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E-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis

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Abstract:

Objective: To review and summarise the current evidence on the uptake of combustible cigarette smoking following e-cigarette use in non-smokers - including never-smokers, people not currently smoking and past smokers - through an umbrella review, systematic review and meta-analysis.

Design: Umbrella review and systematic review

Data sources: PubMed, Scopus, Web of Science, PsychINFO (Ovid), Medline (Ovid) and Wiley Cochrane Library up to April 2020.

Results: Of 6,225 results, 25 studies of non-smokers - never, not current, and former smokers - with a baseline measure of e-cigarette use and an outcome measure of combustible smoking uptake were included. All 25 studies found increased risk of smoking uptake with e-cigarette exposure, although magnitude varied substantially. Using a random-effects model, comparing e-cigarette users versus non-e-cigarette users, among never-smokers at baseline the odds ratio (OR) for smoking initiation was 3.25 (95%CI 2.61-4.05, I^2 85.7%) and among non-smokers at baseline the OR for current smoking was 2.87 (95%CI 1.97-4.19, I^2 90.1%). Among former smokers, smoking relapse was higher in e-cigarette users versus non-users (OR=2.40, 95% CI 1.50-3.83, I^2 12.3%).

Conclusions: Across multiple settings, non-smokers who use e-cigarettes are consistently more likely than those avoiding e-cigarettes to initiate combustible cigarette smoking and become current smokers. The magnitude of this risk varied, with an average of around three times the odds. Former smokers using e-cigarettes have over twice the odds of relapse as non-e-cigarettes users. This study is the first to our knowledge to review and pool data on the latter topic.

Prospero registration number: CRD42020168596

Strengths and Limitations

Strengths

- Comprehensive and systematic literature search with pooled evidence from 25 published studies reviewed according to a pre-specified protocol.
- Inclusion of studies investigating all ages and types of non-smokers (never, not current and former).
- Independent corroboration of results from previous studies, reviews and meta-analyses, while adding evidence on smoking uptake with e-cigarette exposure among former smokers

Limitations

- The evidence is largely reliant on self-reported product use and the studies reviewed were observational in nature as it is not ethical or appropriate to randomise non-smokers to e-cigarette exposure.
- While all studies reported significantly higher uptake of tobacco smoking among non-smokers exposed to e-cigarettes, compared to those not exposed, there was significant variation in the magnitude of the observed increase in risk; the results of the meta-analyses should therefore be considered to be an average of the published studies.

Summary Box

What is already known on the topic: Globally, tobacco smoking is a leading cause of death and disability. There is an existing concern that the use of e-cigarettes in never smokers, particularly youth, may increase the probability that they will use tobacco cigarettes. To our knowledge, no full summaries of the evidence to date across the whole population are currently available.

What this study adds: This umbrella review of systematic reviews and systematic review of new primary studies is the first review to examine the associations between e-cigarette use and cigarette use across the whole population, including youth, adults and former smokers. It provides independent corroboration that non-smokers who use e-cigarettes are substantially more likely to take up tobacco smoking than non-smokers who avoid e-cigarettes. Ex-smokers who use e-cigarettes are significantly more likely to relapse than ex-smokers who do not use e-cigarettes.

Introduction

Globally, combustible tobacco smoking results in over 8 million deaths each year [1]. Due to vigorous public health interventions, smoking prevalence in Australia has declined substantially over the last 50 years [2]. Nevertheless, 9.3% of the total disease burden (in disability-adjusted life years) was attributable to combustible tobacco use in 2015 [3].

E-cigarettes are a diverse group of battery-operated or rechargeable devices that heat a liquid ('e-liquid' or 'e-juice') to produce a vapour that users inhale. Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol and flavouring agents and are commonly used to deliver nicotine [4]. The labelling of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) is not always accurate, with reports of nicotine found in products labelled ENNDS [4, 5].

Studies indicate that in many countries, e-cigarette use among never-smoking youth is increasing [6-11]. In Australia, the proportion of non-smokers aged 14 years or older who had ever used e-cigarettes increased

from 4.9% in 2016 to 6.9% in 2019 [12]. The increase was particularly notable in young adults, with 20% of 18-24 year old non-smokers reporting e-cigarette use [12].

There are concerns that the use of e-cigarettes in never-smokers may increase the probability that they will try combustible tobacco cigarettes and go on to become regular smokers, particularly among youth and young adults [13-15]. Furthermore, use of e-cigarettes could conceivably lead to combustible tobacco smoking relapse in former smokers. If e-cigarette use leads to more people smoking combustible cigarettes, compared with the number of people who have smoked in the absence of e-cigarettes, this would be a source of considerable public health harm [16]. Thus, our primary research question is: among current non-smokers, how does e-cigarette use affect the subsequent risk of smoking combustible tobacco cigarettes? This review aims to systematically update global contemporary population-level evidence on the relationship of e-cigarette use to smoking uptake.

Methods

This summary of the global evidence comprises an umbrella review of systematic reviews and a top-up systematic review of primary research not included in the systematic reviews of the umbrella review. The protocol was published online through PROSPERO (CRD42020168596).

Search strategy

The Population, Intervention, Comparison, Outcome (PICO) format was used to structure the search (Table in S1 Table). Studies investigating the association between ENDS or ENNDS use among non-tobacco smokers and uptake of combustible cigarette smoking were included. For both the umbrella review and the top-up systematic review, six databases (PubMed, Scopus, Web of Science, PsycINFO (Ovid), MEDLINE (Ovid), and Cochrane) were searched on 1 April 2020 (Text in S2). E-cigarette use, cigarette smoking and uptake related search terms and keywords were used (Table A in S2).

Inclusion and exclusion criteria

Systematic reviews and meta-analyses of prospective cohort studies or randomised or non-randomised controlled trials examining the exposure (e-cigarette use) and outcome (smoking uptake in current non-smokers) of interest were included in the umbrella review. For the top-up systematic review, individual prospective cohort studies or randomised or non-randomised controlled trials identified in the search and not included in the umbrella review studies, were included. Cross-sectional studies were excluded due to difficulties in establishing the temporal relationship between e-cigarette exposure and smoking uptake. Studies with a follow up of less than 6 months or with abstracts not published in English were excluded. The full inclusion and exclusion criteria can be found in S2 Table B.

Data screening and extraction

EndNote and Covidence software were used for review management. Two authors of this review (OB and LF) undertook initial screening, study selection, risk of bias assessment, and data extraction. Titles and abstracts identified in the searches were screened using a checklist, followed by full-text screening. A forward and backward reference search using Scopus was performed from the final included articles. After removing duplicates, titles, abstracts, and then full texts were screened for any studies fulfilling the inclusion and exclusion criteria. Data was independently extracted from the included systematic reviews and cohort studies using a pre-specified data extraction template. As it is important to consider whether authors of the studies under review hold any conflicts of interest that could potentially bias their findings, or whether the research was funded by an organisation with a financial interest in the outcomes, information on the source of research sponsorship or external involvement was also extracted. Studies were considered separately if they were funded by the tobacco or nicotine industry.

Risk of bias assessment

Risk of bias for each study included was independently assessed using the AMSTAR 2[17] for the systematic reviews and meta-analyses included in the umbrella reviews, and the Newcastle Ottawa Scale (NOS)[18] for

the studies in the top-up systematic review. For meta-analyses with at least ten studies, risk of bias across studies was assessed and interpreted using the symmetry of funnel plots and superimposed 95% confidence limits [19].

Summary measures and synthesis of results

Findings from the umbrella review and the top-up systematic review were synthesised separately in narrative summaries. Individual prospective primary research studies identified from both the umbrella review and top-up systematic review were then considered in an integrated systematic review. Where appropriate, odds ratios from the studies in the integrated systematic review were combined using a random-effects model. Heterogeneity of study effect estimates were assessed by an I-squared statistic. All analyses were conducted using Stata version 16.1.

Patient and Public Involvement

No patient involved.

Results:

Study Selection

Study selection for this umbrella review and top-up systematic review are shown in the PRISMA flowchart in Figure 1. A total of 6,225 studies were identified for title and abstract screening; 2,659 remained after exclusion of duplicates. After title and abstract screening, 83 articles were identified for full-text screening. Fifteen papers were identified for inclusion; three were systematic reviews that were included in the umbrella review and 12 were primary research studies included in the top-up systematic review. Ten of the latter studies were prospective observational studies and two were secondary analyses of randomised controlled trials (RCT).

From the three systematic review papers included in the umbrella review, 28 primary research studies were identified after removing duplicates. For our meta-analyses, we excluded 15 studies due to ineligible study design (n=10) or data overlap (n=5). No studies were excluded based on their quality assessment scores. The

meta-analyses were thus based on 13 primary research studies identified from the prior systematic reviews, and 12 studies from our top-up systematic review, i.e. a total of 25 primary research studies on e-cigarette use and smoking uptake (Figure 1).

No potential competing interests were identified in the included studies themselves, or by the authors, based on the disclosure statements from the publications. Although one [20] primary research study identified during screening in the top-up systematic review was found to have potential competing interests, as it was funded by the tobacco industry, it was previously excluded due to a large overlap with data presented in a more recent paper by Berry et al. [21].

There is considerable uncertainty regarding the chemical constituents of the e-liquids delivered by the e-cigarettes in the studies included in the review. Where evidence on nicotine content was available, it indicated that a substantial majority of e-cigarettes in those studies delivered nicotine [22-25]. Many publications noted considerable uncertainty regarding nicotine content, including apparent mislabelling, and the need for greater clarity and reliability on this point.

Umbrella review: quality assessment

All three systematic reviews from the selected articles rated moderate in the AMSTAR 2 [17] assessment. Information was lacking regarding study exclusion criteria, stated sources of funding, and detail on data extraction (Table in S3).

Umbrella review:

Table 1 summarises the results of the three systematic reviews included in the umbrella review. All three systematic reviews excluded studies with participants over 30 years of age. Sample sizes for the individual studies varied considerably, ranging from 298 to 17,318. Of the 13 included longitudinal primary research studies (detailed in Table in S4 Table), nine[14, 26-33] were based in the US, two [34, 35] in the UK and one each in Mexico [36], and the Netherlands [37]. Each of the three systematic reviews conducted meta-analyses

and found the odds of smoking initiation were increased for youth and young adult e-cigarette users compared to non-e-cigarette users; these results are summarised in Table 1.

The Khouja et al. (2020) systematic review and meta-analysis included 17 studies published up to November 2018 [38]. The study found that the risk of later smoking in people aged <30 years who had ever used or currently use e-cigarettes was strong; an almost three-fold the odds compared to never users after adjustment for covariates (see Table 1). However, there were high levels of heterogeneity in the summary estimates (adjusted OR I^2 =84.5%), which remained high in adjusted analysis subgrouping by age, ever smoking, risk of bias and location of study. Heterogeneity was reduced when the adjusted ORs were grouped into those examining the relationship between ever e-cigarette use and current smoking (adjusted OR 2.21; 95% CI 1.72 – 2.84, I^2 =5%) and those assessing the relationship of current e-cigarette use to ever smoking (adjusted OR 2.21; 95% CI 1.72 – 2.84, I^2=5%).

Aladeokin & Haighton (2019) aimed to systematically review the evidence on e-cigarette use and initiation of cigarette smoking in adolescents (aged 10-19 years old) in the UK and included eight studies.[39] Their meta-analysis showed e-cigarette users were much more likely than non-users to go on to smoke combustible cigarettes, even after adjusting for covariates (see Table 1); the substantial heterogeneity in the summary estimate should be noted.

The Soneji et al. (2017) systematic review and meta-analysis included nine longitudinal studies of US participants ≤30 years of age [16]. Seven of the included studies assessed the association of baseline ever e-cigarette use with subsequent ever combustible cigarette use at follow-up among baseline never smokers. Soneji et al. also identified two studies that assessed baseline past 30-day e-cigarette use with subsequent past 30-day combustible cigarette use among those reporting no past 30-day use of cigarettes at baseline. The meta-analysis showed a markedly higher odds of combustible cigarette use in those who had used e-cigarettes (Table 1).

Top-up systematic review: quality assessment

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale [18] (NOS). Of the 12 studies, the NOS totals (out of 10 stars) ranged from 5 to 8 (Table in S5). Only one [40] study rated 5, five [23-25, 41, 42] rated 6, two [9, 43] rated 7 and four [21, 44-46] rated 8. No studies received a star for assessment of outcome. The main areas impacting the NOS scores were ascertainment of exposure and adequacy of follow up of cohorts (studies with less than 30% loss to follow up were considered adequate).

Top-up systematic review and integration with primary research studies from the umbrella review

A total of 12 studies published in 2018, 2019 and 2020 were newly-identified for the top-up systematic review (Table 2; Table in S6). Among the 12 included, six were from the US, two from the UK, and one each from Romania, Finland, Taiwan and Canada. Study sample sizes varied considerably, ranging from 374 to 14,623.

Of the six newly-identified studies based on US participants, four[21, 44-46] used Population Assessment of Tobacco and Health (PATH) data from a US nationally representative longitudinal study. Of these, two [45, 46] looked at adult (≥ 18 years old) former smokers, one [44] looked at youth (12-17 years old) and one [21] at a more restricted youth group (12-15 years old). Even though these four studies have the same data source, they were all included in this review as they had different outcome or exposure variables, different populations and included the most recent data.

Of the 12 newly identified studies, five [21, 22, 41, 42, 45] had outcomes assessing ever smoking among never smokers at baseline, seven [23, 24, 40, 42-45] had outcomes assessing current smoking among non-smokers (never or not current smoking) at baseline and three [25, 45, 46] assessed the odds of relapse in former smokers. Results were separated based on these three categories and combined with the 13 primary research studies identified in the umbrella review. Twelve of the seventeen studies in Khouja et al. were included [14, 26, 28-37],three were excluded due to data overlap [47-49], one was excluded as it used retrospective data[50] and one was excluded as it was cross-sectional [51]. Of the eight studies in Aladeokin

& Haighton, two were included [34, 35]; five were excluded for cross-sectional design [52-56] and one for data overlap [49]. From the nine studies identified in Soneji et al., six were included [26-29, 31, 32] after two were excluded as they were abstracts and one excluded for data overlap [57].

Cigarette smoking initiation among never smokers at baseline

Five [21, 22, 41, 42, 45] of the newly-identified studies investigated smoking initiation among never smokers, of which Berry et al. [21] and McMillen et al. [45] used PATH data, focusing on youth (12 to 15 years old) and adults (≥18 years old), respectively (Table 2). Chien et al. examined the association between ever e-cigarette and subsequent combustible smoking initiation in 12,954 youth enrolled in schools in Taiwan between 2014 and 2016 [22]. Conner et al. investigated the association of e-cigarette use at baseline and smoking in adolescents (13 to 14 years old) between Waves 3 and 5 (2014 to 2016) of a cluster RCT in 20 schools in England [42]. Pénzes et al. conducted secondary data analysis from 1,369 9th grade students in the Romanian ASPIRA randomized controlled trial. Details of the studies are given in S6.[41]

All newly-identified studies found that people who used e-cigarettes were significantly more likely than non-users to initiate smoking of combustible cigarettes, with odds ratios varying substantially from 2.1 to 6.6 (I^2=81%; Figure 2a).

Considering these newly identified studies along with 12 studies from the umbrella review, all found significantly increased risk of initiating smoking of combustible cigarettes in people who had used e-cigarettes, compared to those who had not (Figure 2a). Combining the studies from the umbrella review with the newly-identified studies, people exposed to e-cigarettes more likely to take up smoking of combustible cigarettes than people who were not exposed to e-cigarettes (pooled adjusted OR 3.19 (95% CI, 2.44 – 4.16)).

Current (past 30-day) cigarette smoking among non-smokers (never smokers or no current use at baseline)

Seven [23, 24, 40, 42-45] of the newly-identified primary research studies investigated current (past 30-day) use of combustible cigarettes following the use of e-cigarettes (Table 2). Four [24, 42, 43, 45] of these studies looked at never smokers at baseline, while three [23, 40, 44] looked at non-smokers (either never or no current use).

