]
Harrington, 2015 *(46)*	ENDS	14.1[o]	10.3[o]	Not available	21/171
	No ENDS	11.9[o]	9.8[o]	Not available	62/464
Manzoli, 2015 *(43)*	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 *(39)*	ENDS	13.7	12.3	Not available	25/58
	No ENDS	12.4	10.1	Not available	158/356
Prochaska, 2014 *(44)*	ENDS	17.0	10.0	21/101	Not available
	No ENDS	17.0	10.1	162/855	Not available
Vickerman, 2013 *(45)*	ENDS used for one month or more	19.4	13.5	Not available	59/273
	ENDS used for less than one month	18.9	14.0	Not available	73/439
	No ENDS (never tried)	18.1	12.9	Not available	535/1711

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

[b] ENDS1 and ENDS2: the e-cigarette groups received the e-cigarette 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;

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

[d] Control group consisted of received the e-cigarette 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”).

[e] Eight months from start of intervention.

[f] For those reporting smoking at least one cigarette in past seven days.

[g] Data shown as median and interquartile.

[h] At six months after the last laboratory session.

[i] Of the 1000 subjects, 993 responded to the question “How many conventional cigarettes smoked per day during the past 30 days?”

[j] Of the 1000 subjects, 881 responded to the question “How many cigarettes smoked per day during the past 30 days?”

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

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

[m] Number of cigarettes per week divided by seven days.

[n] Not applicable because they followed participants only for four weeks, but the study reported adverse events at one week or longer.

[o] Data for baseline current e-cigarette users.

Table A1.4 (Annex 1) presents the types of e-cigarettes used in the included studies. The majority of the studies used first generation cigalikes *(25, 30–36, 40–42, 47)*.

3.3 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, 31–36)*. RCTs comparing ENDS to other nicotine replacement therapies had additional problems of concealment of randomization *(30)* and blinding *(30–36)*.

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

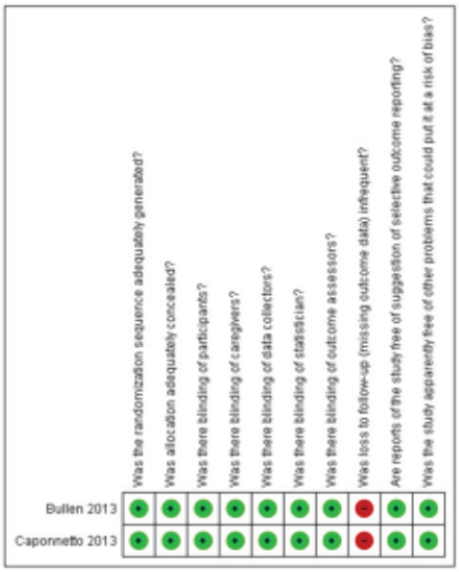


Figure 3. Risk of bias for RCTs comparing ENDS versus other nicotine replacement therapy

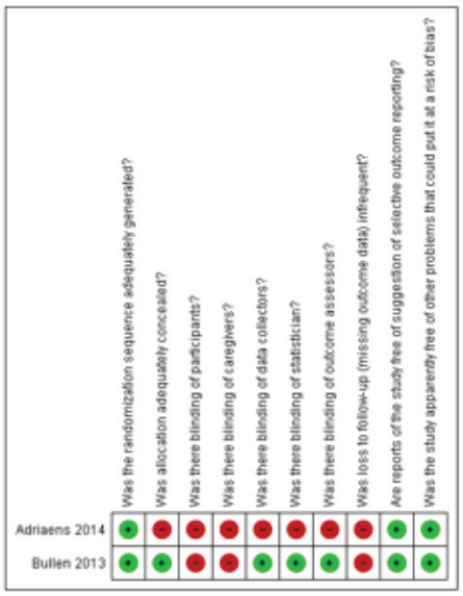


Table 4. Risk of bias assessment for the randomized controlled trials

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?[a]	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 ***(31–36)***	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 ***(30)***	Definitely yes	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no	Definitely no	Probably yes	Probably yes
Bullen, 2013 ***(31–36)***	Definitely yes	Definitely yes	Definitely no	Definitely no	Probably yes	Probably yes	Definitely yes	Definitely no	Definitely yes	Definitely yes

[a] 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.

