CR Review formatting

E-cigarettes review, rewritten to fit prototype format

July 03 2018

A review will have the following sections/pages:

Summary

Full text

Appendices

Related content

Messages for media

Article information

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Top of Summary, Full text and appendices page (the other pages will have just the title and a link to the article pages):

# **Electronic cigarettes for smoking cessation**

Cochrane Systematic Review – Intervention

Published date: 13 September 2016 | Date of last search: January 2016 (see what’s changed)

Authors: Hartmann-Boyce J | McRobbie H | Bullen C | Begh R | Stead LF | Hajek P | View author’s declarations of interest

## \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

SUMMARY

# Background

Electronic cigarettes (ECs) are electronic devices that produce an aerosol (or ‘vapour’) that the user inhales. This vapour typically contains nicotine without most of the toxins smokers inhale with cigarette smoke. Electronic cigarettes have become popular with smokers who want to reduce the risks of smoking. **This review aimed to find out whether electronic cigarettes help smokers stop smoking, and whether it is safe to use ECs to do this.** See more detail about electronic cigarettes.

(Link leads to this text “More detail about electronic cigarettes”):

## What are electronic cigarettes?

Electronic cigarettes (ECs) are known by a variety of names, including vape pens, e-hookahs, mods, tank systems, and e-cigs. ECs are electronic devices that use a battery to aerosolize a liquid, usually containing nicotine, flavouring, and other additives, which is inhaled through a mouthpiece.

## Who can use electronic cigarettes?

Smokers report using ECs to reduce the risks of smoking or to help them quit smoking. The regulation of e-cigarettes varies by country. Because nicotine is highly addictive and can harm the developing adolescent brain, young people are discouraged from using ECs.

## What other options are there?

Options to help people quit smoking include behavioural counselling, nicotine replacement therapy, and other medications. See: Related systematic reviews.

## How do people experience the intervention?

ECs replicate the experience of smoking, delivering a mist with nicotine instead of smoke. They may be perceived as cleaner. Some smokers may experience them as a bit harsher on the back of the throat, and some may experience that cravings return sooner than with smoking.

## Is there anything else someone should know before using the intervention?

It is unknown whether ECs are harmful to others exposed to second-hand aerosol. There may be restrictions on where ECs can be used.

# What this review is based on

Cochrane Reviews are based on systematic and robust selection of relevant studies. We included 24 studies in this review. See what studies we searched for and what we found.

1st link to standard description of what a Cochrane Review is.

2nd link leads to this text, which is a narrative summary of the table in the Full text called “What review authors searched for and found”:

## What studies we searched for

We searched for studies published up to January 2016. We searched for randomized trials in which current smokers (motivated or unmotivated to quit) were randomized to EC or a control condition, and which measured abstinence rates at six months or longer. As the field of EC research is new, we also searched for cohort follow-up studies with at least six months follow-up.

## What we found

We included 24 studies (three randomized trials, two of which were eligible for our cessation meta-analysis, and 21 cohort studies). Eleven of these studies are new for this version of the review. Two randomized trials compared EC with placebo (non-nicotine) EC, with a combined sample size of 662 participants. One trial included minimal telephone support and one recruited smokers not intending to quit. Both used early EC models with low nicotine content and poor battery life.

We identified 27 ongoing studies.

(For more detail, see Methods in the full text of this review.)

# Main findings

→ **Electronic cigarettes compared to placebo:** Electronic cigarettes may increase the proportion of people who abstain from smoking for at least six months (low certainty evidence)

→ **Electronic cigarettes compared to nicotine patches:** It is uncertain how effective electronic cigarettes are compared to nicotine patches (very low certainty evidence)

→ **Adverse effects:** There may be little if any difference in the frequency of adverse events for electronic cigarettes compared to placebo electronic cigarettes or nicotine patches. The most frequently reported adverse events were mouth and throat irritation. None of the included studies reported serious adverse events considered related to using electronic cigarettes (low certainty evidence)

Standard sentences: See current Plain language summary guidance: http://www.cochrane.no/sites/cochrane.no/files/public/uploads/how\_to\_write\_a\_cochrane\_pls\_27th\_march\_2017.pdf

## Summary of findings 1

## Summary of Findings should be numbered when there is more than one. Number 1 should be the one that appears in the summary. This will have consequences for the order of the comparisons listed in the full text.

iSoF generator: See isof.epistemonikos.org.

Create a log-in and let me add you to our organization.

Standard sentences: See current Plain language summary guidance: http://www.cochrane.no/sites/cochrane.no/files/public/uploads/how\_to\_write\_a\_cochrane\_pls\_27th\_march\_2017.pdf

# Authors’ conclusions

Electronic cigarettes may help people to quit smoking for at least six months compared with placebo. However, it is uncertain how effective electronic cigarettes are compared to nicotine patches, and the long-term safety of electronic cigarettes is unknown. The most commonly reported adverse effects of electronic cigarettes are irritation of the mouth and throat.

## \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

See also: Information for decision-makers

See also: Related systematic reviews

See also: Messages for media

(“Information for decision-makers” and “Related systematic reviews” link leads to texts in respective sections. See end of document for these parts. “Messages for media” leads to a section with content that would be created for the most part by other people than authors. )

## \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

FULL TEXT

References in the text will be linked to reference lists in the final published version, but I have not bothered to recreate these links in the prototype sketches.

# Background

Throughout this review, we discuss two types of cigarettes: electronic and conventional tobacco cigarettes. To avoid confusion, all mention of smoking, smoking cessation, cigarette use, smoke intake, etc., concern conventional cigarettes. When the text concerns electronic cigarettes we use the abbreviation ‘ECs’. EC users are sometimes described as vapers, and EC use as vaping. We refer to ECs that do not contain nicotine as placebo ECs.

## Description of the condition

Stopping smoking is associated with large health benefits. Despite most smokers wanting to quit, many find it difficult to succeed in the long term. Almost half who try to quit without support will not manage to stop for even a week, and fewer than five per cent remain abstinent at one year after quitting (Hughes 2004).

Considering the other factors that contribute to tobacco dependence, there is interest in developing smoking cessation products that would not only help relieve the unpleasant effects of nicotine withdrawal but would also act as an effective substitute for smoking behaviour and the rituals and sensations that accompany smoking, without the health risks associated with the inhalation of tobacco smoke.

## Description of the intervention

ECs are electronic vaporizing devices that have in common the ability to heat a liquid, usually comprising propylene glycol and glycerol, with or without nicotine and flavours, and stored in disposable or refillable cartridges or a reservoir, into an aerosol for inhalation. The commonly-used term for this aerosol is vapour, which we use throughout the review. ECs are currently being promoted by retailers to use instead of cigarettes when in smoke-free environments, and to replace conventional cigarettes with a safer alternative.

## Why it is important to do this review

Since ECs appeared on the market in 2006 there has been a steady growth in sales, with some commentators reporting that ECs are a threat to the sales of cigarettes (Herzog 2013). This growth in sales is reflected in population survey data from high-income countries that show an increased awareness and use of ECs over time (ASH 2016; Agaku 2014; Ayers 2011; Gallus 2014; West 2016). Data from lower-income countries also suggest high levels of EC use and awareness (Jiang 2016; Palipudi 2016).

Smokers, healthcare providers and regulators are interested to know if these devices can help smokers quit and if it is safe to use them to do so. In particular, healthcare providers have an urgent need to know what advice they should give to people who smoke. The largest health gains are achieved from stopping smoking completely, as opposed to reducing cigarette consumption, and as such this review focuses on the effectiveness of ECs in aiding smoking cessation.

# Objectives

To evaluate the safety and effect of using electronic cigarettes (ECs) to help people who smoke achieve long-term smoking abstinence.

# Methods

## Criteria for considering studies for this review

### Types of studies

Randomized trials in which smokers are randomized to ECs or to a control condition, and which measure abstinence rates at six months or longer, to determine the effectiveness of ECs in aiding smoking cessation and reduction.

We anticipated that the search would return few randomized trials and so we also considered the results from cohort follow-up studies with six months’ or longer follow-up. In this and the previous version of the review, we include those observational cohort studies which survey existing smokers at baseline, some of whom are already dual users of EC and cigarettes. As discussed in further detail below, these studies are heavily confounded due to the nature of their design. In anticipation of further high-quality studies becoming available, we will exclude this study design for effectiveness outcomes in the next update of this review, and will only include those observational studies where an intervention has been provided.

For adverse events and biomarkers, we included randomized cross-over trials and cohort follow-up studies with follow-up of greater than a week.

We included studies regardless of their publication status or language of publication.

### Types of participants

People defined as current smokers at enrolment into the studies. Participants can be motivated or unmotivated to quit.

### Types of interventions

We compare ECs with placebo ECs, ECs versus alternative smoking cessation aids, including nicotine replacement therapy or no intervention, and ECs added to standard smoking cessation treatment (behavioural or pharmacological or both) with standard treatment alone. As relatively few controlled trials are currently available (some are underway), we also include uncontrolled studies which evaluate ECs (see Types of studies).

### Types of outcome measures

Cessation at the longest follow-up point, which was at least six months from the start of the intervention, measured on an intention-to-treat basis using the strictest definition of abstinence, preferring biochemically-validated results where reported. We collected any data on adverse events at one week or longer, serious and non-serious, from the included studies, including changes in relevant biomarkers.

## Methods for identifying studies

For a detailed description of the strategies that were used to find studies that meet the selection criteria for this review, see: Methods for identifying studies (in *Additional details*).

## Methods for collecting and analysing data

## For a detailed description of the methods used to select studies, extract data from included studies, assess the risk of bias, and synthesize the findings of the included studies, see: Methods for collecting and analysing data (in *Additional details*).

# Results

## Results of the search

Our searches resulted in 24 studies for inclusion in this review. Below, Table 1 presents more detail about what we searched for and found. Figure X illustrates our inclusion and exclusion process in a study flow diagram. Then, in a series of tables and figures, we present the characteristics of included, excluded, and ongoing studies, as well as our judgements about risk of bias. (See Additional details for a list of all results tables and figures.)

‘Figure X’ link is the flow chart of included and excluded studies.