Two [44, 45] of the included studies were based on PATH data. McMillen et al.[45] used data on adult (≥18 years old) never smokers from waves 1 to 2 of the PATH study and Osibogun et al. [44] used data on youth (12-17 years old) non-smokers from waves 1 to 3. A further two [40, 43] of the newly-identified studies used data from the US. Bold et al. surveyed 808 high school students across three waves (2013 to 2015) in Connecticut.[40] Barrington-Trimis et al. collated data on 6,258 youth from three US school-based studies between 2013 and 2015: the Children's Health Study (CHS); the Happiness & Health Study (HH); and the Yale Adolescent Survey Study (YASS) [43]. This study separated results based on ethnicity and found the adjusted odds of dual use at follow up was considerably higher in non-Hispanic whites compared to Hispanic whites (see Table 2), although with considerable overlap in the confidence intervals

The remaining three [23, 24, 42] newly-identified studies used data from Canada, the UK and Finland. Aleyan et al. examined the association between current e-cigarette use and subsequent current smoking among 6,729 Canadian school students using data from a school-based longitudinal cohort study, COMPASS [23]. Conner et al. investigated the association of e-cigarette use at baseline and smoking between Waves 3 and 5 (2014 to 2016) of a cluster RCT assessing a self-regulation anti-smoking intervention from 20 schools in England [42]. Kinnunen et al. used MEtLoFIN a school-based longitudinal cohort dataset in 3,474 Finnish adolescents between 2014 and 2016 [24]. Kinnunen et al., separated the use of e-cigarettes using nicotine content and found among baseline never-smokers, ever use of nicotine-containing e-cigarettes was associated with a nearly 3-fold increase in the odds of uptake of daily smoking (see Table 2)) found no increase in risk associated with use of non-nicotine containing e-cigarettes.

All of the newly-identified studies, and the one relevant study from the umbrella review [27], found a significant increase in the risk of transitioning from being a non-smoker to a current smoker in people who had used e-cigarettes compared to not using e-cigarettes, but with considerable heterogeneity in the estimates (I^2=91%; Figure 2b).

Cigarette smoking relapse among former smokers (at least two months since quit date)

Three [25, 45, 46] newly-identified studies in this review investigated the odds of relapse to combustible cigarette smoking following the use of e-cigarettes in adults aged ≥ 18 years (Table 2). None of the three previously conducted systematic reviews investigated this relationship, so no additional studies from the umbrella review were included. Brose et al. used data from 371 adults who quit ≥2 months prior to baseline in 2016 from a national web-based survey in the UK [25]. The other two studies used PATH data. Dai et al. looked at 3,210 ex-smokers, who had not smoked for >12-months [46]. McMillen et al. looked at data relating to 8,108 adults who had quit ≥5 years prior to baseline; sub-analyses from this study were included in the previous two sections, as the study also provided data on never smokers [45].

All three included studies found the odds of ever relapse was higher among ever e-cigarette users, compared to never e-cigarette users (Figure 2c). Additionally, the odds of ever relapse was higher among current e-cigarette users than non-current e-cigarette users. A meta-analysis of the three newly identified studies found former smokers who used e-cigarettes had 2.4 times greater odds of relapse when compared to those who did not use e-cigarettes, with similar magnitudes of this relationship between studies (I^2 = 12%) (Figure 2c).

Risk of bias across studies

Funnel plots corresponding to the studies included in the meta-analyses are presented in Table in S7 Table. The plot for the seventeen smoking initiation studies of never-smokers is somewhat asymmetrical and seven points lie outside the 95% confidence region, suggesting there may be some selection bias across included

studies, publication bias or possible heterogeneity (as supported by the I^2 statistic; 86%). With less than ten studies investigating current smoking in non-smokers [23, 24, 27, 40, 42-44] and relapse in former smokers [25, 45, 46], test for funnel plot asymmetry was not used as the power of the test would be too low for it to be a reliable indicator of publication bias [19].

Discussion:

Our umbrella and systematic review, along with an updated meta-analysis using data from primary studies, shows strong and consistent evidence that never smokers who have used e-cigarettes are more likely than those who have not used e-cigarettes to try smoking conventional cigarettes and to transition to become regular tobacco smokers. We found that, on average, non-smokers who used e-cigarettes have around three-fold the odds of either initiating smoking or currently smoking combustible cigarettes compared to non-smokers who have not used e-cigarettes. The limited available evidence indicates that former smokers who use e-cigarettes have more than twice the odds of relapse and resumption of current smoking compared to former smokers who have not used e-cigarettes.

This review builds on and has findings consistent with earlier systematic reviews and meta-analyses in the peer-reviewed and grey literature [11, 16, 38, 39, 58, 59]. A 2018 review by the National Academies of Sciences, Engineering, and Medicine (NASEM) on the public health consequences of e-cigarettes concludes that there is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes, and moderate evidence that e-cigarette use increases the frequency and intensity of subsequent combustible tobacco smoking, among youth and young adults [59]. Previous systematic reviews have focused on evidence in those 30 years of age or less, whereas our review included data on adults and former smokers. This is the first systematic review to examine whether e-cigarette use is associated with smoking relapse.

The use of e-cigarettes may represent a risk factor for cigarette smoking initiation, current smoking and relapse to cigarette smoking for several behavioural and physiological reasons. For those who use nicotine-containing e-cigarettes, a resulting addiction to nicotine may leave users at risk of seeking other forms of inhalable nicotine, such as combustible cigarettes [60, 61]. Additionally, as e-cigarettes can mimic behavioural (e.g. hand-mouth) and sensory (e.g. taste) aspects of smoking, associated e-cigarette habits and movements may make the transition to combustible smoking more natural [62, 63]. Further studies should examine potential mediators to better understand possible mechanisms for the association between e-cigarette use and subsequent cigarette use. Although one study showed that an intervention designed to reduce smoking initiation in adolescents through self-regulatory implementation intentions attenuated the odds of smoking uptake in never smokers who used e-cigarettes, a statistically significant increased odds remained [42].

Although studies in this review were consistent in finding increased risks of smoking uptake in non-smokers exposed to e-cigarettes, the magnitude of this increased risk varied substantially between studies. The reason for this variation is unclear, but may relate to the different products, populations and policy environments. In addition, it is challenging to estimate the overall effect of e-cigarettes on smoking initiation due to the variety of ways in which devices (e.g. e-cigarettes, JUULs, pods, vape pens) and users (e.g. never-users, ever-users, current-users, former users) are classified. The high heterogeneity in most of the results from the meta-analyses suggests that pooled odds ratios should be interpreted as an average of disparate results, rather than a reflection of the true underlying effect.

A limitation in this review is that included studies were limited to those written in English. While emerging results from this review and similar studies provide evidence regarding the association between e-cigarette and combustible cigarette use, the evidence is heavily weighted towards US and UK data. Only nine countries were included in this analysis, with a notable lack of data from the Asia-Pacific, Africa and the Middle East. Furthermore, the studies were reliant on self-reported product use, which is likely to be subject to self-reporting bias. All three systematic reviews rated moderate in the AMSTAR 2 risk of bias

assessment and the 12 newly-identified studies rated between 5 to 8 on the Newcastle-Ottawa Scale. Although the consistency of findings across multiple studies and settings supports the likelihood of a causal relationship, given the observational nature of many of the included studies, the findings may be potentially influenced by confounding factors, including socioeconomic status and the tendency for risk behaviours to occur together. As the ability to adjust for such confounding factors varied according to study, the possibility of residual confounding cannot be excluded.

Conclusion:

This review found consistent evidence that use of e-cigarettes, largely nicotine-delivering, is associated with increased risk of subsequent combustible smoking initiation, current combustible smoking and smoking relapse after accounting for known demographic, psychosocial and behavioural risk factors. This is the first review to examine associations between e-cigarette use and cigarette use across the whole population, including youth, adults and former smokers. Intervention efforts and policies surrounding e-cigarettes are needed to reduce the potential of furthering combustible tobacco use in Australia.

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Declarations of interest

The authors declare that they have no competing interests.

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Table 1: Odds ratios and adjusted odds ratios of the association between e-cigarette use and combustible cigarette smoking from systematic reviews and meta-analyses included in the umbrella review

Authors/ Year	Studies included (*n* = total population)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) and heterogeneity (I^2)
Khouja et al., 2020[38]	17 (*n* = 105,448)	4.59 (3.60 – 5.85)	2.92 (2.30 – 3.71) I^2: 84.5%
Aladeokin & Haighton, 2019[39]	8 (*n* = 73,076)	5.55 (3.94 – 1.82)	3.86 (2.18 – 6.82) I^2: 74%
Soneji et al., 2017[16]	9 (*n* = 17,389)	Initiation: 3.83 (3.74 – 3.91) Past 30-day: 5.68 (3.49 – 9.24)	Initiation: 3.50 (2.38 – 5.16) I^2: 56% Past 30-day: 4.28 (2.52 – 7.27) I^2: 0%

Table 2: Odds ratios and adjusted odds ratios of the association between e-cigarette use and subsequent combustible cigarette use for: (1) never-smokers at baseline, (2) non-smokers[a] (never or no current use) at baseline and (3) former smokers at baseline

Authors/ Year	Country	Baseline cigarette use	E-cigarette use	Follow up cigarette use	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
(1) Initiation in never smokers at baseline						
Berry et al., 2019 [21]	US	Never	Ever	Ever		4.09 (2.97 – 5.63)
Chien et al., 2019 [22]	Taiwan	Never	Ever	Ever	2.44 (1.94 – 3.09)	2.14 (1.66 – 2.75)
Conner et al., 2019 [42]	UK (England)	Never	Ever	Ever	4.03 (3.33 – 4.88)	2.78 (2.20 – 3.51)
McMillen et al., 2019 [45]	US	Never	Current[b]	Ever	16.4 (9.8 – 27.5)	6.6 (3.7 – 11.8)
Pénzes et al., 2018 [41]	Romania	Never	Ever	Ever	2.75 (1.52 – 4.96)	3.57 (1.96 – 6.49)
(2) Current use in non-smokers at baseline						
Aleyan et al., 2019 [23]	Canada	Non-smokers[a]	Current[b]	Current[b]		Wave 1 to 2: 1.54 (1.37 – 1.74) Wave 2 to 3: 1.18 (1.08– 1.29)
Barrington-Trimis et al., 2019 [43]	US	Never	Current[b]	Current[b]		*NHW to dual use*: 7.44 (3.63–15.3) *HW to dual use:* 3.64 (1.62–8.18)
Bold et al., 2018 [40]	US	No current[a]	Current[b]	Current[b]		Wave 1 to 2: 7.08 (2.34 – 21.42) Wave 2 to 3: 3.87 (1.86 – 8.06)
Conner et al., 2019 [42]	UK (England)	Never	Ever	Current[b]	3.38 (2.72 – 4.21)	2.17 (1.76 – 2.69)
				Regular[c]	3.60 (2.35 – 5.51)	1.27 (1.17 – 1.39)
Kinnunen et al., 2019 [24]	Finland	Never	Ever nicotine-containing	Daily	11.52 (4.91 –27.01)	8.50 (2.14–29.19) With school clustering: 2.92 (1.09–7.85)
			Ever non-nicotine containing		1.88 (0.25 – 14.45)	2.50 (0.25–12.05) With school clustering: 0.94 (0.22 – 4.08)
McMillen et al., 2019 [45]	US	Never	Ever (not current)	Established[d]	5.9 (1.7 – 20.7)	2.5 (0.6 – 10.9)
			Current[b]		25.5 (10.6 – 61.4)	8.0 (2.8 – 22.7)
Osibogun et al., 2020[44]	US	Non-smokers[a]	Current[b]	Regular[c]	Year 1: 16.4 (7.8 – 34.5) Year 2: 11.1 (3.5 – 35.2)	Year 1: 5.0 (1.9 – 12.8) Year 2: 3.4 (1.0 – 11.5)
(3) Relapse in former smokers at baseline						
Brose et al., 2019 [25]	UK	≥2-month ex-smokers	Ever	Ever	1.52 (0.88 – 2.62)	1.13 (0.61 – 2.07)
			Non-daily		3.32 (1.23 – 8.96)	2.45 (0.85 – 7.08)
Dai et al., 2019 [46]	US	>12-month ex-smokers	Current[b]	Ever	6.36 (4.49 – 9.00)	2.00 (1.25 – 3.20)
			Occasional		5.79 (1.50 – 22.33)	1.56 (0.34 – 7.14)
			Prior		9.68 (4.74 – 19.75)	3.77 (1.48 – 9.65)
McMillen et al., 2019 [45]	US	≥5years ex-smokers	Ever (not current[b])	Ever	5.4 (2.9 – 10.2)	3.3 (1.6 – 6.7)
			Current[b]		7.6 (3.0 – 19.4)	5.2 (1.6 – 16.3)

NHW: Non-Hispanic White; HW: Hispanic White
a - non-smokers defined as never or no current (past 30-day) use
b - current defined as past 30-day use
c - regular defined as ≥20 days/ 30 days
d - established defined as ≥100 combustible cigarettes and currently smokes every day or some

Fig 1: Flow chart for selection of studies for inclusion in umbrella review and top-up systematic review

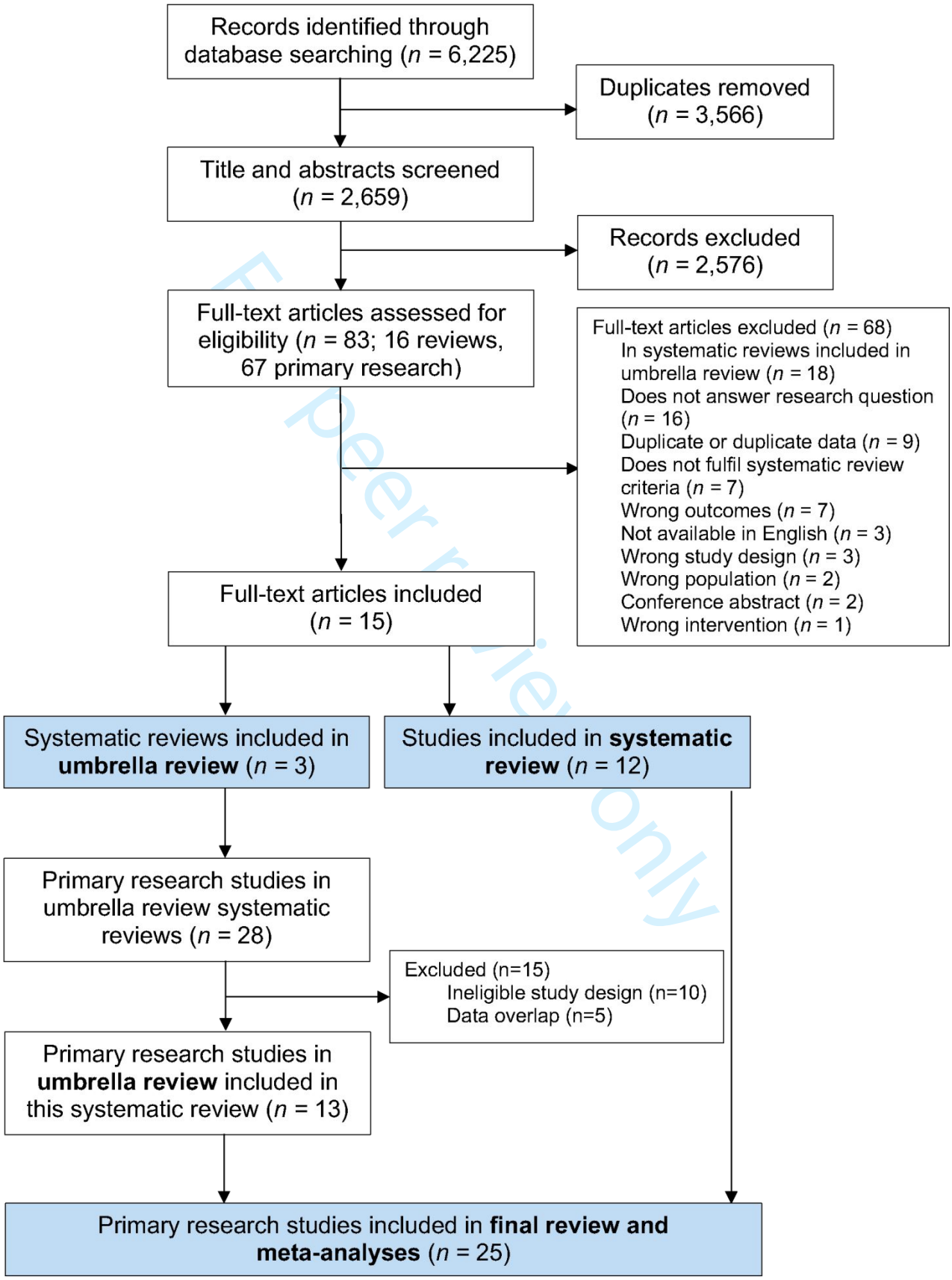


Fig 2: Forest plot and random-effects meta-analysis for the adjusted odds of smoking initiation at follow up among never smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline

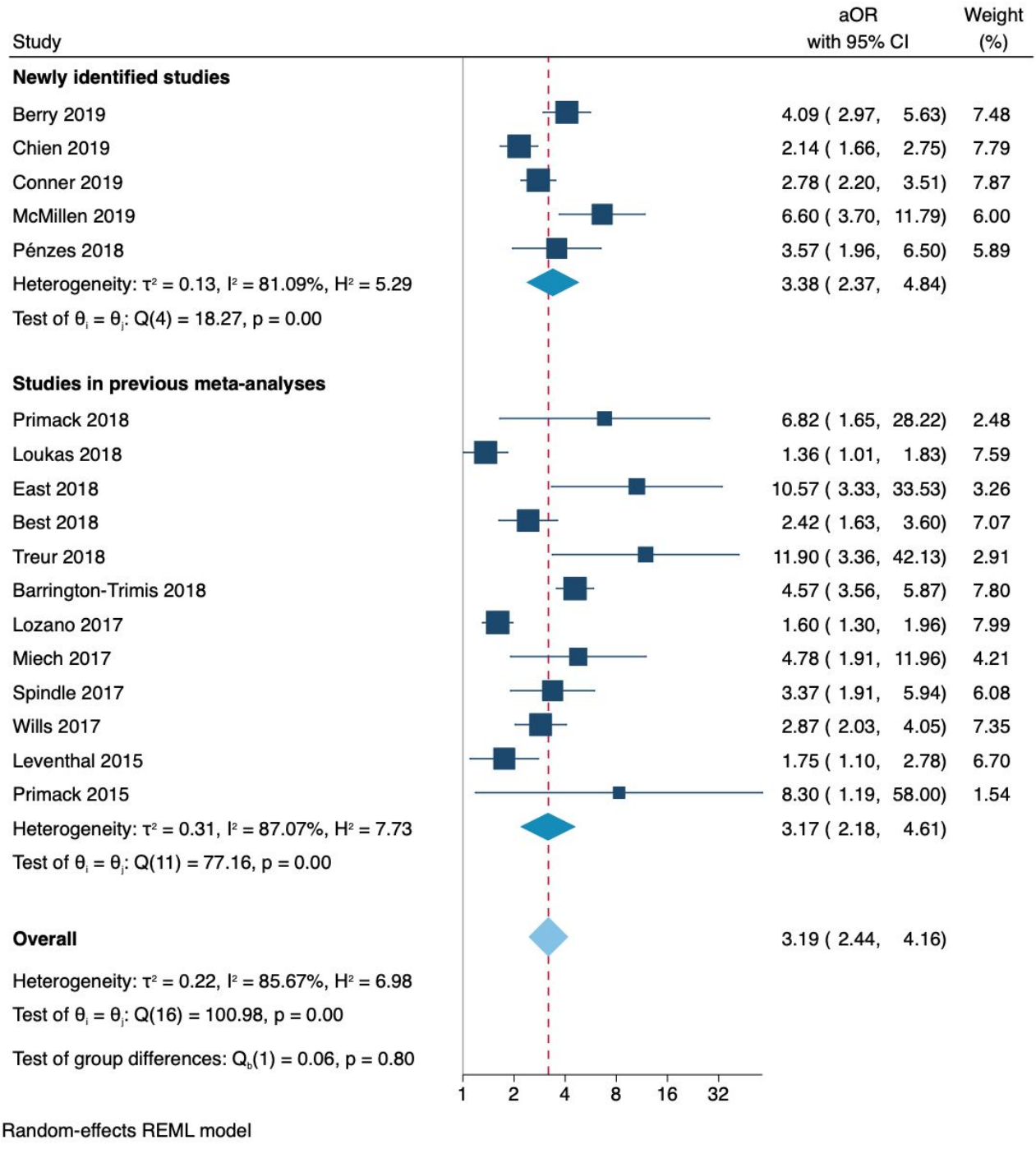


Fig 3: Forest plot and random-effects meta-analysis for the adjusted odds of current (past 30-day) smoking at follow up among non-current smokers and current e-cigarette users at baseline compared with non-current e-cigarette users at baseline

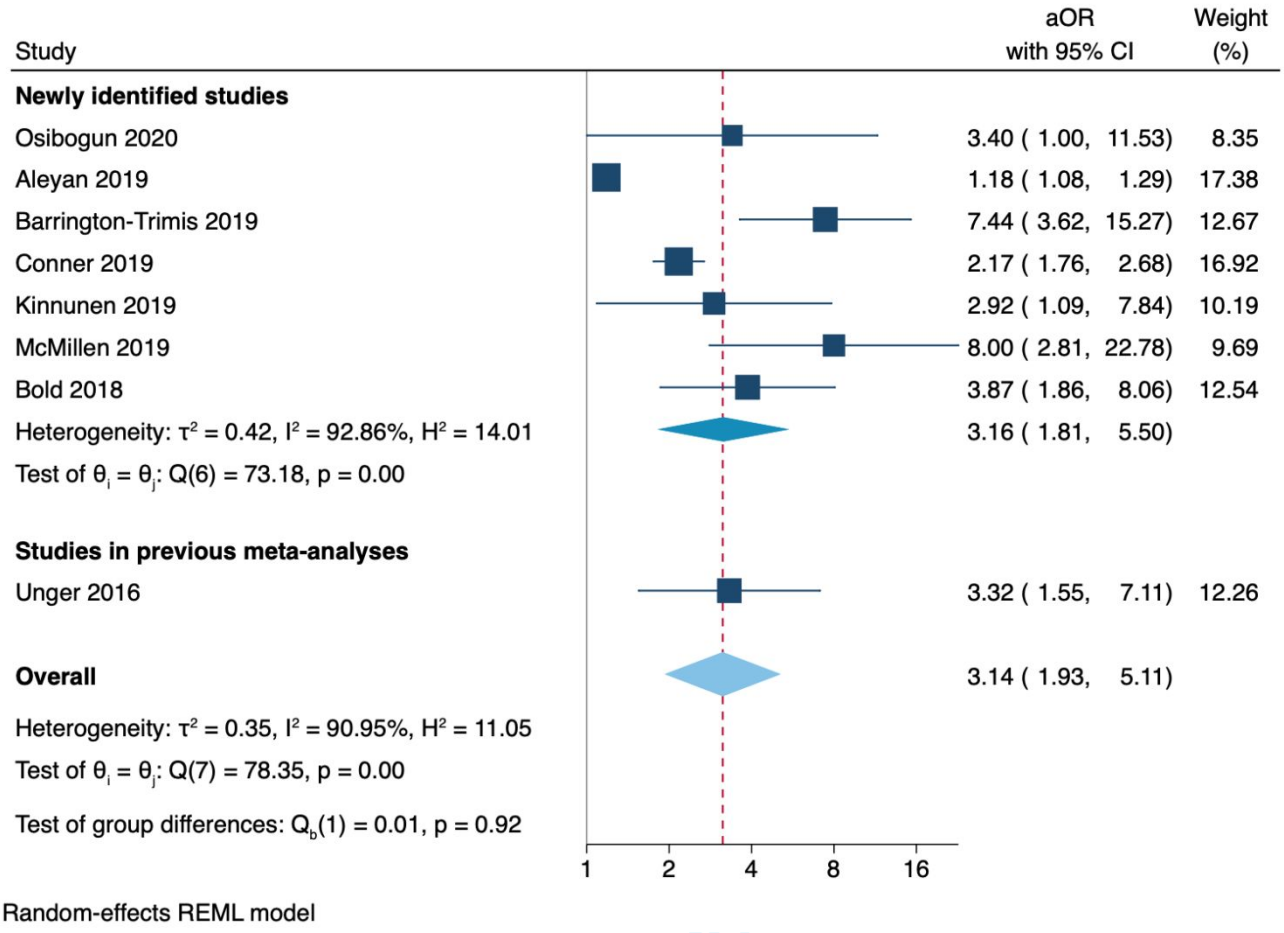
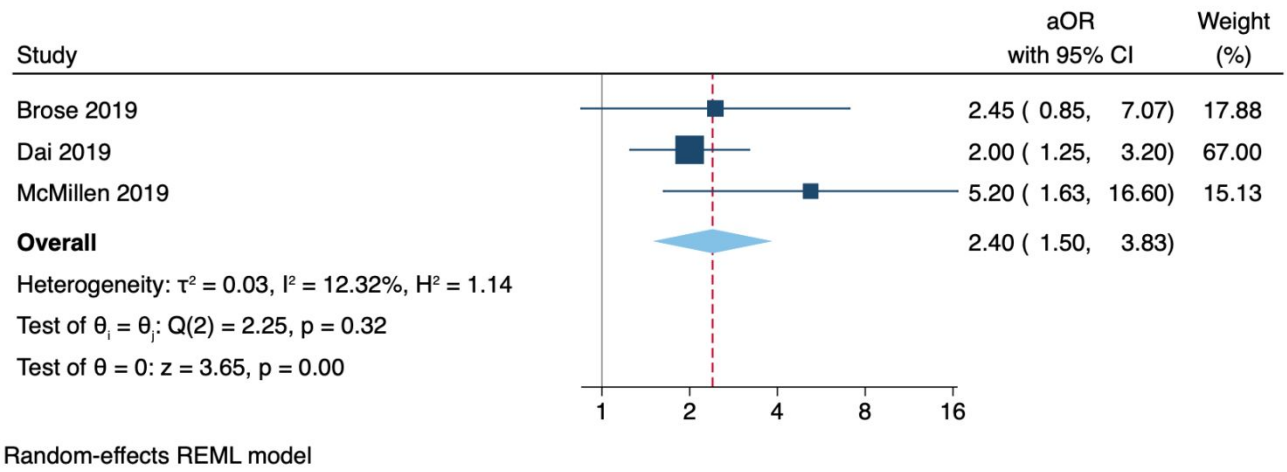


Fig 4: Forest plot and random-effects meta-analysis for the adjusted odds of smoking relapse at follow up among former smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline



Supporting Information

S1 Table: Inclusion and exclusion criteria for umbrella review (of systematic reviews) and systematic review (of primary research)

PICO	Inclusion Criteria	Exclusion Criteria
Population	Non-tobacco smokers - includes never, former or ever users (this includes prior users who have tried smoking but have not used in the past 30 days) Humans, any age (youth, young adults and adults)	Current tobacco smokers (use within the past 30 days) Animal studies, in vitro studies
Intervention	Nicotine-containing or non-nicotine-containing e-cigarettes or e-liquid devices (also referred to as vaping products)	Studies with a focus on heat-not-burn or tobacco containing devices Studies with a focus on the uptake of marijuana, other illicit drugs and harmful substances (as in the CSIRO report [58])
Comparison	No nicotine-containing or non-nicotine containing e-cigarettes or e-liquid devices	
Outcomes	Ever smoking combustible tobacco cigarettes	Studies where smoking cigarettes is not the primary outcome variable
Study	Published, peer-reviewed literature For umbrella review - Systematic reviews and meta-analyses of randomised/non-randomised controlled trials, clinical trials and prospective cohort studies (if a systematic review/meta-analysis includes study designs other than cohort and randomised/ non-randomised controlled trials, the review will only be included if the analysis and/ or results are separated by study design) For systematic review - Randomised/ non-randomised controlled trials, clinical trials (although interventional studies are not expected) - Prospective cohort studies	Systematic reviews that are superseded by a later review which include all studies from the earlier review. - Non-systematic -literature reviews - Intervention trial with no comparator (e.g. before and after study) - Qualitative studies - Retrospective cohort studies - Case-control studies - Cross-sectional (including repeated cross-sectional) - Case studies - Grey literature, conference abstracts, letters, editorials, correspondence, opinion pieces, government reports, position statements *Systematic reviews and meta-analyses will be excluded if they include only the above study designs.*
Follow-up	Minimum 6 months	
Setting	Any country	
Time period	All years	No exclusion
Other	- English - Full-text availability	- Not available in English - Duplicated data

S2 Appendix: Search strategy

MEDLINE, PyschINFO, PubMed, Scopus, Web of Science and Cochrane Library were searched. Papers were imported into an Endnote library, exported to Covidence and duplicates removed. The titles and abstracts were screened by two reviewers (OB and LF) to isolate relevant publications. Full texts were then identified for the relevant publications by two reviewers (OB and LF) and independently assessed the publications against the selection criteria. Any conflicts were discussed and if no consensus was reached the publication was reviewed by a third reviewer (MH).

A forward and backward reference search was performed on the final articles completed using Web of Science and Scopus. After removing duplicates, titles, abstracts and then full texts were screened for any randomised controlled trials fulfilling our inclusion and exclusion criteria by two reviewers (OB and LF).

Data were systematically extracted from the publications using data extraction templates. The quality of the included studies was assessed independently by two reviewers (OB and LF), with discrepancies resolved by discussion and by adjudication of a third reviewer (EB). E-cigarette, cigarette smoking and uptake search terms will be combined with the Boolean operator 'AND' for the final search.

S2A Table: Search terms

E-cigarette related search terms (combined with Boolean operator 'OR')	Combustible **cigarette smoking** related search terms (combined with Boolean operator 'OR')	**Uptake** related search terms (combined with Boolean operator 'OR')
Keywords 1. Electronic cigarette* 2. E-cigarette* 3. Electronic nicotine delivery system* 4. Electronic nicotine de* 5. Electronic non-nicotine de* 6. Vape 7. Vaping 8. Vapo* 9. E-hookah 10. Electronic inhalant device 11. E-liquid MeSH terms 1. Electronic Nicotine Delivery Systems (ENDS)	Keywords 1. Combustible cigarette 2. Tobacco smoking 3. Smoking 4. Cigarette MeSH terms 1. Smokers 2. Non-smokers	Keywords 1. Initiat* 2. Uptak* 3. Subsequent* 4. Predict* 5. Onset

