Electronic cigarette use and tobacco cigarette smoking initiation in adolescents: An evidence review

Authors:

Doireann O'Brien

Jean Long

Caitriona Lee

Anne McCarthy

Joan Quigley

Date May 2020

Disclaimer

Any views expressed in this report are those of the authors and not necessarily those of the Minister for Health, the Department of Health or the Health Research Board.

Published by:

Health Research Board, Dublin

t 353 1 234 5000
f 353 1 661 2335
e hrb@hrb.ie
w www.hrb.ie

Table of Contents

TABLE OF CONTENTS **1**

LIST OF TABLES **3**

LIST OF FIGURES **3**

ABBREVIATIONS **4**

EXECUTIVE SUMMARY **5**

PURPOSE 5
RESEARCH QUESTION 5
METHODS 5
FINDINGS 5
CONCLUSIONS 7

1 INTRODUCTION **9**

1.1 POLICY BACKGROUND 9
1.2 RESEARCH QUESTION 9
1.3 BACKGROUND 9
1.3.1 Prevalence of cigarette smoking in Ireland *9*
1.3.2 Prevalence of e-cigarette use in Ireland *9*
1.3.3 Prevalence of e-cigarette use internationally *10*
1.3.4 Reasons for e-cigarette use *11*

2 METHODS **12**

2.1 CONCEPTUAL METHODS 12
2.2 INCLUSION AND EXCLUSION CRITERIA 12
2.3 INFORMATION SEARCHES 12
2.3.1 Bibliographic databases *13*
2.3.2 Keywords *14*
2.4 SCREENING 14
2.5 DATA EXTRACTION 15
2.6 QUALITY ASSESSMENT 15
2.7 DATA ANALYSIS 15
2.8 LEVEL OF EVIDENCE 16

3 RESULTS **17**

3.1 DESCRIPTIVE CHARACTERISTICS OF INCLUDED STUDIES 17
3.1.1 Measurement of exposure *18*
3.1.2 Measurement of outcome *18*
3.1.3 Covariates *18*
3.1.4 Quality assessment *18*
3.2 FINDINGS 25
3.2.1 Ever e-cigarette use/ever cigarette use *25*
3.2.2 Past-30-day e-cigarette use *33*
3.2.3 Past-30-day cigarette use *33*
3.2.4 Past-30-day e-cigarette and past-30-day cigarette use *34*
3.2.5 Frequency of e-cigarette and cigarette use *34*
3.2.6 Nicotine versus non-nicotine e-cigarettes *34*

4 DISCUSSION **39**

4.1 SUMMARY FINDINGS 39
4.2 COMPARISON WITH PREVIOUS RESEARCH 40
4.2.1 Comparison with other systematic reviews *40*

4.2.2 Public health considerations with respect to e-cigarette use 40
4.3 THEORETICAL IMPLICATIONS 41
4.3.1 Catalyst model 42
4.4 LIMITATIONS 43
4.4.1 E-cigarettes as standard exposure 43
4.4.2 Exposure and outcome measures 43
4.4.3 The issue of confounding and causality 44
4.4.4 Limitations of specific studies 44
4.5 FUTURE RESEARCH 44
4.5.1 Cigarette escalation 44
4.5.2 Future patterns of smoking 45
4.5.3 Vaping and smoking in different contexts 45
4.5.4 What is causing the association? 45
CONCLUSIONS 46

5 REFERENCES 48

APPENDIX 1: LITERATURE SEARCH STRATEGIES AND RESULTS 53

APPENDIX 2: QUALITY ASSESSMENT-TOOL AND RESULTS 66

APPENDIX 3: META-ANALYSIS-FEASIBILITY 69

FEASIBILITY ANALYSIS 69
META-ANALYSIS RESULTS 70
Unadjusted meta-analysis: ever e-cigarette use 70
Sensitivity: only 3-domain covariate adjusted studies retained 70
Sensitivity: only high-quality single time point studies retained 70
Subgroup: pre/post 2014 71
Subgroup: greater and less than 12 months follow up 71
Subgroup: USA and Europe 72
Meta-analysis: past 30 day e-cigarette use 72

List of tables

Table 1 PICO inclusion criteria for review question 12

Table 2 Characteristics of included studies 19

Table 3 AOR for ever e-cigarette and cigarette use among adolescents in the selected longitudinal cohort studies 27

Table 4 Ever use of e-cigarettes and cigarettes among adolescents in the selected longitudinal cohort studies using statistical measures such as ARR, estimates, or standardised coefficient 29

Table 5 Subgroup analyses of data collected pre- and post-2014 32

Table 6 Subgroup analyses of data collected from the USA and Europe 32

Table 7 PAF for four studies 33

Table 8 AORs for different frequencies of e-cigarette and cigarette use among adolescents in the selected longitudinal cohort studies 36

Table 9 ARRs for different frequencies of e-cigarette and cigarette use 38

List of figures

Figure 1 Data from the 2011–2018 *National Youth Tobacco Surveys* in the USA 11

Figure 2 PRISMA flow chart 17

Figure 3 Meta-analysis results, using individual study AOR, for association between ever e-cigarette use and subsequent smoking 31

Figure 4 Schneider and Diehl's illustration of the possible catalyst function of e-cigarettes, along with possible reasons for potential transitions 43

Abbreviations

Abbreviation	Explanation
AOR	adjusted odds ratio
CI	confidence interval
e-cigarette(s)	electronic cigarette(s)
EU	European Union
HRB	Health Research Board
NHLBI	National Heart, Lung, and Blood Institute
OR	odds ratio
PAF	population attributable fraction
PATH Study	Population Assessment of Tobacco and Health Study
PICO	population; intervention or exposure; comparator; outcome
r^2	regression [measure]
RCT	randomised controlled trial
UK	United Kingdom
USA	United States of America

Executive summary

Purpose

In 2013, the Tobacco Policy Review Group published *Tobacco Free Ireland*, a report which set a target for Ireland to reduce smoking prevalence to less than 5% by 2025. The report identified tobacco-related harm reduction as a key issue for consideration. Since e-cigarettes' launch in the European Union (EU) in 2006 and in the United States of America (USA) in 2007, research on their potential benefits in terms of tobacco-related harm reduction, and on the public health harms of e-cigarettes, has grown. This systematic evidence review outlines what is known to date about using e-cigarette and initiation smoking tobacco cigarettes.

Research question

The Department of Health's research question is 'Does e-cigarette use by adolescents who are cigarette-naive at baseline lead to subsequent cigarette smoking?'

Methods

The research presents a systematic review of longitudinal cohort studies that examined whether e-cigarette use leads to subsequent smoking in adolescents who are cigarette naive at baseline. The search covered peer reviewed literature published between 1 January 2005 and 2 October 2019 on e-cigarettes retrieved from one of seven databases and these were Ovid MEDLINE, Cochrane Library, Ovid PsycINFO, Elsevier Embase, PROSPERO, LILACS, Google Scholar, and CORE.ac.uk. Comprehensive searches were completed and updated twice during the review period. There were three rounds of screening, using predefined exclusion criteria, to identify the papers included in this review. The data were extracted from the 21 included papers into the Cochrane Data Extraction Form. The quality of the included studies was assessed using the National Heart, Lung, and Blood Institute's quality assessment tool for observational cohort and cross-sectional studies. The results were described narratively using their summary statistics in the context of their association with the exposure (e-cigarettes), controlling for confounding using covariates. A meta-analysis feasibility assessment was completed in order to decide whether to complete meta-analysis and to decide which meta-analysis method would be most appropriate. A pairwise meta-analysis, to compare outcomes of two-armed longitudinal studies exposures, was completed for the smoking initiation outcomes using the primary studies crude and adjusted odds ratios. Sensitivity and subgroup analyses were also conducted where appropriate. A level of evidence and a GRADE recommendation were assigned to our findings.

Findings

We identified 21 papers for inclusion in the study that comprised 14 unique longitudinal cohort studies. The data were collected between 2013 and 2016 and the longitudinal follow-up period ranged from 4 months to 2.5 years. Only one study had two follow-up time points. Fifteen studies were completed in America and six studies were done in Europe. A variety of questions were asked about e-cigarettes: 17 asked about ever use of e-cigarettes, 4 asked about e-cigarette use in the past 30 days, 4 studies asked about infrequent use of e-cigarettes, and 2 studies examined the use of both nicotine and non-nicotine e-cigarettes. None of the 21 studies provided any specific information about the e-cigarettes type, generation, or liquid. All papers measured cigarette smoking as an outcome variable: 18 papers investigated ever use of cigarettes by follow-up, 4 also asked about past 30-day use of cigarettes, and 5 examined differences between groups in terms of frequency of cigarette use. All publications which conducted regression analysis included potential confounding variables as covariates in their regression model, ranging from the inclusion of 3 to the inclusion of 17. Based on research guidance, we grouped the covariates into three groups: demographic (e.g. ethnicity, family affluence), interpersonal (e.g. number of friends/family members that smoke) or intrapersonal (e.g. such impulsivity, sensation seeking, rebellion). One paper only included variables from one domain while eight papers included variables from two domains, and ten papers included

variables from all three domains. The age of the included population was between 13 and 19 years at baseline.

The most commonly explored association among the 21 included papers was between ever e-cigarette use and subsequent use of cigarettes. All studies which explored this relationship, other than Wills *et al* found that there was a significant positive association between ever using an e-cigarette at baseline and ever using a cigarette at follow-up. Our meta-analysis, which included 9 of the 14 unique studies, found that the combined odds of trying smoking were 4.06 (95%CI: 3.00-5.48) times higher for those who had ever used e-cigarettes at baseline, although this was reduced slightly (to 3.71 times the combined odds, 95%CI: 2.83-4. 86) when only the high-quality studies were included. The main meta-analysis indicated that the model had a moderate to high statistical heterogeneity; however, a sensitivity analysis of only high-quality studies had low to moderate statistical heterogeneity with a slightly reduced combined odds ratio (OR). Using the formula proposed by Zhang and Yu (1998), an approximation of an adjusted relative risk (risk ratio) was calculated for the four high-quality studies. This resulted in a range of values for the population attributable fraction, indicating that between 12% and 29% of those in the four studies who had tried a cigarette had done so due to their initial use of e-cigarettes. In other words, if e-cigarettes did not exist, there would have been between 12% and 29% fewer new adolescent smokers among the study subjects. However, it must be noted that there are limitations to this method, in particular, the fact that the incidence rate used in the calculation is not adjusted, and as such, these results should be interpreted with caution. Subgroup analyses of these studies revealed a higher combined OR for the data collected after 2014, a time point at which e-cigarette use increased substantially, as well as for the data collected in Europe (as compared with the USA).

Four studies which examined the relationship between past-30-day e-cigarette use and initiation of cigarette use using the primary studies adjusted OR also found a significant positive association, although with a lower combined OR than ever trying e-cigarettes; indeed, a meta-analysis of three of these studies found that e-cigarette users had 2.14 times (95%CI: 1.75-2.62) the odds of cigarette smoking compared with non-e-cigarette users. Three studies measured the association between ever e-cigarette use and past-30-day cigarette use, with significant positive associations in the USA samples but no association in a Mexican sample. Neither study which measured past-30-day use of e-cigarettes and subsequent past-30-day cigarette use found a significant association.

Different patterns of use and frequency of use of both e-cigarettes and cigarettes reported significant positive associations. One USA study found significant positive associations between e-cigarettes and 'experimenters', infrequent and frequent users of cigarettes. Two USA studies examined different frequencies of e-cigarette use at baseline on ever cigarette use at follow-up and found significant positive associations between all variations of e-cigarette use and subsequent smoking. Two studies which examined the relationship between e-cigarette use and daily cigarette use found a significant positive association, although this relationship was non-significant when non-nicotine e-cigarettes were examined.

Two studies explored the specific impact of nicotine versus non-nicotine e-cigarettes on subsequent conventional cigarette use. One study which measured ever e-cigarette use and ever smoking found a significant positive association between ever use of e-cigarettes with nicotine and subsequent cigarette use, and between ever use of e-cigarettes without nicotine and subsequent cigarette use, although to a lesser extent. However, a study which explored the impact of nicotine versus non-nicotine e-cigarettes on daily smoking found a significant positive association with nicotine e-cigarettes, but no association between non-nicotine e-cigarettes and daily smoking.