**Table 1: What review authors searched for and found**

|  |  |  |
| --- | --- | --- |
|  | **What the review authors searched for** | **What the review authors found** |
| ***Study designs*** | Randomized trials in which smokers are randomized to ECs or to a control condition.  Cohort follow-up studies with six months’ or longer follow-up.  Observational cohort studies which survey existing smokers at baseline.  For adverse events and biomarkers, randomized cross-over trials and cohort follow-up studies with follow-up of greater than a week. | 24 completed studies (3 randomized trials and 21 cohort studies).  27 ongoing studies. |
| ***Interventions*** | ECs with placebo ECs  ECs versus alternative smoking cessation aids, including nicotine replacement therapy or no intervention  ECs added to standard smoking cessation treatment (behavioural or pharmacological or both) with standard treatment alone. | Two randomized trials compared EC with placebo (non-nicotine) EC and one of those also compared EC with nicotine patches.  Both used early EC models with low nicotine content and poor battery life. |
| ***Participants*** | People defined as current smokers at enrolment into the studies. Participants can be motivated or unmotivated to quit. | People defined as current smokers at enrolment into trials, motivated or unmotivated to quit. |
| ***Settings*** | Any setting | Belgium, USA, UK, New Zealand, Italy, France, UK, Switzerland, South Africa.  Mixed settings (community, laboratory, cancer centre, web-based, research unit, outpatient clinic, inpatients, telephone survey). |
| ***Outcomes*** | Cessation at the longest follow-up point, which was at least six months from the start of the intervention, measured on an intention-to-treat basis using the strictest definition of abstinence, preferring biochemically-validated results where reported.  Any data on adverse events at one week or longer, serious and non-serious, from the included studies, including changes in relevant biomarkers. | The trial with both placebo EC and nicotine patches as comparisons reported cessation at 6 months, any adverse event reported by participants, and the proportion of serious adverse events.  The second trial reported cessation at 12 months, and adverse events thought to be related to EC.  Fourteen cohort studies reported abstinence at six months or longer. Seven cohort studies provided information on adverse events only. |
| ECs: Electronic cigarettes Placebo ECs: non-nicotine electronic cigarettes | | |

**Figure x.** Study flow diagram of searches conducted for this update: An overview of the number of studies that were screened for this version of the review and reasons for excluding studies

**Table x.** Characteristics of included studies: Relevant information about the methods, participants, interventions, and outcome measures for each study included in this review

**Table x.** Characteristics of excluded studies: Reasons for excluding specific studies that might appear to be relevant for this review

**Table x.** Characteristics of ongoing studies: Information about the methods, participants, interventions, and outcome measures of studies for which results have not yet been reported

**Table x.** Risk of bias of included studies: The review authors’ judgements about the risk of specific types of systematic errors (bias) and - the basis for those judgements - for each included study

**Figure x.** Risk of bias summary: An overview of the review authors’ judgements about the risk of specific types of systematic errors (bias) for all of the included studies

## Effects of interventions

This section is written up twice below.

The first time with findings sorted according to outcome, which is the way authors chose to write this actual review. The one summary of findings covers both outcomes. However this is not common.   
The second write up is with dummy text, and demonstrates the desired structure for findings written up according to comparison.

Effects according to outcome:

Summary of findings 1: *This table presents the effects of electronic cigarettes compared to nicotine patches and to placebo*

Overview of analyses (with forestplots)

### Cessation

In the trial comparing EC to patch (Bullen 2013) there was little difference in six-month CO (carbon monoxide)-validated continuous abstinence between the treatment arms (7.3%, 5.8% and 4.1%, in the nicotine EC, patch and placebo EC arms respectively). We made two comparisons. The first compares abstinence rates between nicotine and placebo EC (7.3% versus 4.1%, risk ratio (RR) 1.77, 95% confidence interval (CI) 0.54 to 5.77; 362 participants; Analysis 1.1). The second compares abstinence rates between the nicotine EC and patch arms (7.3% versus 5.8%, RR 1.26, 95% CI 0.68 to 2.34; 584 participants; Analysis 2.1). Fewer than half of all participants across all groups accessed support (39.8%, 35.9%, and 35.6% in the nicotine EC, patch and placebo EC arms respectively).

In the other randomized trial (Caponnetto 2013a) one-year abstinence rates (at least six months of not smoking and CO-validated) were higher in the two nicotine EC arms (13% and 9%) compared with the placebo EC group (4%). In our analysis we combined the two nicotine EC arms and compared these with the placebo group: 11% versus 4%, RR 2.75, 95% CI 0.97 to 7.76; 300 participants (Analysis 1.1).

We combined data from the two studies comparing abstinence rates in nicotine versus placebo EC groups. There was no significant statistical heterogeneity between the studies (Chi² = 0.30, P = 0.58; I² = 0%). The pooled results indicate that use of a nicotine-containing EC may increase the proportion of people who abstain from smoking for at least six months compared to placebo EC use (RR 2.29, 95% CI 1.05 to 4.96, low certainty evidence; Analysis 1.1, Summary of findings 1).

The included cohort studies (Summary of findings 1) share a serious limitation. As these studies only recruited current smokers, they excluded those people from the same population who tried ECs and stopped smoking (e.g. if 100 smokers tried ECs and 50 stopped smoking, these studies would only recruit the 50 who continued to smoke). Following up ‘treatment failures’ is likely to show a low treatment effect, even for treatments that are highly effective. To assess the effects of ECs on smoking, participants need to be recruited prior to initiating EC use. In future versions of this review, we will no longer include this group of studies.

### Adverse events

None of the randomized trials or cohort studies reported any serious adverse events that were considered to be plausibly related to EC use.

Of the people available for six-month follow-up in the ASCEND trial (Bullen 2013), 44.4% of participants in the nicotine EC arm reported any adverse events, compared with 44.7% and 45.6% in the patch and placebo EC arms respectively. Based on this trial, there may be little if any difference in the proportion of people who experienced adverse events for nicotine versus placebo EC (RR 0.97, 95% CI 0.71 to 1.34, low certainty evidence; Analysis 1.2, Summary of findings 1) or for nicotine EC versus patch (RR 0.99, 95% CI 0.81 to 1.12, low certainty evidence; Analysis 2.2, Summary of findings 1).

Effects according to comparison, with dummy text:

## 1

## Comparison 1. *Nictotine EC versus placebo EC*

Key characteristics of included studies 1

Summary of findings 1

### Cessation:

Table x. Analysis 1.1. Nicotine EC versus placebo EC: Cessation

Figure x. Nicotine EC versus placebo EC: Cessation

Text that would go here: summary of effect for this comparison on outcome. The following is dummy text. (Text that would go here: summary of effect for this comparison on outcome. The following is dummy text In the trial comparing EC to patch (Bullen 2013) there was little difference in six-month CO (carbon monoxide)-validated continuous abstinence between the treatment arms (7.3%, 5.8% and 4.1%, in the nicotine EC

### Adverse events:

Table x. Analysis 1.2. Nicotine EC versus placebo EC: Adverse events

Figure x. Nicotine EC versus placebo EC: Adverse events

Text that would go here: summary of effect for this comparison on outcome. The following is dummy text. (Text that would go here: summary of effect for this comparison on outcome. The following is dummy text In the trial comparing EC to patch (Bullen 2013) there was little difference in six-month CO (carbon monoxide)-validated continuous abstinence between the treatment arms (7.3%, 5.8% and 4.1%, in the nicotine EC

## 2

## Comparison 2. *Nictotine EC versus nicotine replacement therapy*

Key characteristics of included studies 2

Summary of findings 2

### Cessation:

Table x. Analysis 2.1. Nicotine EC versus nicotine replacement therapy: Cessation

Figure x. Nicotine EC versus nicotine replacement therapy: Cessation

Text that would go here: summary of effect for this comparison on outcome. The following is dummy text. (Text that would go here: summary of effect for this comparison on outcome. The following is dummy text In the trial comparing EC to patch (Bullen 2013) there was little difference in six-month CO (carbon monoxide)-validated continuous abstinence between the treatment arms (7.3%, 5.8% and 4.1%, in the nicotine EC

### Adverse events:

Table x. Analysis 2.2. Nicotine EC versus nicotine replacement therapy: Adverse events

Figure x. Nicotine EC versus nicotine replacement therapy: Adverse events

Text that would go here: summary of effect for this comparison on outcome. The following is dummy text. (Text that would go here: summary of effect for this comparison on outcome. The following is dummy text In the trial comparing EC to patch (Bullen 2013) there was little difference in six-month CO (carbon monoxide)-validated continuous abstinence between the treatment arms (7.3%, 5.8% and 4.1%, in the nicotine EC

# Discussion

**Key findings and certainty of the evidence**

As with the previous version of this review, a meta-analysis that pooled the results of two randomized trials with 662 participants showed that smokers who used nicotine electronic cigarettes (ECs) may be more likely to stop smoking than smokers using placebo ECs (9% versus 4% after 6 to 12 months). The difference (5%) was small, but not unusual given the low level of behavioural support provided. One randomized trial with 584 participants showed that a first-generation EC with low nicotine delivery compared to nicotine patches may result in similar proportions of smokers who stop smoking (7% versus 6% after 6 months). There was little if any difference (1%; 95% CI 2% fewer to 8% more) in the proportion of smokers who quit.

Although the two randomized trials were well conducted and judged to have a low risk of bias, we assessed the certainty of the evidence overall as low, because of the small number of trials and participants on which the estimates are based. We are encouraged by the increase in the number of ongoing studies that we identified in this update.

None of the included studies reported serious adverse events considered possibly related to EC use. The most commonly reported AEs were local irritation of the throat and mouth.