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 *(37, 38–43, 45, 46)* 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.

Figure 4. Risk of bias for cohort studies:

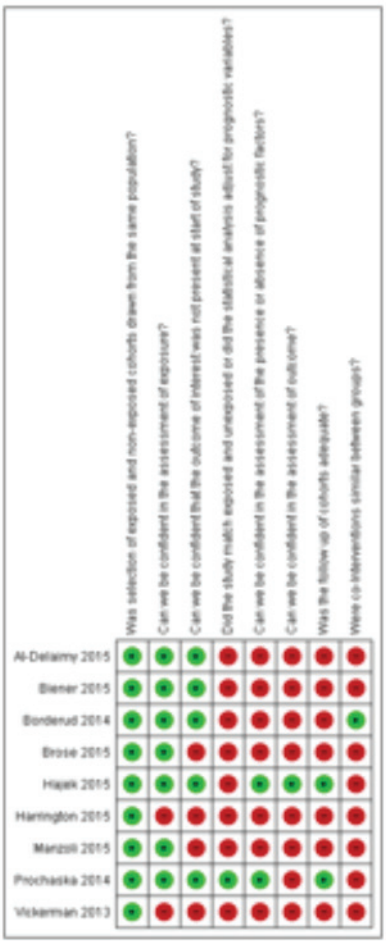


Table 5. Risk of bias assessment of the cohort studies

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?[a]	Was the follow-up of cohorts adequate?[b]	Were co-interventions similar between groups?
Al-Delaimy, 2015 *(37)*	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Biener, 2015 *(38)*	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Brose, 2015 *(40–42)*	Definitely yes	Probably yes	Probably no	Definitely no	Definitely no	Definitely no	Definitely no	Probably no
Hajek, 2015 *(47)*	Probably yes	Probably yes	Probably yes	Definitely no	Probably yes	Probably yes	Probably yes	Probably no
Harrington, 2015 *(46)*	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no
Manzoli, 2015 *(43)*	Definitely yes	Probably yes	Definitely no	Definitely no	Definitely no	Probably no	Definitely no	Probably no
Borderud, 2014 *(39)*	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely yes
Prochaska, 2014 *(44)*	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely no	Definitely yes	Probably No
Vickerman, 2013 *(45)*	Probably yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no

[a] Independent blind assessment or record linkage was considered as adequate outcome assessment. Outcomes self-reported were considered as definitely no for adequate assessment.

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

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

3.4 Outcomes

The mean number of conventional cigarettes/tobacco products used per day at the end of the studies ranged from 0.7 *(31–36)* in both ENDS and ENNDS groups to 13.9 *(40–42)* among non-daily users of ENDS (Table 3). The three RCTs *(25, 30–36)* and one cohort study *(43)* biochemically confirmed nicotine abstinence, while the others presented only self-reported data *(37–42, 44–46)* (Table 3).

Tobacco smoking cessation

Synthesized results from randomized controlled trials. Results from two RCTs *(25, 31–36)* 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) 64/1000 over 6 to 12 months, low-certainty evidence) (Figure 5, Table 6).

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

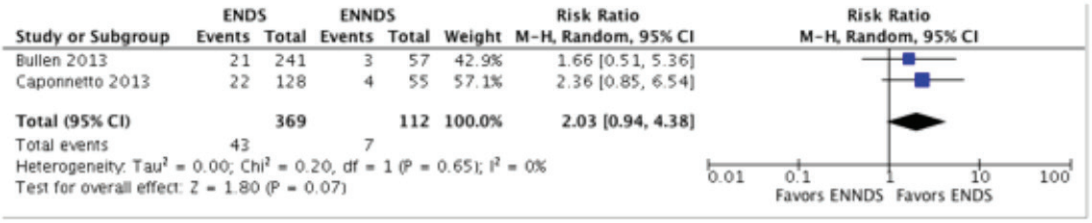


Table 6. GRADE evidence profile for RCTs: electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) for reducing cigarette smoking

