



The Cochrane review of electronic cigarettes for smoking cessation: remaining focused on the evidence

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Reply to C. Pisinger and J. Vestbo:

We are grateful for the opportunity to reply to the commentary on our Cochrane review of electronic cigarettes (EC) for smoking cessation [1] posed by PISINGER and VESTBO [2] with subsequent commentary by McALINDEN *et al.* [3].

Below we list the issues raised and provide our responses.

The decision to include two studies where nicotine levels were judged to be very low as non-nicotine EC was flagged as unusual. This decision was based on what was considered to be a clinically meaningful nicotine concentration (*i.e.* one that might have an effect, as an active ingredient). LEE *et al.* [4] used an EC with a nicotine concentration of $0.01 \text{ mg} \cdot \text{mL}^{-1}$ and VAN STADEN *et al.* [5] used a device with $0.014 \text{ mg} \cdot \text{mL}^{-1}$ of nicotine, *i.e.* concentrations that are unlikely to have any detectable psychoactive effects. Only the study of LEE *et al.* [4] was suitable for inclusion in the efficacy analysis. For the purpose of this letter, we conducted a *post hoc* sensitivity analysis that includes this study in the nicotine EC group (figure 1). The results still show a clinically and statistically significant benefit of EC compared to nicotine replacement therapy (NRT), but statistical heterogeneity has increased (from I^2 of 0% without LEE *et al.* [4], to 58% with).

Combining behavioural support and no support into one group of studies favours EC. Our rationale was to isolate the impact of nicotine EC, as all other elements are balanced across arms. There is no difference in the quit rates observed across studies where all participants are offered behavioural support *versus* studies where the control group receives no behavioural support and the EC group receives only EC, though confidence intervals are wide for all studies contributing data to this analysis.

*The review does not include a comparison of nicotine EC with incentives from the study by HALPERN *et al.* [6].* The study does not allow such a comparison, as the incentive arms also received free cessation aids, which included EC if the standard therapies failed. A control arm did not receive EC or incentives, and the comparison between the EC arm and the control arm is included in the review.

Observational studies were not included. We only included such studies to contribute data on EC safety because of the low number of trials in the field. For efficacy evaluation, Cochrane reviews only consider RCTs.

The authors do not present a balanced scientific view in the review. Our job is not to present a view, but to present the evidence using Cochrane methods, which are considered gold standard. The methods are transparent and readers can make their own decisions about the evidence they generate.

Results from population-based cohort studies showing that dual use might be more harmful than smoking alone are not mentioned. No such results emerged in studies that qualified for inclusion in this review.

Population-based cohort studies are not included. The review uses inclusion criteria dictated by the standard Cochrane guidance. Cohort studies are open to many biases, for example, they have shown that



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Evaluating new and emerging technologies for helping more people who smoke to quit is vital. The authors respond to a previous commentary on the Cochrane review, presenting the evidence using gold standard Cochrane methods. <https://bit.ly/3xDcv8B>

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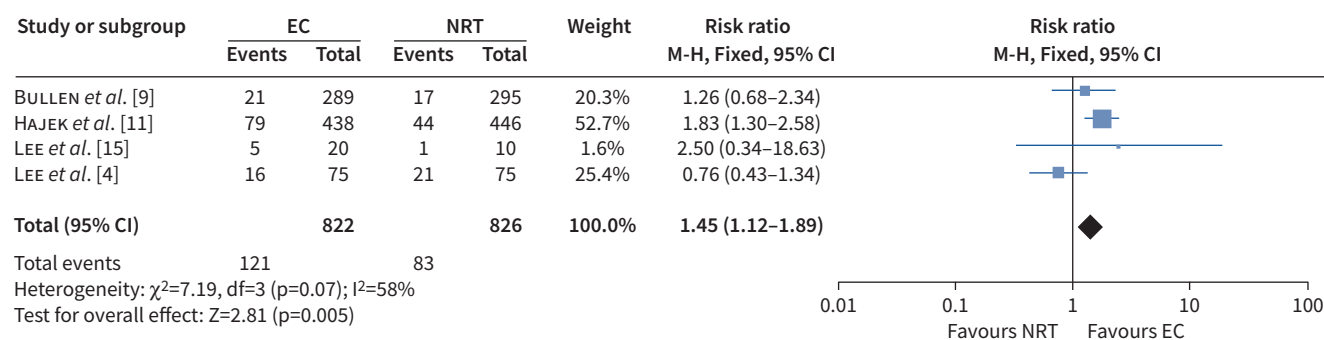


FIGURE 1 Nicotine electronic cigarettes (EC) compared with nicotine replacement therapy (NRT), smoking cessation at 6 months or longer. Sensitivity analysis including LEE *et al.* [4] (low nicotine; 0.01 mg·mL⁻¹ nicotine in e-liquid).

people who use NRT are no more likely to quit smoking [7], and yet NRT is a frontline cessation pharmacotherapy with evidence from over 100 trials showing benefit.

Many of those who use EC for smoking cessation continue using them long-term. In our forthcoming update, we include continued EC use as a secondary outcome. This is an important topic as it is currently not known whether such use has positive or negative effects on, for example, quality of life and risk of relapse.

A large number of in vitro, animal, experimental human and population-based studies have shown negative health effects of EC use. The review synthesises data on safety and health outcomes generated by eligible studies and its conclusions are based on what the data show. The suggestion that the conclusion “we did not detect any clear evidence of harm from nicotine EC, but the longest follow-up was 2 years” should instead refer to 6 months is not justified. The longest follow-up was indeed 2 years.

McALINDEN *et al.* [3] also criticise the review for overlooking the dangers of the “EVALI” (e-cigarette- or vaping-associated lung injury) outbreak in the USA. If any of the studies had detected EVALI, it would obviously be reported. EVALI has been associated with vaping vitamin E acetate in tetrahydrocannabinol oils in illicit products that were sold in the USA [8] and therefore it is unsurprising that it was not detected in our studies of regulated nicotine ECs.

PISINGER and VESTBO [2] note low quit rates in some of the included studies. BULLEN *et al.* [9] tested an early “cig-a-like” EC with low nicotine delivery. HALPERN *et al.* [6] recorded very low quit rates, but this was because trial design resulted in extremely low follow-up rates. The HAMMOND *et al.* [10] study referenced was not a randomised trial. The high quality RCTs cited [11, 12] achieved abstinence rates of 16–18% after 6 or 12 months [1], which exceed validated quit rates achieved by the UK national smoking cessation service [13].

We agree with PISINGER and VESTBO [2] that “E-cigarettes are not a miracle cure for smokers”. Sadly, no such cure exists. The interventions most widely used, with the most evidence, show only modest quit rates, and better methods are needed. Identifying these better methods remains a public health priority. Evaluating new and emerging technologies for helping more people who smoke to quit remains as important as ever.

Note: The review version cited was published in October 2020 and is now superseded by a living systematic review with monthly evidence updates [14].

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