



E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis

Sara Kalkhoran, Stanton A Glantz

Summary

Lancet Respir Med 2016;
4: 116–28

Published Online

January 14, 2016

[http://dx.doi.org/10.1016/S2213-2600\(15\)00521-4](http://dx.doi.org/10.1016/S2213-2600(15)00521-4)

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Department of Medicine,
(S Kalkhoran MD,
Prof S A Glantz PhD) and Center
for Tobacco Control Research
and Education, Cardiovascular
Research Institute
(Prof S A Glantz), University of
California San Francisco,
San Francisco, CA, USA

Correspondence to:
Prof Stanton A Glantz, Center for
Tobacco Control Research and
Education, University of
California, San Francisco,
CA 94143-1390, USA
glantz@medicine.ucsf.edu

Background Smokers increasingly use e-cigarettes for many reasons, including attempts to quit combustible cigarettes and to use nicotine where smoking is prohibited. We aimed to assess the association between e-cigarette use and cigarette smoking cessation among adult cigarette smokers, irrespective of their motivation for using e-cigarettes.

Methods PubMed and Web of Science were searched between April 27, 2015, and June 17, 2015. Data extracted included study location, design, population, definition and prevalence of e-cigarette use, comparison group (if applicable), cigarette consumption, level of nicotine dependence, other confounders, definition of quitting smoking, and odds of quitting smoking. The primary endpoint was cigarette smoking cessation. Odds of smoking cessation among smokers using e-cigarettes compared with smokers not using e-cigarettes were assessed using a random effects meta-analysis. A modification of the ACROBAT-NRSI tool and the Cochrane Risk of Bias Tool were used to assess bias. This meta-analysis is registered with PROSPERO (number CRD42015020382).

Findings 38 studies (of 577 studies identified) were included in the systematic review; all 20 studies with control groups (15 cohort studies, three cross-sectional studies, and two clinical trials) were included in random effects meta-analysis and sensitivity analyses. Odds of quitting cigarettes were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes (odds ratio [OR] 0.72, 95% CI 0.57–0.91). Association of e-cigarette use with quitting did not significantly differ among studies of all smokers using e-cigarettes (irrespective of interest in quitting cigarettes) compared with studies of only smokers interested in cigarette cessation (OR 0.63, 95% CI 0.45–0.86 vs 0.86, 0.60–1.23; $p=0.94$). Other study characteristics (design, population, comparison group, control variables, time of exposure assessment, biochemical verification of abstinence, and definition of e-cigarette use) were also not associated with the overall effect size ($p \geq 0.77$ in all cases).

Interpretation As currently being used, e-cigarettes are associated with significantly less quitting among smokers.

Funding National Institutes of Health, National Cancer Institute, FDA Center for Tobacco Products.

Introduction

E-cigarettes (also known as electronic cigarettes, electronic nicotine delivery systems, vapour pens, and many other terms) are battery-powered devices that heat a solution of humectants (usually propylene glycol or glycerol), nicotine (in most cases), and flavourings (in many cases), to deliver an aerosol that is inhaled by the user. E-cigarette use is increasing in many countries.^{1,2} Adults report various motivations for e-cigarette use, including to help them quit cigarettes and allowing them to continue to use nicotine in areas where smoking is prohibited,^{3–7} which are common themes in e-cigarette marketing and promotion.^{8–10}

In 2015, the US Preventive Services Task Force concluded that evidence was insufficient to recommend e-cigarettes for tobacco cessation in adults because of conflicting and limited evidence available at the time the recommendation was prepared.¹¹ Two meta-analyses of combined results from clinical trials have assessed whether e-cigarette use is associated with smoking cessation.^{12,13} The first,¹² based on two randomised trials,^{14,15} concluded that participants using nicotine e-cigarettes were more likely to have abstained from smoking cigarettes for 6 months (relative risk 2.29,

95% CI 1.05–4.96) than were participants using nicotine e-cigarettes, although the authors had little confidence in the results because of the small number of trials and small sample sizes. The second,¹³ based on six studies (the same two randomised trials,^{14,15} two cohort studies,^{16,17} and two cross-sectional studies^{18,19}) found the proportion of individuals using nicotine-containing e-cigarettes who quit cigarettes to be 20% (95% CI 11–28). These meta-analyses did not compare e-cigarette users to a control group not using e-cigarettes. A third meta-analysis²⁰ of five population-level studies (four longitudinal^{21–24} and one cross-sectional²⁵) found that e-cigarette use was associated with a significant depression in smoking cessation (odds ratio [OR] 0.61, 95% CI 0.50–0.75).

The different results of the meta-analyses of clinical trials and observational studies may relate to discrepancies in how e-cigarettes are used in a controlled study setting versus in the real world. Clinical trials evaluating a treatment or intervention under ideal conditions may differ from observational studies evaluating how a product is actually used in a real-world setting in study design, study population, study environment,²⁶ and ability to control for potential confounders, which can

Panel: Research in context**Evidence before this study**

We searched PubMed and Web of Science between April 27, 2015, and June 17, 2015, for articles that evaluated the association between e-cigarette use and cigarette smoking cessation among adult cigarette smokers. All relevant papers were included, irrespective of where the research was conducted or quality of the studies. There were no language restrictions, although all the papers were written in English. We included two additional studies published while this report was under peer review. Two earlier meta-analyses, one based on two randomised trials, and another based on six studies (the same two randomised trials plus two cohort studies and two cross-sectional studies), suggested that e-cigarettes might assist smokers in quitting cigarettes. These meta-analyses did not compare e-cigarette users to a control group not using e-cigarettes. The first meta-analysis (of two randomised trials) concluded that participants using nicotine e-cigarettes were more likely to have abstained from smoking cigarettes for at least 6 months (relative risk 2.29, 95% CI 1.05–4.96) than were participants using no-nicotine e-cigarettes. The second meta-analysis concluded that the proportion of individuals using nicotine-containing e-cigarettes who quit

cigarettes to be 20% (95% CI 11–28). A third meta-analysis of five population-level observational studies found that e-cigarette use was associated with a significant depression in smoking cessation.

Added value of this study

We include all available (38) studies in our systematic review and all 20 studies with control groups (15 cohort studies, three cross-sectional studies, and two clinical trials) in our meta-analysis. Odds of quitting cigarettes were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes (odds ratio 0.72, 95% CI 0.57–0.91). Sensitivity analysis showed that the results were not affected by a wide range of study design factors.