S2B Table: Search histories

Database	Search	Studies and search date
PubMed	(((Electronic cigarette* or E-cigarette* or Electronic nicotine delivery systems[Mesh] or Electronic non-nicotine delivery* or Electronic nicotine device* or Electronic non-nicotine device* or Vape or Vaping or Vapo* or E-hookah or Electronic inhalant device or E-liquid)) AND (Smoker*[Mesh] or non-smoker*[Mesh] or ex-smoker*[Mesh] or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking)) AND (Initiat* OR Uptak* OR Subsequent* OR Predict* OR Onset)	1187 (01/04/2020)
Scopus	(TITLE-ABS-KEY (("Electronic cigarette*" OR "E-cigarette*" OR "Electronic nicotine delivery system*" OR "Electronic non-nicotine delivery*" OR "Electronic nicotine device*" OR "Electronic non-nicotine device*" OR "Vape" OR "Vaping" OR "Vapo*" OR "E-hookah")) AND TITLE-ABS-KEY (("Smoker*" OR "non-smoker*" OR "ex-smoker*" OR "Combustible cigarette" OR "Tobacco smoking" OR "Smoking" OR "Cigarette" OR "Cigarette smoking" OR "Cigar smoking")) AND TITLE-ABS-KEY (("Initiat*" OR "Uptak*" OR "Subsequent*" OR "Predict*" OR "Onset")))	1289 (01/04/2020)
Web of Science	**ALL FIELDS:** (("Electronic cigarette*" OR E-cigarette* OR "Electronic nicotine delivery system*" OR "Electronic non-nicotine delivery*" OR "Electronic nicotine device*" OR "Electronic non-nicotine device*" OR Vape OR Vaping OR Vapo* OR E-hookah OR "Electronic inhalant device")) *AND* **ALL FIELDS:** ((Smoker* OR non-smoker* OR ex-smoker* OR "Combustible cigarette" OR "Tobacco smoking" OR Smoking OR Cigarette OR "Cigarette smoking" OR "Cigar smoking")) *AND* **ALL FIELDS:** ((Initiat* OR Uptak* OR Subsequent* OR Predict* OR Onset))	1488 (01/04/2020)
PsychINFO (Ovid)	1. (Electronic cigarette* or E-cigarette* or Electronic nicotine delivery system* or Electronic non-nicotine delivery* or Electronic nicotine device* or Electronic non-nicotine device* or Vape or Vaping or Vapo* or E-hookah or Electronic inhalant device or E-liquid).af. 2. (Smoker* or non-smoker* or ex-smoker* or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking).af. 3. (Initiat* or Uptak* or Subsequent* or Predict* or Onset).af. 4. 1 and 2 and 3	874 (01/04/2020)
Medline (Ovid)	1 (Electronic cigarette* or E-cigarette* or Electronic nicotine delivery system* or Electronic non-nicotine delivery* or Electronic nicotine device* or Electronic non-nicotine device* or Vape or Vaping or Vapo* or E-hookah or Electronic inhalant device or E-liquid).af. 2 (Smoker* or non-smoker* or ex-smoker* or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking).af. 3 (Initiat* or Uptak* or Subsequent* or Predict* or Onset).af. 4 1 and 2 and 3	1168 (04/02/2020)
Cochrane	1. MeSH descriptor: [Electronic Nicotine Delivery Systems] explode all trees 2. ("Electronic cigarette" OR E-cigarette OR Vape OR Vaping OR E-hookah OR "Electronic inhalant device" OR E-liquid OR "Electronic Nicotine Delivery Systems"):ti,ab,kw 3. #1 OR #2 4. (Smoker* or non-smoker* or ex-smoker* or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking):ti,ab,kw 5. #4 OR #5 6. (Initiat* OR Uptak* OR Subsequent* OR Progress* OR Predict* OR Duration OR Intens* OR Frequen* OR Onset):ti,ab,kw 7. #3 AND #6 AND #7	219 (01/04/2020)

S3 Table: AMSTAR2[17] rating of included systematic review studies

Criteria	Aladeokin & Haighton 2019[39]	Soneji et al. 2017[16]	Khouja et al. 2020[38]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	No	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes	Partial Yes	Partial Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	No	No	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	Yes
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Yes	Yes
16. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
Rating overall confidence in the results of the review	Moderate	Moderate	Moderate

S4 Table: Primary research studies included in systematic reviews in the umbrella review that were included in the top-up systematic review

Authors/ Year	Title	Systematic review(s) included in	Country and data source(s)	Baseline cigarette use	E-cigarette use	Follow up cigarette use	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Barrington-Trimis et al., 2018[33]	E-cigarette Use and Subsequent Smoking Frequency Among Adolescents	Khouja et al., 2020	US (CA, CT): CHS, HH, YASS	Never	Ever	Ever	3.80 (3.10 – 4.66)	4.57 (3.56 – 5.87)
Best et al., 2018[35]	Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study	Aladeokin & Haighton 2019 Khouja et al., 2020	Scotland (UK): School-based	Never	Ever	Ever	4.62 (3.34 – 6.38)	2.42 (1.63 – 3.60)
East et al., 2018[34]	The Association Between Smoking and Electronic Cigarette Use in a Cohort of Young People	Aladeokin & Haighton 2019 Khouja et al., 2020	England (UK): AOSHGB	Never	Ever	Ever	12.31 (5.06 – 29.94)	10.57 (3.33 – 33.50)
Leventhal et al., 2015[32]	Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence	Khouja et al., 2020 Soneji et al., 2017	US (LA): YBRS - School-based	Never	Ever	Ever	2.95 (1.74 – 4.99)	1.75 (1.10 – 2.77)
Loukas et al., 2018[14]	Exclusive e-cigarette use predicts cigarette initiation among college students	Khouja et al., 2020	US (TX): M-PACT	Never	Ever	Ever	2.72 (2.10 – 3.53)	1.36 (1.01 – 1.83)
Lozano et al., 2017[36]	A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents	Khouja et al., 2020	Mexico: School-based	Never	Ever	Ever	2.46 (1.85 – 3.26)	1.60 (1.31 – 1.97)
Miech et al., 2017[31]	E-cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students	Khouja et al., 2020 Soneji et al., 2017	US: MTD 2014-2015	Never	Ever	Ever	6.32 (1.73 – 23.10)	6.58 (2.04 – 57.88) †
Primack et al., 2015[29]	Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults	Khouja et al., 2020 Soneji et al., 2017	US: Dartmouth media survey 2012-2014	Never	Ever	Ever	5.66 (1.99 – 16.07)	8.3 (1.2 – 58.6)
Primack et al., 2018[30]	Initiation of Traditional Cigarette Smoking after Electronic Cigarette Use Among Tobacco-Naive US Young Adults	Khouja et al., 2020	US: Growth from Knowledge 2013-2014	Never	Ever	Ever	6.06 (2.15 – 17.10)	6.82 (1.65 – 28.25)
Spindle et al., 2017[28]	Electronic cigarette use and uptake of cigarette smoking: A longitudinal examination of U.S. college students	Khouja et al., 2020 Soneji et al., 2017	US: Mid-Atlantic university (S4S project)	Never	Ever	Ever	3.50 (2.41 – 5.09)	3.37 (1.91 – 5.94)
Treur et al., 2018[37]	E-cigarette and waterpipe use in two adolescent cohorts: cross-sectional and longitudinal associations with conventional cigarette smoking	Khouja et al., 2020	Netherlands	Never	Ever**	Ever	10.83 (8.87 – 13.22)	11.9 (3.36 – 42.11)

Unger et al., 2016[27]	E-cigarette use and subsequent cigarette and marijuana use among Hispanic young adults	Soneji et al., 2017	US (LA): Project RED	No current[a]	Current[a]	Current[a]	4.71 (2.27 – 9.77)	3.32 (1.55 – 7.11)
Wills et al., 2017[26]	Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii	Khouja et al., 2020 Soneji et al., 2017	US (HI): School-based	Never	Ever	Ever	4.25 (2.74 – 6.61)	2.87 (2.03 – 4.05)

S5 Table: Newcastle Ottawa Scale[18] (NOS) rating of newly-identified primary research studies

Study	Selection				Comparability	Outcome			Total
	Representativeness of the Exposed Cohort (★)	Selection of the Non-Exposed Cohort (★)	Ascertainment of Exposure (★)	Demonstration That Outcome of Interest Was Not Present at Start of Study (★)	Comparability of Cohorts on the Basis of the Design or Analysis (★★)	Assessment of Outcome (★)	Was Follow-Up Long Enough for Outcomes to Occur (★) *	Adequacy of Follow Up of Cohorts (★) ‡	
Aleyan et al., 2019 [23]	★	★		★	★★		★		6
Barrington-Trimis et al., 2019 [43]	★	★		★	★★		★	★	7
Berry et al., 2019 [21]	★	★	★	★	★★		★	★	8
Bold et al., 2018 [40]	★	★		★	★		★		5
Brose et al., 2019 [25]	★	★		★	★★		★		6
Chien et al., 2019 [22]	★	★		★	★★		★	★	7
Conner et al., 2019 [42]	★	★		★	★★		★		6
Dai et al., 2019 [46]	★	★	★	★	★★		★	★	8
Kinnunen et al., 2019 [24]	★	★		★	★★		★		6
McMillen et al., 2019 [45]	★	★	★	★	★★		★	★	8
Osibogun et al., 2020[44]	★	★	★	★	★★		★	★	8
Pénzes et al., 2018 [41]	★	★		★	★★		★		6

* 6 months considered adequate follow-up time
‡ Studies with less than 30% loss to follow-up considered adequate

S6 Table: Study characteristics from newly-identified studies for the top-up systematic review

Study	Country and data source	Study design	Duration (follow up and date range)	Study population - sample size - baseline age/ grade - % female	Consideration of confounding	NOS[1] score
Aleyan et al., 2019 [23]	Canada (COMPASS Waves 1-3)	Longitudinal cohort	36 months (2014 to 2017)	- 6,729 - 9th or 10th grade - 54.2% female	Gender, grade, ethnicity, friends that smoke, weekly spending money, current cannabis use, and current binge drinking at each wave	6
Barrington-Trimis et al., 2019 [43]	US (CT and CA); CHS; HH; YASS[1]	Longitudinal cohort	12 months (2013 to 2015)	- 6,258 - Grades 9 to 12 - 53.5% female	Gender, grade, and cohort (CHS, H&H, YASS), school (H&H/YASS) or community (CHS)	7
Berry et al., 2019 [21]	US (PATH[3] Waves 1-3)	Longitudinal cohort	24 months (2013 to 2016)	- 6,123 - 12-15 years old, mean 13.4 years (SD 1.2) - 49.5% female	Age, gender, income, race and ethnicity, parental education, urban residence, living with a tobacco user, frequency of noticing health warnings on cigarette packages, and ability to recall a favourite tobacco advertisement. Risk-taking behaviours, sensation-seeking personality traits, and cigarette susceptibility	8
Bold et al., 2018 [40]	US (CT)	Longitudinal cohort	36 months (2013 to 2015)	- 808 - Mean 15.04 years (SD 0.90) - 53% female	School, sociodemographic characteristics (sex, race/ethnicity, SES), and use of other tobacco products.	5
Brose et al., 2019 [25]	UK (National web-based survey 2012-2017)	Longitudinal cohort	12 months (2016 to 2017)	- 374 - Mean 49.2 years (SD 14.1) - 44% female	Time quit smoking, vaping status, gender, income and NRT use	6
Chien et al., 2019 [22]	Taiwan (TAALS[4] Waves 1-2)	Longitudinal cohort	24 months (2014 to 2016)	- 12,954 - 36.9% ever smokers female; 58.1% never smokers female	Smoking susceptibility at baseline, socio-demographic profile, psychological status, and peer support.	7
Conner et al., 2019 [42]	UK (England); RCT Waves 3 and 5	Post-hoc analysis of a cluster RCT	24 months (2014 – 2016)	- 3,994 - 13 to 14 years old - 52.3% female	Sociodemographic (gender, ethnicity, family affluence, percentage of children per school eligible for free school meals); friends' smoking status, family smoking, impulsiveness	6
Dai et al., 2019 [46]	US (PATH[3] Waves 1-2)	Longitudinal cohort	12 months (2013 to 2015)	- 4,094 - Adults (≥18 years) - 45.9% female	Sociodemographic (age, sex, race, education, poverty level, region, and health insurance) and tobacco use characteristics (smoking chronicity, typical number of combustible cigarettes smoked per day during the period of regular smoking, and length of time since quit smoking)	8
Kinnunen et al., 2019 [24]	Finland MetLoFIN[5] (school-based)	Longitudinal cohort	18 months (2014 to 2016)	- 3,474 - Grade 9 (ages 15 to 16 years) - 51.8% female	Gender, socioeconomic background, parents' education, other tobacco product and drug use, school clustering. Crude and adjusted logistic regressions were also conducted with the Firth's bias-reduced logistic regression	6
McMillen et al., 2019 [45]	US (PATH[3] Waves 1-2)	Longitudinal cohort	12 months (2013 to 2015)	- 8,108 - Adults (≥18 years) - 54.4% distant former smoker female; 40.0% never smoker female	Sociodemographic (race/ethnicity, sex, age, education); psychosocial predictors of combustible cigarette smoking risk (household smoking rules and living with someone who smokes)	8
Osibogun et al., 2020[44]	US (PATH[3] Waves 1-3)	Longitudinal cohort	36 months (2013 to 2016)	- 14,623 - Ages 12-17 years - 48% female	Sociodemographic and tobacco-related factors	8
Pénzes et al., 2018 [41]	Romania (ASPIRA[6] RCT)	Secondary analysis from data in cluster RCT	6 months (2014 to 2015)	- 1,369 - Grade 9, mean 14.88 (SD 0.48)	Intervention/control condition, gender, age, the design effect due to the cluster sampling and used schools as cluster units	6

[1] NOS: Newcastle-Ottawa Scale (out of a total of 10)
[2] CHS: Children's Health Study; HH: Happiness & Health Study; YASS: Yale Adolescent Survey Study
[3] PATH: Population Assessment of Tobacco and Health Study
[4] TAALS: The Taiwan Adolescent to Adult Longitudinal Study
[5] MetLoFIN: Metropolitan Longitudinal Finland
[6] ASPIRA: A Smoking Prevention Interactive Experience [Roman acronym for translation of ASPIRE]

S7 Figure: Funnel plots to assess the risk of bias across studies

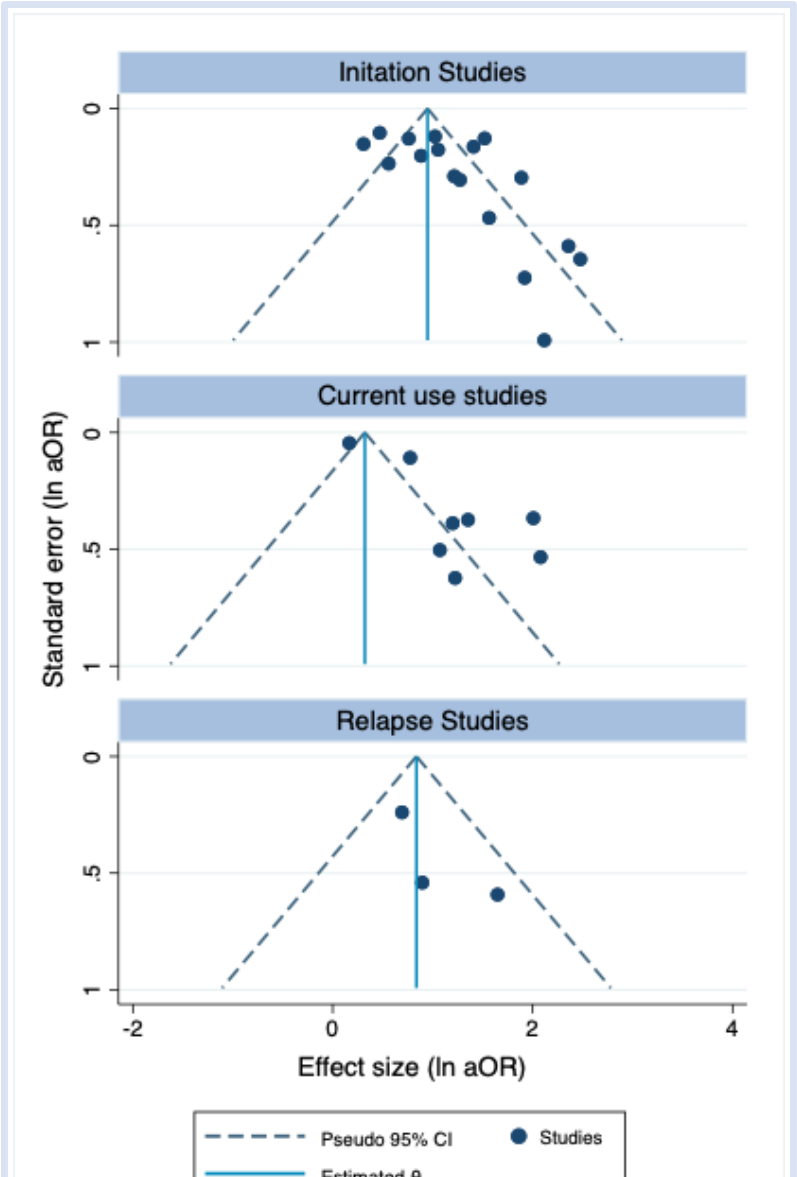


Figure: Funnel plots with pseudo 95% confidence limits

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	1
8	Search strategy, including time period included in the synthesis and key words	5; Table A in S2
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	6
13	List of citations located and those excluded, including justification	Fig 1; Table B in S2
14	Method of addressing articles published in languages other than English	4-5; Fig 1, 22
15	Method of handling abstracts and unpublished studies	5; Fig 1, 22
16	Description of any contact with authors	N/A
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5-6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	-
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5-6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	7, Table 1
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	Table 1 & 2; Fig. 1
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig. 2-4
26	Table giving descriptive information for each study included	Table 1 & 2
27	Results of sensitivity testing (eg, subgroup analysis)	-
28	Indication of statistical uncertainty of findings	8, 9, 12, 13 Table 1

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	13
30	Justification for exclusion (eg, exclusion of non-English language citations)	5; Fig 1; Table B in S2
31	Assessment of quality of included studies	8, 9
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	14-15
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	14-15
34	Guidelines for future research	-
35	Disclosure of funding source	16

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6, S1 Table
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2B Table
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-13 and Table 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, 9; S3; S5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 2, 3, 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	(N/A)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3 and 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

BMJ Open

E-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Smoking and tobacco
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, RESPIRATORY MEDICINE (see Thoracic Medicine)

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E-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis

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Abstract:

Objective: To review and summarise the current evidence on the uptake of combustible cigarette smoking following e-cigarette use in non-smokers - including never-smokers, people not currently smoking and past smokers - through an umbrella review, systematic review and meta-analysis.