We assigned a level of evidence of 3 using *British Medical Journal* guidelines, as this is a systematic review of cohort studies, some of which had high loss to follow-up and/or very small sample sizes. However, with respect to certainty of evidence, the HRB authors have moderate confidence that the true effect is probably close to the estimated effect for trying smoking at follow-up for those who had ever used e-cigarettes at baseline. This is due to the fact that all analyses indicate that there is a significant association between using e-cigarettes at baseline and smoking cigarettes at follow-up,

and this effect size is quite large. Six studies controlled for confounding under three domains (demographic, interpersonal, and intrapersonal) associated with smoking cigarettes, and had a similar, but tighter, significant estimate of effect. The four high-quality studies also had a similar and tighter estimate of effect and lower statistical heterogeneity. The remainder of the studies were judged to be moderate quality because of their small sample sizes and loss to follow-up. In addition, the direction of the findings of the HRB meta-analysis are consistent with two earlier meta-analyses by Soneji *et al.* and Aladeokin *et al*.

Conclusions

We found a four-fold association between ever using e-cigarettes and initiating smoking tobacco cigarettes in adolescents in a combined analysis of nine cohort studies conducted with follow-up periods between 4 and 24 months. Sensitivity and subgroup analysis support the association between ever using e-cigarettes and initiating smoking tobacco cigarettes. The study design used to assess the relationship between e-cigarette use and initiation of cigarette smoking does not allow us to say there is a definitive causal relationship, but it does allow us to say that the findings builds a case towards a causal relationship as the findings are consistent across all studies included in the meta-analysis. Furthermore, the strength of association is statistically significant across all primary research studies in the meta-analysis. In addition, the use of e-cigarettes occurred before initiation of smoking, fulfilling the criteria for a temporal relationship, and two studies have examined the dose response relationship. Moreover, the results of this systematic review are in line with the previous systematic reviews and meta-analyses. Whether there are other additional explanatory factors or not, we need to understand what drives the relationship between e-cigarette and tobacco cigarette use and if the effect is definitively causal. One author recommends large longitudinal epidemiological studies which measure smoking onset, control for confounders, and include a propensity score measure of liability to smoking. Other authors suggest exploring the association using qualitative research approaches.

We identified three theories that attempt to explain the move from e-cigarette use to smoking tobacco cigarettes, and these are: the gateway theory, the common liability theory, and the catalyst model. The gateway theory was developed to explain the observed phenomenon of young people's use of alcohol and drugs in specific stages and sequences, and intimates that e-cigarette use leads to conventional cigarette use. The common liability theory states that there is an underlying common liability within people which increases their propensity to use drugs and other illicit substances, and that the move from e-cigarettes to conventional cigarettes or other drugs is part of their risk behaviours. Recently, however, some authors have proposed that the gateway theory and the common liability theory are not, as some say, opposing, but rather are complementary. They state that use of drugs in general will be explained by common factors, whereas specific factors will explain why young people use drugs in a specific sequence. In a 2016 paper, two authors proposed an alternative model, the catalyst model, to explain the path from e-cigarette use to conventional cigarette use, considering numerous hypotheses and pathways. They separate the process into two stages, from no consumption to e-cigarette consumption, and then from e-cigarette use to conventional cigarette use. Factors such as flavour, health, price, role model, concealment, and acceptance play a role in the first stage by easing the process of initiation, as they appear healthier and more acceptable to some, while the flavours attract others. In the second stage (i.e. the transition from e-cigarettes to cigarettes), the authors hypothesise that addiction, accessibility, and experience may drive the subsequent move to conventional cigarette use. Two factors which exist outside the model but are nevertheless influential are the common liability hypothesis and the renormalisation [of smoking] hypothesis. Despite fierce debates on the merits of different theories, no consensus has been reached on the most likely explanation. Future research should focus on designing studies which specifically set out to test these theories (or elements thereof). It would be beneficial for future research to attempt to isolate and unpick elements of Schneider and Diehl's Catalyst model that describes e-cigarette initiation and subsequent cigarette use in order to further our understanding of this relationship.

The EU has developed regulations to address e-cigarette manufacture, presentation, and sales under the Tobacco Products Directive (2014/40/EU). Ireland are in the process of implementing the European regulations. A population health approach, similar to that successfully used in Ireland to

address tobacco, alcohol and psychoactive drug issues, may need to be extended to tackle use of e-cigarettes; a population health approach to psychoactive substances usually involves addressing price, availability, and marketing to limit use among young and other vulnerable populations.

1 Introduction

1.1 Policy background

In 2013, the Tobacco Policy Review Group published the report *Tobacco Free Ireland*, which set a target for Ireland to reduce smoking prevalence to less than 5% by 2025.[3] *Tobacco Free Ireland* was the first policy document to be launched under the Healthy Ireland framework, and it was endorsed by the Government. Achieving the target in the reduction of smoking prevalence would play a major role in realising the vision set out in Healthy Ireland.

The *Tobacco Free Ireland* report identified tobacco-related harm reduction as a key issue for consideration.[3] It specifically highlighted the role of electronic cigarettes (e-cigarettes) as a potential harm reduction strategy. Since the introduction of e-cigarettes in 2006, research has expanded on their potential benefits in terms of tobacco-related harm reduction and on the public health harms of e-cigarettes.

The Department of Health asked the Health Research Board (HRB) to complete a programme of research and answer five research questions:

1. What are the public health benefits and harms of e-cigarettes?
2. What are the public health benefits and harms of heat-not-burn products?
3. What is the efficacy of e-cigarettes in helping people who smoke to achieve abstinence (smoking cessation)?
4. Examine the efficacy of heat-not-burn products in helping people who smoke to achieve abstinence (smoking cessation)?
5. Does e-cigarette use by adolescents who are cigarette naive at baseline lead to subsequent cigarette smoking?

1.2 Research question

We answered Question 5 in this review:

Does e-cigarette use by adolescents who are cigarette-naive at baseline lead to subsequent cigarette smoking?

1.3 Background

1.3.1 Prevalence of cigarette smoking in Ireland

The *Healthy Ireland Survey 2019* reported that 17% of respondents aged 15 years and older were current cigarette smokers and 14% smoked daily.[4] A study carried out by the *European School Survey Project on Alcohol and Other Drugs* (ESPAD) found that in Ireland 32.3% of second-level students aged 15–16 years reported ever using a cigarette, while 13% had smoked at least once in the last 30 days.[5] Just under 7% of respondents in the ESPAD survey reported smoking daily, and of students who had ever smoked a cigarette, almost one-half reported that they were 13–14 years old when they first smoked.[5]

1.3.2 Prevalence of e-cigarette use in Ireland

The *Healthy Ireland Survey 2018* reported that 92% of smokers were aware of e-cigarettes.[6] The *Healthy Ireland Survey 2019* reported that 5% of the population were using e-cigarettes, and a further 12% had tried them at some point in the past. Furthermore, 10% of current smokers were using e-cigarettes, 13% of ex-smokers were using them, and 1% of never smokers were using them.[4] The *Prevalence of Drug Use and Gambling in Ireland and Drug Use in Northern Ireland* survey carried out in 2014-2015 reported that in the Republic of Ireland, 13.6% of respondents aged 15 or older had ever used e-cigarettes and 3.1% had used them in the month prior to the survey.[7] The same survey also found that the prevalence of ever using an e-cigarette varied with age, with the highest use being

reported among respondents aged 25–34 years (21.5%) and the lowest use being reported among those aged 65 years or older (4.6%).[7] Among respondents aged 15–24 years, 14.7% had ever used e-cigarettes. The 2016 Irish ESPAD survey reported that 23% of second-level students aged 15–16 years reported ever using an e-cigarette, and 10.1% reported using an e-cigarette in the 30 days prior to the survey.[5] Slightly more than half (52.7%) of respondents who were e-cigarette users reported that they were 15 years old when they first used an e-cigarette. The sixth Health Behaviour in School-aged Children study, completed in 2018, found that the proportion of children who had ever used an e-cigarette increased with age, from 11.5% of 13-year olds to 30% of 17-year olds. The same trend was noted for ever use of an e-cigarette in the month prior to the survey but the proportions were lower, with 4.8% of 13-year olds and 10.6% of 17-year olds reporting e-cigarette use. [8]

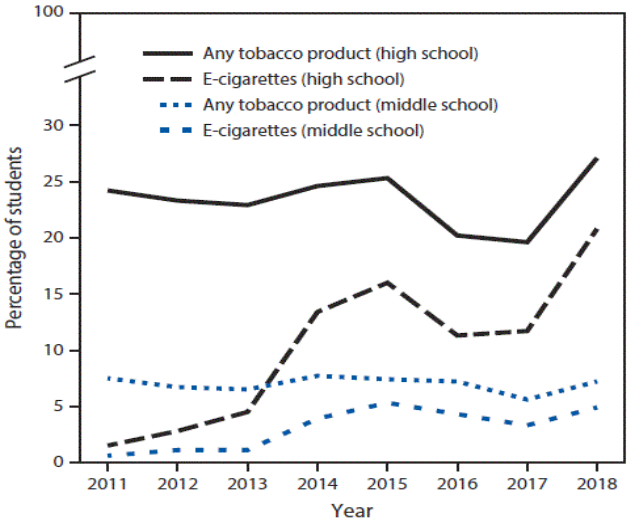
1.3.3 Prevalence of e-cigarette use internationally

A study based on Eurobarometer surveys reported that 63 million people living in European Union (EU) member states aged 15 or older had ever used e-cigarettes by 2017 (95% confidence interval [CI]: 59.9 million–66.2 million), and 7.6 million (95% CI: 6.5 million–8.9 million) were regular e-cigarette users.[9] Among participants who had ever used e-cigarettes, those aged 15–24 years were less likely to be regular users than those aged 55 years or older (16.9% versus 38.1%). In addition, never smokers were less likely to be regular e-cigarette users than current and former smokers (12.8% versus 27.0% versus 41.3%). The proportion of people aged 15 years or older who were regular e-cigarette users in 2017 ranged from 4.7% in the UK to 0.2% in Bulgaria.

A study examining data from a representative cross-sectional survey of EU citizens found that 31.1% (95% CI: 30.0–32.2%) of current smokers reported ever having used e-cigarettes, 10.8% (95% CI: = 10.0–11.7%) of former smokers reported ever having used them, and 2.3% (95% CI: 2.1–2.6%) of never smokers reported ever having used them. Past experimentation (7.2% [95% CI: 6.9–7.5%]) was more common than both current use (1.8% [95% CI: 1.6–1.9%]) and past use (2.6% [95% CI: 2.4–2.8%]). The authors extrapolated these findings to the whole population, estimating that approximately 48.5 million EU citizens were ever e-cigarette users, with 76.8% of them using nicotine-containing e-cigarettes.[10]

Bauld *et al.* reported e-cigarette use among 60,000 people aged 11–16 years across the UK.[11] Their data were derived from several large surveys that were completed between 2015 and 2017– the Youth Tobacco Policy Survey; the School Health Research Network survey based in Wales; two Action on Smoking and Health Smokefree Great Britain Youth Surveys; and the Scottish Schools Adolescent Lifestyle and Substance Use Survey – with different designs and sampling strategies. When examining the compiled results, Bauld *et al.* found that between 7% and 18% of 11–16-year-old children had ever used e-cigarettes. They also found that between 67% and 92% of 11–16-year-old regular smokers in the UK had ever used e-cigarettes in 2015–2016, while between 7% and 38% of regular smokers had used them once per week in the same time period. The surveys' range for ever use of e-cigarettes among 11–16-year-olds who regularly smoked conventional cigarettes (i.e. dual users) was between 4% and 10% in 2015–2016, while the range for regular e-cigarette use among the same cohort was between 0.1% and 0.5%.

In the USA, data from the 2011-2018 *National Youth Tobacco Surveys* (Figure 1) found that current e-cigarette use among high school students increased from 1.5% in 2011 to 20.8% in 2018.[12] In addition, current e-cigarette use among middle school students in the USA increased from 0.6% (60,000 students) in 2011 to 4.9% (570,000 students) in 2018.



Source: Cullen *et al*., 2018[12]

Figure 1 Data from the 2011–2018 *National Youth Tobacco Surveys* in the USA

1.3.4 Reasons for e-cigarette use

The 2017 Eurobarometer reported that most e-cigarette users in the EU initiated use in order to try to curb their tobacco intake; however, this was effective only for a minority of users.[13] Specifically, of the 15% of EU citizens who had ever used e-cigarettes, 61% of EU respondents and 58% of Irish respondents who started using e-cigarettes did so in order to reduce or stop their tobacco intake. Just 14% of EU and 23% of Irish e-cigarette users stated that they stopped smoking tobacco entirely due to taking up e-cigarette usage, whereas 10% of EU respondents and 15% of Irish respondents said that they stopped smoking tobacco but then started again. Furthermore, 17% of EU respondents and 20% of Irish respondents said that they reduced their tobacco intake but did not stop smoking.[13]

The *Healthy Ireland Survey 2018* reported that 44% of 7,500 respondents who had smoked in the 12 months prior to the survey had tried to quit during that period.[6] More than one-half of current smokers (57%) were thinking about quitting, while 40% of current smokers had tried to quit in the past 12 months. Most of those who had tried to quit smoking in the past 12 months did so due to concerns about their health. The possible link between e-cigarette use and smoking cessation or reduction was not presented in the report's findings.