Implications of all the available evidence

As currently being used, e-cigarettes are associated with significantly less quitting among smokers. According to the results of our systematic review and meta-analysis, e-cigarettes should not be recommended as effective smoking cessation aids until there is evidence that, as promoted and used, they assist smoking cessation.

compromise the generalisability of results of observational studies.²⁷ These differences are potentially important for e-cigarettes, which, unlike prescription-only nicotine inhalers, are mass-marketed consumer products. We conducted a systematic review and meta-analysis of clinical trials and observational real-world studies to assess the association between e-cigarettes (as available and used) and cigarette smoking cessation among adults, including all smokers as well as only those interested in quitting smoking.

Methods**Data sources and searches**

To identify studies, we began by manually searching the references from the three earlier meta-analyses^{12,13,20} and completed a comprehensive literature search of PubMed and the Web of Science Core Collection between April 27, 2015, and June 17, 2015. As detailed in the appendix, search terms included “electronic cigarette”, “e-cigarette”, “electronic nicotine delivery”, “stop”, “quit”, “cessation”, “abstain”, and “abstinence”. Search results were not limited by language, but all identified studies were in English. There was no search limitation on publication dates. We continued to monitor the scientific literature after completing the formal search; this report includes two studies that were published while it was in initial peer review.^{28,29} Both abstracts and full manuscripts were considered.

Study selection

One investigator (SK) did the search, data extraction, and risk of bias assessment, which was subsequently

reviewed by a second investigator (SAG). Clinical trials, whether randomised and controlled or not, cohort studies, and cross-sectional studies were all considered. We included studies that evaluated the relationship between e-cigarette use and cigarette smoking cessation among adult cigarette smokers; therefore, two studies on adolescents were excluded.^{30,31} We considered all study populations that were defined as “adult” by the study authors (youngest age varied from 15 to 30 years in the studies that defined “adult”; detailed descriptions of each article are provided in the appendix). We included studies of participants who were interested in quitting cigarette smoking and studies of all smokers irrespective of interest in quitting. We excluded one cross-sectional study²⁵ because the primary outcome was e-cigarette use, not smoking cessation.

Data extraction

Studies that included cigarette smoking cessation as a primary outcome were evaluated for inclusion. The definitions of cigarette smoking cessation included in this systematic review and meta-analysis included both self-reported abstinence from smoking cigarettes and biochemically-validated measures of abstinence (eg, cotinine or exhaled carbon monoxide measurements). All studies were included irrespective of the duration of abstinence from cigarettes. Those who quit cigarettes could have still been using e-cigarettes; quitting e-cigarettes was not used as an outcome.

Data extracted from each study included study location, design, population, definition and prevalence of e-cigarette use, comparison group (if applicable),

See Online for appendix

	Location	Years	Population	Prevalence and definition of e-cigarette use	Comparison group	Confounders		Definition of quitting	Odds of quitting (95% CI)
						Level of dependence	Other		
Cohort studies of real-world use of e-cigarettes, e-cigarette use assessed at baseline									
Borderud et al (2014) ³⁴	USA	2012–13 and follow-up 6–12 months later	1074 smokers with cancer in a tobacco programme	285 (27%) reported any e-cigarette use in the past 30 days at enrolment	No e-cigarette use in the past 30 days at baseline	Fagerstrom Test for Nicotine Dependence; e-cigarette users: mean 4.6 (SD 2.7); non-e-cigarette users: 3.3 (2.7)	Past quit attempts, cancer diagnosis	Self-reported 7 day cigarette abstinence	1.0 (0.6–2.0), adjusted; ITT analysis: 0.5 (0.3–0.8), adjusted
Choi et al (2014) ²¹	USA	2010–11 and follow-up 1 year later	346 young adult smokers in Midwestern USA	Used e-cigarettes >1 day in the past 30 days at baseline	Never e-cigarette use	..	Demographics and baseline cigarette consumption	Self-reported 30 day cigarette abstinence	0.93 (0.19, 4.63), adjusted
Grana et al (2014) ²²	USA	2011 and follow-up 1 year later	949 current adult smokers	88 (9%) reported using e-cigarettes in the past 30 days (even once) at baseline	No e-cigarette use in the past 30 days (at baseline)	<30 min to first cigarette smoked: (69%) baseline e-cigarette users, (58%) baseline non-e-cigarette users	Intention to quit, cigarette consumption	Response of “Yes, I do not smoke now” to the question “Have you ever tried to quit smoking?” and reporting no past 30 day e-cigarette use	0.76 (0.36–1.60), adjusted
Prochaska et al (2014) ³⁵	USA	2009–13	956 adult daily smokers (at least five cigarettes per day) with serious mental illness in the San Francisco Bay Area (part of a randomised controlled trial)	Reported e-cigarette use when asked about “other tobacco use”: 0/35 (0%) participants in 2009, 5/348 (1%) in 2010, 21/225 (9%) in 2011, 38/202 (19%) in 2012, and 37/146 (25%) in 2013	Non-e-cigarette users	78.5% smoked within 30 min of waking	Demographics, study factors, psychiatric variables, and tobacco-related variables	Past 7 day tobacco abstinence (self-report and biochemical verification)	1.16 (0.65–2.05),* adjusted
Al-Delaimy et al (2015) ³⁶	USA	2011–12 and follow-up 1 year later	1000 current adult smokers in California aged 18–59 years; 368 individuals used in final analysis	236 (24%) reported they “have used e-cigarettes” at baseline	“Will never use e-cigarettes” at baseline and follow-up	<30 min to first cigarette smoked: 595 (61%) among entire study sample	Demographics and intention to quit	Self-reported 30 day cigarette abstinence	0.41 (0.18–0.93), adjusted
Harrington et al (2015) ³⁷	USA	2012–13 (baseline and 6 month follow-up)	979 hospitalised cigarette smokers (825 with follow-up) at one hospital	171 (21%) reported current e-cigarette use at baseline, 247 (30%) reported e-cigarette use at follow-up (98 [12%] at both times)	Did not use e-cigarettes at baseline	Those who reported quitting smoking	0.90 (0.54–1.50),† unadjusted
Hitchman et al (2015) ³⁸	UK	2012 and follow-up in 2013	1643 current adult cigarette smokers	348 (21%) reported any e-cigarette use at baseline, 587 (36%) at follow-up	Never e-cigarette use at baseline	Strength of urges to smoke (5 point scale from no urges to extremely strong urges) at initial assessment (0: 126 [8%], 1: 212 [13%], 2: 764 [47%], 3: 387 [24%], 4: 105 [6%], 5: 49 [3%])	Motivation to stop smoking at baseline and demographics	Those who reported that they “do not smoke cigarettes at all” or “stopped smoking completely”	0.83 (0.52–1.30), adjusted
Manzoli et al (2015) ³⁹	Italy	2013 with follow-up 1 year later	236 e-cigarette only users, 491 cigarette smokers, and 232 dual users of cigarettes and e-cigarettes	232 dual users of cigarettes and e-cigarettes (used cigarettes and e-cigarettes within the same week for past 6 months); 81 dual users continued using e-cigarettes at 1 year	Cigarette smokers not using e-cigarettes	..	Demographics, body-mass index, alcohol use, self-rated health, medical comorbidities, and years of tobacco smoking	Self-reported past 30 day smoking abstinence (25% verified with CO)	0.83 (0.53–1.29), adjusted