## Applicability of evidence

**Table 2:** *Applicability of evidence*

|  |  |
| --- | --- |
| Findings | *Interpretation* |
| All the included studies were conducted in high-income countries except one done in a middle-income country (South Africa). | *It is uncertain how applicable the findings are to low-income settings.* |
| Caponnetto 2013a used only a placebo EC control, which does not allow comparison with standard smoking cessation treatments. | *Effects in routine (non-research) settings may be different, given different smoking cessation interventions that are in use and differences in the motivation of smokers to quit.* |
| In Bullen 2013 EC was couriered directly to participants, whereas nicotine patches were supplied via a voucher that participants had to take to a community pharmacist. | *These differences in the way that participants received their allocated product might have influenced outcomes.* |
| Bullen 2013 and Caponnetto 2013a used first-generation cartridge ‘cigalike’ ECs that were widely available at the time but that have now been surpassed by newer models. The EC used in the ASCEND trial (Bullen 2013) delivered little nicotine and not particularly quickly (Cmax of 1.3 ng/ml was achieved after 10 minutes of use). The EC used in the ECLAT trial (Caponnetto 2013a) also performed poorly and was discontinued before the trial was published. | *Products with better nicotine delivery might have better effects.* |

## Agreements and disagreements with other studies or reviews

**Table 3:** *Agreements and disagreements with other studies or reviews*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Systematic reviews of EC safety or efficacy or both for smoking cessation (2014-2016) | | | | | |
| Author / Year | Cessation  reported? | Safety  reported? | Study types included | No. of  included studies | Summary of main conclusions |
| Gualano 2015 | Yes  (Narrative only) | Yes  (Narrative only) | Experimental and observational studies | 12 | EC can reduce the number of cigarettes smoked and withdrawal symptoms.  AEs reported are mainly related to a short period of use.  Long-term studies are needed to evaluate the effects of ECs after chronic exposure. |
| Hagstrom 2014 | Yes  (Narrative only) | Yes  (Narrative only) | RCTs and observational studies | 5 | Limited scientific data to support or refute their use as an option for smoking cessation.  Side effects were similar across studies, including cough, local irritation, and headache.  Length of follow-up was too short to assess other, more concerning side effects such as respiratory disorders or malignancy. |
| Harrell 2014 | Yes.  Meta-analysis  (OR 2.29, 95% CI 1.09 to 4.96 for nicotine EC vs no-nicotine EC) | Yes  (Narrative only) | All | 20 | Further research is needed to examine the longer-term safety, potential for long-term use and efficacy as a cessation aid. |
| Hua 2016 | No | Yes  (Narrative only) | Published case reports | 26 | EC use can be accompanied by negative and, less frequently, positive health ­effects.  ECs have their own set of health effects that need to be better characterized and understood. |
| Kalkhoran 2016 | Yes.  Meta-analysis (includes 15 cohort, 3 cross-sectional, 2 RCTs; OR for quitting 0.72, 95% CI 0.57 to 0.91 in EC users vs non-EC users) | No | Clinical trials, cohort studies, cross-sectional studies. Only studies with control groups included in meta-analysis | 38 | As currently being used, ECs are associated with significantly less quitting among smokers.  ECs should not be recommended as effective smoking cessation aids until there is evidence that, as promoted and used, they assist smoking cessation. |
| Waghel 2015 | Yes  (Narrative only) | No | All English-language clinical trials assessing cessation, reduction, desire to smoke, and/or withdrawal symptoms | 7 | Limited evidence available suggests EC may be effective as monotherapy for smoking cessation and reduction.  Superiority to nicotine replacement ­therapy­ was not proven |

# Authors’ conclusions

## Implications for practice

Only three randomized trials have been reported up to now. More data are needed to strengthen confidence in the estimated effects of electronic cigarettes (ECs). There is evidence from the pooled results of two trials that ECs with nicotine, compared with placebo ECs, may help smokers to stop smoking for at least 6 to 12 months (low certainty evidence). This corresponds to findings from placebo-controlled trials of nicotine replacement therapy (Stead 2012). It is uncertain how effective electronic cigarettes are compared to nicotine patches

(very low certainty evidence). ECs are an evolving technology and the effects of newer devices with better nicotine delivery are uncertain.

None of the included studies (short- to mid-term; up to two years) detected serious adverse events considered possibly related to EC use. The most commonly reported adverse effects were irritation of the mouth and throat. The long-term safety of ECs is uncertain.

## Implications for research

**Table 4:** *Implications for research*

|  |  |
| --- | --- |
| **Trialists** | Although placebo ECs were important in testing ECs with metrics used in evaluating nicotine replacement therapy products, future studies should focus on comparing ECs with ‘usual care’ or minimal treatment, and with alternative pharmacological and behavioural treatments.  Data are also needed on the proportions of smokers who successfully quit smoking with the help of ECs and who continue to use ECs long-term, and the proportion who eventually become nicotine-free. To assess the effects of ECs on smokers at the population level, data are needed on relationships between trajectories of vaping and smoking rates in countries where both products are available.  Given the variety of EC products on the market and the product evolution, future studies need to select ECs with good nicotine delivery that are representative of the best current standard in terms of reliability and user satisfaction.  Further RCTs also need to be adequately powered, and should consider providing ECs in a way that would be used in real-world settings (e.g. taking into account individual preferences for strengths and flavours of e-liquids and even EC devices). |
| **Systematic  reviewers** | None |
| **Other researchers** | None |

# References

Jump to: Included studies | Excluded studies | Ongoing studies | Other references | Other published versions of this review

## Included studies

Adriaens 2014

Adriaens K, Van Gucht D, Declerck P, Baeyens F. Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. International Journal of Environmental Research and Public Health 2014;11(11):11220-48.

Al-Delaimy 2015

Al-Delaimy WK, Myers MG, Leas EC, Strong DR, Hofstetter CR. E-cigarette use in the past and quitting behavior in the future: a population-based study. American Journal of Public Health 2015;105(6):1213-9.

Borderud 2014

Borderud SP, Li Y, Burkhalter JE, Sheffer CE, Ostroff JS. Electronic cigarette use among patients with cancer: characteristics of electronic cigarette users and their smoking cessation outcomes. Cancer 2014;120(22):3527-35.

Brose 2015

Brose LS, Hitchman SC, Brown J, West R, McNeill A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. Addiction 2015;110(7):1160-8.

Bullen 2013

Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 2013;382(9905):1629-37.

Caponnetto 2013a

Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. PloS One 2013;8(6):e66317.

Caponnetto 2013b

Caponnetto P, Auditore R, Russo C, Cappello GC, Polosa R. Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. International Journal of Environmental Research and Public Health 2013;10(2):446-61.

## Excluded studies

Adkison 2013

Adkison SE, O’Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong HH, et al. Electronic nicotine delivery systems: international tobacco control four-country survey. American Journal of Preventive Medicine 2013;44(3):207-15.

Battista 2013

Battista L, Di Iorio M, Tancredi M, Acconcia MC, Torromeo C, Barilla F, et al. Cardiovascular effects of electronic cigarettes. Circulation 2013;128:A16755.

Biener 2015

Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: Association with smoking cessation and motivation to quit. Nicotine & Tobacco Research 2015;17(2):127-33.

## Brown 2014a

Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. Addiction 2014;109(9):1531-40.

Bullen 2010

Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tobacco Control 2010;19(2):98-103.

Chausse 2015

Chausse P, Naughton G, Dutheil F. Electronic cigarettes: the resistance value of the heating filament could be the key to lung toxicity. Chest 2015;148(1):e29-30.

Chorti 2012

James SA, Meier EM, Wagener TL, Smith KM, Neas BR, Beebe LA. E-Cigarettes for immediate smoking substitution in women diagnosed with cervical dysplasia and associated disorders. International Journal of Environmental Health Research 2016;13(3):E288.

Czogala 2012

Czogala J, Cholewinski M, Kutek A, Zielinska-Danch W. [Evaluation of changes in hemodynamic parameters after the use of electronic nicotine delivery systems among regular cigarette smokers]. [Polish]. Przeglad lekarski 2012;69(10):841-5.

Dawkins 2012

Dawkins L, Turner J, Hasna S, Soar K. The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. Addictive Behaviors 2012;37(8):970-3.

Dawkins 2013a

Dawkins L, Turner J, Crowe E. Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers. Psychopharmacology 2013;227(3):377-84.

## Ongoing studies

Caponnetto 2014

Caponnetto P, Polosa R, Auditore R, Minutolo G, Signorelli M, Maglia M, et al. Smoking cessation and reduction in schizophrenia (SCARIS) with e-cigarette: study protocol for a randomized control trial. Trials [electronic resource] 2014; 15:88.

Fraser 2015

Fraser D, Borland R, Gartner C. Protocol for a randomised pragmatic policy trial of nicotine products for quitting or long-term substitution in smokers. BMC Public Health 2015;15:1026.

ISRCTN60477608

ISRCTN60477608. The efficacy of e-cigarettes compared with nicotine replacement therapy, when used within the UK stop smoking service. ISRCTN60477608 2014 (accessed 15 August 2016).

KCT0001277

KCT0001277. Effect of an electronic cigarette for smoking reduction and cessation in Korean male smokers: a randomized, controlled study. KCT0001277 2014 (accessed 15 August 2016).

Lopez 2016

Lopez AA, Cobb CO, Yingst JM, Veldheer S, Hrabovsky S, Yen MS, et al. A transdisciplinary model to inform randomized clinical trial methods for electronic cigarette evaluation. BMC Public Health 2016;16(1):217.

Lucchiari 2016

Lucchiari C, Masiero M, Veronesi G, Maisonneuve P, Spina S, Jemos C, et al. Benefits of e-cigarettes among heavy smokers undergoing a lung cancer screening program: randomized controlled trial protocol. JMIR Research Protocols 2016;5(1):e21.

NCT01842828

NCT01842828. E-Cigarettes as an addition to multi-component treatment for tobacco dependence: a pilot study. clinicaltrials.gov/show/NCT01842828 (accessed 16 July 2014).

NCT01989923

NCT01989923. Immediate smoking cessation for patients at risk for cervical dysplasia, cervical cancer and lower genital tract dysplasia and cancer - a feasibility study comparing nicotine replacement therapy with the electronic nicotine delivery system. clinicaltrials.gov/show/NCT01989923 (accessed 16 July 2014).

NCT02004171

NCT02004171. Electronic nicotine delivery devices (ENDDs) or nicotine inhaler for smoking cessation. clinicaltrials.gov/show/NCT02004171 (accessed 16 July 2014).

NCT02029196

NCT02029196. A randomised, parallel group, multi-centre study to evaluate the safety profile of the ITG EVP G1 product. clinicaltrials.gov/show/NCT02029196 (accessed 16 July 2014).

## Other references

Agaku 2014

Agaku IT, King BA, Husten CG, Bunnell R, Ambrose BK, Hu SS, et al. Tobacco product use among adults - United States, 2012-2013. MMWR - Morbidity & Mortality Weekly Report 2014;63(25):542-7.

ASH 2016

Action on Smoking and Health. Use of electronic cigarettes (vapourisers) among adults in Great Britain. www.ash.org.uk/files/documents/ASH\_891.pdf (accessed 21 July 2016).

Ayers 2011

Ayers JW, Ribisl KM, Brownstein JS. Tracking the rise in popularity of electronic nicotine delivery systems (electronic cigarettes) using search query surveillance. American Journal of Preventive Medicine 2011;40(4):448-53.

Balfour 2004

Balfour D. The neurobiology of tobacco dependence: A preclinical perspective on the role of dopamine projections to the nucleus. Nicotine & Tobacco Research 2004;6(6):899-912.

Barbeau 2013

Barbeau AM, Burda J, Siegel M. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach. Addiction Science & Clinical Practice 2013;8:5.

Barrett 2010

Barrett SP. The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. Behavorial Pharmacology 2010;21(2):144-52.

Bein 2011

Bein K, Leikauf GD. Acrolein - a pulmonary hazard. Molecular Nutrition & Food Research 2011;55(9):1342-60.

