Longitudinal patterns in smoking abstinence in trials of e-cigarettes for smoking cessation: secondary analysis of data from a systematic review, with meta-analyses

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Abstract

Introduction: We set out to better understand patterns of smoking abstinence and relapse in trials of e-cigarettes for smoking cessation.

Methods: Secondary analysis of studies from a Cochrane review. Studies had to test any type of e-cigarette intervention for smoking cessation. They had to follow-up for at least 6 months and report either: abstinence at multiple time points; abstinence using multiple definitions; relapse. We narratively synthesized data and conducted meta-analyses.

Results: We included 15 studies (n=7,233 participants). Using the Cochrane risk of bias tool v1, 5 were judged to be at high risk of bias, 8 were at low risk, and 2 at unclear risk. Absolute continuous abstinence rates tended to decline over time, but varying slopes. For absolute point prevalence abstinence, three studies demonstrated a shallow decline over time, two a steep decline, and three the opposite - an increase in abstinence over time. Data on relative abstinence rates (e-cigarettes versus control) were mixed. There were multiple instances of differences between point prevalence and continuous/sustained abstinence rates, both in trajectories over time and in terms of relative abstinence. The few studies addressing relapse highlighted mixed demographic and behavioural characteristics associated with relapse rates.

Conclusions: Smoking trajectories vary between trials of e-cigarettes for smoking cessation. Risk ratios may not be stable over time and may increase or decrease in favor of e-cigarettes depending on the study. Further data are needed, especially on relapse rates in early quitters who use e-cigarettes versus those who use other or no stop-smoking aids.

Implications: While some have posited e-cigarettes might increase smoking relapse when used as a cessation tool, others have posited that combustible cigarette quit rates may increase over time in the same studies due to ‘accidental quitting’. We set out to investigate this empirically and found considerable variation in smoking trajectories in e-cigarette trials. Data suggest risk ratios may not be stable over time and may increase or decrease in favor of e-cigarettes depending on the study. Further data are needed, especially on relapse rates in early quitters who use e-cigarettes versus those who use other or no stop-smoking aids.

Background

There is high certainty evidence that nicotine e-cigarettes help more people stop smoking at six months or longer than traditional nicotine replacement therapies (NRTs)[1]. However, questions remain about the longitudinal trajectories of cigarette use in people using e-cigarettes to quit smoking.

Firstly, the role of e-cigarettes in smoking relapse is unclear[2]. Some people have postulated that people who use e-cigarettes to help them quit smoking may be more likely to relapse to smoking, given the behavioral similarities between smoking and vaping, and the high nicotine content of many e-cigarettes. Others have hypothesized that, because people tend to use e-cigarettes for longer periods of time than traditional NRTs during an attempt to quit smoking, e-cigarettes might better protect against smoking relapse than other ways of quitting smoking.

Additionally, most smoking cessation interventions instruct people to quit smoking at the start of the intervention, meaning cigarette abstinence rates are often highest soon after the quit attempt, and decline over time. However, this can be affected by the way smoking abstinence is measured - best practice in the field is to measure continuous abstinence, such that to be classified as abstinent at six months, someone must have been abstinent (depending on definitions, sometimes allowing minor lapses) since a target quit date specified by the intervention[3]. However, due to the phenomena of 'accidental quitting' - when people not planning to quit smoking end up gradually doing so after starting to vape – and a potential higher likelihood of the use of e-cigarettes to reduce smoking before quitting, it has also been postulated that quit patterns in people using e-cigarettes might not match up with those of people using other quit aids. This could mean that unlike attempts to quit using other support, with e-cigarettes, smoking abstinence rates may increase over time[3].

In this paper, we set out to better understand patterns of smoking abstinence and relapse in trials of e-cigarettes interventions for smoking cessation through systematically reviewing and analyzing cigarette abstinence data across all reported time points and using all reported definitions of abstinence in randomized controlled trials of e-cigarettes for smoking cessation. As well as providing a better understanding smoking and e-cigarette use behavior, this could help to inform how smoking cessation should optimally be measured in future research.

Methods

We pre-registered plans for this analysis on Open Science Framework (https://osf.io/32fa7).

Studies were identified from those already included in the Cochrane living systematic review of e-cigarettes for smoking cessation (the 'parent review')[1]. In addition to inclusion criteria for the parent review, to be included in this paper studies must have reported smoking cessation at six months or longer and smoking cessation at multiple time points or using different methods (e.g.

continuous and point prevalence abstinence; as these can reflect differences in trajectories over time). Alternatively, they could have reported an analysis of smoking relapse.