(Table 1 continues on next page)

	Location	Years	Population	Prevalence and definition of e-cigarette use	Comparison group	Confounders		Definition of quitting	Odds of quitting (95% CI)
						Level of dependence	Other		
(Continued from previous page)									
Pavlov et al (2015) ⁴⁰	Canada	Not available (baseline and 3 month follow-up)	3073 cigarette smokers enrolled in a smoking cessation programme at a primary care clinic in Toronto, CA	363 (12%) did not use e-cigarettes at enrolment but began using e-cigarettes during the programme	Participants who did not start using e-cigarettes during the programme	Heaviness of smoking index (unclear if adjusted for)	Education, employment, income, quit confidence, and motivation to quit (unclear if adjusted for)	Definition unclear	0.68 (0.54–0.87) unclear if adjusted
Sutfin et al (2015) ⁴¹	USA	2010–13	271 college students in North Carolina and Virginia who smoked cigarettes and had not tried an e-cigarette at baseline	118 (44%) had ever tried e-cigarettes by study wave 5 (none at baseline)	Did not use e-cigarettes during study	..	Baseline smoking frequency, lifetime other tobacco use, demographics, membership in Greek organisation, [‡] sensation seeking at baseline, and number of friends and family who smoke	Did not continue to smoke at study wave 6 (derived from inverse of those who continued to smoke)	0.40 (0.21–0.76), [†] adjusted
Cohort studies of real-world use of e-cigarettes, e-cigarette use assessed at follow-up									
Adkison et al (2013) ³³	Canada, USA, UK, Australia	2008–09 and follow-up 1 year later	5939 adults age >18 years who were current or former cigarette smokers	3% reported currently using an e-cigarette	Current non-users of e-cigarettes at follow-up	Self-reported quitting since previous study wave	0.81 (0.43–1.53),* unadjusted
Vickerman et al (2013) ³⁴	USA	2011–12	2758 adult tobacco quitline callers age >18 years in six US states surveyed 7 months after enrolment	765 (31%) had ever used e-cigarettes	Never use of e-cigarettes	Self-reported 30 day tobacco abstinence at 7 month follow-up	0.50 (0.40–0.63), [†] unadjusted
Pearson et al (2014) ⁴²	USA	2012–13, and 3 month follow-up	2123 current smokers in the USA participating in a web-based smoking cessation trial	672 (32%) reported using an e-cigarette to quit smoking cigarettes in the past 3 months	No e-cigarette use in the past 3 months	Fagerstrom score: e-cigarette for cessation, median 6 (IQR 4–7); no e-cigarette for cessation, 5 (4–7)	Demographics, quitting-related variables, other quit methods	Self-reported 30 day abstinence from cigarettes	0.68 (0.53–0.87), adjusting for all factors but other quit methods; 0.77 (0.59–1.00), adjusting also for other quit methods
Biener et al (2015) ⁷	USA	2011–12, and follow-up in 2014	695 adult smokers in two US metropolitan areas (Texas and Indiana)	111 (23%) were intensive e-cigarette users (defined as daily e-cigarette use for at least 1 month), 220 (29%) were intermittent e-cigarette users (defined as regular but not daily use for more than 1 month), and 364 (48%) were either non-users of e-cigarette or had tried e-cigarettes no more than two times (self-trial)	Never used e-cigarettes or tried e-cigarettes no more than two times	Heavy smoker (>20 cigarettes per day and first cigarette <30 min of waking): 21% (95% CI 11–34) in non-users/self-trial; 28% (11–54) in intermittent users; 68% (40–87) in intensive users	Demographics	Self-reported 30 day abstinence from cigarettes	Intensive users: 6.07 (1.11–33.18), adjusted; intermittent users: 0.31 (0.04–2.80), adjusted

(Table 1 continues on next page)

Location	Years	Population	Prevalence and definition of e-cigarette use	Comparison group	Confounders		Definition of quitting	Odds of quitting (95% CI)	
					Level of dependence	Other			
(Continued from previous page)									
Shi et al (2015) ⁴³	USA	2010, and follow-up 1 year later	2454 US cigarette smokers in the 2010 Tobacco Use Supplement to the Current Population Survey	279 (11%) reported having ever used e-cigarettes	No smoking cessation aid use	Baseline cigarette dependence level assessed and controlled for in analysis	Demographics	Cigarette abstinence for >30 days	0.44 (0.24-0.79), adjusted
Cross-sectional studies of real-world use of e-cigarettes									
Brown et al (2014) ³⁸	UK	2009-14	5863 adult smokers in England in 2009-14 as part of the Smoking Toolkit Study	489 (8%) answered e-cigarettes to which "of the following did you try to help you stop smoking during the most recent serious quit attempt?"	Over the counter NRT or no aid	Strength of urges to smoke (0-5 score): e-cigarettes, mean 2.0 (SD 1.2); NRT, 2.2 (1.1); no aid, 1.8 (1.1); time spent with urges to smoke (0-5); e-cigarettes, 1.9 (1.3); NRT, 2.2 (1.3); no aid, 1.8 (1.3)	Demographics, time since start of quit attempt, past year quit attempts, abrupt vs gradual quitting, year, and interaction terms	Those who answered "I am still not smoking" when asked "how long did your most recent serious quit attempt last before you went back to smoking"	1.63 (1.17-2.27) compared with NRT, adjusted; 1.61 (1.19-2.18) compared with no aid, adjusted
Christensen et al (2014) ⁴⁴	USA	2012-13	9656 adults via the telephone-based Kansas Adult Tobacco Survey	12% had ever used an e-cigarette; 3% had used an e-cigarette at least once in the past month	Never tried e-cigarettes or currently do not use e-cigarettes	..	Demographics	Self-reported cigarette abstinence	Ever e-cigarette use: 0.43 (0.24-0.79), adjusted; current e-cigarette use: 0.16 (0.07-0.36), adjusted
McQueen et al (2015) ³⁸	USA	2014	106 patients with head and neck cancer at an otolaryngology clinic in Alabama aged >19 years who were current or past daily tobacco users	23 (22%) reported using e-cigarettes as part of their quit programme	Did not use e-cigarettes as part of their quit programme	Self-reported 30 day abstinence from all tobacco products, including e-cigarettes	0.25 (0.09-0.65), † unadjusted
Randomised clinical trials with control groups									
Bullen et al (2013) ³⁴	New Zealand	2011-13	657 adult cigarette smokers interested in quitting, recruited through newspaper advertising	Intervention arm: 16 mg nicotine e-cigarettes	21 mg nicotine patches (n=295), no-nicotine e-cigarettes (n=73)	Fagerstrom mean 5.6 (SD 2) in e-cigarette group, 5.5 (2) in patch group, 5.5 (2) in no-nicotine e-cigarette group	Randomised groups with similar demographics, age started smoking, years smoking, type of tobacco smoked, past year quit attempt, living with smokers, smoking behavioural questionnaire, autonomy over smoking scale, self-efficacy to quit	Smoking abstinence 6 months after quit day, defined as self-reported abstinence of the follow-up period with <5 cigarettes total, verified by exhaled carbon monoxide	RR 1.77 (0.54-5.77) compared with non-nicotine e-cigarette; unadjusted; RR 1.26 (0.68-2.34) compared with patches, unadjusted
Non-randomised clinical trials with control groups									
Hajek et al (2015) ³⁹	UK	2015	100 smokers accessing Stop Smoking Services	69 (69%) accepted e-cigarettes as part of their smoking cessation treatment	Did not accept e-cigarettes	Self-reported abstinence from cigarettes at 4 weeks, biochemically verified by exhaled carbon monoxide	RR 1.44 (0.94-2.21), † unadjusted