Cahill 2016

Cahill K, Lindson-Hawley N, Thomas K, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD006103. DOI: 10.1002/14651858.CD006103.pub7.

## Other published versions of this review

McRobbie 2012

McRobbie H, Bullen C, Hajek P. Electronic cigarettes for smoking cessation and reduction [Protocol]. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.

McRobbie 2014

McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub2.

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Methods for collecting and analysing data

Difference between protocol and review (in About this review)

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Analysis 1.2 . Nicotine EC vs placebo EC (outcome: adverse events)

Analysis 2.1 . Nicotine EC vs Nicotine replacement therapy (outcome: smoking cessation)

Analysis 2.2. Nicotine EC vs Nicotine replacement therapy (outcome: adverse events)

**Appendices**

Appendix 1 Summary of proportion of participants abstinent from smoking at follow-up: cohort studies

# Methods for identifying studies

Electronic searches

We searched the following databases in January 2016:

* Cochrane Tobacco Addiction Group Specialized Register
* Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2016, Issue 1)
* MEDLINE (OVID SP) (2004 to 2016 January week 2, & MEDLINE in process/In data review Feb 1 2016)
* Embase (OVID SP) (2004 to 2016 week 5)
* PsycINFO (OVID SP) (2004 to 2016 January week 4)

For the first version of the review we also searched CINAHL (EBSCO Host) (2004 to July 2014). We did not search this database for this review update as it did not contribute additional search results to the first version of the review.

The search terms were broad and included e-cig$ OR elect$ cigar$ OR electronic nicotine. The search for the 2016 update added the terms vape or vaper or vapers or vaping. The search date parameters are limited to 2004 to the present, because ECs were not available before 2004.

Searching other resources

We searched the reference lists of studies found in the literature search and the metaRegister of controlled trials database (www.isrctn.com/page/mrct). We also contacted authors of known trials and other published EC studies.

MEDLINE search strategy

1. e-cig$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. electr$ cigar$.mp.
3. electronic nicotine.mp.
4. (vape or vaper or vapers or vaping).ti,ab.
5. 1 OR 2 OR 3 OR 4

Identical terms used for other databases.

Line 4 added to search strategy for 2016 update.

# Methods for collecting and analysing data

## Selection of studies

Two review authors (from JHB, HM, LS or RB) independently prescreened all titles and abstracts obtained from the search, using a screening checklist. Where there was disagreement, we obtained the full-text version and resolved the disagreement by discussion or by referral to a third review author (PH).

Two review authors (from JHB, HM and RB) obtained and independently screened full-text versions of the potentially relevant papers for inclusion. We resolved any disagreements by discussion or with a third review author (PH).

## Data extraction and management

Two review authors (from JHB, HM or LS) extracted data from the included studies, and checked them against each other. A third review author (PH) was available to review and resolve any discrepancies. We extracted data on:

* Author
* Date and place of publication
* Study design
* Inclusion and exclusion criteria
* Setting
* Summary of study participant characteristics
* Summary of intervention and control conditions
* Number of participants in each arm
* Smoking cessation outcomes
* Type of biochemical validation (if any)
* Adverse events (AEs), serious adverse events (SAEs), and relevant biomarkers
* Assessment time points
* Risk of bias in the domains specified below
* Additional comments

We adopted a broad focus to detect a variety of adverse events.

One review author then entered the data into Review Manager 5 software for analyses, and another checked them.

## Assessment of risk of bias in included studies

Two review authors (JHB and HM or LS) independently assessed the risk of bias for each included study, following the approach recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). This approach uses a domain-based evaluation that addresses seven different areas: random sequence generation; allocation concealment; blinding of participants and providers; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other potential sources of bias. We assigned a grade (low, high, or unclear) for risk of bias for each domain. We resolved disagreements by discussion or by consulting a third author (PH).

## Measures of treatment effect

We analyzed dichotomous data by calculating the risk ratio (RR), using the longest follow-up data reported. For cessation, we calculated the RR as ((number of events in intervention condition/intervention denominator) / (number of events in control condition/control denominator)) with a 95% confidence interval (CI).

We analyzed continuous data (other measures of tobacco exposure) by comparing the difference between the mean change from baseline to the longest follow-up point in the intervention and control groups.

## Unit of analysis issues

We extracted data on smoking outcomes only from RCTs in which individuals were the unit of randomization. In the case of trials with multiple arms, we combined all relevant experimental intervention groups of the study into a single group, and combined all relevant control intervention groups into a single control group.

We offer a narrative synthesis of data from cohort studies.

## Dealing with missing data

For smoking cessation, we used a conservative approach as is standard for the Cochrane Tobacco Addiction Group, treating participants with missing data as still smoking. We based the proportion of people affected by adverse events on the number of people available for follow-up, and not the number randomized.

## Assessment of heterogeneity

We assessed the clinical and methodological diversity between studies to guide our decision as to whether data should be pooled. We were also guided by the degree of statistical heterogeneity, assessed by calculating the I² statistic (Higgins 2003); we considered a value greater than 50% as evidence of substantial heterogeneity.

Assessment of reporting biases

Reporting bias is best assessed using funnel plots, where 10 or more RCTs contribute to an outcome. However, there are currently insufficient studies to support this approach.

## Data synthesis

We provide a narrative summary of the included studies. Where appropriate, we have pooled data from these studies in meta-analyses. For dichotomous data, we used a fixed-effect Mantel-Haenszel model to calculate the risk ratio with a 95% confidence interval, in accord with the standard methods of the Cochrane Tobacco Addiction Group for cessation studies.

We had planned to calculate the summary estimates for continuous outcomes (e.g. biomarkers of tobacco exposure) using the inverse variance approach (also with a 95% CI). However, there were insufficient data with which to do so.

For adverse events, we originally planned to enter the most commonly-reported adverse events into meta-analyses to determine if there were any significant differences between the EC and control groups. We also originally planned to include data from cross-over trials in a meta-analysis using paired data obtained from reports. However, there were again insufficient data with which to do so, and hence we have summarized adverse event data narratively.

Subgroup analysis and investigation of heterogeneity

We had planned to undertake subgroup analyses to investigate differences between studies, such as:

* Intensity of behavioural support used;
* Type of control group (e.g. placebo EC, NRT);
* Type of participants (e.g. experience of EC use).

However, there were too few studies to conduct such analyses. Should further studies become available in future, we will follow this approach.

## Sensitivity analysis

We had planned to undertake sensitivity analyses to assess the effect of removing studies judged to be at high risk of bias. However, there were too few studies to conduct such analyses. Should further studies become available in subsequent updates, we will adopt this approach.

## Summary of findings table

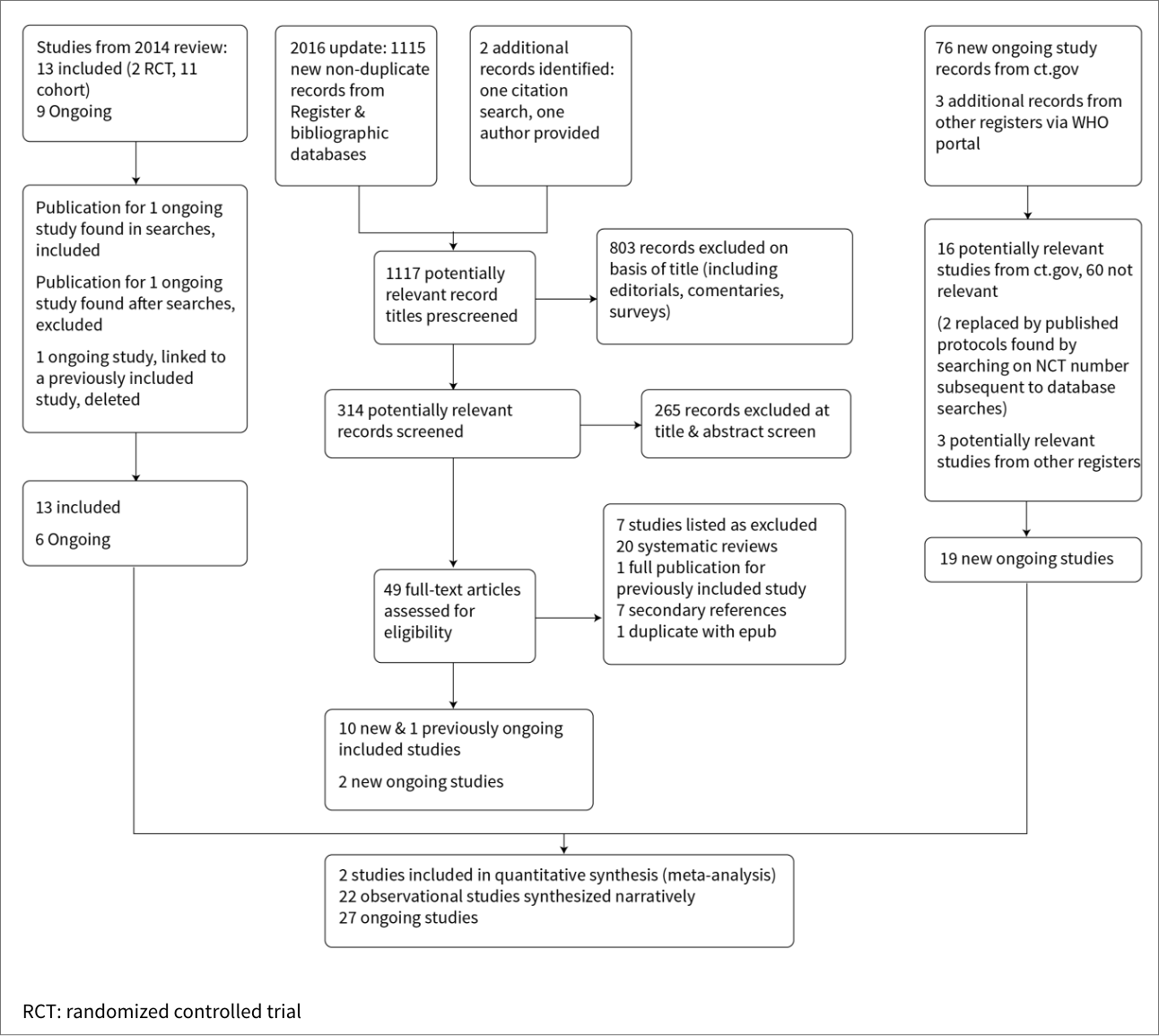
Following standard Cochrane methodology, we created a 'Summary of findings' table for both outcomes. For cessation, the 'Summary of findings' table only includes data from randomized controlled trials. Also following standard Cochrane methodology, we used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome, and to draw conclusions about the quality of evidence within the text of the review.