Data was extracted from the parent review; we defined abstinence as abstinence from combustible tobacco (not necessarily from nicotine). In addition, we extracted data on the following from the original papers: definitions of abstinence used; time points at which abstinence data was collected; abstinence at every available time point and using every reported abstinence measure, including number of participants (per arm) followed up at this time point; and number of participants (per arm) considered abstinent at each time point. We also extracted any data on smoking relapse. Risk of bias assessments relied on those from the parent review, which were conducted using the Cochrane risk of bias tool v1.

For each study, we calculated the absolute and relative abstinence rates at all available time points. As is standard practice in the field, participants lost to follow up were considered to be continuing to smoke[4]. We plotted individual study data in Excel, with line charts showing absolute proportion abstinent in nicotine e-cigarette arms, and a separate set of charts showing risk ratios over time, grouped by comparator (comparators defined as per parent review). Within comparator groups, where two or more studies reported data at two or more similar time points, we pooled data using random effects Mantel-Haenzel meta-analyses, and present point estimates and 95% confidence intervals (CI). Where relevant, meta-analyses were subgrouped based on definition of abstinence (point prevalence versus continuous or sustained measures). We used I^2 to evaluate subgroup differences, interpreting a value of >50% as indicating potential heterogeneity between subgroups. We also used the Chi^2 test for subgroup differences as a potential indication of subgroup differences, in which p values <0.05 were taken to indicate statistically significant subgroup differences. Data on relapse, where reported, was synthesized narratively.

Results

We screened studies from the Cochrane review of e-cigarettes for smoking cessation published in 2024[1]. Overall, we included 15 studies, representing 7,233 participants. Details can be found in Supplementary Table 1; details on e-cigarettes can be found in Supplemental Table 2. The main reason for exclusion was that studies did not report cessation at six months or longer (52 studies). The remaining studies (n=23) were excluded because they only reported abstinence at one time point, didn't say anything on relapse AND didn't include multiple definitions of abstinence. Overall, 5 studies were judged to be at high risk of bias, 8 studies were judged to be at low risk of bias, and 2 studies were judged to be at unclear risk of bias.

Absolute smoking abstinence rates

As seen in Figure 1, absolute continuous abstinence rates trended downwards over time (note, this is to be expected given the way in which continuous abstinence is defined). In some instances, abstinence rates were higher at later follow-up points due to higher levels of follow-up (for example, where 6 months was the primary outcome, abstinence rates were sometimes higher than for interim outcomes due to additional resource dedicated to data collection). Trends in

point prevalence abstinence varied considerably by study (Figure 1), with three studies demonstrated a shallow decline over time, two a steep decline, and three the opposite - an increase in abstinence rates over time.

Smoking abstinence rates relative to other study arms

(Note: for the meta-analyses, studies were restricted to those which reported abstinence at common time points to ensure comparability over time, meaning these analyses are substantially less powered than those in the Cochrane review, and should not be used as definitive results for abstinence outcomes.)

E-cigarettes with nicotine versus e-cigarettes without nicotine

As seen in Figure 2a, there was no clear pattern in the six eligible studies. Meta-analyses showed no clear pattern based on time point or measure used (Chi^2 test for subgroup differences $p>0.30$ in all analyses; I^2 for subgroup differences=0%; and pooled CIs were wide and overlapped at all reported time points, see supplemental figures 1 and 2 (3 months 95% CI 1.00 to 2.01; 6 months 95% CI 0.79 to 3.00)).

E-cigarettes with nicotine versus usual care

In the three studies reporting abstinence at multiple time points, relative effects appeared to slightly decline over time (Figure 2b). Meta-analyses showed no clear pattern based on time point or measure used (Chi^2 test for subgroup differences $p>0.60$ in all analyses; I^2 for subgroup differences=0% in all analyses; and pooled CIs were wide and overlapped at all reported time points, see supplemental figures 3 and 4 (3 months 95% CI 1.20 to 3.68; 6 months 95% CI 1.00 to 2.65)).

E-cigarettes with nicotine versus nicotine replacement therapy

The trajectory of relative effects varied across the three studies contributing data (Figure 2c), with one showing a decline over time and others showing increases. Pooled data again showed no clear difference based on time point, with CIs overlapping (3 months 1.28 to 1.72; 6 months 1.04 to 2.49). All studies contributing data to meta-analysis used continuous/sustained definitions of abstinence (supplemental figures 5 and 6).