The Irish ESPAD survey reported that the most common reason for those aged 15–16 years trying e-cigarettes was "curiosity", at 60%, and the second most frequent answer was that "friends were using them", at 21.4%.[5] Fifty-one students (17.3%) reported using e-cigarettes to quit smoking tobacco and 29 students (9.8%) reported smoking e-cigarettes as an alternative to tobacco.

2 Methods

2.1 Conceptual methods

A single standard systematic search approach was used for the five questions outlined in Section 1.1. Published studies and other material were sourced via database and supplemental searches. Articles were double-screened, until a final core set of relevant articles that would speak to the five review questions were agreed upon. For the question on smoking initiation, which dealt with peer-reviewed investigations (using longitudinal cohort studies), data were extracted from the material using an adapted Cochrane Data Extraction Form.[14]

2.2 Inclusion and exclusion criteria

The examination of the relationship between the initiation of smoking cigarettes among young people as a result of vaping e-cigarettes required that we included longitudinal cohort studies only, as such studies can measure incidence.

For the question on smoking initiation, the date limits used are 2005-2019, as 2005 is considered the date of introduction of e-cigarettes as they are currently understood.

No language limit was imposed initially (apart from the implicit limit of using databases that index primarily English-language research). However, on immersion in the full extent of the topic, it became clear that a rudimentary translation of non-English-language articles would not be adequate to understand such technical material and there would not be time or resources to have all the non-English results translated professionally. Thus, reluctantly, non-English language articles were screened out from the articles put forward for full analysis. However, the authors are aware that a body of research published in other languages exists which could add to the review body of literature.

Where duplicate articles occurred, only one of the two articles was included. Despite 'deduplicating' the articles prior to screening, some duplicates were noted at 'title and abstract' and at full-text screening stages. These are likely to have got through the deduplication process due to inaccurate or incomplete information in some of the search fields, for example, wrong or missing titles or authors, missing digital object identifiers, or other information types.

The study inclusion criteria for 'Does e-cigarette use lead to subsequent smoking in adolescents (who are cigarette naive at baseline)?', are described in Table 1.

Table 1 PICO inclusion criteria for review question

Element	Description
Population	Adolescents who are cigarette naive at baseline. The age of the included population was between 13 and 19 years or under at baseline.
Exposure	Electronic cigarette vaping at baseline or in the past
Comparators	Non-electronic cigarette user
Outcomes	Initiation of cigarette smoking at follow-up
Study design	Cohort studies
Search dates	2005-2019 for e-cigarettes

2.3 Information searches

Following scoping searches on the topic of e-cigarettes and heat-not-burn products in Ovid MEDLINE and Ovid PsycINFO, and in the search engine Google, a search plan was designed by the information specialist to capture relevant studies and other data. The plan included literature searches using bibliographic databases, registries, repositories, and search engines. Supplemental searches were planned, including forward and backward citation searching of recent systematic reviews, and

authoritative reports. Follow-up searches of Ovid MEDLINE were scheduled to be carried out after the initial main search, to maintain currency of the review.

'Search development' database work was carried out from 4 to 10 April 2019 and the finalized searches for each database were run on the 15 April. These results were combined using EndNote X7 and uploaded to EPPI-Reviewer 4 (V. 4.11.0.0)[15] Subsequent supplemental searches were carried out on the 12 August and 2 October 2019 August and October 2019.

2.3.1 Bibliographic databases

General scoping searches were carried out in late March 2019 using Ovid MEDLINE and PsycINFO, and using the search engine Google, to estimate the size of the body of published information and to test search terms. The primary database searches were carried out on the 15 April 2019. The databases included were:

- Ovid MEDLINE (Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to April 12, 2019)
- Elsevier Embase
- Ovid PsycINFO
- Wiley Cochrane Database of Systematic Reviews
- Wiley Cochrane Central Register of Controlled Trials
- LILACS (including the databases LILACS, IBECS, CUMED, BDENF – Nursing, BBO – Dentistry, WHO IRIS, PAHO IRIS, Index Psychology – Scientific journals and MedCarib)
- PROSPERO (Centre for Reviews and Dissemination, University of York)

Peer review of the search strategy by another information specialist, as recommended in the Peer Review of Electronic Search Strategies (PRESS) guidelines,[16] was not carried out as resources were unavailable when conducting the searches. However, every effort was made by the information specialist to critically appraise the search strategies using the checklist outlined in the PRESS guidelines in order to follow the PRESS recommendations.

On the 12 August 2019, a two-part supplemental search was carried out. This included a literature search using Ovid MEDLINE (with the same search terms as the original search but limited to recent articles), and a citation search based on core reviews and reports. The list of reports and reviews used for this search is included in Appendix 1. The review titles were sourced by combining the Ovid MEDLINE e-cigarette and heat-not-burn searches with a customised version of the Ovid Expert Searches systematic review filter and then limiting them to publications from the previous five years. The titles were screened for clinical relevance in accordance with PICO (e.g. smoking cessation, harms, benefits, and initiation) by the information specialist and titles were confirmed for inclusion with the lead reviewer. The results from these searches were added to EndNote X7 and screened initially for duplicates, then for relevance using the review PICO (see Table 1), and then for originality (whether they were already included in the original search results).

On 2 October 2019, a second simple supplemental search was carried out using Ovid MEDLINE, with the same search terms as before. The results were screened initially by the information specialist to eliminate articles that had already been screened in other searches, and to eliminate highly irrelevant articles (e.g. articles not relating to e-cigarettes or heat-not-burn devices). The results were screened by the researchers and any relevant articles were retained.

The full search strategies used in the initial searches for Ovid MEDLINE and other databases are included in Appendix 1. The MEDLINE searches used in the supplemental searches were the same as the initial MEDLINE strategy.

The searches were broadly comprehensive but not exhaustive. The use of journal hand-searching, follow-up of relevant authors, and more exhaustive searches with other databases were considered

for this review, but due to time considerations, it was not possible to incorporate all these methods in this project.

2.3.2 Keywords

Keywords for these searches were compiled from scoping searches on the topic carried out in MEDLINE and Google, and with the assistance of PubMed PubReMiner,[17] the PubMed text-mining software. This software allowed the easy capture of relevant medical subject headings (MeSH) terms.

The keywords used in building the searches were based on variations of terms for e-cigarette and heat-not-burn products, for example, e-cig*, e-liquid, vape, vaping, cigalike, HnB (heat-not-burn products), heatsticks, electronic nicotine delivery system (ENDS), and electronic non-nicotine delivery. Non-English terms for these concepts were also included, for example, e-sigaret*, E-zigarette, and e-papieros. Some high-profile brand names such as JUUL and IQOS were included.

For databases with a controlled vocabulary, such as MEDLINE, Cochrane, PsycINFO, PROSPERO and Embase, terms from the relevant thesaurus (MeSH, Emtree, PsycINFO Thesaurus) were also incorporated.

Given the considerable body of literature published to date mentioning e-cigarettes and heat-not-burn products and the limited amount of time available to complete the review, additional search terms were used to broadly exclude some categories of study, for example, MeSH and free terms for animal studies and cell line studies.

Rather than split the single e-cigarette/heat-not-burn products search into three separate searches for smoking cessation, harms and benefits, and initiation studies, a single search was used for all three subtopics, and results were filtered via the screening process to the appropriate subtopic. It was anticipated that several results would be relevant to more than one question.

2.4 Screening

A comprehensive screening process was carried out. Results (n=6,510 after deduplication) from the literature searches were exported to EPPI-Reviewer 4. 'Title and abstract' screening was carried out by two researchers (AMcC and DOB) and the information specialist (CL). A pilot group consisting of 10% of the results were initially screened to test the screening questions and process. The remainder of the results was then screened using the same criteria. The screening questions comprised the five review questions. Where there was doubt about the relevance of an article, it was included for the next round of screening.

Inclusion and exclusion criteria for the title and abstract screening process were those outlined in Section 2.2.

After the title and abstract stage of screening, 130 papers relating to the research question were retained. The full texts of the relevant 130 papers were sourced and then screened to answer specific inclusion queries that could not be answered using the published abstract alone. This screening was carried out by two of the researchers (AMcC, and DOB), using the same inclusion and exclusion criteria as before.

After this extended preliminary screening, 46 papers were carried forward to the full-text screening process. Despite a thorough screening process, some articles had to be excluded on deep examination during the data extraction process, as on close reading, they did not fulfill the inclusion criteria of the study. In some cases, details of study type or methods were unclear. Some of the articles included inadequate descriptions of the analyses carried out, which required contact with the original authors to obtain full details. Following full-text analysis, 18 papers were included for data extraction.

The results of the two supplemental searches (described in Section 2.3.1) were screened by title and abstract by the information specialist to eliminate obviously out of scope results. Potentially relevant results were then screened by a researcher (DOB). Of 109 supplemental results, only three additional

relevant results were retrieved. These were added to the 18 papers remaining after screening and resulted in 21 papers eligible for data extraction.

2.5 Data extraction

One researcher (DOB) extracted data from the 21 included papers into the bespoke Cochrane Data Extraction Form[14] under the following headings: 'study identifier', 'general information', 'study characteristics', 'participants', 'exposure group 1', 'exposure group 2', 'outcomes', 'data and analysis' and 'other information'. JL validated the extraction and any disagreements were resolved by consensus. DOB noted during extraction that a number of the papers were based on data from the same datasets and so identified studies that were linked and grouped them for analysis and presentation. As stated above, the final total included 14 unique studies published in 21 journal papers.

2.6 Quality assessment

DOB and JL assessed the quality of the included studies using the National Heart, Lung, and Blood Institute's (NHLBI's) quality assessment tool for observational cohort and cross-sectional studies.[18] This tool uses 14 items to assess the quality of cohort studies (Appendix 2).

Each study was independently assessed by two researchers (DOB and JL), with any disagreements being resolved by consensus. The results of the quality assessment are presented in Appendix 2. Quality assessment results were not used to exclude studies from the main analysis, but the assessment was used to describe the main strengths and limitations of the studies. In addition, the quality assessment results were used to inform our choice of high-quality studies for one of the sensitivity analyses.

2.7 Data analysis

The results were described narratively using summary statistics and describing the influence of covariates. They are presented according to different categories of frequency of both e-cigarette use at baseline and tobacco smoking at follow-up, taking account of different follow-up periods.

Meta-analysis is the statistical pooling of two or more trials comparing the same two interventions.[19] A core assumption underpinning meta-analysis is that the studies being pooled are homogeneous; all sources of heterogeneity and variation must be assessed before meta-analysis can be carried out.[19 20] A feasibility analysis is an assessment of variation in study and patient characteristics across comparisons that affect the summary measures of effects (such as the odds ratio) for the exposure or interventions of interest relative to an overall reference exposure or treatment.[20-22] The feasibility assessment was completed in order to decide whether to complete meta-analysis, as well as to decide which meta-analysis method would be most appropriate. The feasibility analysis considered outcome, exposure, unit of measurement, and length of time to follow-up (Appendix 3). Based on these criteria, 12 studies were considered eligible for pairwise meta-analysis so as to compare outcomes of two armed longitudinal studies exposures. A separate meta-analysis was done using both the primary studies' crude odds ratio and their adjusted odds ratio (AOR) for 'ever use' of e-cigarettes and cigarettes (n=9), and for 'past 30-day use' of e-cigarettes (n=3). We also completed sensitivity analysis and subgroup analysis on the 'ever use' data. We used the 'Metagen' package for the R programming language.[23 24] This package uses the inverse variance method for weighting of studies.[23 24] The I^2 statistic describes the percentage of the variability in treatment effects that is due to statistical heterogeneity rather than sampling error (chance).[19] Random and fixed effects models were run, although the random effects model is preferred due the underlying statistical heterogeneity in the studies. Odds ratios and their associated 95% confidence intervals (CI) were calculated. Where data from the included studies were unclear, we did not include them in meta-analysis.

One of our sensitivity analyses explored the impact of studies which appropriately controlled for confounding. Based on Glasser *et al.*, we defined the three domains of covariates (which may be confounders) in the e-cigarette and cigarette use topic area as demographic (such as ethnicity or

family affluence), interpersonal (such as number of friends/family members that smoke) or intrapersonal (such as impulsivity or sensation seeking).[25] Studies which included covariates in all three domains were considered well-controlled studies.