# Study characteristics

**Table 1:** *What review authors searched for and found*

Same as above in Full text

**Figure x.** *Study flow diagram of searches conducted for this update*



**Table x.** *Characteristics of included studies*

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**Table x.** *Characteristics of excluded studies*

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| --- | --- |
| **Study** | **Reason for exclusion** |
| *Adkison 2013* | Although this study uses a prospective cohort design, no data on EC use were collected at baseline, with EC use data only being available at follow-up |
| *Battista 2013* | Short-term EC use only |
| *Biener 2015* | Cohort study, but EC use evaluated retrospectively only |
| *Brown 2014a* | Cross-sectional survey |
| *Bullen 2010* | Short-term EC use only |
| *Chausse 2015* | Ineligible study design |
| *Chorti 2012* | Short-term EC use only |
| *Czogala 2012* | Short-term EC use only |
| *Dawkins 2012* | Short-term EC use only |
| *Dawkins 2013a* | Short-term EC use only |

**Table x.** *Characteristics of ongoing studies*

# Risk of bias

**Table x.** *Risk of bias of included studies*

**Adriaens 2014**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | Low risk | Block randomization was performed by using a randomization tool available on the website www.randomizer.org  (But high for abstinence outcome as non-randomized for our purposes) |
| Allocation concealment  (selection bias) | Unclear risk | Not specified |
| Blinding of participants  and personnel  (performance bias) | Low risk | Unblinded but as this review only includes data on objective measurements and not cessation judged unlikely to affect outcomes. |
| Blinding of outcome assessment  (detection bias) | Low risk | Unblinded but as this review only includes data on objective measurements and not cessation judged unlikely to affect outcomes. |
| Incomplete outcome data  (attrition bias) | Low risk | 36 out of 48 completed follow-up (11/16 in EC1 group, 12/17 in EC2 group, 13/17 in control group) |
| Selective reporting (reporting bias) | Unclear risk | Outcome reporting somewhat non-traditional; for example, collecting complaints but not explicitly adverse events, and incidence of AEs not reported. Unable to find prospectively registered protocol |
| Other bias | Unclear risk |  |

**Al-Delaimy 2015**

|  |  |  |
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| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | HIgh risk | Observational study |
| Allocation concealment  (selection bias) | HIgh risk | Observational study |
| Blinding of participants  and personnel  (performance bias) | Low risk | Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on performance |
| Blinding of outcome assessment  (detection bias) | Low risk | Telephone report, unblinded, but given nature of the study differential misreport seems unlikely |
| Incomplete outcome data  (attrition bias) | HIgh risk | Greater loss to follow-up for ‘will never use’ than users |
| Selective reporting (reporting bias) | Unclear risk | Unable to determine prespecified outcomes |
| Other bias | Unclear risk |  |

**Borderud 2014**

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| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | High risk | Observational study |
| Allocation concealment  (selection bias) | High risk | Observational study |
| Blinding of participants  and personnel  (performance bias) | Low risk | Although there is no blinding, the study design means that there is unlikely to be significantly impact on performance |
| Blinding of outcome assessment  (detection bias) | Low risk | Self-report only but differential misreport across EC conditions judged to be unlikely |
| Incomplete outcome data  (attrition bias) | High risk | Large number of participants (285) lost to follow-up (of eligible, 59.5% followed up). A further 82 deceased “significantly higher percentage of E-cigarette users dropped out of tobacco treatment and were lost to follow-up than non–E-cigarette users”. Complete-case analysis not significant, ITT analysis significant. |
| Selective reporting (reporting bias) | Unclear risk | Unable to determine prespecified outcomes |
| Other bias | Unclear risk |  |

**Brose 2015**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | HIgh risk | Observational study |
| Allocation concealment  (selection bias) | HIgh risk | Observational study |
| Blinding of participants  and personnel  (performance bias) | Low risk | Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on performance |
| Blinding of outcome assessment  (detection bias) | Low risk | Online survey, differential misreport seems unlikely |
| Incomplete outcome data  (attrition bias) | High risk | 43.3% (1759) followed up. 1687 used in analyses due to missing data or baseline pipe or cigar smoking. 1473 used in quit attempt analysis (further missing data) |
| Selective reporting (reporting bias) | Unclear risk | Unable to determine prespecified outcomes |
| Other bias | Unclear risk |  |

**Bullen 2013**

|  |  |  |
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| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | Low risk | Computerised block randomization |
| Allocation concealment  (selection bias) | Low risk | Computerised via study statistician |
| Blinding of participants  and personnel  (performance bias) | Low risk | NEC and PEC were blind to treatment condition in relation to one another. No blinding for NEC/PEC vs PATCH conditions, but as NEC and PATCH were both active treatments performance bias judged unlikely |
| Blinding of outcome assessment  (detection bias) | Low risk | Biochemical validation used |
| Incomplete outcome data  (attrition bias) | Low risk | LTFU 22% (all considered smokers). Patch group had a higher LTFU and withdrawal than EC (loss to follow-up 17% NEC, 27% patches, 22% PEC). However, minimal difference in per-protocol and ITT analyses |
| Selective reporting (reporting bias) | Unclear risk | All prespecified outcomes reported |
| Other bias | Unclear risk |  |

**Caponnetto 2013a**

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| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | Low risk | Computer-generated, block size 15 (5:5:5 ratio) |
| Allocation concealment  (selection bias) | Low risk | Randomization carried out by pharmacy, who did not have direct contact with the participants |
| Blinding of participants  and personnel  (performance bias) | Low risk | Double-blind. “Blinding was ensured by the identical external appearance of the cartridges. The hospital pharmacy was in charge of randomization and packaging of the cigarettes” |
| Blinding of outcome assessment  (detection bias) | Low risk | Biochemical validation used |
| Incomplete outcome data  (attrition bias) | Low risk | 211 (70.3%) and 183 (61%) attended 6- and 12-month follow-up (at 12m, 35% lost in 7.2 group; 37% lost in 5.4 group; 45% lost in no-nicotine group) |
| Selective reporting (reporting bias) | Unclear risk | Unclear if original intention was to combine groups A+B or not. In sample size calculation they compared A+B with C, but results are not reported in this way |
| Other bias | Unclear risk |  |

**Caponnetto 2013b**

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| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | High risk | Prospective cohort; no randomization |
| Allocation concealment  (selection bias) | High risk | Not randomized |
| Blinding of participants  and personnel  (performance bias) | High risk | No blinding |
| Blinding of outcome assessment  (detection bias) | Low risk | Biochemical validation used |
| Incomplete outcome data  (attrition bias) | Low risk | 0/14 lost to follow-up |
| Selective reporting (reporting bias) | Unclear risk | Unable to determine prespecified outcomes |
| Other bias | Unclear risk |  |

**Choi 2014**

|  |  |  |
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| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | High risk | Prospective cohort |
| Allocation concealment  (selection bias) | High risk | Not randomized |
| Blinding of participants  and personnel  (performance bias) | Low risk | Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on performance |
| Blinding of outcome assessment  (detection bias) | Low risk | Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on detection |
| Incomplete outcome data  (attrition bias) | Unclear risk | Unable to determine attrition bias |
| Selective reporting (reporting bias) | Unclear risk | Unable to determine prespecified outcomes |
| Other bias | Unclear risk |  |

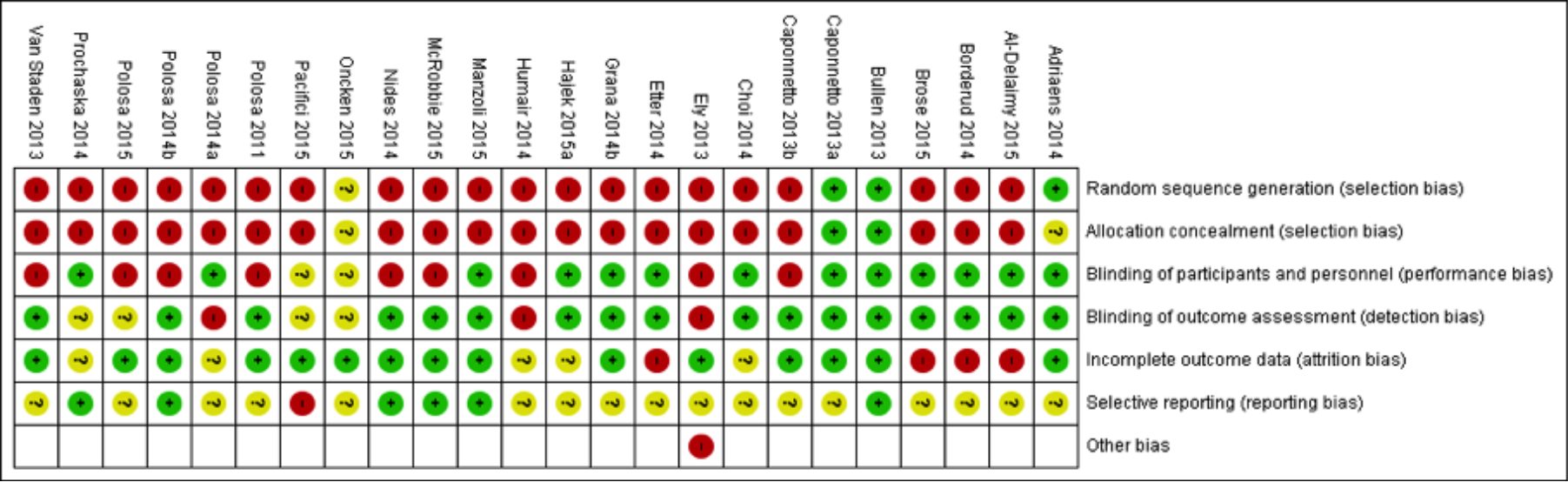
**Ely 2013**

|  |  |  |
| --- | --- | --- |
| Bias | Author’s judgement | Support for judgment |
| Random sequence generation  (selection bias) | High risk | Prospective cohort |
| Allocation concealment  (selection bias) | High risk | Not randomized |
| Blinding of participants  and personnel  (performance bias) | High risk | No blinding |
| Blinding of outcome assessment  (detection bias) | High risk | No blinding |
| Incomplete outcome data  (attrition bias) | Low risk | 4/48 lost to follow-up |
| Selective reporting (reporting bias) | Unclear risk | Unable to determine prespecified outcomes |
| Other bias | High risk | No definition of abstinence provided  Not clear if ‘completed programme’ was at 6 months. |