Quality assessment						**Summary of findings**					**Certainty in estimates**
						Study event rates		Relative risk (95% CI)	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[a]	ENDS		ENNDS[a]	ENDS	Quality of evidence
Cessation/nicotine abstinence (includes self-reported and biochemically validated by eCO)											
481 (2) 6–12 months	Serious limitations[b]	No serious limitations	No serious limitations	Serious imprecision[c]	Undetected	7/112	43/369	2.03 (0.94–4.38)	213 per 1000	219 more per 1000 (13 fewer to 720 more)	LOW
Self-report of reduction in cigarettes of > 50%											
481 (2) 6–12 months	Serious limitations[b]	Serious limitations	No serious limitations	Serious imprecision[c]	Undetected	45/112	184/369	0.97 (0.57–1.66)	213 per 1000	7 fewer per 1000 (92 fewer to 140 more)	LOW

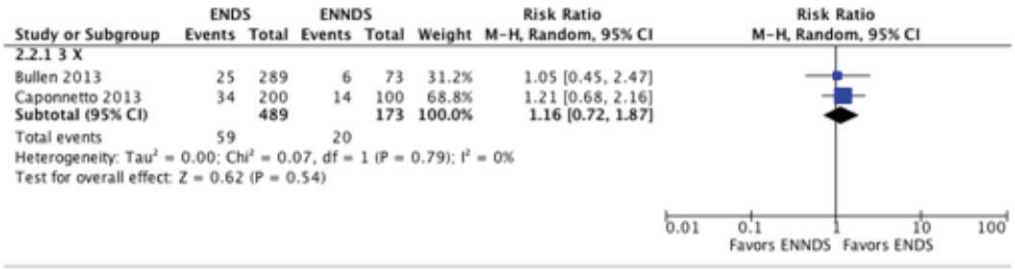
[a] The estimated risk control was taken from the median estimated control risks of the cohort studies.

[b] Two studies presented high risk of bias for missing outcome data. Moreover, one was not blinded to participants and caregivers *(34–39)* and another *(41)* also was not blinded to data collectors, statisticians 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.

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

A plausible worst-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; $P = 0.54$; $I^2 = 0\%$) (Figure 6). 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 *(31–36)*, caregivers, data collectors, statisticians and outcome assessors in the ENDS versus other nicotine replacement therapy studies *(48)* (Figure 2, Tables 4 and 6).

Figure 6. Sensitivity analysis of RCTs on smoking cessation comparing ENDS versus ENNDS

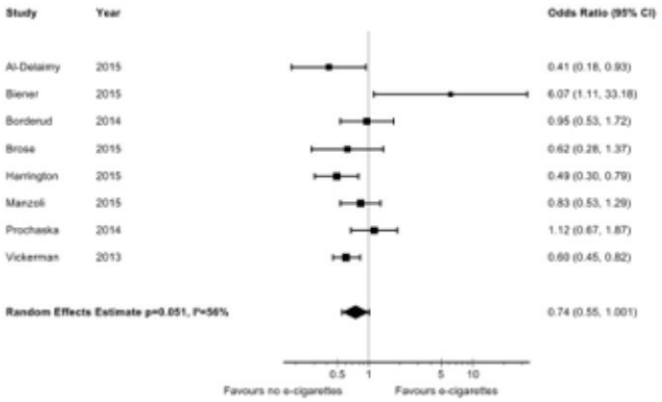


Adriaens *(30)* also compared two types of ENDS (i.e. Joyetech eGo-C and Kanger T2-CC) versus ENDS and e-liquid; results failed to show a difference between the ENDS groups with a very wide confidence interval (RR 1.15, 95% CI 0.28, 4.76; $P = 0.84$).