We calculated the population attributable fraction (PAF) for the high-quality studies included in the main meta-analysis. The PAF is the excess risk of disease in the study population due to the presence of the exposure (in this case, e-cigarettes). It is used to assess the public health impact of the exposure (e-cigarettes) on conventional cigarette use. It is the percentage of cigarette smoking, among the study population that used e-cigarettes, that could be prevented if e-cigarettes were removed.[26] In order to calculate the fraction for the included studies in this report, the following three steps were taken:

1. Used four high-quality studies
2. Converted AORs to risk ratios,[27] and
3. Calculated PAF using risk ratios.[28] [26]

However, it must be noted that there are limitations with the method used in this analysis,[27] particularly the fact that the incidence rate used in the calculation is not adjusted, and as such, these results should be interpreted with caution.[29] [30]

2.8 Level of evidence

We used the *British Medical Journal* guidelines to assign the level of evidence,[31] and the GRADE certainty of evidence,[32] to write our strength of evidence recommendation. The levels of evidence range from one to four. The certainty of evidence can be high, moderate, low or of very low quality. The quality of evidence drives the strength of recommendation, which is one of the last translational steps of research, most proximal to patient care.

3 Results

3.1 Descriptive characteristics of included studies

The PRISMA flow chart (Figure 2) shows the numbers of articles examined at each stage of the review process. From an initial 6,619 studies (6,510 papers from the initial searches, plus 109 papers from supplemental searches), 14 unique studies in 21 papers met the inclusion criteria for this systematic review. Of these papers, the majority (n=12) were from the USA, 3 were from the UK, 2 were from Canada, 1 was from Finland, 1 was from Germany, 1 was from Mexico, and 1 was from the Netherlands. As per the inclusion criteria, the age of the included population was 19 years or under at baseline. Most studies had one follow-up period, although one reported follow-up data at two time points.[33] The follow-up periods ranged from 4 months to 2.5 years, with data collected between 2013 and 2016 (Table 2).

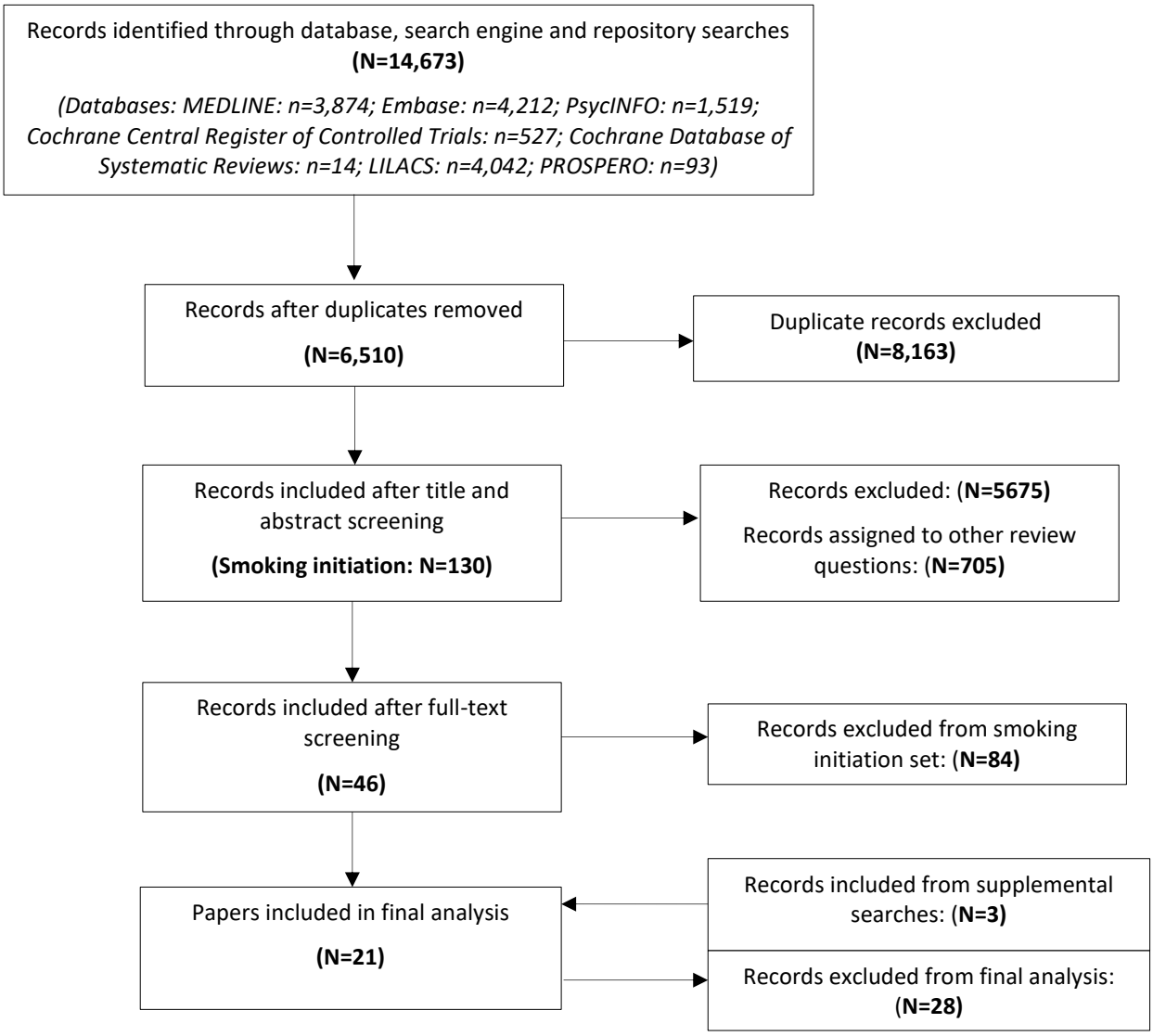


Figure 2 PRISMA flow chart

3.1.1 Measurement of exposure

The exposure variable for all papers was the use of e-cigarettes at baseline, although the frequency of exposure differed among studies. The majority (n=17) asked about ever use of e-cigarettes at baseline,[33-49], four studies asked about e-cigarette use in the past 30 days,[50 38 51 43] two studies asked about any prior use of e-cigarettes[38 52] and four studies asked about infrequent use of e-cigarettes [39 52 47 48] and frequent use of e-cigarettes [39 52 47 48] Two studies examined the use of both nicotine and non-nicotine e-cigarettes.[44 49] None of the 21 studies provided any specific information about the e-cigarette type, generation or liquid. Apart from Treur *et al.*[44] and Kinnunen *et al.*[49], all other authors assumed that e-cigarettes contained nicotine.

3.1.2 Measurement of outcome

All papers measured cigarette smoking as an outcome variable. The majority (n=18) investigated ever use of cigarettes by follow-up; [33 34 36-48 50-52] however, some also asked about past-30-day use of cigarettes (n=4)[37 38 41 43] or examined differences between groups in terms of frequency of cigarette use (for example, experimenters, infrequent smokers, or frequent smokers) (n=5). [35 39 49 50 53]

3.1.3 Covariates

All publications which conducted regression analysis included potential confounding variables as covariates in their regression model, ranging from the inclusion of 3 variables[48] to the inclusion of 17 variables.[37]

Based on Glasser *et al.*, we defined the three domains of covariates in this topic area as demographic (e.g. ethnicity, family affluence), interpersonal (e.g. number of friends/family members that smoke), and intrapersonal (e.g. impulsivity, sensation seeking).[25] Although the majority included covariates from all three domains, there was some diversity in the number of covariates included in each study; one paper [35] only included variables from one domain, eight papers included variables from two domains[34 42 44 46 47 49-51] and 10 papers included variables from all three domains. [33 37-41 43 45 48 53]

Of the 19 papers that conducted regression analysis on the association between e-cigarette use and conventional cigarette use, 10 studies controlled for covariates in all three main domains: demographic, interpersonal, and intrapersonal.

3.1.4 Quality assessment

Overall, using the NHLBI quality assessment tool, we determined that there was a variation in the quality of our included papers.[18] We judged that there were four high-quality studies as they had a representative and clearly defined sample with a participation rate of more than 50%, a loss to follow-up rate of 20% or less, and a sample size justification or variance calculation for the main outcomes.

Table 2 Characteristics of included studies

Study ID	Study design	Objective	Years followed	Follow-up period	Country	Mean age (age range) or school grade baseline✞	Loss to follow-up	Baseline sample
Aleyan *et al.* (2018)[53]	Prospective cohort study (COMPASS study)	The authors examined whether baseline use of e-cigarettes among a Canadian sample of susceptible and non-susceptible never-smoking youth was associated with cigarette smoking initiation over a 2-year follow-up.	2013–2016	2 years	Canada	9th–12th grade	20.1%	9,501
Hammond *et al.* (2017)[50]	Cohort study (COMPASS study)	The authors examined e-cigarette use in a large longitudinal sample of Canadian youth, including the extent to which e-cigarette use was associated with cigarette-smoking initiation at 1-year follow-up.	2013–2015	1 year	Canada	14–18	23.0%	19,310
Barrington-Trimis *et al.* (2018a)[35]	Prospective cohort study (Children's Health Study; Happiness and Health Study; Yale Adolescent Survey Study)	The authors evaluated the association of baseline e-cigarette use (never or ever) with cigarette use frequency at follow-up. Also, to evaluate transitions between baseline ever or past-30-day single or dual product use and past-30-day single or dual product use at follow-up.	2013–2016	Not reported	USA	9th–12th grade	Follow-up 1 6.1% Follow-up 2 40%	6,147
Barrington-Trimis *et al.* (2018b)[36]	Prospective cohort study (Children's Health Study)	The authors examined the sensitivity, specificity, and predictive value of the susceptibility to smoking index in a prospective cohort study of non-smoking Southern California adolescents as they turned 18, the legal age for smoking at the time of the study.	2014–2016	Approx. 16 months	USA	11th and 12th grade	25.3%	1,266

Study ID	Study design	Objective	Years followed	Follow-up period	Country	Mean age (age range) or school grade baseline✞	Loss to follow-up	Baseline sample
Barrington-Trimis *et al.* (2016)[34]	Prospective cohort study (Children's Health Study)	The authors examined whether e-cigarette use among older adolescents in the transition to adulthood leads to greater likelihood of initiation of cigarettes as they reach the legal age to purchase cigarettes.	2014–2016	Approx. 16 months	USA	17.4 (11th and 12th grade)	30% e-cigarette users; 27.7% never e-cigarette users	298
Berry *et al.* (2019)[37]	Cohort study (Population Assessment of Tobacco and Health (PATH) Study)	The authors evaluated the associations of prior e-cigarette and other noncigarette tobacco product use with subsequent cigarette initiation over approximately 2 years.	2013–2016	2 years	USA	13.4 (12–15)	19.1%	6,123
Watkins *et al.* (2018)[38]	Cohort study [PATH Study]	The authors simultaneously assessed e-cigarettes, hookah, noncigarette combustible tobacco, and smokeless tobacco as determinants of future cigarette smoking, including whether poly use of noncigarette products has a greater association with future smoking compared with use of 1 product alone.	2013–2015	1 year	USA	14.3 (12–17)	12.1%	10,384
Conner *et al.* (2018)[39]	Longitudinal study (controls from a randomised controlled trial (RCT))	This study investigated the extent to which baseline ever use of e-cigarettes was associated with the initiation or escalation of cigarette use (objectively validated) 12 months later in a sample of UK adolescents aged 13–14 years. The impact of controlling for various smoking risk factors such as	2014–2015	12 months	UK	13.8 (13–14) (never smokers)	21.4%	2,836