**Etter 2014**

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| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | High risk | Prospective cohort |
| Allocation concealment  (selection bias) | High risk | Not randomized |
| Blinding of participants  and personnel  (performance bias) | Low risk | Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on performance |
| Blinding of outcome assessment  (detection bias) | Low risk | Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on detection |
| Incomplete outcome data  (attrition bias) | High risk | 28% (N = 367) for those who answered the baseline survey (N = 1329) provided data at 1-year follow-up |
| Selective reporting (reporting bias) | Unclear risk | Unable to determine prespecified outcomes |
| Other bias | Unclear risk |  |

**Figure x.** *Risk of bias summary*

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# Evidence tables

(A GRADE evidence profile should come directly after its corresponding Summary of findings table, so when there are more than one set, they appear in pairs)

**Summary of findings 1**

Interactive table: <http://bit.ly/isof-e-cigarettes-test>

Or see:

Isof.epistemonikos.org

For examples

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# Analyses with forest plots

*Overview of analyses with forest plots*

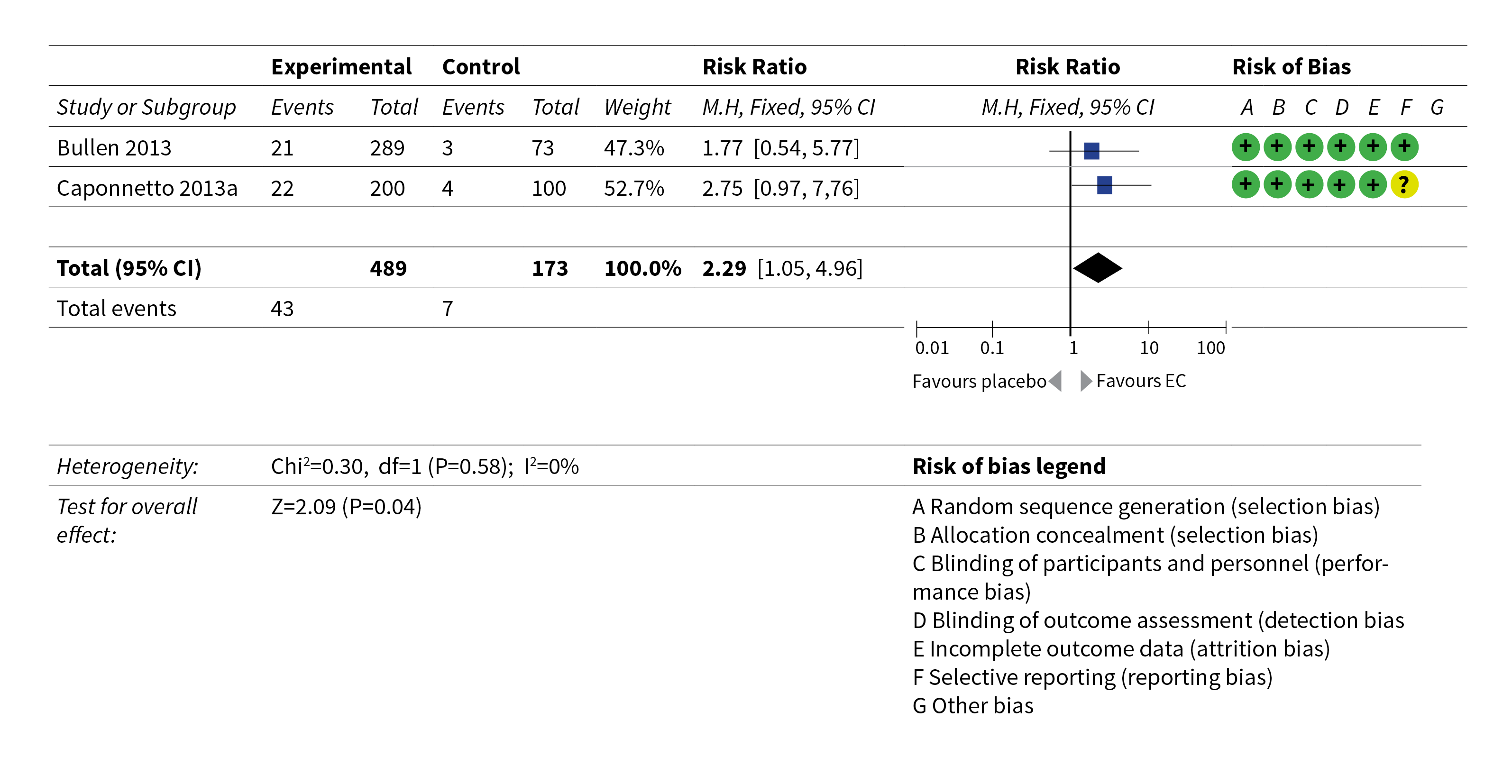
**Comparison 1:** Nicotine EC vs Placebo

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Analysis** | **Outcome or subgroup** | **Studies** | **Participants** | **Statistical method** | **Effect estimate** |
| Analysis 1.1 | Smoking cessation | 2 | 662 | Risk Ratio (M-H, Fixed, 95% CI) | 2.29 [1.05, 4.96] |
| Analysis 1.2 | Proportion of participants reporting adverse events | 1 | 298 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.71,1.34] |

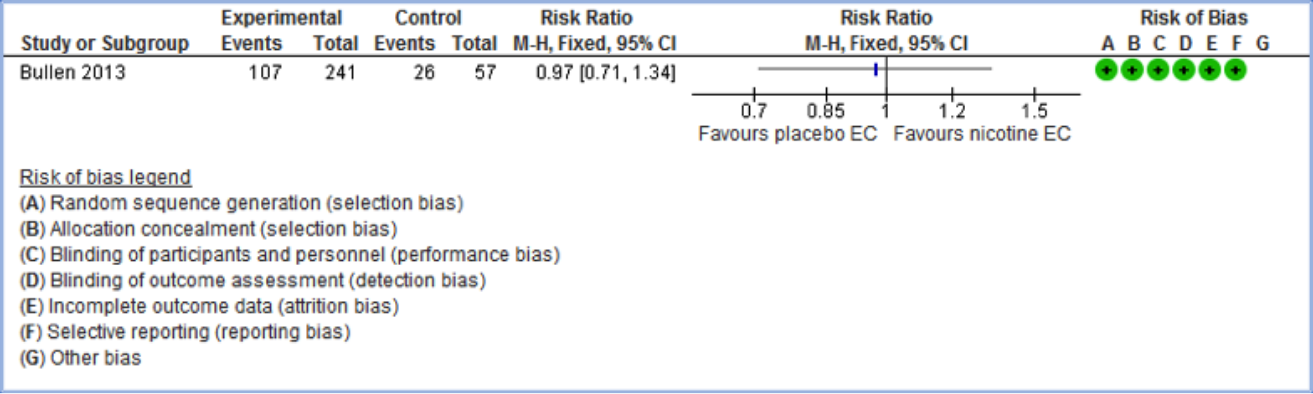
**Comparison 2:** Nicotine EC vs nicotine replacement therapy

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| --- | --- | --- | --- | --- | --- |
| **Analysis** | **Outcome or subgroup** | **Studies** | **Participants** | **Statistical method** | **Effect estimate** |
| Analysis 2.1 | Smoking cessation | 1 | 584 | Risk Ratio (M-H, Fixed, 95% CI) | 1.26 [0.68, 2.34] |
| Analysis 2.2 | Proportion of participants reporting adverse events | 1 | 456 | Risk Ratio (M-H, Fixed, 95% CI) | 0.99 [0.81,1.22] |

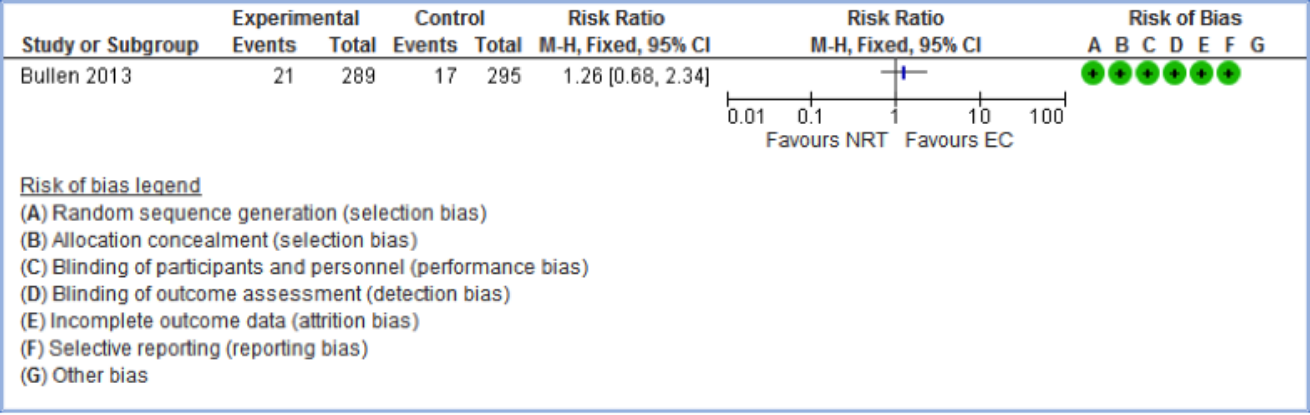
**Analysis 1.1.** Nicotine EC vs placebo EC (outcome: smoking cessation)



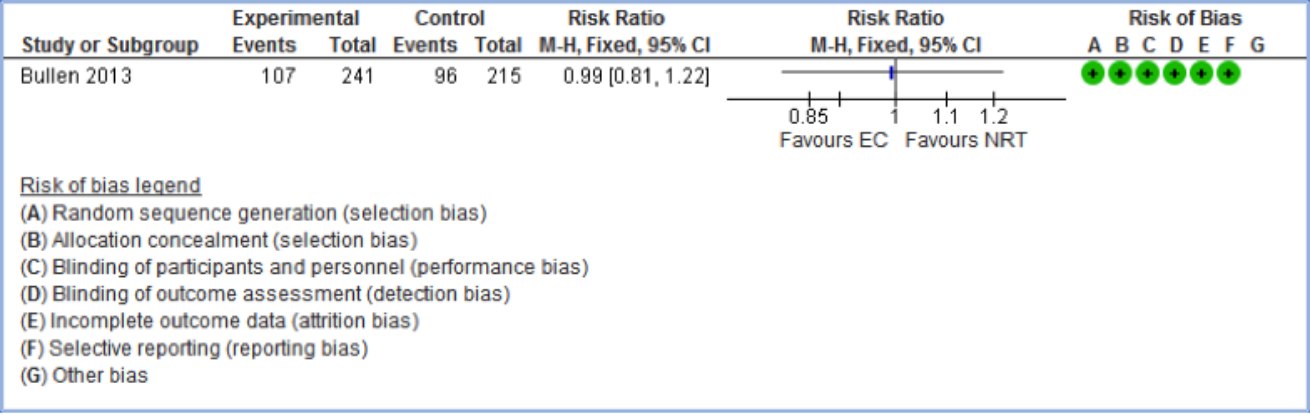
**Analysis 1.2 .** Nicotine EC vs placebo EC (outcome: adverse events)