Bullen *(31–36)* also compared ENDS and ENNDS with nicotine replacement therapy; 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 *(37–46)* comparing ENDS to no ENDS without reported concomitant interventions failed to show a benefit in smoking cessation (OR 0.74, 95% CI 0.55, 1.00; $P = 0.051$; $I^2 = 56\%$) (Figure 7).

Figure 7. Meta-analysis of cohort studies on smoking cessation with adjusted ORs



A sensitivity analysis from the eight cohort studies *(37–46)* using any rather than daily use of ENDS for the Brose study *(40–42)*, both intensive use (used e-cigarettes daily for at least one month) and intermittent use (used regularly, but not daily for more than one month) of ENDS for the Biener study *(38)*, and any use versus never used for the Vickerman study *(45)* suggested a reduction in smoking cessation rates with ENDS (adjusted OR 0.69, 95% CI 0.53, 0.91; $P = 0.01$; $I^2 = 59\%$) (Figure 8). Certainty in evidence from the observational studies was rated down from low to very low because of risk of bias due to missing outcome data, imprecision in the assessment of prognostic factors and outcomes (Figure 4, Tables 5 and 7), and inconsistency in the results.

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

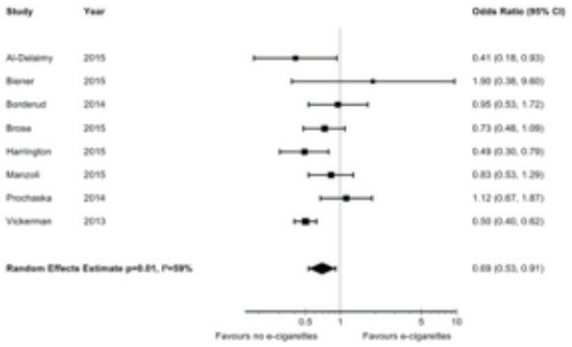
Quality assessment						Summary of findings					Certainty in estimates
						Study event rates		Relative risk (95% CI)	Anticipated absolute effects over 6–12 months		OR Quality of evidence
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication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

[a] The estimated risk control was taken from the median estimated control risks of the cohort studies.

[b] 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.

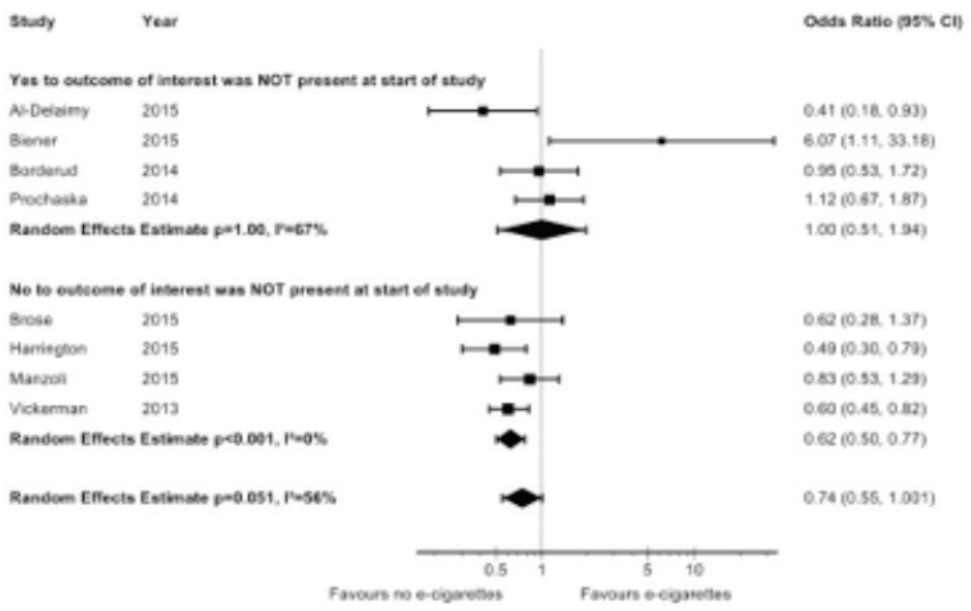
[c] 95% CI for absolute effects include clinically important benefit and no benefits.