Advice to use e-cigarettes versus standard advice

Only one study tested this comparison and provided sufficient data to contribute to this paper; in this study, relative abstinence declined over time (Figure 2d)[18.]

Smoking relapse

Six studies provided some information or commentary on smoking relapse; none provided definitions for the term ‘relapse’, but it is assumed that this includes participants who met individual studies’ definitions of abstinence at earlier time points but at a later time point did not. Methodological heterogeneity precluded any statistical synthesis of these data. Two studies

commented on relapse rates in e-cigarette arms as compared to other conditions. Hajek 2019[12] noted that time to relapse and relapse rates at 52 weeks among participants with sustained abstinence at 4 weeks did not differ substantially between two trial groups (nicotine e-cigarettes versus NRT; hazard ratio for time to relapse: 1.14; 95% CI 0.96 to 1.34; RR of relapse at 52 weeks 1.27, 95% CI 0.93 to 1.73). Bullen 2013[7] noted that most participants relapsed within 50 days. Among those who relapsed, median time to relapse was more than twice as long in the nicotine e-cigarettes group (35 days, 95% CI 15–56) than in the NRT group (14 days, 95% CI 8–18; p<0·0001) or the non-nicotine e-cigarettes group (12 days, 5–34; p=0·09).

Four studies provided some commentary on who was most likely to relapse, and/or reasons for relapse. Conditions associated with relapse included: early dual use (as opposed to early complete switching)[8]; mental illness[19]; and reporting issues with the e-cigarettes.[20] Myers Smith 2022[17] found that abstainers using e-cigarettes at 4 weeks had a lower rate of relapse than those who were not using e-cigarettes, although the difference was not statistically significantly (46.3 versus 65.21%, RR = 0.71, 95% CI = 0.43–1.17).

Discussion

Data from 15 randomized controlled trials of e-cigarettes for smoking cessation showed mixed results in terms of absolute and relative abstinence rates over time. As expected, (due to the nature of the measure), absolute continuous abstinence rates tended to decline over time, but with variation in the slope of the decline. For point prevalence abstinence, two studies demonstrated a shallow decline over time, one a steep decline, and the fourth study the opposite - an increase in abstinence rates over time. These results suggest that smoking trajectories vary between trials of e-cigarettes for smoking cessation and point to the need for further research in this space, including observational data analysis and individual participant data analysis to further understand the ways in which vaping interventions affect smoking abstinence over time.

Data on relative abstinence rates (from trials comparing e-cigarettes to control conditions) was similarly mixed, particularly in trials comparing nicotine e-cigarettes versus NRT, with some trials showing reductions in relative abstinence and others showing increases over time. Again, this warrants further investigation, including through analysis of individual participant data. The possibility that risk ratios may not be stable over time and may increase or decrease in favor of e-cigarettes depending on the study, sounds a note of caution on any assertions that are made regarding trajectories of smoking abstinence in people given e-cigarettes compared to other interventions.
There are some important limitations to note. Given that the included studies span from 2013 to 2022 the product characteristics ECs in these trials, such as device type, availability of flavor, and nicotine content, have changed a lot during this period. These trials took places in multiple countries, possibly with different regulations on ECs, which could impact outcomes. Another limitation is the lack of clear definitions of relapse, which could impact the results[21].

There were multiple instances of differences between point prevalence and continuous/sustained abstinence rates, both in terms of trajectories over time and in terms of relative abstinence rates, and a minority of studies reported any information on smoking relapse. One study reported both continued and 7-day point prevalence abstinence[12]. As future trials of e-cigarettes continue to

advance the literature, we suggest the following: 1) trials report both continuous abstinence and point prevalence outcomes and 2) report more precise metrics of both lapse and relapse (e.g., median to each).

Data availability statement: All data is all from published literature, and data extraction sheets are available upon request.