ORs were adjusted for all factors in the confounders column except as noted. ORs provided for observational studies, RRs provided for randomised trials. OR=odds ratio. NRT=nicotine replacement therapy. RR=relative risk. *Obtained by contacting authors. †Calculated from numbers provided by authors. ‡Social clubs for university students.

Table 1: Summary of studies on the relationship between e-cigarette use and cigarette smoking

cigarette consumption, level of nicotine dependence, other confounders measured, definition of quitting smoking, and odds of quitting smoking. We attempted to contact study investigators for missing information. Risk of bias was assessed using a modification of the ACROBAT-NRSI tool³² for observational studies and the Cochrane Risk of Bias Tool³³ for clinical trials, implemented as detailed in the appendix.

Data synthesis

For studies comparing nicotine e-cigarettes with nicotine replacement therapy (NRT), no-nicotine e-cigarettes, or no cessation aid, all ORs are presented; when several ORs were provided, we included only the comparison with no e-cigarette use (when available) or no cessation aid in the meta-analysis. Adjusted ORs were used when available, otherwise unadjusted ORs were used. For one cohort study,⁷ two different ORs were reported for e-cigarette users of different intensities and a pooled estimate was not provided; the ORs for those two groups are presented separately.

Statistical analysis

We computed pooled estimates of the odds of smoking cessation among smokers using e-cigarettes compared with smokers not using e-cigarettes using a random effects meta-analysis with the metan command in Stata version 13.0. Adjusted ORs were used when available, with unadjusted ORs for the remaining studies in the meta-analysis. Statistical heterogeneity was assessed using the I^2 statistic.

We did a sensitivity analysis of the effects of study type (real world *vs* clinical), longitudinal versus cross-sectional data analysis, sample frame (smokers interested in quitting *vs* all smokers), control group (NRT users *vs* all no-e-cigarette users), study population (mental illness or no mental illness), whether the study controlled for level of nicotine dependence, time of e-cigarette assessment (whether e-cigarette use was assessed at baseline or follow-up in longitudinal studies), whether abstinence was biochemically defined, and whether the definition of e-cigarette use was current (past 30 day) use versus ever-use or not within the past 30 days on the results using separate random effects meta-regressions with each factor entered as a dummy variable with the Stata metareg command. We considered the nine sensitivity analyses to be a family of comparisons and controlled for multiple comparisons using the Holm-Sidak method to obtain adjusted p values. We tested for the presence of publication bias using a funnel plot and Egger's test.

The meta-analysis was registered with PROSPERO on May 11, 2015, number CRD42015020382.

Role of the funding source

The funders had no role in the study design, collection, analysis, or interpretation of the data, or writing of the

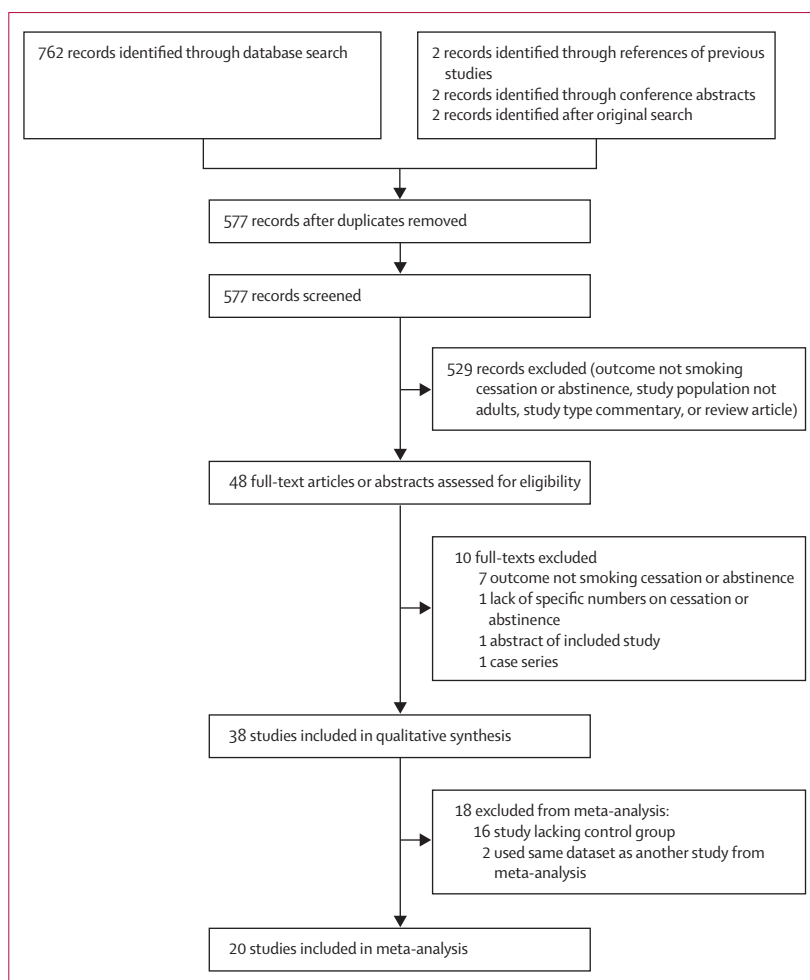


Figure 1: Study profile

report. Both authors had access to the raw data. Both authors had full access to all of the data the study and had final responsibility for the decision to submit for publication.