Study ID	Study design	Objective	Years followed	Follow-up period	Country	Mean age (age range) or school grade baseline✞	Loss to follow-up	Baseline sample
		friends and family smoking and their moderating effects was also explored.						
East *et al.* (2018)[40]	Longitudinal survey (Action on Smoking and Health)	This study explored the associations between e-cigarette use and smoking initiation among young people in Great Britain.	2016	4–6 months	Great Britain	(11–18)	50%	2,916
Leventhal *et al.* (2015)[33]	Longitudinal survey	This study investigated whether adolescents entering the 9th grade in Los Angeles, California, who reported ever using e-cigarettes were more likely to initiate the use of combustible tobacco during the subsequent year.	2013–2014	6 months and 1 year	USA	14.06 (9th grade) [never smokers]	3% at 6-month 3.4 at 12-month	2,530 (never smokers)
Leventhal *et al.* (2016)[52]	Longitudinal study	Associations of vaping with subsequent smoking frequency and heaviness pattern among adolescents were examined.	2014–2015	6 months	USA	15.5 years [analytic sample]	3%	2,966 (never smokers)
Lozano *et al.* (2017)[41]	Longitudinal survey	The aim of this study was to evaluate if e-cigarette trial among Mexican youth who had not previously smoked cigarettes or used marijuana increased the likelihood of trial and use of conventional cigarettes or marijuana use at 20-month follow-up.	2015–2016	20 months	Mexico	(11–13) [analytic sample]	37%	10,435
Miech *et al.* (2017)[51]	Longitudinal survey	This study prospectively examined vaping as a predictor of future cigarette smoking among youth with and without previous cigarette smoking experience. A secondary aim is to investigate whether vaping may	2014–2015	13.4 months	USA	42% modal age 19 at follow-up	58%	347

Study ID	Study design	Objective	Years followed	Follow-up period	Country	Mean age (age range) or school grade baseline✞	Loss to follow-up	Baseline sample
		desensitise youth to the dangers of smoking.						
Morgenstern *et al.* (2018)[42]	Longitudinal survey	The aim of this study was to evaluate whether e-cigarette use in adolescence can increase the risk of conventional cigarette use.	2015–2016	6 months	Germany	15.61	7.3%	2,358
Spindle *et al.* (2017)[43]	Longitudinal survey	The present study examined the extent to which e-cigarette use among never cigarette smokers at time 1 of the study was predictive of cigarette smoking status at time 2 (one year later), while controlling for other relevant variables that independently may predict the uptake of cigarettes. A secondary purpose of this study was to examine if several factors previously predictive of the onset of cigarette smoking (anxiety, depression, peer deviance, stressful life events, impulsivity, and the use of other tobacco products and marijuana) predicted the onset of e-cigarette use among initial never users of either cigarettes or e-cigarettes.	2014–2015	1 year	USA	18.5 [analytic sample]	35%	5,779
Treur *et al.* (2018)[44]	Cohort study	The authors aimed to 1): investigate the prevalence and sociodemographic patterning of three major types of alternative tobacco (e-cigarettes with nicotine, e-cigarettes without nicotine and waterpipe) and 2): investigate the association between alternative tobacco	2014–2015	6 months	Netherlands	13.8 [complete sample]	69.3%	6,819

Study ID	Study design	Objective	Years followed	Follow-up period	Country	Mean age (age range) or school grade baseline✞	Loss to follow-up	Baseline sample
		and conventional smoking, cross-sectionally in the total sample and longitudinally in a subsample whereby we take adolescents' propensity to smoke into account.						
Wills *et al.* (2016)[45]	Longitudinal study	The authors tested the role of cognitive and social factors for mediating the relation between e-cigarette use and smoking onset.	2013–2014	1 year	USA	14.7 (14–16)	44.4%	1,984
Wills *et al.* (2017a)[46]	Longitudinal study	The authors tested whether the effect of e-cigarette use for smoking onset differs for youth who are lower versus higher on propensity to smoke.	2013–2014	1 year	USA	14.8	44.4%	1,984
Wills *et al.* (2017b)[47]	Longitudinal study	The authors primary aim was to test whether e-cigarette use is related to the onset of smoking; thus, among adolescents who had never smoked at time 1 (T1), we determined the likelihood of smoking at time 2 (T2) as a function of previous e-cigarette use. A second aim was to determine longitudinal predictors for e-cigarette uptake.	2013–2014	1 year	USA	14.7 (14–16)	44.4%	1,984
Best *et al.* (2018)[48]	Prospective cohort study	This study examined whether young never smokers in Scotland, UK who have tried an e-cigarette are more likely than those who have not, to try a cigarette during the following year.	2015–2016	1 year	Scotland	14.4 (11–18)	29.6%	3,001
Kinnunen *et al.* (2019)[49]	Longitudinal study	This longitudinal study explored whether nicotine and non-nicotine e-cigarette uses predict the daily use of two different	2014–2016	2.5 years	Finland	15–16	55.1%	7,738

Study ID	Study design	Objective	Years followed	Follow-up period	Country	Mean age (age range) or school grade baseline✞	Loss to follow-up	Baseline sample
		nicotine products, namely conventional cigarettes and nicotine e-cigarettes.						

✞ Grade is shown as a proxy for age when data on age were not provided.

3.2 Findings

3.2.1 Ever e-cigarette use/ever cigarette use

Fourteen papers (11 unique studies) explored the relationship between ever e-cigarette use at baseline and subsequent trial of cigarettes at follow-up. Most of these papers used regression models to produce adjusted odds ratios (AORs), including varying numbers of covariates, with all except Wills *et al.* (2016)[45] finding significant associations (Table 3).

In the USA, using data from the Children's Health Study, Barrington-Trimis *et al.* (2016)[34] measured ever use of cigarettes at a 16-month follow-up among baseline ever e-cigarette and cigarette users in two different models.[34] Both the model which included demographic covariates only (AOR: 6.17; 95% CI: 3.3–11.6), and the model which also included use of alternative tobacco products as covariates (AOR: 5.48; 95% CI: 2.69–11.2), found a significant positive association between ever use of e-cigarettes at baseline and initiating smoking cigarettes at follow-up.[34] Berry *et al.* (2019), using data from the USA PATH Study, produced a model which adjusted for all three domains of covariates, finding a significant positive association between ever e-cigarette use and initiating cigarette use during a 2-year follow-up (AOR: 4.09; 95% CI: 2.97–5.63).[37] Watkins *et al.* (2018) – who used the same cohort, although with data from a 12-month follow-up point – also found a significant positive association between ever e-cigarette use and initiating smoking cigarettes during follow-up (AOR: 2.53; 95% CI: 1.8–3.56).[38] Leventhal *et al.* (2015) explored the association at a 6-month and 12-month follow-up in a convenience sample based in California.[33] Using a model which adjusted for variables in all three domains and averaged across the two time points, they found a significant positive association (AOR: 1.75; 95% CI: 1.1–2.77).[33] Spindle *et al.* (2017), again using a sample population from the USA, also found a significant positive association between ever e-cigarette use and ever cigarette use (AOR: 3.37; 95% CI: 1.91–5.94). [43] One Hawaiian study, controlling for demographic and intrapersonal variables, also found a significant effect (AOR: 2.87; 95% CI: 2.03–4.05).[47] Wills *et al.* (2017a) explored the same relationship in the same sample, this time including propensity to smoke as a variable, and also found a significant positive association (estimate 0.8, SE 0.18).[46]

Wills *et al.* (2016), using the same Hawaiian sample as above, explored the mediating effect of social and cognitive factors on the relationship between e-cigarette use and subsequent cigarette use (Table 3).[45] Their autoregressive model showed that e-cigarette use was related to all the mediators (in particular marijuana use (r^2 = 0.51) and smoking expectancies (r^2 =0.4)) collected at the second time point, resulting in a non-significant direct positive effect between e-cigarette use and cigarette use, in a model which accounted for 34% of the variance (r^2 =0.34). In order to address temporal ambiguity, the authors also produced a model in which data for the mediators collected at the first time point were considered, which found a significant direct positive association between e-cigarette use and subsequent smoking (r^2 =0.18).[45] The discrepancies in these results demonstrate that more complex, or sophisticated, measures of confounders (including different data collection points) can alter causal interpretations.[54]

In the UK, Conner *et al.* (2018) explored associations between baseline e-cigarette use with ever cigarette use at a 12-month follow-up, adjusting for covariates across the three main domains.[39] They found that there was a significant difference between those who had used e-cigarettes and those who had not in terms of subsequent cigarette use (AOR: 4.06; 95% CI: 2.94–5.6).[39] East *et al.* (2018) also explored this relationship in the UK, although at a 4–6-month follow-up, controlling for variables across the three main domains, and found a significant positive association (AOR: 10.57; 95% CI: 3.33–33.5).[40] Similarly, Best *et al.* (2018), controlling for interpersonal and intrapersonal variables in a UK sample, also found a significant positive association at 1 year (AOR: 2.42; 95% CI: 1.63–3.6).[48]

Two studies analysed the relationship between baseline e-cigarette use with ever cigarette use using adjusted risk ratio (ARR) as outputs (Table 4). Lozano *et al.* (2017) explored the association between ever e-cigarette use at baseline and initiated ever cigarette use at a 20-month follow-up in Mexico.[41] Using a model which adjusted for variables in all three main domains, they found that the risk of cigarette use increased for e-cigarette users (ARR: 4.4; 95% CI: 1.22–1.6). Morgenstern *et al.* (2018) explored the association between ever use of e-cigarettes and subsequent cigarette use at a 6-month

follow-up in a German sample.[42] Controlling for demographic and intrapersonal variables, they also found a significant positive association (ARR: 2.18; 95% CI: 1.68–2.83).[42]

One Dutch study explored the relationship between both nicotine and non-nicotine e-cigarette use at baseline and subsequent use of cigarettes.[44] Adjusting for demographic and intrapersonal variables, the authors found a significant positive association between ever use of e-cigarettes with nicotine and subsequent cigarette use (AOR: 11.9; 95% CI: 3.36–42.12) and for ever use of e-cigarettes without nicotine (AOR: 5.36; 95% CI: 2.73–10.52).[44]

Table 3 AOR for ever e-cigarette and cigarette use among adolescents in the selected longitudinal cohort studies

Study ID	Outcome (cigarette)	Exposure (e-cigarette)	AOR	Lower 95% CI	Upper 95% CI	Covariates	Demographic	Interpersonal	Intrapersonal
Barrington-Trimis *et al.* (2016)[34]	Ever use	Ever use	6.17*	3.3	11.6	Gender; ethnicity; grade; highest parental education	Y	N	N
Barrington-Trimis *et al.* (2016)[34]	Ever use	Ever use	5.48*	2.69	11.2	Gender; ethnicity; grade; highest parental education; use of hookah; use of cigar; use of pipe	Y	N	Y
Berry *et al.* (2019)[37]	Ever use	Ever use	4.09*	2.97	5.63	Sex; age; race/ethnicity; parental education; urban or rural residence; living with tobacco user; noticing tobacco warnings; tobacco advertisement receptivity; ever alcohol use; ever marijuana use; prescription drug abuse; enjoying frightening things; liking new and exciting experiences; preferring unpredictable friends; willingness to smoke in next year; curiosity about cigarettes; susceptibility to cigarette peer pressure from friends	Y	Y	Y
Watkins *et al.* (2018)[38]	Ever use	Ever use	2.53*	1.8	3.56	Hookah use; non-combustible cigarettes; smokeless tobacco use; gender; age; race/ethnicity; parental education; urban residence; sensation seeking; ever used alcohol; living with tobacco user; notice of cigarette warning labels; tobacco advertising receptivity; summer season	Y	Y	Y
Conner *et al.* (2018)[39]	Initiation	Ever use	4.06*	2.94	5.6	Friend smokers; gender; family smokers; intention; attitudes; norms; perceived behavioural control; self-efficacy; free school meals	Y	Y	Y
East *et al.* (2018)[40]	Initiation	Ever use	10.57*	3.33	33.5	Age; gender; school performance; problem behaviour; monthly alcohol use; smoking susceptibility; e-cigarette susceptibility; some friends smoke; some friends use e-cigarettes; at least one parent smokes; at least one parent uses e-cigarettes; sibling(s) smoke; sibling(s) use e-cigarettes; public approve of smoking; public approval of e-cigarettes	Y	Y	Y

Study ID	Outcome (cigarette)	Exposure (e-cigarette)	AOR	Lower 95% CI	Upper 95% CI	Covariates	Demographic	Interpersonal	Intrapersonal
East *et al.* (2018)[40]	Initiation	Ever use	11.89*	3.56	39.72	Age; gender; school performance; problem behaviour; monthly alcohol use; smoking susceptibility; e-cigarette susceptibility; some friends smoke; some friends use e-cigarettes; at least one parent smokes; at least one parent uses e-cigarettes; sibling(s) smoke; sibling(s) use e-cigarettes; public approve of smoking; public approval of e-cigarettes; follow-up e-cigarette use			
Leventhal *et al.* (2015)[33]	Ever use	Ever use	1.75*	1.1	2.77	Gender; ethnicity; living with biological parents; substance use; family history of smoking; age; parental education; peer smoking; scale for depressive symptoms; subscale for impulsivity; delinquent behaviour; smoking susceptibility; smoking expectancies; time; ever e-cigarette use by time	Y	Y	Y
Spindle *et al.* (2017)[43]	Ever use	Ever use	3.37*	1.91	5.94	Gender; age; ethnicity; depression; anxiety; negative urgency; positive urgency; lack of premeditation; lack of perseverance; sensation seeking; stressful life events; peer deviance; other tobacco use	Y	Y	Y
Treur *et al.* (2018)[44]	Ever use	Ever use of nicotine e-cigarette	11.9*	3.36	42.11	Sex; age; educational level; propensity to smoke; interaction	Y	N	Y
Treur *et al.* (2018)[44]	Ever use	Ever use of non-nicotine e-cigarette	5.36*	2.73	10.52				
Wills *et al.* (2017b)[47]	Ever use	Ever use	2.87*	2.03	4.05	Age; gender; ethnicity; parental education; parental support; rebelliousness	Y	N	Y
Best *et al.* (2018)[48]	Ever use	Ever use	5.97*	3.12	11.40	Sex; age; family affluence scale; ethnic group; school; susceptibility to smoking at baseline; any family member smokes at baseline; at least some friends smoke at baseline; interactions between e-cigarettes and susceptibility; interactions between e-cigarettes and friends smoking	Y	Y	Y

* Statistically significant at the level determined by the study.