Figure 8. Meta-analysis of cohort studies on smoking cessation with adjusted ORs using a sensitivity analysis with an assumed correlation = 0.5



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; $P = 1.00$; $I^2 = 67\%$) and the high risk of bias group (adjusted OR 0.62, 95% CI 0.50, 0.77; $p < 0.001$; $I^2 = 0\%$), the difference is easily explained by chance (interaction *P*-value was 0.19) (Figure 9).

Figure 9. Sensitivity analysis of cohort studies on cessation smoking separately by confidence in whether the outcome was present at the beginning of the study

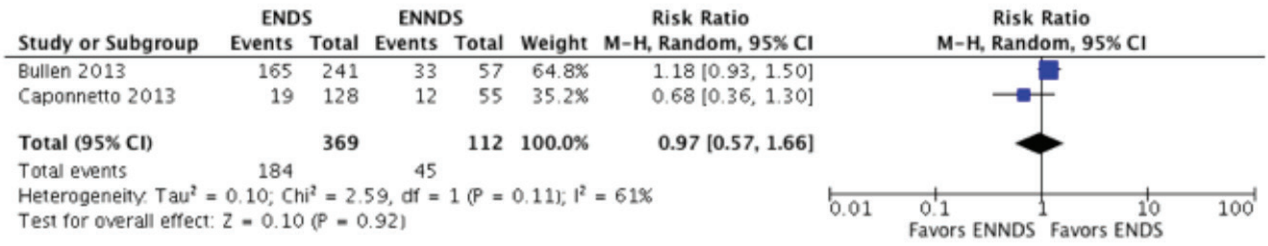


Borderud *(39)* reported smoking cessation in 25 out of 58 cancer patients using ENDS plus behavioural and pharmacologic treatment versus 158 out of 356 cancer patients who received only behavioural and pharmacologic treatment (adjusted OR 0.97, 95% CI 0.71 to 1.33).

Reduction in cigarette use of at least 50%

Synthesized results from randomized controlled trials. The results of two RCTs *(25, 31–36)* failed to show a difference between ENDS-type cigalikes and the ENNDS group with regard to reduction in cigarettes, but with a very wide confidence interval (RR 0.97, 95% CI 0.57, 1.66; $P = 0.92$; $I^2 = 61\%$) (Figure 10). Certainty in evidence was rated low because of imprecision and risk of bias *(25, 31–36)* (Figure 2, Tables 4 and 6).

Figure 10. Meta-analysis of RCTs on reduction comparing ENDS versus ENNDS



Synthesized results from cohort studies. Two studies *(38, 40–42)* suggested increased reduction rates in those with greater versus lesser use of ENDS. Biener *(38)* 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 *(40–42)* 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's study *(31–36)* 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 six 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 a 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 included death (n = 1, in the nicotine e-cigarettes group), life-threatening illness (n = 1, in the nicotine e-cigarettes group), admission to hospital or prolongation of hospital stay (12% of all events in the nicotine e-cigarettes group, 8% in the patches group and 11% in the placebo e-cigarettes group), persistent or significant disability or incapacity, and other medically important events (6% of all events in the nicotine e-cigarettes group, 4% in the patches group and 3% in the placebo e-cigarettes group).

The Adriaens study *(30)* reported no serious adverse events in either ENDS group or the eliquid 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 et al. *(25)* observed no serious adverse events during the study, and the authors found a significant reduction in frequency of reported symptoms compared to the baseline.

Synthesized results from cohort studies. Manzoli *(43)* reported no significant differences in self-reported serious side-effects, but observed four cases of pneumonia, four exacerbations of chronic obstructive pulmonary disease, 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), and four among tobacco and ENDS smokers.

Hajek *(47)* reported one leak irritating a participant's mouth and some reports of irritation at the back of the throat and minor coughing.