Design: Umbrella review, systematic review and meta-analysis

Data sources: PubMed, Scopus, Web of Science, PsychINFO (Ovid), Medline (Ovid) and Wiley Cochrane Library up to April 2020.

Results: Of 6,225 results, 25 studies of non-smokers - never, not current, and former smokers - with a baseline measure of e-cigarette use and an outcome measure of combustible smoking uptake were included. All 25 studies found increased risk of smoking uptake with e-cigarette exposure, although magnitude varied substantially. Using a random-effects model, comparing e-cigarette users versus non-e-cigarette users, among never-smokers at baseline the odds ratio (OR) for smoking initiation was 3.25 (95%CI 2.61-4.05, I^2 85.7%) and among non-smokers at baseline the OR for current smoking was 2.87 (95%CI 1.97-4.19, I^2 90.1%). Among former smokers, smoking relapse was higher in e-cigarette users versus non-users (OR=2.40, 95% CI 1.50-3.83, I^2 12.3%).

Conclusions: Across multiple settings, non-smokers who use e-cigarettes are consistently more likely than those avoiding e-cigarettes to initiate combustible cigarette smoking and become current smokers. The magnitude of this risk varied, with an average of around three times the odds. Former smokers using e-cigarettes have over twice the odds of relapse as non-e-cigarettes users. This study is the first to our knowledge to review and pool data on the latter topic.

Prospero registration number: CRD42020168596

Strengths and Limitations

Strengths

- Comprehensive and systematic literature search with pooled evidence from 25 published studies reviewed according to a pre-specified protocol.
- Inclusion of studies investigating all ages and types of non-smokers (never, not current and former).
- Independent corroboration of results from previous studies, reviews and meta-analyses, while adding evidence on smoking uptake with e-cigarette exposure among former smokers

Limitations

- The evidence is largely reliant on self-reported product use and the studies reviewed were observational in nature as it is not ethical or appropriate to randomise non-smokers to e-cigarette exposure.
- While all studies reported significantly higher uptake of tobacco smoking among non-smokers exposed to e-cigarettes, compared to those not exposed, there was significant variation in the magnitude of the observed increase in risk; the results of the meta-analyses should therefore be considered to be an average of the published studies.

Introduction

Globally, combustible tobacco smoking results in over 8 million deaths each year [1]. Due to vigorous public health interventions, smoking prevalence in Australia has declined substantially over the last 50 years [2]. Nevertheless, 9.3% of the total disease burden (in disability-adjusted life years) was attributable to combustible tobacco use in 2015 [3].

E-cigarettes are a diverse group of battery-operated or rechargeable devices that heat a liquid ('e-liquid' or 'e-juice') to produce a vapour that users inhale. Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol and flavouring agents and are commonly used to deliver nicotine [4]. The labelling of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) is not always accurate, with reports of nicotine found in products labelled ENNDS [4, 5].

Studies indicate that in many countries, e-cigarette use among never-smoking youth is increasing [6-11]. In Australia, the proportion of non-smokers aged 14 years or older who had ever used e-cigarettes increased from 4.9% in 2016 to 6.9% in 2019 [12]. The increase was particularly notable in young adults, with 20% of 18-24 year old non-smokers reporting e-cigarette use [12]. E-cigarette use among youth is predominantly driven by curiosity and experimentation rather than smoking cessation [13-15]. Evidence also suggests that most people who report ever e-cigarette do not graduate to regular e-cigarette use [15, 16]. Although the identification of risk factors for initiation of e-cigarette use is complex, it appears as though many are similar to those for smoking initiation [17, 18].

There are concerns that the use of e-cigarettes in never-smokers may increase the probability that they will try combustible tobacco cigarettes and go on to become regular smokers, particularly among youth and young adults [19, 20]. Furthermore, use of e-cigarettes could conceivably lead to combustible tobacco smoking relapse in former smokers. If e-cigarette use leads to more people smoking combustible

cigarettes, compared with the number of people who have smoked in the absence of e-cigarettes, this would be a source of considerable public health harm [21]. Thus, our primary research question is: among never smokers, current non-smokers and former smokers, how does e-cigarette use affect the subsequent risk of initiating use, current use and relapse to combustible tobacco cigarettes? This review aims to systematically update global contemporary population-level evidence on the relationship of e-cigarette use to smoking uptake.

Methods

This summary of the global evidence comprises an umbrella review of systematic reviews and a top-up systematic review of primary research not included in the systematic reviews of the umbrella review. The protocol was published online through PROSPERO (CRD42020168596).

Search strategy

The Population, Intervention, Comparison, Outcome (PICO) format was used to structure the search (Supplementary Table 1). Studies investigating the association between ENDS or ENNDS use among non-tobacco smokers and uptake of combustible cigarette smoking were included. E-cigarette use, cigarette smoking and uptake related search terms and keywords were used (Supplementary Table 2). For both the umbrella review and the top-up systematic review, six databases (PubMed, Scopus, Web of Science, PsycINFO (Ovid), MEDLINE (Ovid), and Cochrane) were searched on 1 April 2020 (Supplementary Table 3).

Inclusion and exclusion criteria

Systematic reviews and meta-analyses of prospective cohort studies or randomised or non-randomised controlled trials examining the exposure (e-cigarette use) and outcome (smoking uptake in current non-smokers) of interest were included in the umbrella review. For the top-up systematic review, individual prospective cohort studies or randomised or non-randomised controlled trials identified in the search and not included in the umbrella review studies, were included. Cross-sectional studies were excluded due to difficulties in establishing the temporal relationship between e-cigarette exposure and smoking uptake.

Studies with a follow up of less than 6 months or with abstracts not published in English were excluded. The full inclusion and exclusion criteria can be found in Supplementary Table 1.

Data screening and extraction

EndNote and Covidence software were used for review management. Two authors of this review (OB and LF) undertook initial screening, study selection, risk of bias assessment, and data extraction. Titles and abstracts identified in the searches were screened using a checklist, followed by full-text screening. A forward and backward reference search using Scopus was performed from the final included articles. After removing duplicates, titles, abstracts, and then full texts were screened for any studies fulfilling the inclusion and exclusion criteria. Data were independently extracted from the included systematic reviews and cohort studies using a pre-specified data extraction template. As it is important to consider whether authors of the studies under review hold any conflicts of interest that could potentially bias their findings, or whether the research was funded by an organisation with a financial interest in the outcomes, information on the source of research sponsorship or external involvement was also extracted. Studies were considered separately if they were funded by the tobacco or nicotine industry.

Risk of bias assessment

Risk of bias for each study included was independently assessed using the AMSTAR 2[22] for the systematic reviews and meta-analyses included in the umbrella reviews, and the Newcastle Ottawa Scale (NOS)[23] for the studies in the top-up systematic review. For meta-analyses with at least ten studies, risk of bias across studies was assessed and interpreted using the symmetry of funnel plots and superimposed 95% confidence limits [24].

Summary measures and synthesis of results

Findings from the umbrella review and the top-up systematic review were synthesised separately in narrative summaries. Individual prospective primary research studies identified from both the umbrella review and

top-up systematic review were then considered in an integrated systematic review. Where appropriate, odds ratios from the studies in the integrated systematic review were combined using a random-effects model. Heterogeneity of study effect estimates were assessed by an I-squared statistic. All analyses were conducted using Stata version 16.1.

Patient and Public Involvement

No patient involved.

Results:

Study Selection

Study selection for this umbrella review and top-up systematic review are shown in the PRISMA flowchart in Figure 1. A total of 6,225 studies were identified for title and abstract screening; 2,659 remained after exclusion of duplicates. After title and abstract screening, 83 articles were identified for full-text screening. Fifteen papers were identified for inclusion; three were systematic reviews that were included in the umbrella review and 12 were primary research studies included in the top-up systematic review. Ten of the latter studies were prospective observational studies and two were secondary analyses of randomised controlled trials (RCT).

From the three systematic review papers included in the umbrella review, 28 primary research studies were identified after removing duplicates. For our meta-analyses, we excluded 15 studies due to ineligible study design (n=10) or data overlap (n=5). No studies were excluded based on their quality assessment scores. The meta-analyses were thus based on 13 primary research studies identified from the prior systematic reviews, and 12 studies from our top-up systematic review, i.e. a total of 25 primary research studies on e-cigarette use and smoking uptake (Figure 1).

No potential competing interests were identified in the included studies themselves, or by the authors, based on the disclosure statements from the publications. Although one [25] primary research study identified during screening in the top-up systematic review was found to have potential competing

interests, as it was funded by the tobacco industry, it was previously excluded due to a large overlap with data presented in a more recent paper by Berry et al. [26].

There is considerable uncertainty regarding the chemical constituents of the e-liquids delivered by the e-cigarettes in the studies included in the review. Where evidence on nicotine content was available, it indicated that a substantial majority of e-cigarettes in those studies delivered nicotine [27-30]. Many publications noted considerable uncertainty regarding nicotine content, including apparent mislabelling, and the need for greater clarity and reliability on this point.

Umbrella review: quality assessment

All three systematic reviews from the selected articles rated moderate in the AMSTAR 2 [22] assessment. Information was lacking regarding study exclusion criteria, stated sources of funding, and detail on data extraction (Supplementary Table 4).

Umbrella review:

Table 1 summarises the results of the three systematic reviews included in the umbrella review. All three systematic reviews excluded studies with participants over 30 years of age. Sample sizes for the individual studies varied considerably, ranging from 298 to 17,318. Of the 13 included longitudinal primary research studies (detailed in Supplementary Table 5), nine[20, 31-38] were based in the US, two [39, 40] in the UK and one each in Mexico [41], and the Netherlands [42]. Each of the three systematic reviews conducted meta-analyses and found the odds of smoking initiation were increased for youth and young adult e-cigarette users compared to non-e-cigarette users; these results are summarised in Table 1.

Table 1: Odds ratios and adjusted odds ratios of the association between e-cigarette use and combustible cigarette smoking from systematic reviews and meta-analyses included in the umbrella review

Authors/ Year	Studies included (*n* = total population)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) and heterogeneity (I^2)
Khouja et al., 2020[43]	17 (*n* = 105,448)	4.59 (3.60 – 5.85)	2.92 (2.30 – 3.71) I^2: 84.5%
Aladeokin & Haighton, 2019[44]	8 (*n* = 73,076)	5.55 (3.94 – 1.82)	3.86 (2.18 – 6.82) I^2: 74%
Soneji et al., 2017[21]	9 (*n* = 17,389)	Initiation: 3.83 (3.74 – 3.91) Past 30-day: 5.68 (3.49 – 9.24)	Initiation: 3.50 (2.38 – 5.16) I^2: 56% Past 30-day: 4.28 (2.52 – 7.27) I^2: 0%

The Khouja et al. (2020) systematic review and meta-analysis included 17 studies published up to November 2018 [43]. The study found that the risk of later smoking in people aged <30 years who had ever used or currently use e-cigarettes was strong; an almost three-fold the odds compared to never users after adjustment for covariates (see Table 1). However, there were high levels of heterogeneity in the summary estimates (adjusted OR I^2 =84.5%), which remained high in adjusted analysis subgrouping by age, ever smoking, risk of bias and location of study. Heterogeneity was reduced when the adjusted ORs were grouped into those examining the relationship between ever e-cigarette use and current smoking (adjusted OR 2.21; 95% CI 1.72 – 2.84, I^2 =5%) and those assessing the relationship of current e-cigarette use to ever smoking (adjusted OR 2.21; 95% CI 1.72 – 2.84, I^2=5%).

Aladeokin & Haighton (2019) aimed to systematically review the evidence on e-cigarette use and initiation of cigarette smoking in adolescents (aged 10-19 years old) in the UK and included eight studies.[44] Their meta-analysis showed e-cigarette users were much more likely than non-users to go on to smoke combustible cigarettes, even after adjusting for covariates (see Table 1); the substantial heterogeneity in the summary estimate should be noted.

The Soneji et al. (2017) systematic review and meta-analysis included nine longitudinal studies of US participants ≤30 years of age [21]. Seven of the included studies assessed the association of baseline ever e-cigarette use with subsequent ever combustible cigarette use at follow-up among baseline never smokers. Soneji et al. also identified two studies that assessed baseline past 30-day e-cigarette use with subsequent past 30-day combustible cigarette use among those reporting no past 30-day use of cigarettes at baseline. The meta-analysis showed a markedly higher odds of combustible cigarette use in those who had used e-cigarettes (Table 1).

Top-up systematic review: quality assessment

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale [23] (NOS). Of the 12 studies, the NOS totals (out of 10 stars) ranged from 5 to 8 (Supplementary Table 6). Only one [45] study rated 5, five [28-30, 46, 47] rated 6, two [9, 48] rated 7 and four [26, 49-51] rated 8. No studies received a star for assessment of outcome. The main areas impacting the NOS scores were ascertainment of exposure and adequacy of follow up of cohorts (studies with less than 30% loss to follow up were considered adequate).

Top-up systematic review and integration with primary research studies from the umbrella review

A total of 12 studies published in 2018, 2019 and 2020 were newly-identified for the top-up systematic review (Table 2; Supplementary Table 7). Among the 12 included, six were from the US, two from the UK, and one each from Romania, Finland, Taiwan and Canada. Study sample sizes varied considerably, ranging from 374 to 14,623.