**Analysis 2.1 .** Nicotine EC vs Nicotine replacement therapy (outcome: smoking cessation)

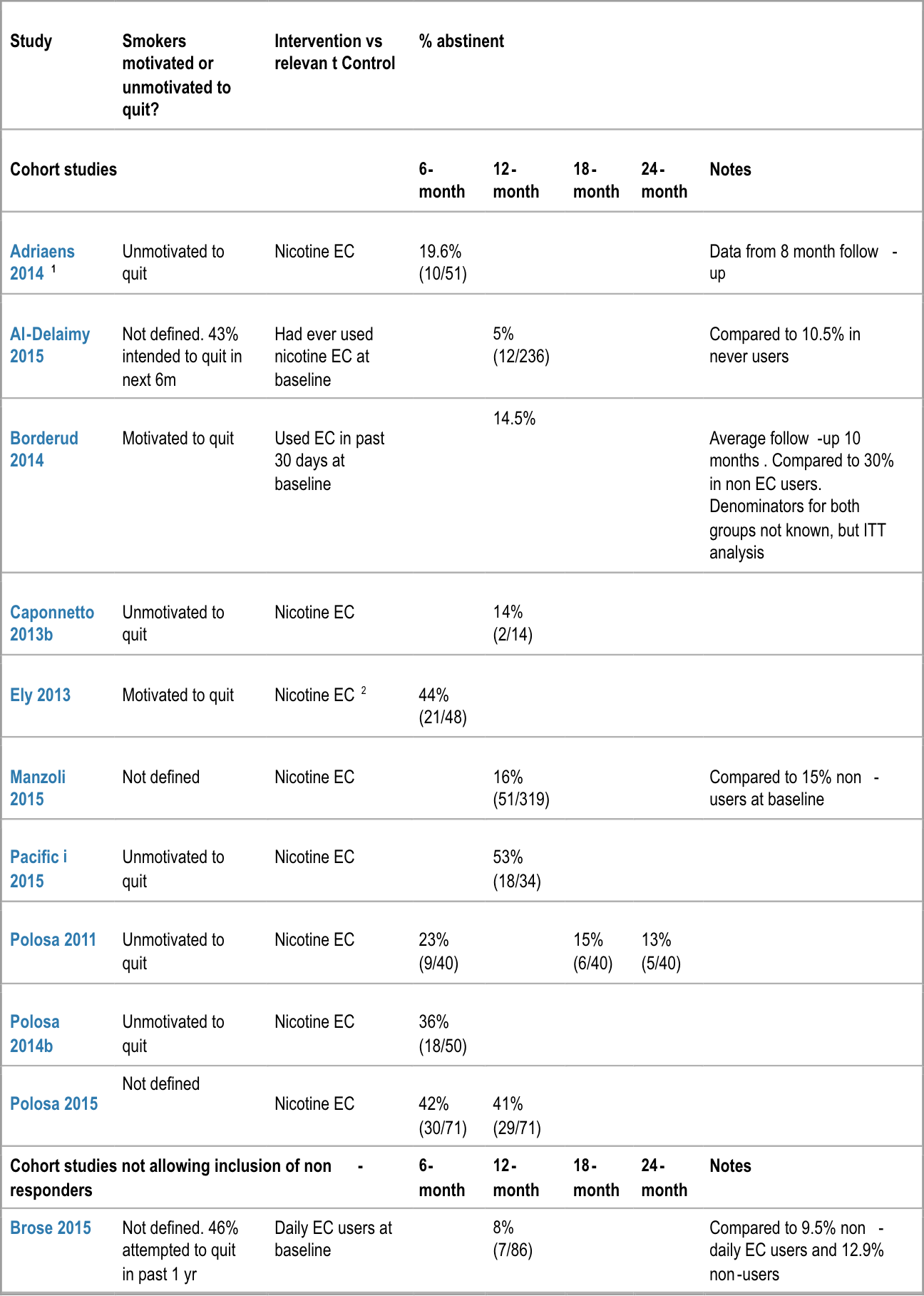


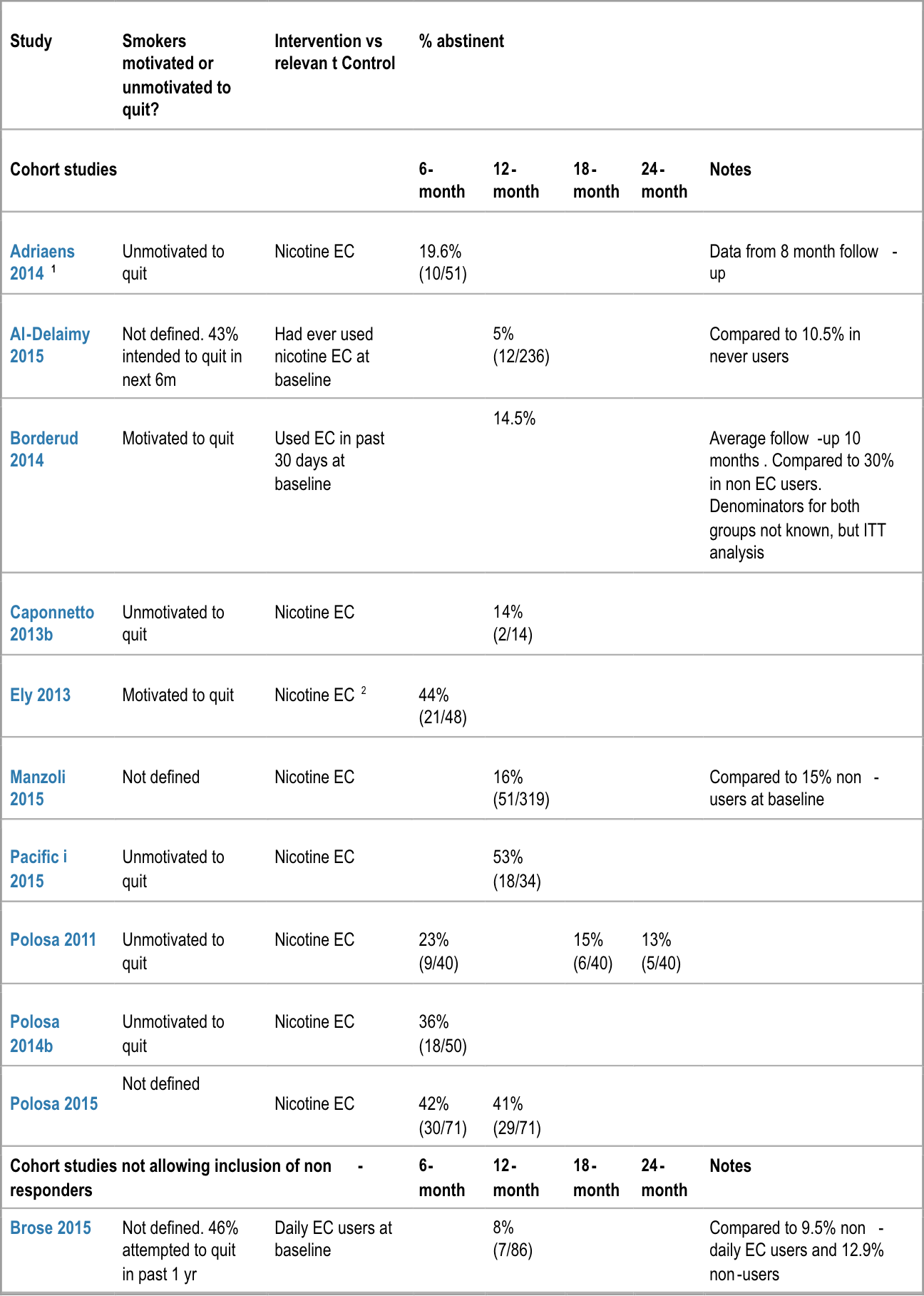
**Analysis 2.2.** Nicotine EC vs Nicotine replacement therapy (outcome: adverse events)



# Appendices

**Table x.** Summary of proportion of participants abstinent from smoking at follow-up: cohort studies





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Information for Decision makers

# For patients and the public

## What are electronic cigarettes?

Electronic cigarettes (ECs) are known by a variety of names, including vape pens, e-hookahs, mods, tank systems, and e-cigs. ECs are electronic devices that use a battery to aerosolize a liquid, usually containing nicotine, flavouring, and other additives, which is inhaled through a mouthpiece.

## Who can use electronic cigarettes?

Smokers report using ECs to reduce the risks of smoking or to help them quit smoking. The regulation of e-cigarettes varies by country. Because nicotine is highly addictive and can harm the developing adolescent brain, young people are discouraged from using ECs.

## What other options are there?

Options to help people quit smoking include behavioural counselling, nicotine replacement therapy, and other medications. See: systematic reviews of other options (below).

## How do people experience the intervention?

ECs replicate the experience of smoking, delivering a mist with nicotine instead of smoke. They may be perceived as cleaner. Some smokers may experience them as a bit harsher on the back of the throat, and some may experience that cravings return sooner than with smoking.

## Is there anything else someone should know before using the intervention?

It is unknown whether ECs are harmful to others exposed to second-hand aerosol. There may be restrictions on where ECs can be used.

# For health professionals

## Indications and contraindications

Although electronic cigarettes (ECs) are promoted to help people quit smoking, their safety and effectiveness are uncertain. Smokers may therefore want to consider other options

Young people are discouraged from using ECs, because nicotine is highly addictive and might harm the developing adolescent brain.

Nicotine replacement products, rather than ECs, should be considered to manage nicotine withdrawal symptoms in hospitalized smokers.

## Delivery

There are hundreds of different brands and models of ECs available. There is also wide variation in the composition of the fluid in the cartridge or in the EC reservoir (nicotine content, flavours, and other components). ECs may deliver very low amounts of nicotine to new users. However, even in the absence of good nicotine delivery, they can alleviate the urge to smoke.