4. Discussion

4.1 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 worst-case sensitivity analysis to assess the risks of bias associated with missing participant data yielded results that were inconsistent with the primary complete case analysis (Figure 6). Furthermore, in all these RCTs, the ENDS tested were earlier generation; it is possible that later generations of ecigarettes 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 9). As with 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, when enrolling smokers already using ENDS and still smoking, cohort studies may be choosing participants who are already failing, and may thus underestimate the beneficial effects of ENDS. 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.

4.2 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 in 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 increased rates of 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 non-daily 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 seem logical, nicotine delivery from ENDS depends on other factors, such as the efficiency of the device in aerosolizing 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 smoking cessation 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 were not available to conduct a subgroup analysis addressing this hypothesis. Subsequent trials should help provide information regarding whether their impact on smoking cessation depends on whether users were intending to quit smoking, as well as the other unresolved issues.

Another limitation of this review was the 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 ecigarette, and type of e-cigarette);
- concomitant interventions in both e-cigarette 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 subgroup. 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 arguments in favour of the second rather than the third are as follows: (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 the researcher might as well commit 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 represents our view of the matter.

4.3 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 ENNDS. We excluded observational studies included in that Cochrane review as they were either case series or cross-sectional or did not include one arm with ENDS/ENNDS compared to alternative strategies, and included one additional RCT *(30)* and nine new cohort studies *(37–47)*. The authors of the review found that ENDS is a useful method to stop smoking in the long term compared with ENNDS.

Another review *(10)* including two of our three RCTs *(25, 31–36)*, a further two case series and two cross-sectional studies assessed the efficacy 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-cigarettes are associated with smoking cessation – similar to the findings in our meta-analysis comparing ENDS versus ENNDS (Figure 5), although they commented on the need for further RCTs. Similarly, the Khoudigian review *(11)* showed a non-statistically significant trend towards smoking cessation in adults using nicotine e-cigarettes compared with other therapies or a placebo. However, the Kalkhoran and Glantz review *(9)* concluded that e-cigarettes are associated with significantly less quitting among smokers.

A review with a different purpose *(48)* describes the variety of e-cigarette products and summarizes 82 articles describing the chemical constituents, cytotoxicity, nicotine absorption, concept of marketing and media research, policy recommendations, and awareness of e-cigarettes.

4.4 Implications

Existing smoking reduction aids such as nicotine replacement therapy are effective, but their impact is limited: the increased proportion of those desiring to quit that succeeds in quitting is very 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 are 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.