Table 4 Ever use of e-cigarettes and cigarettes among adolescents in the selected longitudinal cohort studies using statistical measures such as ARR, estimates, or standardised coefficient

Study ID	Outcome (cigarette)	Exposure (e-cigarette)	ARR	Lower 95% CI	Upper 95% CI	Standardised coefficient	Estimate (SE)	Covariates	Demographic	Interpersonal	Intrapersonal
Lozano *et al.* (2017)[41]	Ever use	Ever use	1.4*	1.22	1.6			Sex; age; parents' socioeconomic status (SES); sensation seeking; friends that smoke; parents that smoke; siblings that smoke; tried alcohol; binge drinking; Internet tobacco product advertising	Y	Y	Y
Morgenstern *et al.* (2018)[42]	Ever use	Ever use	2.18*	1.68	2.83			Sex; age; federal state; school type; migration background; school-leaving qualification of parents; SES; sensation seeking; impulsivity; anxiety; sensitivity; hopelessness; extraversion; agreeableness; conscientiousness; neuroticism; openness; ever e-cigarettes use; ever alcohol use; ever binge drinking; ever cannabis use; ever other illegal drugs use	Y	N	Y
Wills *et al.* (2016)[45]	Ever use	Ever use				.08¥		Smoker prototypes; smoking expectancies; peer smoker affiliations; marijuana score; gender; ethnicity; family structure; parental education	Y	Y	Y

Wills *et al.* (2016)[45]	Ever use	Ever use	0.18*		Gender; ethnicity; family structure; parental education	Y	N	N
Wills *et al.* (2017a)[46]	Initiation	Ever use		0.8 (0.18)*	Gender; ethnicity; father education; propensity to smoke; e-cigarette use by propensity	Y	N	Y

*Statistically significant at the level determined by the study. ¥ Non-significant results at the level determined by the study.

3.2.1.1 Meta-analysis

In order to ascertain whether a meta-analysis was feasible, or indeed appropriate, a feasibility analysis was conducted, taking outcome, exposure, unit of measurement, and length of time to follow-up into account as they employed the same method of analysis. Based on these criteria, nine studies with 16,808 participants were considered eligible for meta-analysis. Appendix 3 presents the full feasibility analysis. Several subgroup and sensitivity analyses were conducted to assess the influence of issues (such as quality, control for covariates, time to follow-up, study location and data collection year) raised in the feasibility assessment, as described below.

Using the 'Metagen' package,[23 24] we conducted a meta-analysis on studies which explored the association between ever use of e-cigarettes at baseline and ever use of cigarettes at follow-up, in cigarette-naive adolescents at baseline (Figure 3).

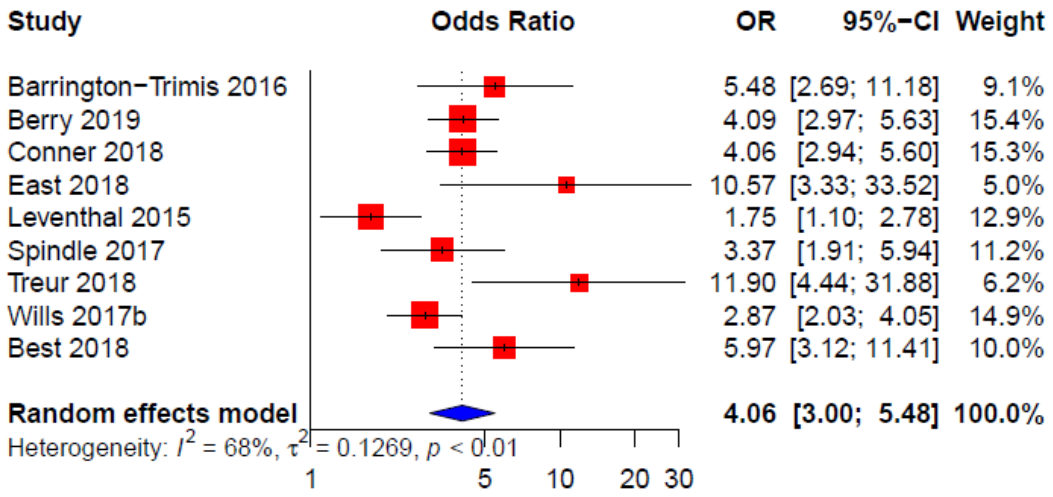


Figure 3 Meta-analysis results, using individual study AOR, for association between ever e-cigarette use and subsequent smoking

The meta-analysis displays a statistically significant positive effect on ever e-cigarette use and subsequent smoking (AOR: 4.06; 95% CI: 3–5.48; I^2: 68%), using AORs in a random effects model, which estimates different, yet related, intervention effects (see Appendix 3 for a meta-analysis of crude or unadjusted odds ratios). A random effects analysis allows us to address statistical heterogeneity that cannot be readily explained by other factors.[19]. The I^2 of 68% indicates that there is moderate to high statistical heterogeneity between studies. In examining the model, it is apparent that East *et al.*, Treur *et al.* and Leventhal *et al.* are outliers in the group. [33 40 44] This may be explained, in part, by the fact that East *et al.* had very small numbers in the exposed group, [40] Treur *et al.* examined e-cigarettes with nicotine specifically and the number in the exposed group is unknown,[44] and Leventhal *et al.* used a convenience sample [33]

3.2.1.2 Sensitivity analysis

In addition to the main analysis, two sensitivity analyses were conducted; one to assess the impact of the low-quality studies on the overall result, and one to assess the impact of the studies which did not control for the three confounder categories (demographic, intrapersonal, and interpersonal factors) in the regression models results.

Four studies were deemed to be of 'high quality', answering 'yes' to at least three of the four bulleted questions listed below, and thus indicating a high-quality study design.[37 43 47 48] A question addressing the inclusion of confounding variables was not included, as this was accounted for in the second sensitivity analysis.

- Were all subjects selected or recruited from the same or similar populations (including same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
- Was the participation rate of eligible persons at least 50%?
- Was loss to follow-up 20% or less?
- Was a sample size justification, power description, or variance and effect estimates provided? This final question was weighted more heavily, as any study which answered 'no' to this question was excluded from the meta-analysis subgroup. [18]

Four studies[37 43 47 48] were included in the meta-analysis for high-quality studies, and the AOR was 3.71 (95% CI: 2.83–4.86; I^2 35%), which represents a reduced AOR, with narrower CIs, once the lower-quality studies are removed. Of note, the level of statistical heterogeneity is almost halved at 35%, indicating low to moderate statistical heterogeneity which may be explained by representative sampling and adequate sample sizes. A further sensitivity analysis was conducted on the six studies[33 37 39 40 43 48] which appropriately controlled for the three domains of covariates – that is, demographic, interpersonal, and intrapersonal factors. The results of this analysis (AOR: 3.82; 95% CI: 2.66–5.48; I^2 69%) were very similar to the results for the high-quality studies assessment, but the level of heterogeneity remains moderate to high.

3.2.1.3 Subgroup analyses

In addition to the sensitivity analyses, three subgroup analyses were conducted. The first considered studies which collected data pre-2014[33 37 47]in comparison with those which collected their initial data post-2014,[34 39 40 43 44 48] due to the increase in e-cigarette use that was observed around this time.[55] As seen in Table 5, the AOR for studies which collected data from 2014 onwards increased substantially.

Table 5 Subgroup analyses of data collected pre- and post-2014

Subgroup	AOR	Lower 95% CI	Upper 95% CI
Pre-2014	2.81	2.45	3.72
Post-2014	5.16	3.69	7.21

The second subgroup analysis considered the length of time to follow-up, as studies included in the analyses had follow-up periods which ranged from 4 months to 2 years. However, as only two studies had follow-up periods of less than 1 year,[40 44] including one study which had a very small sample size, the meta-analysis did not provide meaningful results.

Finally, given the importance of the context of these studies (including social norms, regulatory environment, etc.), we conducted a subgroup analysis of the European studies as compared with the studies from the USA. As seen in Table 6, the AOR is higher in the European studies [39 40 44 48] as compared with the USA studies. [33 34 37 43 47] However the confidence intervals overlap.

Table 6 Subgroup analyses of data collected from the USA and Europe

Subgroup	AOR	Lower 95% CI	Upper 95% CI
USA studies	3.18	2.26	4.47
European studies	6.22	3.73	10.38

3.2.1.4 Population attributable fraction

We calculated the population attributable fraction (PAF) for the high-quality studies included in the main meta-analysis. The PAF is the excess risk of disease in the study population due to the presence

of the exposure (in this case e-cigarettes). It is used to assess the public health impact of the exposure (e-cigarettes) on conventional cigarette use. It is the percentage of cigarette smoking among the study population that used e-cigarettes that could be prevented if e-cigarettes were removed.[26] In order to calculate the fraction for the included studies in this report, the following steps were taken:

1. Used four high-quality studies,
2. Converted AORs to risk ratios (RRs),[27] and
3. Calculated PAF using RRs [26 28]

Table 7 PAF for four studies

Study ID	Country	AOR	RR	PAF
Berry (2019)[37]	USA	4.09	3.66	14.89%
Spindle (2017)[43]	USA	3.37	2.69	18.48%
Wills (2017b)[47]	USA	2.87	2.61	12.04%
Best (2018)[48]	UK	5.97	3.65	29.35%

Table 7 shows that in the USA studies, between 12% and 18% of conventional smoking is attributable to e-cigarette smoking, while in the one UK study, this increases to 29% population attributable risk. However, it must be noted that there are limitations to the method used in this analysis,[27] particularly the fact that the incidence rate used in the calculation is not adjusted, and as such, these results should be interpreted with caution[29 30]

3.2.2 Past-30-day e-cigarette use

Four studies examined the impact of past-30-day e-cigarette use at baseline and subsequent cigarette smoking at follow-up (Table 8). Using an adjusted model (including covariates from two of the three main domains), Hammond *et al.* (in a Canadian sample) found that those who had smoked e-cigarettes in the past 30 days at baseline were more likely to have initiated smoking cigarettes at follow-up (AOR: 2.12; 95% CI: 1.68–2.66).[50] Watkins *et al.* conducted their analysis using two separate models, adjusting for different amounts of covariates in each, also finding a positive association between past-30-day e-cigarette use and conventional cigarette use (AOR: 3.61; 95% CI: 1.82–7.16 with 3 covariates, and AOR: 2.65; 95% CI: 1.38–5.1 with 14 covariates).[38] Miech *et al.* also explored the association between those who had recently vaped (past 30-day use) and cigarette use at a follow-up (13.4 months later) in a USA sample (Table 9).[51] Controlling for demographic and intrapersonal variables, they found a significant positive association between vaping and smoking (ARR: 4.78; 95% CI: 1.91–11.96).[51] Finally, Spindle *et al.* (again in a USA sample), using a model which controlled for three of the main variable domains, also found a significant positive association between past-30-day e-cigarette use and ever cigarette use (OR: 3.41; 95% CI: 1.57–7.41).[43]

A meta-analysis was conducted, including 30,018 participants from three of four studies measuring past-30-day e-cigarette use at baseline, and found a significant positive association between past-30-day e-cigarette use at baseline and subsequent cigarette smoking initiation at follow-up (AOR: 2.14; 95% CI: 1.75–2.62; I^2 0%).[38 43 50]The forest plot is presented in Appendix 3.