Acknowledgements
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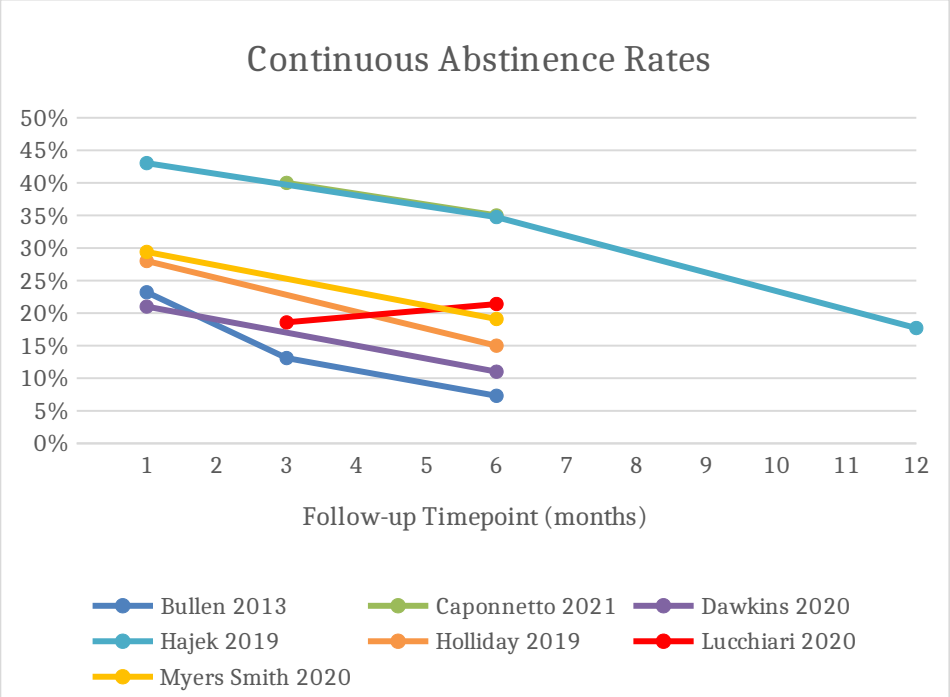
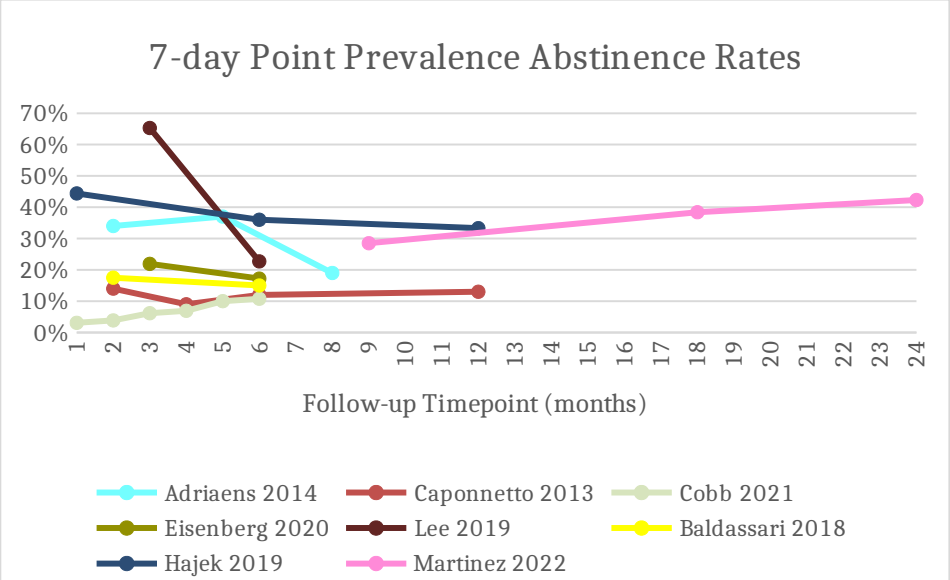
Declarations of interest
None to declare

Figure 1. Smoking abstinence rates in arms given a nicotine e-cigarette



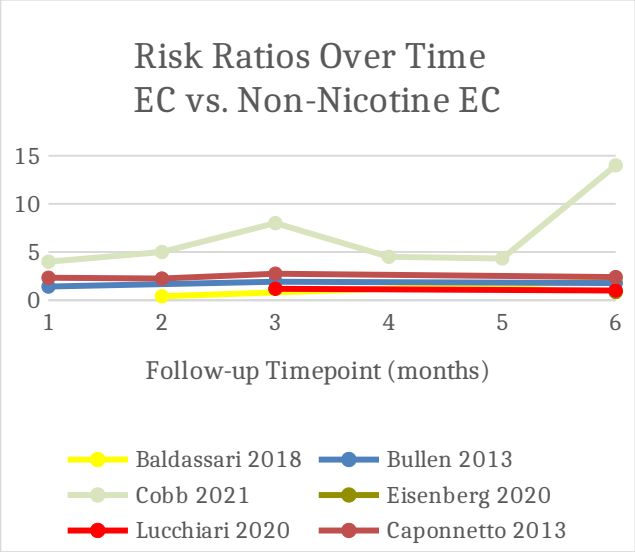
a) Continuous abstinence
Alt text: This graph shows smoking abstinence rates in arms given nicotine e-cigarettes. Absolute continuous abstinence rates tended to decline over time, but with variation in the slope of the decline.