Results

Of 577 studies identified, 38 were included in the systematic review (appendix) and 20 (table 1) in the meta-analysis. Studies excluded from the systematic review did not include smoking cessation as an outcome, did not include adults as the study population, were opinion pieces or commentaries, or were review articles (figure 1). Of the 38 studies included in the systematic review, 16 were excluded from the meta-analysis because they lacked a control group that did not use e-cigarettes,^{15–17,19,45–56} and two^{57,58} were excluded because they used the same dataset as another study included in the meta-analysis.^{14,38} 15 of the studies included in the meta-analysis were longitudinal cohort studies (ten assessed e-cigarette use at baseline, five assessed e-cigarette use only at follow-up), three were cross-sectional studies, and two were clinical trials.

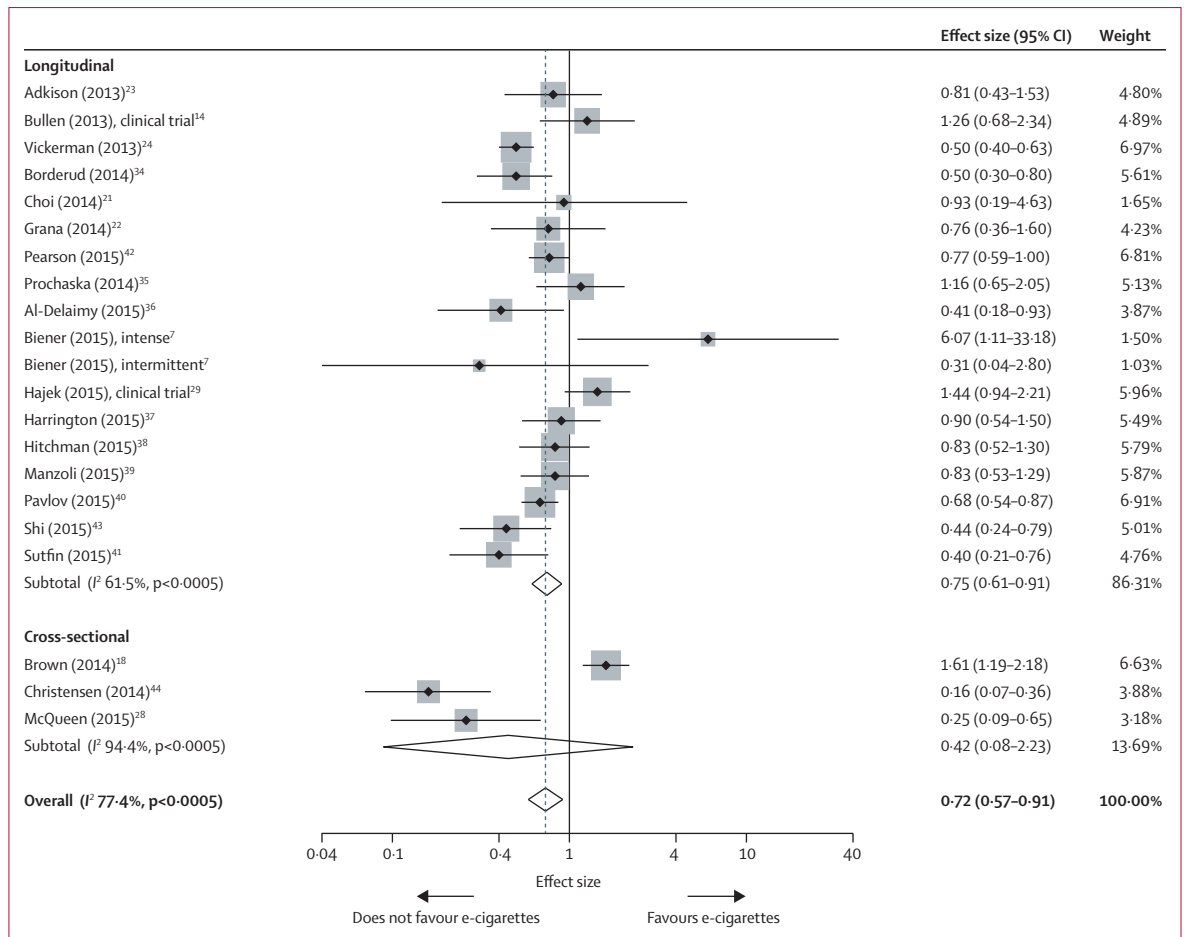


Figure 2: Odds of quitting smoking, stratified by longitudinal versus cross-sectional studies
 Figure shows odds of quitting among e-cigarette users compared with non-e-cigarette users. The overall odds of quitting cigarettes is 0.72 (95% CI 0.57-0.91) irrespective of how studies are stratified.

Odds of quitting (only provided for studies with a control group) are described with point estimates and 95% CIs and whether these point estimates differed significantly from 1.00.

15 longitudinal real-world studies assessing smoking cessation in e-cigarette users compared with those who did not use e-cigarettes.^{7,21-24,34-43} Point estimates in 13 of the 15 studies indicated decreased smoking cessation among those who used e-cigarettes, six of which reported statistically significant results.^{24,34,36,40,41,43} One study⁷ found that intensive e-cigarette users (those who used e-cigarettes daily for at least 1 month) had significantly increased smoking cessation and that intermittent e-cigarette users had a non-significant decrease in smoking cessation. In three studies without control groups (excluded from the meta-analysis),^{16,45,46} smoking cessation rates among e-cigarette users ranged from 17% at 8 weeks,⁴⁵ to 41% at 1 year,⁴⁶ to 46% at 1 year.¹⁶