3.2.3 Past-30-day cigarette use

Four papers (three unique studies) explored the association between e-cigarette use and past-30-day cigarette use (Table 8). Berry *et al.* used a model which adjusted for all three domains of covariates in a USA sample (the PATH Study) and found a significant positive association between e-cigarette use and past-30-day cigarette use at the 24-month follow-up point (AOR: 2.75; 95% CI: 1.6–4.73).[37] Watkins *et al.* used the same cohort, although with data from a 12-month follow-up point, to investigate the relationship between different categories of e-cigarette use and cigarette use at

follow-up, using one model which adjusted only for alternative tobacco products and one model which adjusted for covariates in all three domains.[38] E-cigarette use at baseline was associated with past-30-day cigarette use at follow-up (AOR: 2.39; 95% CI: 1.42–4.00 with 3 covariates, and AOR: 1.87; 95% CI: 1.15–3.05 with 14 covariates).[38] Spindle *et al.*, using a sample from the USA, explored the associations between ever and past-30-day e-cigarette use with ever and past-30-day cigarette use at follow-up.[43] Using a model which controlled for three covariate domains, they found a significant positive association between ever e-cigarette use and current (past-30-day) cigarette use (AOR: 3.3; 95% CI: 1.2–9.05).[43]

Lozano *et al.*[41] explored the association between ever e-cigarettes at baseline and past-30-day cigarette use at a 20-month follow-up in Mexico (Table 9). Using a model which adjusted for variables in all three covariate domains, they found a non-significant increase among e-cigarette users in cigarette use in the past 30 days (ARR: 1.43; 95% CI: 0.94–2.16).[41]

3.2.4 Past-30-day e-cigarette and past-30-day cigarette use

Two studies explored the association between past-30-day e-cigarette use and past-30-day cigarette use (Table 8). Spindle *et al.*, using a sample from the USA, found that the association between past-30-day e-cigarette use and past-30-day cigarette use was not significant (OR: 1.15; 95% CI: 0.15–9.06).[43] Similarly, Watkins *et al.*, using data from the USA PATH Study, found no association for 3 covariates (AOR: 2.48; 95% CI: 0.91–6.78) or for 14 covariates (AOR: 2.08; 95% CI: 0.81–5.4).[38]

3.2.5 Frequency of e-cigarette and cigarette use

Five studies explored the association between baseline e-cigarette use and frequency of subsequent smoking at follow-up (Table 8). Hammond *et al.*[50] and Kinnunen *et al.*[49] analysed the relationship between e-cigarette use at baseline and daily cigarette use, Hammond *et al.* at a 1-year follow-up, and Kinnunen *et al.* at a 2.5-year follow-up, both adjusting for demographic and intrapersonal variables.[49 50] Hammond *et al.* found a significant positive association between baseline past-30-day e-cigarette use and daily smoking initiation (AOR: 1.79; 95% CI: 1.41–2.28),[50] while Kinnunen *et al.* found a significant positive association between ever use of nicotine e-cigarettes and daily smoking (AOR: 2.92; 95% CI: 1.09–7.85) but no association between ever use of non-nicotine e-cigarettes and daily smoking (AOR: 0.94; 95%CI 0.22-4.08).[49]

Barrington-Trimis *et al.*, using three cohort studies in California and Connecticut, explored the association between ever e-cigarette users at baseline and cigarette use (to varying degrees) at follow-up. They examined those who subsequently experimented with cigarettes (AOR: 4.57; 95% CI: 3.56–5.87), those who were infrequent users of cigarettes (AOR: 4.27; 95% CI: 2.5–6.62), and those who frequently used cigarettes (AOR: 3.51; 95% CI: 1.97–6.24), controlling for demographic variables only; all findings demonstrated an increased likelihood of cigarette smoking.[35]

Wills *et al.* explored the impact of different frequencies of e-cigarette use at baseline on smoking onset at follow-up.[47] They found significant positive associations for one to two times e-cigarette ever use (OR: 2.88; 95% CI: 1.96–4.22), for three to four times e-cigarette use (OR: 2.29; 95% CI: 1.35–3.87), for yearly/monthly use (OR: 4.17; 95% CI: 2.03–8.57), and for weekly/daily e-cigarette use (OR: 4.09; 95% CI: 2.43–6.88).[47] Leventhal *et al.*, using a USA convenience sample, explored associations across different frequencies of e-cigarette use at baseline and cigarette use at follow-up.[52] They found a positive association between baseline vaping and follow-up smoking frequency (AOR: 2.51; 95% CI: 2.30–2.75), controlling for covariates in the three main domains.

3.2.6 Nicotine versus non-nicotine e-cigarettes

Two studies explored the specific impact of nicotine versus non-nicotine e-cigarettes on subsequent conventional cigarette use (Table 8). Adjusting for demographic and intrapersonal variables, one Dutch study found a significant positive association between ever use of e-cigarettes with nicotine and subsequent cigarette use (OR: 11.9; 95% CI: 3.36–42.12) and to a lesser extent between ever use of e-cigarettes without nicotine and subsequent cigarette use (OR: 5.36; 95% CI: 2.73–10.52).[44] Kinnunen *et al.* explored the association between ever trying either nicotine or non-nicotine e-cigarettes at baseline and daily smoking at a 2.5-year follow-up in a Finnish sample.[49] Using a model

which controlled for demographic and intrapersonal variables, they found a positive significant association between ever use of nicotine e-cigarettes and daily smoking (OR: 2.92; 95% CI: 1.09–7.85) but no association between ever use of non-nicotine e-cigarettes and daily smoking (OR: 0.94; 95% CI: 0.22–4.08).[49]

Table 8 AORs for different frequencies of e-cigarette and cigarette use among adolescents in the selected longitudinal cohort studies

Study ID	Outcome (cigarette)	Exposure (e-cigarette)	AOR	Lower 95% CI	Upper 95% CI	Covariates	Demographic	Interpersonal	Intrapersonal
Hammond *et al.* (2017)[50]	Initiation	Past-30-day use	2.12*	1.68	2.66	Schools; age; sex; race/ethnicity; spending money; smoking status	Y	Y	N
Hammond *et al.* (2017)[50]	Daily smoking initiation	Past-30-day use	1.79*	1.41	2.28				
Barrington-Trimis *et al.* (2018a)[35]	Experimented	Ever use	4.57*	3.56	5.87				
Barrington-Trimis *et al.* (2018a)[35]	Infrequent	Ever use	4.27*	2.75	6.62	Sex; race and/or ethnicity; grade; study (e.g. cohort 1, 2 or 3)	Y	N	N
Barrington-Trimis *et al.* (2018a)[35]	Frequent	Ever use	3.51*	1.97	6.24				
Berry *et al.* (2019)[37]	Past-30-day use	Ever use	2.75*	1.6	4.73	Sex; age; race/ethnicity; parental education; urban or rural residence; living with tobacco user; noticing tobacco warnings; tobacco advertisement receptivity; ever alcohol use; ever marijuana use; prescription drug abuse; enjoying frightening things; liking new and exciting experiences; preferring unpredictable friends; willingness to smoke in next year; curiosity about cigarettes; susceptibility to cigarette peer pressure from friends	Y	Y	Y
Watkins *et al.* (2018)[38]	Ever use	Former use	2.58*	1.77	3.761	Hookah use; non-combustible cigarette use; smokeless tobacco use; gender; age; race/ethnicity; parental education; urban residence; sensation seeking; ever alcohol use; living with tobacco user; notice of cigarette warning labels; tobacco advertising receptivity; summer season	Y	Y	Y
Watkins *et al.* (2018)[38]	Ever use	Past-30-day use	1.87*	1.15	3.05				
Watkins *et al.* (2018)[38]	Past-30-day use	Ever use	2.65*	1.38	5.10				

Study ID	Outcome (cigarette)	Exposure (e-cigarette)	AOR	Lower 95% CI	Upper 95% CI	Covariates	Demographic	Interpersonal	Intrapersonal
Watkins *et al.* (2018)[38]	Past-30-day use	Former use	1.84*	1.07	3.15				
Watkins *et al.* (2018)[38]	Past-30-day use	Past-30-day use	2.08¥	0.81	5.4				
Leventhal *et al.* (2016)[52]	Smoking frequency	Ever use	2.51*	2.3	2.75	Age; sex; ethnicity; highest parental education; whether student lived with both parents; ever use of alcohol or drugs; ever use of combustible tobacco product; family history of smoking; depressive symptoms; impulsivity: lack of premeditation; impulsivity: sensation seeking; delinquent behaviour; peer smoking; smoking susceptibility; smoking expectancies	Y	Y	Y
Spindle *et al.* (2017)[43]	Ever use	Past-30-day use	3.41*	1.57	7.41	Gender; age; ethnicity; depression; anxiety; negative urgency; positive urgency; lack of premeditation; lack of perseverance; sensation seeking; stressful life events; peer deviance; other tobacco use	Y	Y	Y
Spindle *et al.* (2017)[43]	Past-30-day use	Ever use	3.3*	1.2	9.05				
Spindle *et al.* (2017)[43]	Past-30-day use	Past-30-day use	1.15¥	0.15	9.06				
Wills *et al.* (2017b)[47]	Ever use	Use 1–2 times	2.88*	1.96	4.22	Age; gender; ethnicity; parental education; parental support; rebelliousness	Y	N	Y
Wills *et al.* (2017b)[47]	Ever use	Use 3–4 times	2.29*	1.35	3.87				
Wills *et al.* (2017b)[47]	Ever use	Use yearly/monthly	4.17*	2.03	8.57				
Wills *et al.* (2017b)[47]	Ever use	Use weekly/daily	4.09*	2.43	6.88				
Kinnunen *et al.* (2019)[49]	Daily smoking	Ever use non-nicotine e-cigarettes	0.94¥	0.22	4.08	Gender; socioeconomic background (measured by parental background); other tobacco product use; school clustering	Y	N	Y

Study ID	Outcome (cigarette)	Exposure (e-cigarette)	AOR	Lower 95% CI	Upper 95% CI	Covariates	Demographic	Interpersonal	Intrapersonal
Kinnunen *et al.* (2019)[49]	Daily smoking	Ever use nicotine e-cigarettes	2.92*	1.09	7.85				

*Statistically significant at the level determined by the study. ¥ Non-significant results at the level determined by the study.

Table 9 ARRs for different frequencies of e-cigarette and cigarette use

Study ID	Outcome (cigarette)	Exposure (e-cigarette)	ARR	Lower 95% CI	Upper 95% CI	Covariates	Demographic	Interpersonal	Intrapersonal
Lozano *et al.* (2017)[41]	Past-30-day use	Ever use	1.43¥	0.94	2.16	Sex; age; parent SES; sensation seeking; friends that smoke; parents that smoke; siblings that smoke; tried alcohol; binge drinking; Internet tobacco product advertising	Y	Y	Y
Miech *et al.* (2017)[51]	Ever use	Past-30-day use	4.78*	1.91	11.96	Binge drinking in last 30 days [baseline]; marijuana used in last 30 days [baseline]; female; non-white	Y	N	Y

*Statistically significant at the level determined by the study.

¥ Non-significant results at the level determined by the study.

4 Discussion

4.1 Summary findings

The most commonly explored association among the included studies was between ever e-cigarette use and subsequent use of cigarettes. All studies which explored this relationship, other than Wills *et al,*[45] found that there was a significant positive association between ever using an e-cigarette at baseline and ever using a cigarette at follow-up. Our meta-analysis which included 9 of the 14 unique studies and was based on primary study adjusted odds ratios, found that the combined odds of trying smoking were 4.06 times higher for those who had ever used e-cigarettes at baseline, although this was reduced slightly (to 3.71 times the odds) when only the high-quality studies were included. The main meta-analysis indicated that the model had a moderate to high statistical heterogeneity; however, a sensitivity analysis of only high-quality studies had low to moderate statistical heterogeneity with a slightly reduced combined OR. Using the formula proposed by Zhang and Yu (1998),[27] an approximation of an adjusted relative risk [risk ratio] was calculated for the four high-quality studies.[37 43 47 48] This resulted in a range of values for the PAF, indicating that between 12% and 29% of those in the four studies who had tried a cigarette had done so due to their initial use of e-cigarettes. In other words, if e-cigarettes did not exist, there would have been between 12% and 29% fewer adolescent smokers. However, it must be noted that there are limitations to this method, in particular the fact that the incidence rate used in the calculation is not adjusted, and as such, these results should be interpreted with caution.[29 30] Subgroup analyses of these studies revealed a higher OR for the data collected after 2014, a time point at which e-cigarette use increased substantially,[10] as well as for the data collected in Europe (as compared with the USA).