Table 2: Odds ratios and adjusted odds ratios of the association between e-cigarette use and subsequent combustible cigarette use for: (1) never-smokers at baseline, (2) non-smokers[a] (never or no current use) at baseline and (3) former smokers at baseline

Authors/ Year	Country	Baseline cigarette use	E-cigarette use	Follow up cigarette use	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
(1) Initiation in never smokers at baseline						
Berry et al., 2019 [26]	US	Never	Ever	Ever		4.09 (2.97 – 5.63)
Chien et al., 2019 [27]	Taiwan	Never	Ever	Ever	2.44 (1.94 – 3.09)	2.14 (1.66 – 2.75)
Conner et al., 2019 [47]	UK (England)	Never	Ever	Ever	4.03 (3.33 – 4.88)	2.78 (2.20 – 3.51)
McMillen et al., 2019 [50]	US	Never	Current[b]	Ever	16.4 (9.8 – 27.5)	6.6 (3.7 – 11.8)
Pénzes et al., 2018 [46]	Romania	Never	Ever	Ever	2.75 (1.52 – 4.96)	3.57 (1.96 – 6.49)
(2) Current use in non-smokers at baseline						
Aleyan et al., 2019 [28]	Canada	Non-smokers[a]	Current[b]	Current[b]		Wave 1 to 2: 1.54 (1.37 – 1.74) Wave 2 to 3: 1.18 (1.08– 1.29)
Barrington-Trimis et al., 2019 [48]	US	Never	Current[b]	Current[b]		*NHW to dual use*: 7.44 (3.63–15.3) *HW to dual use:* 3.64 (1.62–8.18)
Bold et al., 2018 [45]	US	No current[a]	Current[b]	Current[b]		Wave 1 to 2: 7.08 (2.34 – 21.42) Wave 2 to 3: 3.87 (1.86 – 8.06)
Conner et al., 2019 [47]	UK (England)	Never	Ever	Current[b]	3.38 (2.72 – 4.21)	2.17 (1.76 – 2.69)
				Regular[c]	3.60 (2.35 – 5.51)	1.27 (1.17 – 1.39)
Kinnunen et al., 2019 [29]	Finland	Never	Ever nicotine-containing	Daily	11.52 (4.91 –27.01)	8.50 (2.14–29.19) With school clustering: 2.92 (1.09–7.85)
			Ever non-nicotine containing		1.88 (0.25 – 14.45)	2.50 (0.25–12.05) With school clustering: 0.94 (0.22 – 4.08)
McMillen et al., 2019 [50]	US	Never	Ever (not current)	Established[d]	5.9 (1.7 – 20.7)	2.5 (0.6 – 10.9)
			Current[b]		25.5 (10.6 – 61.4)	8.0 (2.8 – 22.7)
Osibogun et al., 2020[49]	US	Non-smokers[a]	Current[b]	Regular[c]	Year 1: 16.4 (7.8 – 34.5) Year 2: 11.1 (3.5 – 35.2)	Year 1: 5.0 (1.9 – 12.8) Year 2: 3.4 (1.0 – 11.5)
(3) Relapse in former smokers at baseline						
Brose et al., 2019 [30]	UK	≥2-month ex-smokers	Ever	Ever	1.52 (0.88 – 2.62)	1.13 (0.61 – 2.07)
			Non-daily		3.32 (1.23 – 8.96)	2.45 (0.85 – 7.08)
Dai et al., 2019 [51]	US	>12-month ex-smokers	Current[b]	Ever	6.36 (4.49 – 9.00)	2.00 (1.25 – 3.20)
			Occasional		5.79 (1.50 – 22.33)	1.56 (0.34 – 7.14)
			Prior		9.68 (4.74 – 19.75)	3.77 (1.48 – 9.65)
McMillen et al., 2019 [50]	US	≥5years ex-smokers	Ever (not current[b])	Ever	5.4 (2.9 – 10.2)	3.3 (1.6 – 6.7)
			Current[b]		7.6 (3.0 – 19.4)	5.2 (1.6 – 16.3)

NHW: Non-Hispanic White; HW: Hispanic White

a - non-smokers defined as never or no current (past 30-day) use

b - current defined as past 30-day use

c - regular defined as ≥20 days/ 30 days

d - established defined as ≥100 combustible cigarettes and currently smokes every day or some

Of the six newly-identified studies based on US participants, four[26, 49-51] used Population Assessment of Tobacco and Health (PATH) data from a US nationally representative longitudinal study. Of these, two [50, 51] looked at adult (≥ 18 years old) former smokers, one [49] looked at youth (12-17 years old) and one [26] at a more restricted youth group (12-15 years old). Even though these four studies have the same data source, they were all included in this review as they had different outcome or exposure variables, different populations and included the most recent data.

Of the 12 newly identified studies, five [26, 27, 46, 47, 50] had outcomes assessing ever smoking among never smokers at baseline, seven [28, 29, 45, 47-50] had outcomes assessing current smoking among non-smokers (never or not current smoking) at baseline and three [30, 50, 51] assessed the odds of relapse in former smokers. Results were separated based on these three categories and combined with the 13 primary research studies identified in the umbrella review. Twelve of the seventeen studies in Khouja et al. were included [20, 31, 33-42], three were excluded due to data overlap [52-54], one was excluded as it used retrospective data [55] and one was excluded as it was cross-sectional [56]. Of the eight studies in Aladeokin & Haighton, two were included [39, 40]; five were excluded for cross-sectional design [57-61] and one for data overlap [54]. From the nine studies identified in Soneji et al., six were included [31-34, 36, 37] after two were excluded as they were abstracts and one excluded for data overlap [62].

Cigarette smoking initiation among never smokers at baseline

Five [26, 27, 46, 47, 50] of the newly-identified studies investigated smoking initiation among never smokers, of which Berry et al. [26] and McMillen et al. [50] used PATH data, focusing on youth (12 to 15 years old) and adults (≥18 years old), respectively (Table 2). Chien et al. examined the association between ever e-cigarette and subsequent combustible smoking initiation in 12,954 youth enrolled in schools in Taiwan between 2014 and 2016 [27]. Conner et al. investigated the association of e-cigarette use at baseline and smoking in adolescents (13 to 14 years old) between Waves 3 and 5 (2014 to 2016) of a cluster RCT in 20 schools in England [47]. Pénzes et al. conducted secondary data analysis from 1,369 9th grade students in the Romanian ASPIRA randomized controlled trial. Details of the studies are given in Supplementary Table 7 [46].

All newly-identified studies found that people who used e-cigarettes were significantly more likely than non-users to initiate smoking of combustible cigarettes, with odds ratios varying substantially from 2.1 to 6.6 (I^2=81%; Figure 2).

Considering these newly identified studies along with 12 studies from the umbrella review, all found significantly increased risk of initiating smoking of combustible cigarettes in people who had used e-cigarettes, compared to those who had not (Figure 2). Combining the studies from the umbrella review with the newly-identified studies, people exposed to e-cigarettes more likely to take up smoking of combustible cigarettes than people who were not exposed to e-cigarettes (pooled adjusted OR 3.19 (95% CI, 2.44 – 4.16)).

Current (past 30-day) cigarette smoking among non-smokers (never smokers or no current use at baseline)

Seven [28, 29, 45, 47-50] of the newly-identified primary research studies investigated current (past 30-day) use of combustible cigarettes following the use of e-cigarettes (Table 2). Four [29, 47, 48, 50] of these studies looked at never smokers at baseline, while three [28, 45, 49] looked at non-smokers (either never or no current use).

Two [49, 50] of the included studies were based on PATH data. McMillen et al.[50] used data on adult (≥18 years old) never smokers from waves 1 to 2 of the PATH study and Osibogun et al. [49] used data on youth (12-17 years old) non-smokers from waves 1 to 3. A further two [45, 48] of the newly-identified studies used data from the US. Bold et al. surveyed 808 high school students across three waves (2013 to 2015) in Connecticut [45]. Barrington-Trimis et al. collated data on 6,258 youth from three US school-based studies between 2013 and 2015: the Children's Health Study (CHS); the Happiness & Health Study (HH); and the Yale Adolescent Survey Study (YASS) [48]. This study separated results based on ethnicity and found the adjusted

odds of dual use at follow up was considerably higher in non-Hispanic whites compared to Hispanic whites (see Table 2), although with considerable overlap in the confidence intervals

The remaining three [28, 29, 47] newly-identified studies used data from Canada, the UK and Finland. Aleyan et al. examined the association between current e-cigarette use and subsequent current smoking among 6,729 Canadian school students using data from a school-based longitudinal cohort study, COMPASS [28]. Conner et al. investigated the association of e-cigarette use at baseline and smoking between Waves 3 and 5 (2014 to 2016) of a cluster RCT assessing a self-regulation anti-smoking intervention from 20 schools in England [47]. Kinnunen et al. used MEtLoFIN a school-based longitudinal cohort dataset in 3,474 Finnish adolescents between 2014 and 2016 [29]. Kinnunen et al., separated the use of e-cigarettes using nicotine content and found among baseline never-smokers, ever use of nicotine-containing e-cigarettes was associated with a nearly 3-fold increase in the odds of uptake of daily smoking (see Table 2)) found no increase in risk associated with use of non-nicotine containing e-cigarettes.

All of the newly-identified studies, and the one relevant study from the umbrella review [32], found a significant increase in the risk of transitioning from being a non-smoker to a current smoker in people who had used e-cigarettes compared to not using e-cigarettes, but with considerable heterogeneity in the estimates (I^2=91%; Figure 3).

Cigarette smoking relapse among former smokers (at least two months since quit date)

Three [30, 50, 51] newly-identified studies in this review investigated the odds of relapse to combustible cigarette smoking following the use of e-cigarettes in adults aged ≥ 18 years (Table 2). None of the three previously conducted systematic reviews investigated this relationship, so no additional studies from the umbrella review were included. Brose et al. used data from 371 adults who quit ≥2 months prior to baseline in 2016 from a national web-based survey in the UK [30]. The other two studies used PATH data. Dai et al. looked at 3,210 ex-smokers, who had not smoked for >12-months [51]. McMillen et al. looked at data relating

to 8,108 adults who had quit ≥5 years prior to baseline; sub-analyses from this study were included in the previous two sections, as the study also provided data on never smokers [50].

All three included studies found the odds of ever relapse was higher among ever e-cigarette users, compared to never e-cigarette users (Figure 4). With respect to more detailed findings, in addition to the pre-specified meta-analyes, Brose et al. reported lower odds of relapse among recent ex-smokers who vaped daily versus those who vaped non-daily, while Dai et al. and McMillen et al. showed past 30-day regular e-cigarette use had greater odds of relapse than non-current use [30, 50, 51]. Within the Dai et al. study, regular e-cigarette use in recent smokers (quit ≤ 12 months) was not associated with smoking relapse [51]. However, regular e-cigarette use in those who had ceased smoking for more than 12 months was associated with a significant increase in the odds of relapse. A meta-analysis of the three newly identified studies found former smokers who used e-cigarettes had 2.4 times greater odds of relapse when compared to those who did not use e-cigarettes, with similar magnitudes of this relationship between studies (I^2 = 12%) (Figure 4).

Risk of bias across studies

Funnel plots corresponding to the studies included in the meta-analyses are presented in Supplementary Figure 1. The plot for the seventeen smoking initiation studies of never-smokers is somewhat asymmetrical and seven points lie outside the 95% confidence region, suggesting there may be some selection bias across included studies, publication bias or possible heterogeneity (as supported by the I^2 statistic; 86%). With less than ten studies investigating current smoking in non-smokers [28, 29, 32, 45, 47-49] and relapse in former smokers [30, 50, 51], test for funnel plot asymmetry was not used as the power of the test would be too low for it to be a reliable indicator of publication bias [24].

Discussion:

Our umbrella and systematic review, along with an updated meta-analysis using data from primary studies, shows strong and consistent evidence that never smokers who have used e-cigarettes are more likely than

those who have not used e-cigarettes to try smoking conventional cigarettes and to transition to become regular tobacco smokers. We found that, on average, non-smokers who used e-cigarettes have around three-fold the odds of either initiating smoking or currently smoking combustible cigarettes compared to non-smokers who have not used e-cigarettes. The limited available evidence indicates that former smokers who report current e-cigarette use within the previous 30-days have more than twice the odds of relapse and resumption of current smoking compared to former smokers who have not used e-cigarettes.

This review builds on and has findings consistent with earlier systematic reviews and meta-analyses in the peer-reviewed and grey literature [11, 21, 43, 44, 63, 64]. A 2018 review by the National Academies of Sciences, Engineering, and Medicine (NASEM) on the public health consequences of e-cigarettes concludes that there is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes, and moderate evidence that e-cigarette use increases the frequency and intensity of subsequent combustible tobacco smoking, among youth and young adults [64]. Previous systematic reviews have focused on evidence in those 30 years of age or less, whereas our review included data on adults and former smokers. This is the first systematic review to examine whether e-cigarette use is associated with smoking relapse.

The use of e-cigarettes may represent a risk factor for cigarette smoking initiation, current smoking and relapse to cigarette smoking for several behavioural and physiological reasons. For those who use nicotine-containing e-cigarettes, a resulting addiction to nicotine may leave users at risk of seeking other forms of inhalable nicotine, such as combustible cigarettes [65, 66]. Additionally, as e-cigarettes can mimic behavioural (e.g. hand-mouth) and sensory (e.g. taste) aspects of smoking, associated e-cigarette habits and movements may make the transition to combustible smoking more natural [67, 68]. Further studies should examine potential mediators to better understand possible mechanisms for the association between e-cigarette use and subsequent cigarette use. Although one study showed that an intervention designed to reduce smoking initiation in adolescents through self-regulatory implementation intentions

attenuated the odds of smoking uptake in never smokers who used e-cigarettes, a statistically significant increased odds remained [47].

Although studies in this review were consistent in finding increased risks of smoking uptake in non-smokers exposed to e-cigarettes, the magnitude of this increased risk varied substantially between studies. The reason for this variation is unclear, but may relate to the different products, populations and policy environments. In addition, it is challenging to estimate the overall effect of e-cigarettes on smoking initiation due to the variety of ways in which devices (e.g. e-cigarettes, JUULs, pods, vape pens) and users (e.g. never-users, ever-users, current-users, former users) are classified. The high heterogeneity in most of the results from the meta-analyses suggests that pooled odds ratios should be interpreted as an average of disparate results, rather than a reflection of the true underlying effect.

A limitation in this review is that included studies were limited to those written in English. While emerging results from this review and similar studies provide evidence regarding the association between e-cigarette and combustible cigarette use, the evidence is heavily weighted towards US and UK data. Only nine countries were included in this analysis, with a notable lack of data from the Asia-Pacific, Africa and the Middle East. Furthermore, the studies were reliant on self-reported product use, which is likely to be subject to self-reporting bias. All three systematic reviews rated moderate in the AMSTAR 2 risk of bias assessment and the 12 newly-identified studies rated between 5 to 8 on the Newcastle-Ottawa Scale. Although the consistency of findings across multiple studies and settings supports the likelihood of a causal relationship, given the observational nature of many of the included studies, the findings may be potentially influenced by confounding factors, including socioeconomic status and the tendency for risk behaviours to occur together. As the ability to adjust for such confounding factors varied according to study, the possibility of residual confounding cannot be excluded.

Conclusion:

This review found consistent evidence that use of e-cigarettes, largely nicotine-delivering, is associated with increased risk of subsequent combustible smoking initiation, current combustible smoking and smoking relapse after accounting for known demographic, psychosocial and behavioural risk factors. This is the first review to examine associations between e-cigarette use and cigarette use across the whole population, including youth, adults and former smokers. Intervention efforts and policies surrounding e-cigarettes are needed to reduce the potential of furthering combustible tobacco use in Australia and beyond.

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Declarations of interest

The authors declare that they have no competing interests.

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Contribution Statement

OB, LF and EB all contributed to the study conception and design and interpretation of data. GJ and AY assisted with statistical analysis and interpretation of data. All authors were involved in revising the manuscript.

Data Sharing

All data used in the manuscript are from published research.