Three cross-sectional studies compared e-cigarette users to those who did not use e-cigarettes:^{18,28,44} two^{28,44}

showed significantly lower smoking cessation among smokers using e-cigarettes compared with those who did not, and the other study¹⁸ (of smokers who had made a quit attempt in the past year) found significantly higher smoking cessation in those who used e-cigarettes compared with those who used NRT or no smoking cessation aid. Cigarette quit rates in cross-sectional studies that included only e-cigarette users (ie, studies without control groups, which were excluded from the meta-analysis) ranged from 10% to 66%.^{19,47-49}

The one randomised controlled trial comparing cigarette quit rates of e-cigarette users with those of NRT users showed a non-significant increase in quitting associated with e-cigarette use.¹⁴ A secondary analysis of a subset of participants with mental illness in this study showed a non-significant decrease in quitting among those who used e-cigarettes compared with those who used NRT.⁵⁸ A non-randomised clinical trial found a non-significant increase in quitting among individuals electing to use e-cigarettes for smoking cessation compared with those not using e-cigarettes.²⁹

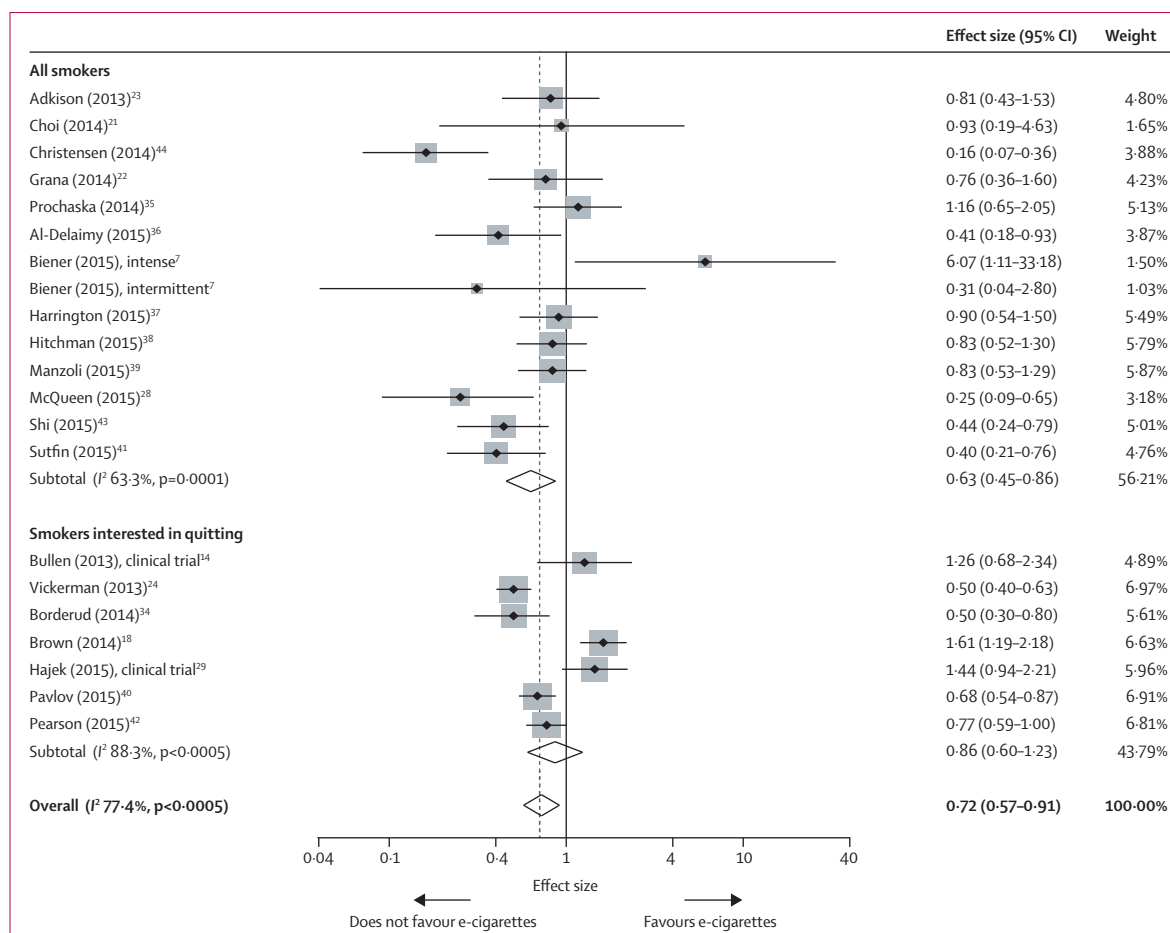


Figure 3: Odds of quitting smoking, stratified by all smokers versus those with an interest in quitting

Figure shows odds of quitting among e-cigarette users compared with non-e-cigarette users. The overall odds of quitting cigarettes is 0.72 (95% CI 0.57-0.91) irrespective of how studies are stratified.

For trials without control groups^{17,50-56} (ie, all participants used e-cigarettes), cigarette quit rates ranged from 12.5% to more than 40%. A randomised trial comparing users of e-cigarettes with and without nicotine (without a control group of non-e-cigarette users or conventional smoking cessation therapy) found a non-significant increase in quitting cigarettes for those using nicotine-containing e-cigarettes compared with those using non-nicotine e-cigarettes.¹⁵

Combining the 18 real-world studies^{7,18,21-24,28,34-44} (treating one study⁷ with estimates for two types of e-cigarette users as two studies, yielded 19 real-world estimates of the relationship between e-cigarette use and quitting smoking) and the two clinical trials^{14,29} in a random effects meta-analysis (figures 2, 3) indicated that the odds of quitting smoking were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes (OR 0.72, 95% CI 0.57-0.91).

Studies that included only smokers interested in quitting cigarettes yielded a pooled OR for quitting of 0.86 (0.60-1.23) for those using e-cigarettes compared

with those not using e-cigarettes. Studies of all smokers (irrespective of motivation to quit) yielded a pooled OR of 0.63 (0.45-0.86), which is not significantly different from studies limited to smokers interested in quitting ($p=0.94$).

All of the observational studies had low risk of selection bias, half (nine of 18) controlled for confounders, and seven of 15 longitudinal studies had follow-up periods of at least 6 months (appendix). The overall risk of bias from exposure measurement was unclear, given that the definition of e-cigarette use in all but two^{7,39} of the studies could have included people who only used e-cigarettes once; risk of bias from outcome assessment was unclear or high due to objective or poorly defined measurements.