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Annex 1. Tables

Annex 1. Tables

Table A1.1 Search strategy for Ovid Medline

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

Table A1.2 Potential studies retrieved at the clinicaltrials.gov

Investigator	Title	NCT	Web address	Date of access
Pasquale Caponnetto	Caponnetto P, Polosa R, Auditore R, Minutolo G, Signorelli M, Maglia M, Alamo A, Palermo F, Aguglia E. Smoking cessation and reduction in schizophrenia (SCARIS) with e-cigarette: study protocol for a randomized control trial. Trials. 2014 Mar 22;15:88. doi: 10.1186/1745-6215-15-88. (Published study protocol)	NCT01979796	https://ClinicalTrials.gov/show/NCT01979796	7 Oct 2015
Laura A Beebe	Smoking Cessation in Women With Gynecological Conditions	NCT01989923	https://ClinicalTrials.gov/show/NCT01989923	7 Oct 2015
Natalie Walker	The Use of Nicotine Patches Together With E-cigarettes (With and Without Nicotine) for Smoking Cessation	NCT02521662	https://ClinicalTrials.gov/show/NCT02521662	7 Oct 2015
Amy J Arouni	e-Cigarettes Versus NRT Gum for Smoking Cessation	NCT01925781	https://ClinicalTrials.gov/show/NCT01925781	7 Oct 2015
Mark J Eisenberg	Evaluating the Efficacy of E-Cigarette Use for Smoking Cessation (E3) Trial	NCT02417467	https://ClinicalTrials.gov/show/NCT02417467	7 Oct 2015
Barney Vaughan	Electronic Cigarettes or Nicotine Inhaler for Smoking Cessation	NCT02004171	https://ClinicalTrials.gov/show/NCT02004171	7 Oct 2015
Susan M Lee	The END Perioperative Smoking Pilot Study	NCT02482233	https://ClinicalTrials.gov/show/NCT02482233	7 Oct 2015
Jed E Rose	Electronic Nicotine Delivery Systems as a Smoking Cessation Treatment	NCT02487953	https://ClinicalTrials.gov/show/NCT02487953	7 Oct 2015
Scott Halpern	Randomized Clinical Trial to Reduce Harm From Tobacco	NCT02328794	https://ClinicalTrials.gov/show/NCT02328794	7 Oct 2015
Peter Hajek	Spain-UK-Czech E-cigarette Study	NCT01842828	https://ClinicalTrials.gov/show/NCT01842828	7 Oct 2015
Michael R Gartner	Characterization of Biomarkers of Tobacco Exposure, Urge-to-Smoke Following Exclusive and Dual Ad Lib Use of Electronic Cigarettes	NCT02385227	https://ClinicalTrials.gov/show/NCT02385227	7 Oct 2015
Hayden J McRobbie	Effect of the Electronic Cigarette on Withdrawal Symptoms	NCT01454362	https://ClinicalTrials.gov/show/NCT01454362	7 Oct 2015
Claudio Lucchiari	Benefits of Tobacco Free Cigarette	NCT02422914	https://ClinicalTrials.gov/show/NCT02422914	7 Oct 2015

Carlo Cipolla	Early Smoking Reduction or Cessation by Means of no Nicotine Electronic Cigarette Added to Standard Counselling	NCT01733706	https://ClinicalTrials.gov/show/NCT01733706	7 Oct 2015

Table A1.3 Information about contact with the authors of the included studies

Author, year	Email sent by the reviewers	Did the author of the study reply?	Did the author provide the requested data?
Adriaens, 2014 ***(30)***	Yes	Yes	Yes
Bullen, 2013 ***(31–36)***	Yes	Yes	Yes
Caponnetto, 2013 ***(25)***	Yes	Yes	No (however author replied stating that will contact us later)
Al-Delaimy, 2015 ***(37)***	Yes	Yes	Yes
Biener, 2015 ***(38)***	Yes	Yes	Yes
Brose, 2015 ***(40–42)***	Yes	Yes	Yes
Hajek, 2015 ***(47)***	Yes	No	No
Harrington, 2015 ***(46)***	Yes	Yes	Yes
Manzoli, 2015 ***(43)***	Yes	Yes	No (however author replied stating that will contact us later)
Borderud, 2014 ***(39)***	Yes	Yes	Yes
Prochaska, 2014 ***(44)***	Yes	Yes	Yes
Vickerman, 2013 ***(45)***	Yes	Yes	Yes

Table A1.4 Types of e-cigarettes used in the included studies

Study	Device				E-liquid			Use	
	Type	Brand and model	Battery voltage	Metal in heating resistance	Nicotine concentration	Flavours in the e-liquid	Conveyants	Puff regime during study	Amount of e-liquid consumed/day
Adriaens, 2014 ***(30)***	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	18 mg of nicotine per mL for both types	Tobacco-flavoured (Dekang "Turkish Blend") for both types	Not reported	Not reported	Not reported
Bullen, 2013 ***(31–36)***	Cigalike	Elusion	Not reported	Not reported	Labelled 16 mg (commissioned analyses showed 10–16 mg of nicotine per mL)	Not reported	Not reported	Participants used e-cigarette 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 7.2 mg and 5.4 mg 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	1) Cigalike	1) Gamucci			1) With a choice of				

(47)	2) Tank	2) Basic EVOD tank system, The EVODs were later replaced with an Aspire product due to issues with leakage from the cheap EVOD model	Not reported	Not reported	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 *(44)*	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

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