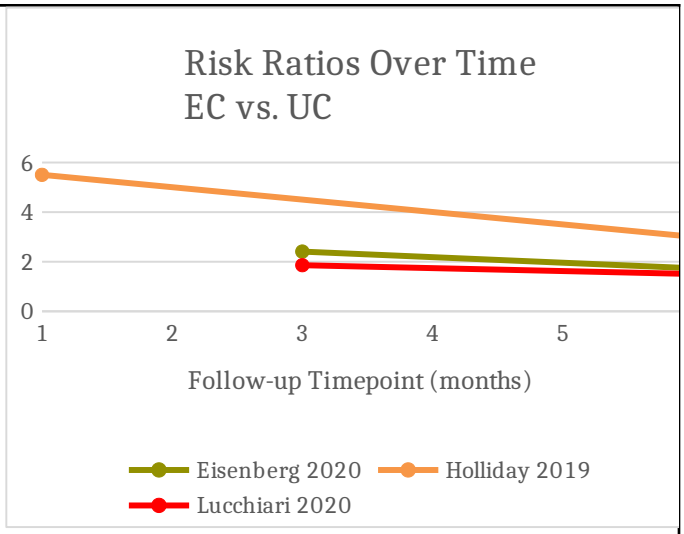
b) Point prevalence

Alt text: This graph shows point prevalence abstinence rates. Two studies demonstrated a shallow decline over time, one a steep decline, and the fourth study the opposite - an increase in abstinence rates over time.

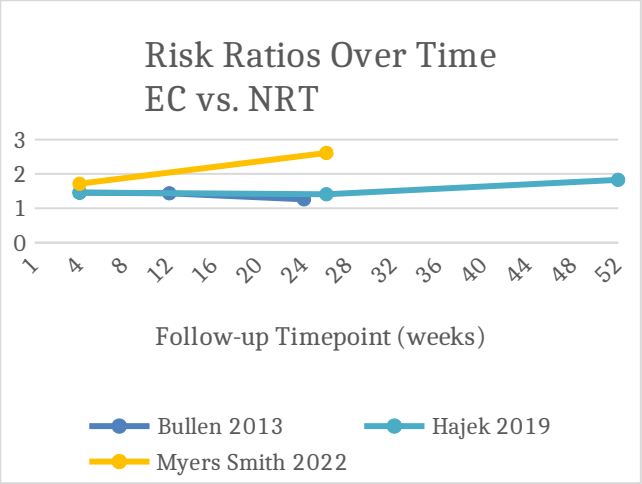
Figure 2. Risk ratios plotted over time



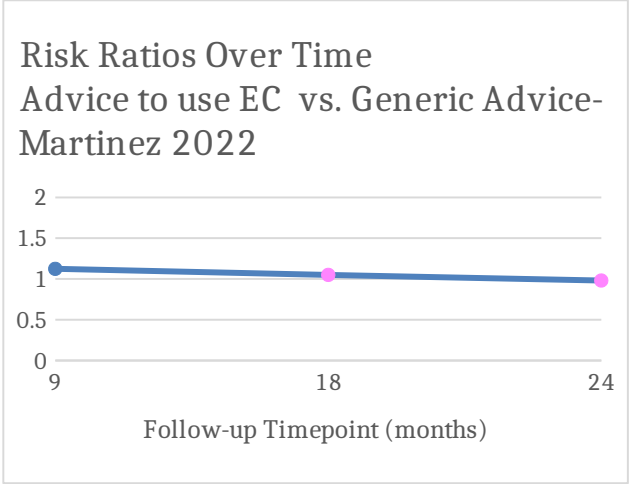
a) E-cigarettes with nicotine versus e-cigarettes without nicotine (note overlap between Lucchiari and Eisenberg partially obscures Eisenberg)



b) E-cigarettes with nicotine versus usual care



c) E-cigarettes with nicotine versus nicotine replacement therapy



d) Advice to use e-cigarettes versus standard advice

Alt text: The following graphs show the risk ratios over time of people given e-cigarettes compared to other interventions. It shows that risk ratios may not be stable over time and may increase or decrease in favor of e-cigarettes depending on the study, sounds a note of caution on any assertions that are made regarding trajectories of smoking abstinence in people given e-cigarettes compared to other interventions.

Citations:

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