The one randomised clinical trial¹⁴ had a low risk of selection, detection, and reporting bias, but a high risk of performance and attrition bias, because participants randomly assigned to e-cigarettes were provided with the e-cigarettes, whereas the individuals randomly assigned to nicotine patches were provided a voucher that they

	n	OR (95% CI)	p value*
Sample frame			0.94
All smokers	14	0.63 (0.45-0.86)	
Smokers interested in quitting cigarettes	7	0.86 (0.60-1.23)	
Study type			0.90
Real world	19	0.67 (0.52-0.85)	
Clinical trial	2	1.38 (0.97-1.96)	
Longitudinal vs cross-sectional			0.98
Longitudinal	18	0.75 (0.61-0.91)	
Cross-sectional	3	0.42 (0.08-2.23)	
Control group for study			0.90
All non-e-cigarette users	20	0.70 (0.55-0.89)	
NRT	1	1.26 (0.68-2.34)	
Study population			0.89
All individuals	20	0.70 (0.55-0.89)	
Individuals with mental illness	1	1.16 (0.65-2.05)	
Controlling for level of nicotine dependence			0.79
Controlled for dependence	11	0.84 (0.60-1.17)	
Did not control for dependence	10	0.62 (0.45-0.85)	
Time of e-cigarette assessment in cohort studies			0.93
Baseline	10	0.71 (0.59-0.85)	
Follow-up	6	0.66 (0.45-0.95)	
Biochemical verification of abstinence			0.77
Biochemical verification	4	1.14 (0.88-1.48)	
No biochemical verification	17	0.63 (0.49-0.82)	
Definition of e-cigarette use			0.87
Current or past 30 days	11	0.80 (0.54-1.17)	
Ever use or not within the past 30 days	10	0.66 (0.49-0.90)	

OR=odds ratio. NRT=nicotine replacement therapy. *Holm-Sidak corrected p for a family of 9 comparisons; $p(\text{corrected}) = 1 - (1 - p(\text{uncorrected}))^{9-1}$.

Table 2: Sensitivity analysis

could take to a pharmacy to obtain the patches; additionally, the nicotine patch group had a higher loss to follow-up than did the e-cigarette group (appendix). The non-randomised controlled trial²⁹ had low risk of detection, attrition, and reporting bias, but high risk of selection and performance bias because participants were not randomised and had chosen to use e-cigarettes.

We did not find evidence of publication bias by Egger's test ($p=0.91$) or by visualisation of the funnel plot (appendix).

There was evidence of heterogeneity of the studies (I^2 77.4%, $p<0.0005$). In particular, heterogeneity was higher for the cross-sectional studies (I^2 94.4%, $p<0.0005$) than the longitudinal studies (I^2 61.5%, $p<0.0005$). In addition to using a random effects model to control for heterogeneity, we assessed the possible reasons for heterogeneity in a sensitivity analysis (table 2). In the sensitivity analyses, sample frame, study type (longitudinal vs cross-sectional data analysis), control group, study population, level of nicotine dependence, time of e-cigarette assessment (in longitudinal studies), biochemical verification of smoking cessation, and

definition of e-cigarette use were not associated with overall effect size ($p\geq 0.77$ in all cases).

Discussion

In this systematic review and meta-analysis, pooled results from 18 real-world observational studies and two clinical trials showed 28% (OR 0.72, 95% CI 0.57-0.91) lower odds of cigarette smoking cessation among those who used or had used e-cigarettes compared with those who had not used e-cigarettes. This conclusion was insensitive to a wide range of study design factors, including whether or not the study population consisted only of smokers interested in smoking cessation, or all smokers (irrespective of quit intention).

The results of this meta-analysis are consistent with those of the previous meta-analysis of five real-world studies,²⁰ which found a pooled OR for quitting of 0.61 (95% CI 0.50-0.75) for those who used e-cigarettes compared with those who did not use e-cigarettes.

By contrast, two previous meta-analyses,^{12,13} which both included the same two clinical trials to compare nicotine e-cigarette users with non-nicotine e-cigarette users,^{14,15} showed the odds of quitting cigarettes to be twice as high in those using e-cigarettes with nicotine compared with those using e-cigarette without nicotine (2.29, 95% CI 1.05-4.96).¹² One of the previous meta-analyses,¹³ based on six studies, found that 20% (95% CI 11-28) of users of nicotine-containing e-cigarettes went on to quit cigarettes. By contrast with our analysis, the estimates did not include a comparison to standard therapy or no e-cigarette use, so they cannot be used to determine whether e-cigarettes are associated with greater cigarette abstinence than current practice.

So far, no clinical trials have done a true head-to-head comparison of e-cigarettes with standard therapies (ie, nicotine patch, gum, or inhaler) approved by the US Food and Drug Administration for smoking cessation. The one randomised clinical trial included in this meta-analysis¹⁴ compared e-cigarettes with nicotine patches, but was subject to performance bias because individuals randomly assigned to e-cigarettes were provided with them by the investigators, whereas participants randomly assigned to NRT were given only a voucher that they could redeem at a pharmacy to obtain NRT patches. Although this practice is consistent with standard care in the country in which the study was done (New Zealand), it potentially biases the study against NRT. As a result, true head-to-head comparisons of e-cigarettes with approved therapies in a clinical setting are needed to evaluate the usefulness of e-cigarettes for smoking cessation. In the USA, such studies require Investigational New Drug approval from the Food and Drug Administration Center for Drug Evaluation and Research. If e-cigarette companies do not request this approval (as has been the case to date), such studies will be difficult, if not impossible, to conduct, unless at the request of the companies.

Heterogeneity was higher for the cross-sectional studies (I^2 94.4%, $p < 0.0005$) than the longitudinal studies (I^2 61.5%, $p < 0.0005$). This increased heterogeneity might result from the fact that there were only three cross-sectional studies (compared with 18 longitudinal estimates), and that they differed in terms of countries (one in the UK¹⁸ and two in the USA^{28,44}), study population (two only of smokers interested in quitting,^{18,28} one of all smokers⁴⁴), comparator group (one compared e-cigarettes with NRT¹⁸ and the other two compared with no e-cigarette use^{28,44}), and adjustment for nicotine dependence (one¹⁸ was adjusted, two^{28,44} were not). There was no evidence of study type (longitudinal vs cross-sectional) being associated with the overall effect size.