There are differences between smoking a cigarette and smoking ECs. Smoking ECs too much at a time or smoking them for too long can lead to throat irritation and soreness. Nicotine absorption occurs more slowly with ECs than with smoking tobacco cigarettes, so smokers may need to get used to waiting longer to get a nicotine fix.

## Cautions

The effects of long-term use of ECs, EC cessation, and interventions to help people quit using ECs are unknown.

## Counselling patients

These points might be covered in response to questions by smokers about using ECs to help them quit smoking:

* The main findings of this review regarding the safety and effectiveness of ECs
* More detail about ECs
* Using ECs is probably less harmful than smoking conventional cigarettes, but we do not know how safe they are for users or those around them. The health consequences of vapor exposure are unknown, and inhaling
* EC flavourings might adversely affect respiratory function.
* There are other options that can help them to stop smoking (see above).

# For policy makers and citizens

## Policy options

Policy options for electronic cigarettes (ECs) include: requiring disclosure of ingredients, regulating nicotine levels, regulating the composition of fluids (e.g. banning flavours with high toxicity), regulating disposal of devices and fluids, restrictions on advertising, requiring product warnings, taxation policies, restrictions on where ECs can be used, and banning ECs altogether.

Policy options targeted at preventing use of ECs by children and young people include requiring child-resistant packaging, restricting flavours with high youth appeal, restricting advertising targeted at young people, and restricting sale of ECs to young people.

## Equity considerations

Use of ECs likely costs less than smoking. Therefore, to the extent that ECs are found to be safe and effective, affordability might not be a barrier to shifting from tobacco to ECs.

## Economic considerations

There are many EC producers, including tobacco manufacturers, promoting ECs through advertising and social media. In addition to considering taxation policies and the cost of ECs relative to tobacco cigarettes, consideration needs to be given to how the cost of ECs might affect uptake by non-smokers, particularly young people.

## Monitoring and evaluation

The impacts of policies aimed at encouraging or discouraging smokers to use ECs or to prevent youth from using ECs are uncertain. The effects of implementing such policies should be evaluated.

Because the safety and effectiveness of ECs is uncertain, rigorous evaluation is needed to inform future policy decisions. In the most recent update of this review, 15 ongoing randomised trials with follow-up of six months or longer were found.

# Other options

## Cochrane Reviews of other options to help people quit smoking

Mobile phone‐based interventions for smoking cessation

Robyn Whittaker, Hayden McRobbie, Chris Bullen, Anthony Rodgers, Yulong Gu | 10 Apr 2016

Aversive smoking for smoking cessation

Peter Hajek, Lindsay F Stead | 23 Jul 2001

Telephone counselling for smoking cessation

Lindsay F Stead, Jamie Hartmann‐Boyce, Rafael Perera, Tim Lancaster | 12 Aug 2013

Hypnotherapy for smoking cessation

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Nicotine replacement therapy for smoking cessation

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Print‐based self‐help interventions for smoking cessation

Jamie Hartmann‐Boyce, Tim Lancaster, Lindsay F Stead | 3 Jun 2014

Relapse prevention interventions for smoking cessation

Peter Hajek, Lindsay F Stead, Robert West, Martin Jarvis, Jamie Hartmann‐Boyce, Tim Lancaster | 20 Aug 2013

## Other related Cochrane reviews

Interventions to reduce harm from continued tobacco use

Nicola Lindson‐Hawley, Jamie Hartmann‐Boyce, Thomas R Fanshawe, Rachna Begh, Amanda Farley, Tim Lancaster | 13 Oct 2016

Physician advice for smoking cessation

Lindsay F Stead, Diana Buitrago, Nataly Preciado, Guillermo Sanchez, Jamie Hartmann‐Boyce, Tim Lancaster | 31 May 2013

See also: Related systematic reviews

## \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

messages for media

This section is for content generated for dissemination – press releases, blogshots, videos, etc.

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More by this author on the Cochrane Library

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Chris Bullen

Rachna Begh

Lindsay F Stead

Peter Hajek

## Authors’ contributions

All authors contributed to the writing of this review.

JHB, HM and LS extracted data, with discrepancies and disagreements referred to PH.

As principal investigator of one of the included trials, CB was not involved with data extraction or assessment of study quality.

# Declarations

## Authors’ declarations of interest

Within the last three years HM has received honoraria for speaking at research symposia and received benefits in kind and travel support from, and has provided consultancy to, the manufacturers of smoking cessation medications.

Within the last three years PH has provided consultancy for and received research funding from GSK, Pfizer, Novartis and other manufacturers of smoking cessation medications.

Two authors (HM, CB) have additional declarations:

CB and HM were investigators on a study of ECs from an EC manufacturer (Ruyan Group, Beijing and Hong Kong). Ruyan supplied the ECs used in the trial and contracted with Health NZ Ltd. to undertake the study. Health New Zealand Ltd funded The University of Auckland to conduct the trial, independently of Ruyan Group (Holdings) Ltd. The trial design conduct, analysis and interpretation of results were conducted independently of the sponsors.

CB and HM were investigators on the ASCEND EC trial funded by the Health Research Council of New Zealand that used product supplied at no charge from PGM international, a retailer of ECs.

JHB, RB and LS have no conflicts of interest to declare.

## Acknowledgements

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## Sources of support

### Internal support

• Queen Mary University of London, UK.

provides salary, office space and library resources for HM and PH

• The University of Auckland, New Zealand

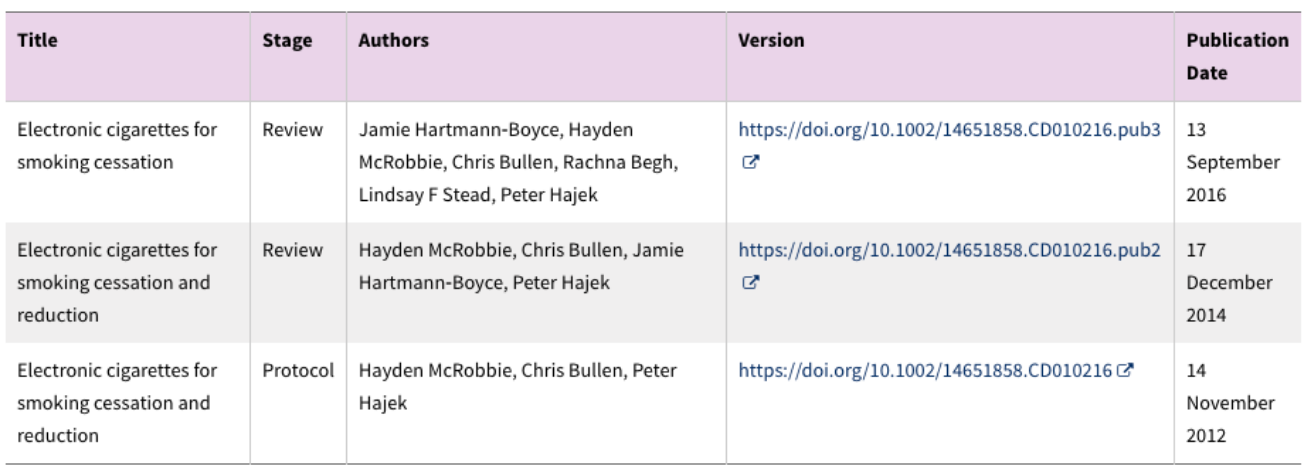
provides salary, office space and library resources for CB

### External support

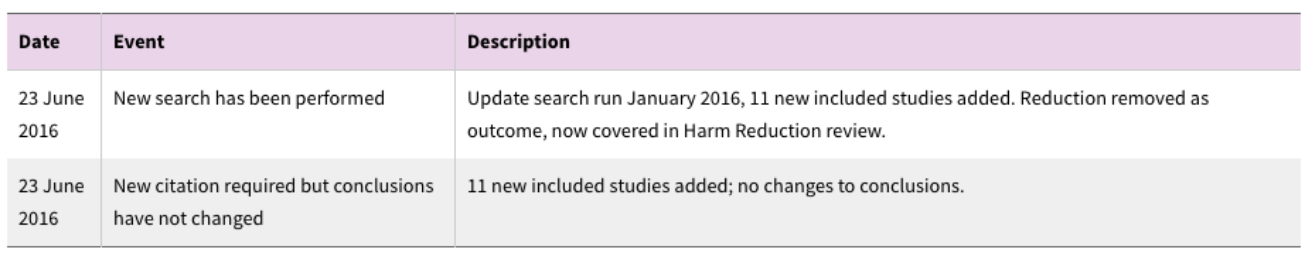
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# History

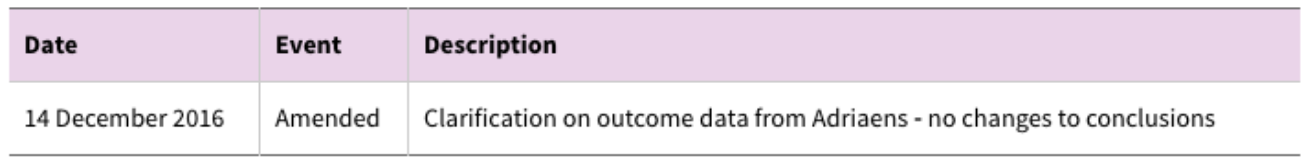
## Version history



## Search history



## What’s changed



## Difference between protocol and review

Originally, the protocol did not specify a minimum follow‐up period for data on adverse events. The Methods section has been changed to clarify that we will exclude follow‐up data at less than a week.

The original version of this review included reduction as a secondary outcome. The 2016 update removed reduction as an outcome, to bring the review into line with other reviews of cessation treatments produced by the Cochrane Tobacco Addiction Group and to prevent substantial overlap with the update of the group’s review of interventions for harm reduction (Stead 2007, update forthcoming).

# Keywords

Medical Subject Headings (MeSH) Keywords

\*Electronic Nicotine Delivery Systems [adverse effects, instrumentation];

\*Smoking Prevention;

Cohort Studies;

Nicotine [administration & dosage];

Nicotinic Agonists [administration & dosage];

Publication Bias;

Randomized Controlled Trials as Topic;

Smoking [epidemiology];

Smoking Cessation [\*methods];

Tobacco Use Cessation Products;

Medical Subject Headings Check Words:

Humans;

Middle Aged;

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RElated systematic reviews

# Related Cochrane Reviews

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Peter Hajek, Lindsay F Stead | 23 Jul 2001

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# Related Cochrane protocols

(consider separating this from list of reviews)

# Other related systematic reviews

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Nicola Lindson‐Hawley, Jamie Hartmann‐Boyce, Thomas R Fanshawe, Rachna Begh, Amanda Farley, Tim Lancaster | 13 Oct 2016

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