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Figure 1: Flow chart for selection of studies for inclusion in umbrella review and top-up systematic review

Figure 2: Forest plot and random-effects meta-analysis for the adjusted odds of smoking initiation at follow up among never smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline

Figure 3: Forest plot and random-effects meta-analysis for the adjusted odds of current (past 30-day) smoking at follow up among non-current smokers and current e-cigarette users at baseline compared with non-current e-cigarette users at baseline

Figure 4: Forest plot and random-effects meta-analysis for the adjusted odds of smoking relapse at follow up among former smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline

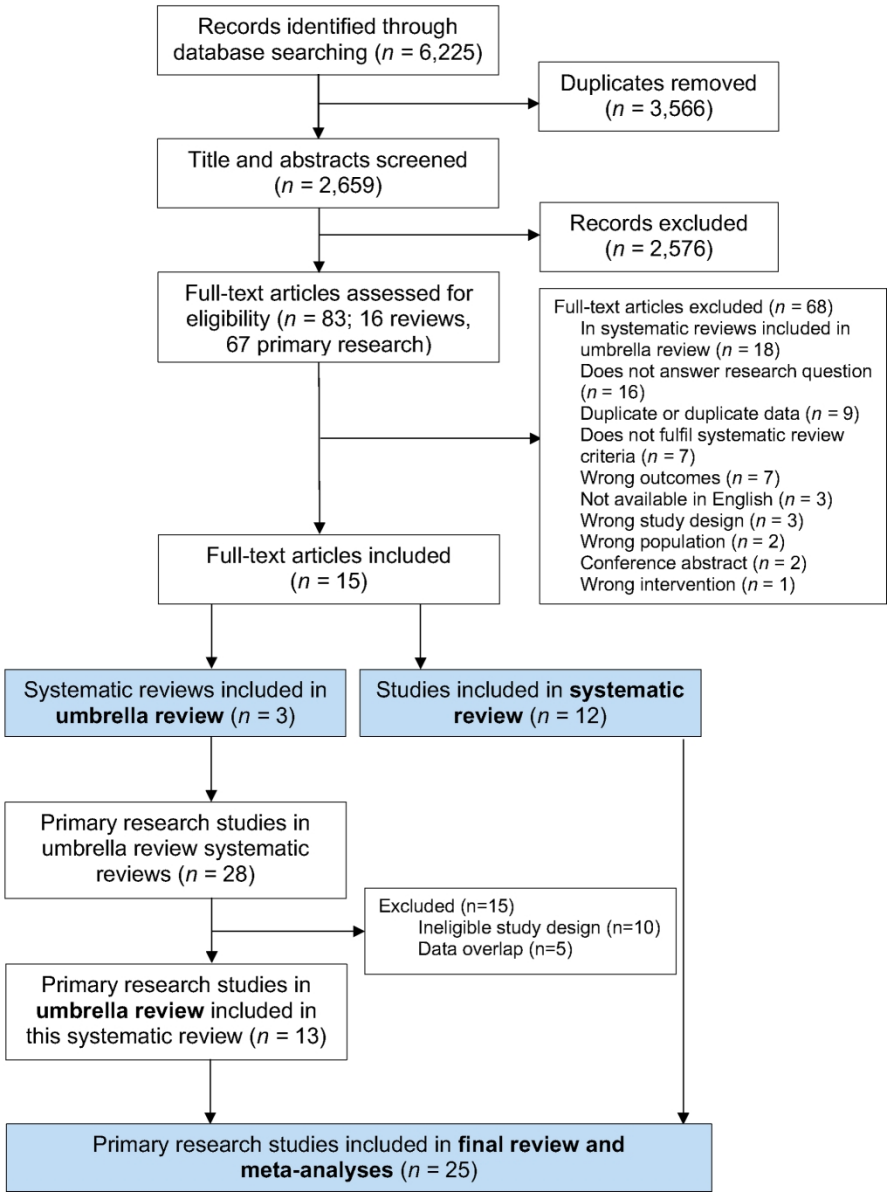

Figure 1: Flow chart for selection of studies for inclusion in umbrella review and top-up systematic review

169x227mm (300 x 300 DPI)

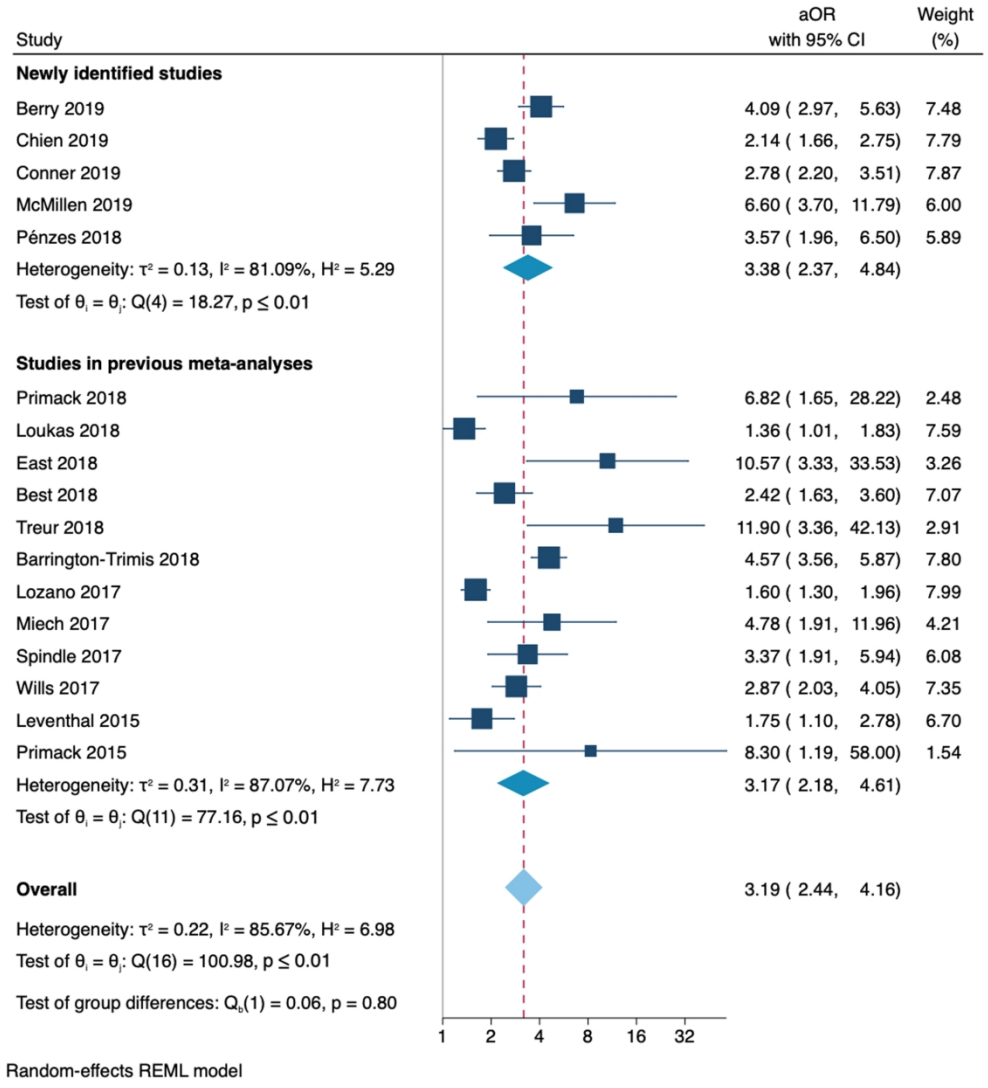

Figure 2: Forest plot and random-effects meta-analysis for the adjusted odds of smoking initiation at follow up among never smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline

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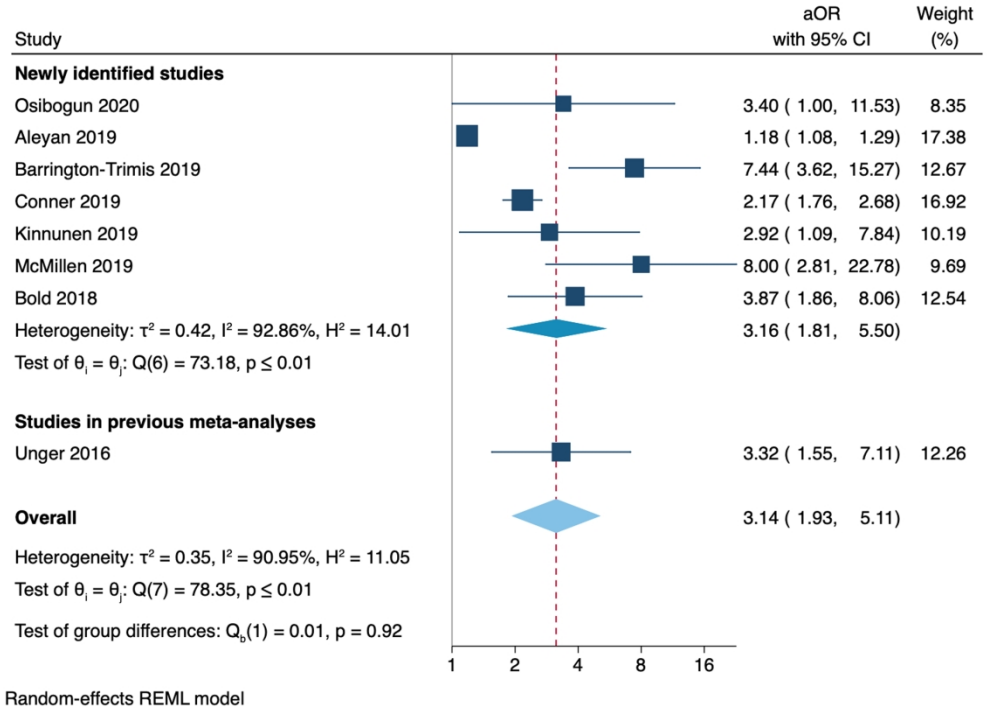

Figure 3: Forest plot and random-effects meta-analysis for the adjusted odds of current (past 30-day) smoking at follow up among non-current smokers and current e-cigarette users at baseline compared with non-current e-cigarette users at baseline

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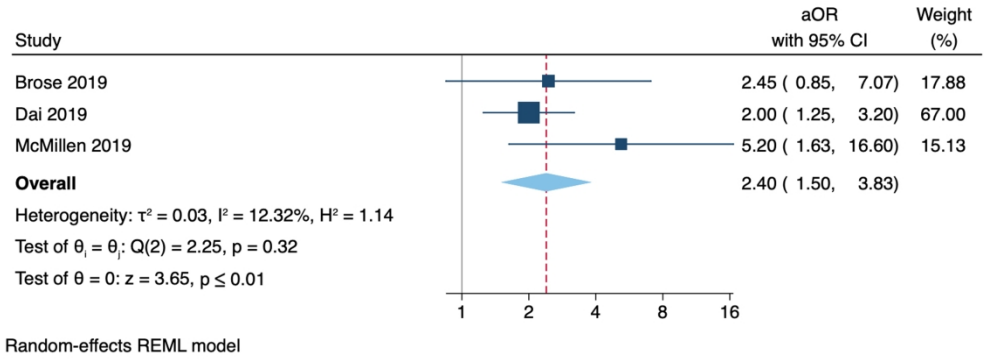

Figure 4: Forest plot and random-effects meta-analysis for the adjusted odds of smoking relapse at follow up among former smokers and current e-cigarette users at baseline compared with never e-cigarette users at baseline

293x110mm (300 x 300 DPI)

Supporting Information

Supplementary Table 1: Inclusion and exclusion criteria for umbrella review (of systematic reviews) and systematic review (of primary research)

PICO	Inclusion Criteria	Exclusion Criteria
Population	Non-tobacco smokers - includes never, former or ever users (this includes prior users who have tried smoking but have not used in the past 30 days) Humans, any age (youth, young adults and adults)	Current tobacco smokers (use within the past 30 days) Animal studies, in vitro studies
Intervention	Nicotine-containing or non-nicotine-containing e-cigarettes or e-liquid devices (also referred to as vaping products)	Studies with a focus on heat-not-burn or tobacco containing devices Studies with a focus on the uptake of marijuana, other illicit drugs and harmful substances (as in the CSIRO report [58])
Comparison	No nicotine-containing or non-nicotine containing e-cigarettes or e-liquid devices	
Outcomes	Ever smoking combustible tobacco cigarettes	Studies where smoking cigarettes is not the primary outcome variable
Study	Published, peer-reviewed literature For umbrella review - Systematic reviews and meta-analyses of randomised/non-randomised controlled trials, clinical trials and prospective cohort studies (if a systematic review/meta-analysis includes study designs other than cohort and randomised/ non-randomised controlled trials, the review will only be included if the analysis and/ or results are separated by study design) For systematic review - Randomised/ non-randomised controlled trials, clinical trials (although interventional studies are not expected) - Prospective cohort studies	Systematic reviews that are superseded by a later review which include all studies from the earlier review. - Non-systematic -literature reviews - Intervention trial with no comparator (e.g. before and after study) - Qualitative studies - Retrospective cohort studies - Case-control studies - Cross-sectional (including repeated cross-sectional) - Case studies - Grey literature, conference abstracts, letters, editorials, correspondence, opinion pieces, government reports, position statements *Systematic reviews and meta-analyses will be excluded if they include only the above study designs.*
Follow-up	Minimum 6 months	
Setting	Any country	
Time period	All years	No exclusion
Other	- English - Full-text availability	- Not available in English - Duplicated data

Supplementary Appendix: Search strategy

MEDLINE, PyschINFO, PubMed, Scopus, Web of Science and Cochrane Library were searched. Papers were imported into an Endnote library, exported to Covidence and duplicates removed. The titles and abstracts were screened by two reviewers (OB and LF) to isolate relevant publications. Full texts were then identified for the relevant publications by two reviewers (OB and LF) and independently assessed the publications against the selection criteria. Any conflicts were discussed and if no consensus was reached the publication was reviewed by a third reviewer (MH).

A forward and backward reference search was performed on the final articles completed using Web of Science and Scopus. After removing duplicates, titles, abstracts and then full texts were screened for any randomised controlled trials fulfilling our inclusion and exclusion criteria by two reviewers (OB and LF).

Data were systematically extracted from the publications using data extraction templates. The quality of the included studies was assessed independently by two reviewers (OB and LF), with discrepancies resolved by discussion and by adjudication of a third reviewer (EB). E-cigarette, cigarette smoking and uptake search terms will be combined with the Boolean operator 'AND' for the final search.

Supplementary Table 2: Search terms

E-cigarette related search terms (combined with Boolean operator 'OR')	Combustible **cigarette smoking** related search terms (combined with Boolean operator 'OR')	**Uptake** related search terms (combined with Boolean operator 'OR')
Keywords 1. Electronic cigarette* 2. E-cigarette* 3. Electronic nicotine delivery system* 4. Electronic nicotine de* 5. Electronic non-nicotine de* 6. Vape 7. Vaping 8. Vapo* 9. E-hookah 10. Electronic inhalant device 11. E-liquid MeSH terms 1. Electronic Nicotine Delivery Systems (ENDS)	Keywords 1. Combustible cigarette 2. Tobacco smoking 3. Smoking 4. Cigarette MeSH terms 1. Smokers 2. Non-smokers	Keywords 1. Initiat* 2. Uptak* 3. Subsequent* 4. Predict* 5. Onset

Supplementary Table 3: Search histories

Database	Search	Studies and search date
PubMed	(((Electronic cigarette* or E-cigarette* or Electronic nicotine delivery systems[Mesh] or Electronic non-nicotine delivery* or Electronic nicotine device* or Electronic non-nicotine device* or Vape or Vaping or Vapo* or E-hookah or Electronic inhalant device or E-liquid)) AND (Smoker*[Mesh] or non-smoker*[Mesh] or ex-smoker*[Mesh] or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking)) AND (Initiat* OR Uptak* OR Subsequent* OR Predict* OR Onset)	1187 (01/04/2020)
Scopus	(TITLE-ABS-KEY (("Electronic cigarette*" OR "E-cigarette*" OR "Electronic nicotine delivery system*" OR "Electronic non-nicotine delivery*" OR "Electronic nicotine device*" OR "Electronic non-nicotine device*" OR "Vape" OR "Vaping" OR "Vapo*" OR "E-hookah")) AND TITLE-ABS-KEY (("Smoker*" OR "non-smoker*" OR "ex-smoker*" OR "Combustible cigarette" OR "Tobacco smoking" OR "Smoking" OR "Cigarette" OR "Cigarette smoking" OR "Cigar smoking")) AND TITLE-ABS-KEY (("Initiat*" OR "Uptak*" OR "Subsequent*" OR "Predict*" OR "Onset")))	1289 (01/04/2020)
Web of Science	**ALL FIELDS:** (("Electronic cigarette*" OR E-cigarette* OR "Electronic nicotine delivery system*" OR "Electronic non-nicotine delivery*" OR "Electronic nicotine device*" OR "Electronic non-nicotine device*" OR Vape OR Vaping OR Vapo* OR E-hookah OR "Electronic inhalant device")) *AND* **ALL FIELDS:** ((Smoker* OR non-smoker* OR ex-smoker* OR "Combustible cigarette" OR "Tobacco smoking" OR Smoking OR Cigarette OR "Cigarette smoking" OR "Cigar smoking")) *AND* **ALL FIELDS:** ((Initiat* OR Uptak* OR Subsequent* OR Predict* OR Onset))	1488 (01/04/2020)
PsychINFO (Ovid)	1. (Electronic cigarette* or E-cigarette* or Electronic nicotine delivery system* or Electronic non-nicotine delivery* or Electronic nicotine device* or Electronic non-nicotine device* or Vape or Vaping or Vapo* or E-hookah or Electronic inhalant device or E-liquid).af. 2. (Smoker* or non-smoker* or ex-smoker* or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking).af. 3. (Initiat* or Uptak* or Subsequent* or Predict* or Onset).af. 4. 1 and 2 and 3	874 (01/04/2020)
Medline (Ovid)	1 (Electronic cigarette* or E-cigarette* or Electronic nicotine delivery system* or Electronic non-nicotine delivery* or Electronic nicotine device* or Electronic non-nicotine device* or Vape or Vaping or Vapo* or E-hookah or Electronic inhalant device or E-liquid).af. 2 (Smoker* or non-smoker* or ex-smoker* or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking).af. 3 (Initiat* or Uptak* or Subsequent* or Predict* or Onset).af. 4 1 and 2 and 3	1168 (04/02/2020)
Cochrane	1. MeSH descriptor: [Electronic Nicotine Delivery Systems] explode all trees 2. ("Electronic cigarette" OR E-cigarette OR Vape OR Vaping OR E-hookah OR "Electronic inhalant device" OR E-liquid OR "Electronic Nicotine Delivery Systems"):ti,ab,kw 3. #1 OR #2 4. (Smoker* or non-smoker* or ex-smoker* or Combustible cigarette or Tobacco smoking or Smoking or Cigarette or Cigarette smoking or Cigar smoking):ti,ab,kw 5. #4 OR #5 6. (Initiat* OR Uptak* OR Subsequent* OR Progress* OR Predict* OR Duration OR Intens* OR Frequen* OR Onset):ti,ab,kw 7. #3 AND #6 AND #7	219 (01/04/2020)