There could be a number of explanations for why e-cigarette use was associated with less quitting in this meta-analysis combining observational and clinical studies. When considering e-cigarettes as a potential smoking cessation aid, the fact that they are freely available consumer products could be important. The situation may be similar to the differences between the clinical efficacy of approved NRT therapies for smoking cessation in clinical trials versus actual use in non-clinical settings. A few studies have evaluated the association of other forms of over-the-counter nicotine with smoking cessation. Data from the large population-based California Tobacco Surveys, showed that NRT was associated with long-term success in quitting cigarettes when available by prescription only, but this association was lost when NRT became available over the counter.⁵⁹ In a prospective cohort study of adult smokers in England, prescription medication combined with behavioural counselling was associated with increased smoking cessation, whereas over-the-counter NRT was associated with a significant reduction in smoking cessation (OR 0.68, 95% CI 0.49–0.94) that was similar to the association between e-cigarette use and quitting smoking that we observed.⁶⁰

In observational studies evaluating e-cigarette use, participants are choosing to use e-cigarettes unlike clinical trials where they are being randomly assigned to receive them. From one perspective, this self-selection of product use by individuals would be a potential source of selection bias⁶¹ when evaluating e-cigarettes as a smoking cessation aid. However e-cigarettes are not being used just as smoking cessation devices in the real world. Indeed, one important motivation for using e-cigarettes is to self-administer nicotine in places where smoking is prohibited.^{3,62}

Interest in quitting cigarette smoking is a common reason for using e-cigarettes,^{3,4} probably because claims of efficacy as a cessation aid have appeared in e-cigarette advertisements in the USA,⁹ UK,⁸ and China¹⁰ even though such claims had not been accepted by regulatory authorities. E-cigarettes are also marketed as a way to circumvent smoke-free policies,^{8,9} and could be used as

such by nicotine-dependent individuals who have lower baseline intentions of quitting.

Subgroup analyses in two of the studies suggest that specific use patterns may be important. Biener and colleagues⁷ found that intermittent e-cigarette users (more than once or twice but less than daily use) were less likely to quit smoking one year later than non-e-cigarette users, but those who had used e-cigarettes daily for at least one month were significantly more likely to quit cigarettes. Similarly, Hitchman and colleagues³⁸ found that all “cig-alike” users and non-daily tank system users had lower odds of quitting cigarettes, whereas daily tank system users were significantly more likely to quit. By contrast, Manzoli and colleagues³⁹ found a non-significant (OR 0.83, 95% CI 0.53–1.29) reduction in quitting cigarettes among cigarette smokers who regularly used e-cigarettes (defined as using both cigarettes and e-cigarettes within the same week for 6 months) compared with cigarette-only smokers. These data suggest that e-cigarette use patterns might be important in the association between e-cigarettes and smoking cessation.

E-cigarette regulation has the potential to influence marketing and reasons for use. The inclusion of e-cigarettes in smoke-free laws and voluntary smoke-free policies could help decrease use of e-cigarettes as a cigarette substitute and, perhaps, increase their effectiveness for smoking cessation. The way e-cigarettes are available on the market—for use by anyone and for any purpose—creates a disconnect between the provision of e-cigarettes for cessation as part of a monitored clinical trial and the availability of e-cigarettes for use by the general population. Therefore, careful attention to how the products are marketed and actually used will be necessary in evaluating e-cigarettes as a smoking cessation aid and their ultimate public health impact.⁶³

The studies we reviewed controlled for many confounding variables, including level of nicotine dependence, whether the subject was trying to quit smoking cigarettes, demographics, past quit attempts, medical and psychiatric comorbidities, cigarette consumption, intention or motivation to quit, study factors, tobacco-related variables and behaviours, alcohol use, sensation seeking, number of friends and family who smoke, use of other quit methods, and type of tobacco smoked (table 1). Future research should focus on determining standard definitions of e-cigarette use; evaluating the association of different extents of use and different devices with smoking cessation; conducting more randomised clinical trials comparing e-cigarettes to standard therapies such as NRT; evaluating the effect of e-cigarette use on factors such as motivation to quit; and distinguishing e-cigarette users by their reasons for using the products. An ideal study (whether a clinical trial or observational study) would control for all these variables, and be a longitudinal

study that assessed e-cigarette use at both the start and end, including product type used and frequency of use. Additionally, having clear definitions of e-cigarette use (ever use, past 30 day use, whether experimentation with e-cigarettes once or twice are included) is important, as is how cessation is defined. It will, unfortunately, likely be difficult to obtain all these details in any one study.

This study is subject to eight limitations. First, given that there have been very few controlled clinical trials exploring e-cigarette use for smoking cessation; all but two of the studies used in this meta-analysis were observational studies. Second, the definition of smoking cessation used in the studies included in the meta-analysis varied in terms of length of abstinence from cigarettes and how smoking cessation was defined. Because we aimed for a comprehensive review, we included all definitions of quit as defined by the authors. Third, most—but not all—of the observational studies controlled for confounders such as nicotine dependence. Sensitivity analysis showed that controlling for nicotine dependence was not associated with overall effect size. Other potential confounding variables were controlled for in some of the studies, however, sensitivity analyses could not be conducted on each of these variables. Nevertheless, it is always possible that other unidentified confounders, including biases introduced by those who self-selected to use e-cigarettes, might affect the results. Fourth, only two studies^{7,39} assessed the extent of e-cigarette use in their analyses. It is possible that in some included studies, e-cigarettes were only used once, which would not be a good predictor of smoking cessation. Fifth, there was variability in the quality of the studies. We included them all to provide a comprehensive review of the literature and avoid concerns that the results of the analysis were affected by bias in selecting which studies to exclude and include. The sensitivity analysis showed that the results of the meta-analysis were insensitive to a wide range of aspects of study design. Sixth, in the cross-sectional studies, e-cigarette use and cessation were assessed at the same time, raising concerns about recall bias. Seventh, e-cigarettes are rapidly evolving products and different types and generations of e-cigarettes may have different effects in terms of cessation. Finally, both e-cigarette products and the marketing and regulatory environment are rapidly evolving, all of which could affect the relationship between e-cigarette use and quitting smoking.

As use patterns and product types continue to evolve, the association between e-cigarettes and cigarette quit rates may change. In the current regulatory environment, e-cigarette use is increasing and, although quitting smoking is a common marketing claim and is often cited as a reason for use among cigarette smokers, the overall conclusion from the available studies is that e-cigarette use is associated with reduced smoking cessation in the real world.

Contributors

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

Declaration of interests

SAG is Truth Initiative Foundation Distinguished Professor of Tobacco Control. We declare no competing interests.

Acknowledgments

We thank Pamela M Ling, Margarete C Kulik, Lauren M Dutra, and Elaine Allen (University of California San Francisco, CA, USA) for their review of and feedback on the manuscript. SK's work was supported by NIH NRSA T32HP19025. SAG's work reported in this publication was supported by grant 1P50CA180890 from the National Cancer Institute and FDA Center for Tobacco Products (CTP). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration.

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