Supplementary Table 4: AMSTAR2[17] rating of included systematic review studies

Criteria	Aladeokin & Haighton 2019[39]	Soneji et al. 2017[16]	Khouja et al. 2020[38]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	No	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes	Partial Yes	Partial Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	No	No	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	Yes
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	Yes	Yes
16. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
Rating overall confidence in the results of the review	Moderate	Moderate	Moderate

Supplementary Table 5: Primary research studies included in systematic reviews in the umbrella review that were included in the top-up systematic review

Authors/ Year	Title	Systematic review(s) included in	Country and data source(s)	Baseline cigarette use	E-cigarette use	Follow up cigarette use	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Barrington-Trimis et al., 2018[33]	E-cigarette Use and Subsequent Smoking Frequency Among Adolescents	Khouja et al., 2020	US (CA, CT): CHS, HH, YASS	Never	Ever	Ever	3.80 (3.10 – 4.66)	4.57 (3.56 – 5.87)
Best et al., 2018[35]	Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study	Aladeokin & Haighton 2019 Khouja et al., 2020	Scotland (UK): School-based	Never	Ever	Ever	4.62 (3.34 – 6.38)	2.42 (1.63 – 3.60)
East et al., 2018[34]	The Association Between Smoking and Electronic Cigarette Use in a Cohort of Young People	Aladeokin & Haighton 2019 Khouja et al., 2020	England (UK): AOSHGB	Never	Ever	Ever	12.31 (5.06 – 29.94)	10.57 (3.33 – 33.50)
Leventhal et al., 2015[32]	Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence	Khouja et al., 2020 Soneji et al., 2017	US (LA): YBRS - School-based	Never	Ever	Ever	2.95 (1.74 – 4.99)	1.75 (1.10 – 2.77)
Loukas et al., 2018[14]	Exclusive e-cigarette use predicts cigarette initiation among college students	Khouja et al., 2020	US (TX): M-PACT	Never	Ever	Ever	2.72 (2.10 – 3.53)	1.36 (1.01 – 1.83)
Lozano et al., 2017[36]	A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents	Khouja et al., 2020	Mexico: School-based	Never	Ever	Ever	2.46 (1.85 – 3.26)	1.60 (1.31 – 1.97)
Miech et al., 2017[31]	E-cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students	Khouja et al., 2020 Soneji et al., 2017	US: MTD 2014-2015	Never	Ever	Ever	4.32 (1.73 – 23.10)	6.58 (2.04 – 57.88) †
Primack et al., 2015[29]	Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults	Khouja et al., 2020 Soneji et al., 2017	US: Dartmouth media survey 2012-2014	Never	Ever	Ever	5.66 (1.99 – 16.07)	8.3 (1.2 – 58.6)
Primack et al., 2018[30]	Initiation of Traditional Cigarette Smoking after Electronic Cigarette Use Among Tobacco-Naive US Young Adults	Khouja et al., 2020	US: Growth from Knowledge 2013-2014	Never	Ever	Ever	6.06 (2.15 – 17.10)	6.82 (1.65 – 28.25)
Spindle et al., 2017[28]	Electronic cigarette use and uptake of cigarette smoking: A longitudinal examination of U.S. college students	Khouja et al., 2020 Soneji et al., 2017	US: Mid-Atlantic university (S4S project)	Never	Ever	Ever	3.50 (2.41 – 5.09)	3.37 (1.91 – 5.94)
Treur et al., 2018[37]	E-cigarette and waterpipe use in two adolescent cohorts: cross-sectional and longitudinal associations with conventional cigarette smoking	Khouja et al., 2020	Netherlands	Never	Ever**	Ever	10.83 (8.87 – 13.22)	11.9 (3.36 – 42.11)

Unger et al., 2016[27]	E-cigarette use and subsequent cigarette and marijuana use among Hispanic young adults	Soneji et al., 2017	US (LA): Project RED	No current[a]	Current[a]	Current[a]	4.71 (2.27 – 9.77)	3.32 (1.55 – 7.11)
Wills et al., 2017[26]	Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii	Khouja et al., 2020 Soneji et al., 2017	US (HI): School-based	Never	Ever	Ever	4.25 (2.74 – 6.61)	2.87 (2.03 – 4.05)

Supplementary Table 6: Newcastle Ottawa Scale[18] (NOS) rating of newly-identified primary research studies

Study	Selection				Comparability	Outcome			Total
	Representativeness of the Exposed Cohort (★)	Selection of the Non-Exposed Cohort (★)	Ascertainment of Exposure (★)	Demonstration That Outcome of Interest Was Not Present at Start of Study (★)	Comparability of Cohorts on the Basis of the Design or Analysis (★★)	Assessment of Outcome (★)	Was Follow-Up Long Enough for Outcomes to Occur (★) *	Adequacy of Follow Up of Cohorts (★) ‡	
Aleyan et al., 2019 [23]	★	★		★	★★		★		6
Barrington-Trimis et al., 2019 [43]	★	★		★	★★		★	★	7
Berry et al., 2019 [21]	★	★	★	★	★★		★	★	8
Bold et al., 2018 [40]	★	★		★	★		★		5
Brose et al., 2019 [25]	★	★		★	★★		★		6
Chien et al., 2019 [22]	★	★		★	★★		★	★	7
Conner et al., 2019 [42]	★	★		★	★★		★		6
Dai et al., 2019 [46]	★	★	★	★	★★		★	★	8
Kinnunen et al., 2019 [24]	★	★		★	★★		★		6
McMillen et al., 2019 [45]	★	★	★	★	★★		★	★	8
Osibogun et al., 2020[44]	★	★	★	★	★★		★	★	8
Pénzes et al., 2018 [41]	★	★		★	★★		★		6

* 6 months considered adequate follow-up time
‡ Studies with less than 30% loss to follow-up considered adequate

Supplementary Table 7: Study characteristics from newly-identified studies for the top-up systematic review

Study	Country and data source	Study design	Duration (follow up and date range)	Study population - sample size - baseline age/ grade - % female	Consideration of confounding	NOS[1] score
Aleyan et al., 2019 [23]	Canada (COMPASS Waves 1-3)	Longitudinal cohort	36 months (2014 to 2017)	- 6,729 - 9th or 10th grade - 54.2% female	Gender, grade, ethnicity, friends that smoke, weekly spending money, current cannabis use, and current binge drinking at each wave	6
Barrington-Trimis et al., 2019 [43]	US (CT and CA); CHS; HH; YASS[1]	Longitudinal cohort	12 months (2013 to 2015)	- 6,258 - Grades 9 to 12 - 53.5% female	Gender, grade, and cohort (CHS, H&H, YASS), school (H&H/YASS) or community (CHS)	7
Berry et al., 2019 [21]	US (PATH[3] Waves 1-3)	Longitudinal cohort	24 months (2013 to 2016)	- 6,123 - 12-15 years old, mean 13.4 years (SD 1.2) - 49.5% female	Age, gender, income, race and ethnicity, parental education, urban residence, living with a tobacco user, frequency of noticing health warnings on cigarette packages, and ability to recall a favourite tobacco advertisement. Risk-taking behaviours, sensation-seeking personality traits, and cigarette susceptibility	8
Bold et al., 2018 [40]	US (CT)	Longitudinal cohort	36 months (2013 to 2015)	- 808 - Mean 15.04 years (SD 0.90) - 53% female	School, sociodemographic characteristics (sex, race/ethnicity, SES), and use of other tobacco products.	5
Brose et al., 2019 [25]	UK (National web-based survey 2012-2017)	Longitudinal cohort	12 months (2016 to 2017)	- 374 - Mean 49.2 years (SD 14.1) - 44% female	Time quit smoking, vaping status, gender, income and NRT use	6
Chien et al., 2019 [22]	Taiwan (TAALS[4] Waves 1-2)	Longitudinal cohort	24 months (2014 to 2016)	- 12,954 - 36.9% ever smokers female; 58.1% never smokers female	Smoking susceptibility at baseline, socio-demographic profile, psychological status, and peer support.	7
Conner et al., 2019 [42]	UK (England); RCT Waves 3 and 5	Post-hoc analysis of a cluster RCT	24 months (2014 – 2016)	- 3,994 - 13 to 14 years old - 52.3% female	Sociodemographic (gender, ethnicity, family affluence, percentage of children per school eligible for free school meals); friends' smoking status, family smoking, impulsiveness	6
Dai et al., 2019 [46]	US (PATH[3] Waves 1-2)	Longitudinal cohort	12 months (2013 to 2015)	- 4,094 - Adults (≥18 years) - 45.9% female	Sociodemographic (age, sex, race, education, poverty level, region, and health insurance) and tobacco use characteristics (smoking chronicity, typical number of combustible cigarettes smoked per day during the period of regular smoking, and length of time since quit smoking)	8
Kinnunen et al., 2019 [24]	Finland MetLoFIN[5] (school-based)	Longitudinal cohort	18 months (2014 to 2016)	- 3,474 - Grade 9 (ages 15 to 16 years) - 51.8% female	Gender, socioeconomic background, parents' education, other tobacco product and drug use, school clustering. Crude and adjusted logistic regressions were also conducted with the Firth's bias-reduced logistic regression	6
McMillen et al., 2019 [45]	US (PATH[3] Waves 1-2)	Longitudinal cohort	12 months (2013 to 2015)	- 8,108 - Adults (≥18 years) - 54.4% distant former smoker female; 40.0% never smoker female	Sociodemographic (race/ethnicity, sex, age, education); psychosocial predictors of combustible cigarette smoking risk (household smoking rules and living with someone who smokes)	8
Osibogun et al., 2020[44]	US (PATH[3] Waves 1-3)	Longitudinal cohort	36 months (2013 to 2016)	- 14,623 - Ages 12-17 years - 48% female	Sociodemographic and tobacco-related factors	8
Pénzes et al., 2018 [41]	Romania (ASPIRA[6] RCT)	Secondary analysis from data in cluster RCT	6 months (2014 to 2015)	- 1,369 - Grade 9, mean 14.88 (SD 0.48)	Intervention/control condition, gender, age, the design effect due to the cluster sampling and used schools as cluster units	6

[1] NOS: Newcastle-Ottawa Scale (out of a total of 10)
[2] CHS: Children's Health Study; HH: Happiness & Health Study; YASS: Yale Adolescent Survey Study
[3] PATH: Population Assessment of Tobacco and Health Study
[4] TAALS: The Taiwan Adolescent to Adult Longitudinal Study
[5] MetLoFIN: Metropolitan Longitudinal Finland
[6] ASPIRA: A Smoking Prevention Interactive Experience [Roman acronym for translation of ASPIRE]

Supplementary Figure 1: Funnel plots to assess the risk of bias across studies

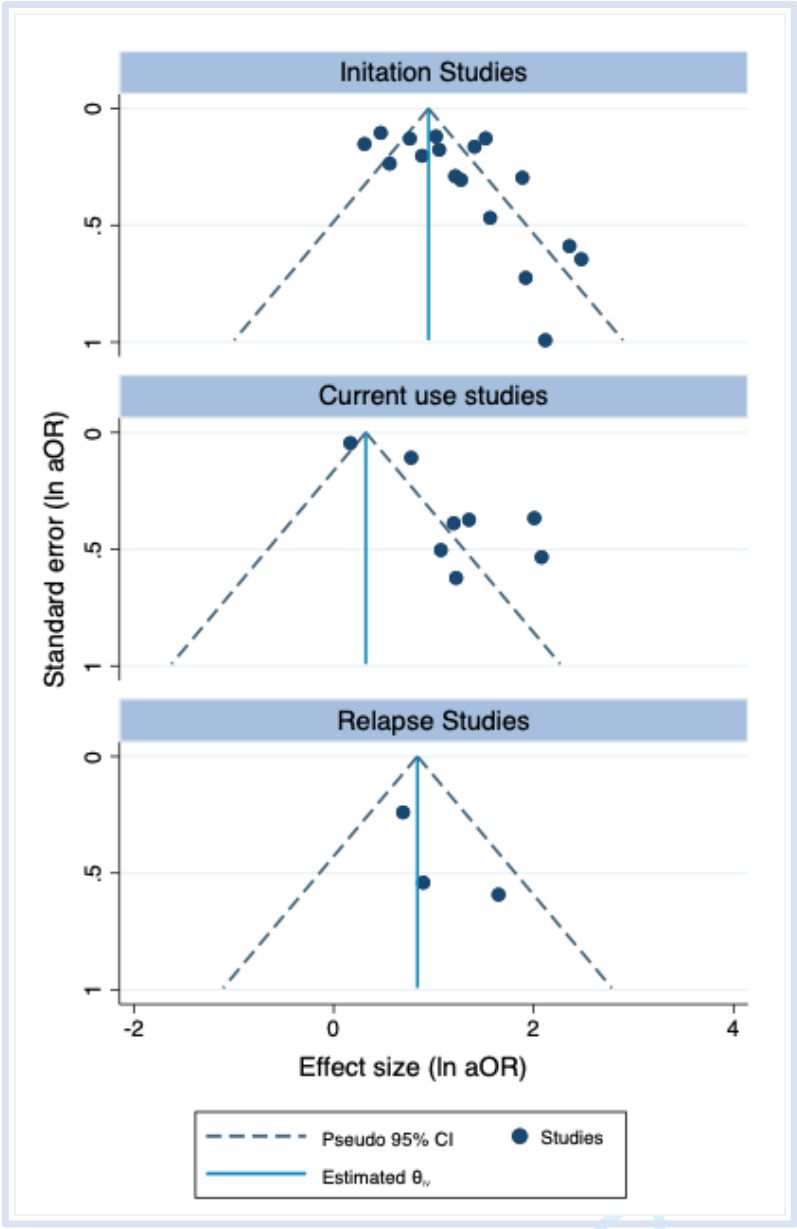

Figure: Funnel plots with pseudo 95% confidence limits

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3 – 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6, Supplementary Table 3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, 6, Supplementary Table 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7, Figure 1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 – 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-13 and Table 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, 9; Supplementary Table 4 and 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1 and 2, Supplementary Figure 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2, 3 and 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	(N/A)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15 – 17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3, 16, 17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	5
2	Hypothesis statement	-
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	7
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Title page
8	Search strategy, including time period included in the synthesis and key words	5; Supplementary Table 3
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5; Supplementary Table 3
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	-
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	4-5; Figure 1
15	Method of handling abstracts and unpublished studies	4-5; Figure 1
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	-
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	16
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8, 10
22	Assessment of heterogeneity	13, 15, Table 1, Figures 2, 3 and 4
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6 – 7
24	Provision of appropriate tables and graphics	Table 1 & 2 and Figures 1, 2, 3 and 4
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 2, 3 and 4
26	Table giving descriptive information for each study included	Table 1 and Table 2
27	Results of sensitivity testing (eg, subgroup analysis)	-
28	Indication of statistical uncertainty of findings	13, 15, Table 1, Figures 2, 3 and 4

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	15, Supplementary Figure 1
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1 and Supplementary Table 1
31	Assessment of quality of included studies	10, 15, Supplementary Tables 4 and 6
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	15-17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	18
34	Guidelines for future research	-
35	Disclosure of funding source	18

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.