Based on primary study adjusted odds ratios, four studies examined the relationship between past-30-day e-cigarette use and initiating cigarette use also found a significant positive association, although with a lower combined OR than ever trying e-cigarettes; indeed, a meta-analysis of three of these studies found that e-cigarette users had 2.14 times the combined odds of cigarette smoking compared with non-e-cigarette users. Three studies measured the association between ever e-cigarette use and past-30-day cigarette use, with significant positive associations in the USA samples[37 38 43] but no association in a Mexican sample.[41] Neither study which measured past-30-day use of e-cigarettes and subsequent past-30-day cigarette use found a significant positive association.[43 38]

Different patterns of use and frequency of use of both e-cigarettes and cigarettes retained significant positive associations. One USA study found significant positive associations between e-cigarettes and 'experimenters', infrequent and frequent users of cigarettes.[35] In the inverse, two USA studies examined different frequencies of e-cigarette use at baseline on ever cigarette use at follow-up and found significant positive associations between all variations of e-cigarette use and subsequent smoking.[47 52] Two studies which examined the relationship between e-cigarette use and daily cigarette use found a significant positive association, [49 50] although this relationship was non-significant when non-nicotine e-cigarettes were examined.[49]

Two studies explored the specific impact of nicotine versus non-nicotine e-cigarettes on subsequent conventional cigarette use.[44 49] One study which measured ever e-cigarette use and ever smoking found a significant positive association between ever use of e-cigarettes with nicotine and subsequent cigarette use, and between ever use of e-cigarettes without nicotine and subsequent cigarette use, although to a lesser extent.[44] However, a study which explored the impact of nicotine versus non-nicotine e-cigarettes on daily smoking found a significant positive association with nicotine e-cigarettes, but no association between non-nicotine e-cigarettes and daily smoking.[49]

We assigned a level of evidence of 3 using *British Medical Journal* guidelines,[31] as this is a systematic review of cohort studies, some of which had high loss to follow-up and/or very small sample sizes. However, with respect to certainty of evidence,[32] the HRB authors have moderate confidence that the true effect is probably close to the estimated effect for trying smoking at follow-up for those who had ever used e-cigarettes at baseline, as all meta-analyses indicate that there is a significant positive association between using e-cigarettes at baseline and smoking cigarettes at follow-up, and this effect size is quite large; the findings are statistically significant, consistent and the exposure occurred before the outcome. Six studies controlled for confounding under three domains (demographic, interpersonal, and intrapersonal) associated with smoking cigarettes, and had a similar, but tighter, significant estimate of effect in meta-analysis. The four high-quality studies also had a similar and tighter estimate of effect and lower statistical heterogeneity. The remainder of the studies were judged to be moderate quality because of their small sample sizes and/or high loss to follow-up. The findings of the HRB meta-analysis are consistent with two earlier meta-analyses by Soneji *et al.* [56] and Aladeokin *et al*.[57]

4.2 Comparison with previous research

4.2.1 Comparison with other systematic reviews

A previous systematic review and meta-analysis, conducted in 2017, also examined the association between initial use of e-cigarettes and subsequent smoking.[56] Although this study investigated both adolescents and young adults (with an age range of 14–30 years), many of the studies investigated were similar to the ones in the present review, albeit without the more recently published papers. Similarly to the HRB review, Soneji *et al.* found that e-cigarette use is associated with an increased risk of future cigarette smoking initiation and current cigarette smoking, even after adjusting for potential confounding by demographic, psychosocial and behavioural risk factors (AOR: 3.5; 95% CI: 2.38–5.16; I^2 56%). The Soneji *et al.* meta-analysis included seven studies, whereas the HRB meta-analysis included nine studies[56]. We did not include three of the studies from the Soneji *et al.* meta-analysis. Miech *et al.* was not included in this meta-analysis because the data were analysed using RR and an ARR, and we could not convert the ARR to an AOR.[51] The two Primack studies were excluded because their respondents' average age exceeded 19 years. The results also correspond to a more recent meta-analysis which found a significant positive association between e-cigarette use and subsequent smoking in a UK context only.[57] Although we focused on adolescents only, other studies have found this positive association in older age groups such as Primack *et al.* and Unger *et al.* described in the meta-analysis by Soneji *et al*.[56] A narrative review conducted by Glasser *et al*. (2019) concluded that while e-cigarette use is associated with subsequent smoking, it is difficult to draw strong conclusions because of methodological limitations, and urged future research to address vulnerabilities in young people which may explain the relationship.[25] The World Health Organization based on the Academies of Sciences systematic narrative review reported that there is moderate evidence that young never-smokers who experiment with electronic cigarettes are at least twice more likely to experiment with smoking later.[58]

4.2.2 Public health considerations with respect to e-cigarette use

Soneji *et al.,* in their systematic review, suggested that in order to minimise the potential public health harm from e-cigarette use, regulatory authorities and public health agencies need to enforce age limitations when buying e-cigarettes, place restrictions on advertising campaigns that may be viewed by adolescents, limit characterising flavours, and report nicotine content in e-liquid.[56] Aladeokin and Haighton suggested that public health policy makers in the UK still need clear conclusions about the effects and safety of e-cigarettes.[57] The EU has developed regulations to address e-cigarette manufacture, presentation and sales under the Tobacco Products Directive (2014/40/EU).[59] The Directive lays down rules prohibiting sales to persons under 18 years. In addition, Article 20 of the new regulations prohibit promotional elements on e-cigarette packaging, and cross-border advertising and promotion of e-cigarettes, sets limits on maximum concentrations of nicotine in liquids, limits maximum volumes of liquid that can be sold in a single container, requires childproof and tamper-proof packaging of liquid, sets requirements on purity of ingredients, requires that the devices deliver consistent doses of vapour, requires disclosure of ingredients and nicotine content, and allows member state regulators to act if the regulations are violated. In addition, warning labels can be placed on e-cigarettes. However, the regulations do not ban vaping in public places.[59] Ireland are in the process of implementing the European regulations. A population health approach, similar to that successfully used in Ireland to address tobacco, alcohol and psychoactive drug issues may need to be extended to tackle use of e-cigarettes; a population health approach to psychoactive substances usually involves addressing price, availability, and marketing to limit use among young and vulnerable populations. Kennedy *et al*. reviewed the global approaches to regulating e-cigarettes and found that 22 countries regulate e-cigarettes using existing regulations, 7 countries made amendments to existing legislation, and 14 countries use a combination of new/amended and existing regulation. In addition, 25 countries enacted new policies to regulate e-cigarettes.[60] Kennedy *et al.* identified several regulation domains including product prohibitions or restrictions related to e-cigarette manufacturing, distribution, importation, sale and minimum age of purchase; They also identified use restrictions on use including vape-free public places. They identified that a number of countries prohibited or restricted advertising, promotion, and/or sponsorship.[60] Some countries introduced taxation of e-cigarettes to increase price or affordability. Some countries introduced requirements such as health warning labelling, listing of ingredients including flavours, listing nicotine volume/concentration, reporting of adverse events associated with e-cigarettes and their liquids, and the introduction of child-safety packaging. Kennedy *et al.* also found that e-cigarettes were banned in 25 countries and market authorisation was required in 17 other countries.[60] The authors go on to say that minimum age-of-purchase policies was common in countries permitting the sale of e-cigarettes (with the age of purchase ranging between the age of 18 and 21 years). E-cigarette use was banned in enclosed

public spaces such as bars, restaurants and other workplaces in 25 countries. Advertising and promoting e-cigarettes were banned in 35 countries.[60]

Kennedy *et al.* identified 14 countries that required e-cigarettes to have health warning labels, and 13 that regulated ingredients and flavours that were to be used in e-cigarettes.[60] In 14 countries, nicotine concentrations did not exceed 20 mg/mL of e-liquid. Child-safety standards for e-cigarettes and/or e-liquid bottles were required in 11 countries. Regulations on importation of e-cigarettes were in place in 14 countries. Manufacturing standards for e-cigarettes marketed as medicines were required in 13 countries.[60] The distribution of e-cigarettes marketed as medicines was regulated in 21 countries. Manufacturers/retailers are required to notify the appropriate authority prior to marketing e-cigarettes in 13 countries. Specific safety standards were required for e-cigarettes or e-liquids in 26 countries. Venezuela prohibited the registration of e-cigarettes as a brand/patent. Six countries applied a tax to e-cigarettes. The list of regulatory options identified by Kennedy *et al.* provides policy makers with a broad menu of possibilities.[60]

4.3 Theoretical implications

It is clear from the above results that there is a strong positive association between e-cigarette use and subsequent cigarette trial; however, it is not clear what is driving this association. One commonly proposed explanation is the 'gateway theory', which was developed by Denise Kandel in the 1970s as a hypothesis to explain the observed phenomenon of young people's use of alcohol and drugs in specific stages and sequences.[61] The theory has been developed since then, most recently exploring the effects of nicotine on the brains of mice, and had been applied to the e-cigarette debate:

> "Our findings also provide initial biologic insights that may help inform the current debate about electronic cigarettes, which have been promoted as a tool to stop smoking and reduce the harmful effects of combustible tobacco use in the population. Although e-cigarettes eliminate some of the morbidity associated with combustible tobacco, they and related products are pure nicotine-delivery devices. They have the same effects on the brain as those reported here for nicotine, …and they pose the same risk of addiction to other drugs and experiences. [1(p7-8)]"

However, the gateway theory has received criticism, both in general and in relation to e-cigarettes.[62 63] A commonly reported refrain from detractors of the gateway theory is that it is difficult to test.[63] Etter states that Hill's (1945) nine aspects of causality need to be employed in order to decide whether an association is causal: 1) strength of the association; 2) consistency (across trials, investigators, individuals, research methods, replications); 3) specificity (can other things cause it?); 4) temporal precedence (do we know if cause precedes effect?); 5) dose responsivity; 6) plausibility (biological and psychological); 7) coherence (consistent with other lines of evidence); 8) experiment; and 9) analogy (do similar agents act similarly?).[63]

In order to try to explore the roots of causality, Etter recommends large longitudinal epidemiological studies which measure smoking onset, control for confounders, and include a propensity score measure of liability to smoking. Many of the studies included in this review are designed as such; indeed, some (such as Treur *et al.*[44]) have explicitly addressed Etter's suggestions of study characteristics that are needed to provide evidence for this theory.[44 63] Others, such as Berry *et al*.,[37] have demonstrated that propensity for risk is unlikely to be the sole reason for initiation in this gateway, as the association in their study was especially pronounced in the low-risk group. Some studies have evaluated other aspects, such as dose responsivity. Wills *et al*.[47] and Leventhal *et al*.[52] provided some evidence for different frequencies of vaping at baseline, but this result needs to be further explored. The study design used to assess the relationship between e-cigarette use and initiation of cigarette smoking does not allow us to say there is a definitive causal relationship but it does allow us to say that the findings build a case towards a causal relationship as the findings are consistent across all studies included in the meta-analysis. Furthermore, the strength of association is statistically significant across all primary research studies. In addition, the use of e-

cigarettes occurred before initiating smoking fulfilling the criteria for a temporal relationship and two studies have examined the dose response relationship.

Whether there are other additional explanatory factors or not, we need to understand what drives the relationship between e-cigarette and tobacco cigarette use and if the effect is definitively causal. Critics of the gateway theory often propose the common liability theory, which states that there is an underlying common liability within people which increases their propensity to use drugs. [64-67] Despite this, one strong argument against the common liability theory is that some studies have shown that young people with typically low risk of initiating smoking have reported the strongest association between e-cigarette use and subsequent smoking. Indeed, studies included in this review have found this; for example, Morgenstern *et al*. found, in a German sample, that the association between e-cigarettes and subsequent smoking initiation was stronger among adolescents with low sensation-seeking scores and without any experience of alcohol intoxication.[42] Similarly, in a Canadian sample, Aleyan *et al*.[53] found that the relationship between e-cigarette use and subsequent smoking was stronger among non-susceptible young people than susceptible young people – a result that mirrored Barrington-Trimis *et al.*'s (2016)[34] finding that associations were stronger in adolescents with no intention of smoking at initial evaluation. Berry *et al*. also found that the association of prior e-cigarette use with cigarette initiation was stronger among low-risk youths, and Wills *et al*. (2017a) found that the relation between e-cigarette use at one time point and smoking onset at a subsequent time point was stronger among participants with lower levels of rebelliousness and willingness and higher levels of parental support.[37 46] Conner *et al*. (2018) found that the association between ever use of e-cigarettes and initiation of cigarette use was particularly strong among adolescents with no friends who smoked, a group usually considered to be less susceptible to smoking initiation.[39] Furthermore, Miech *et al*. found that among never-smokers at baseline, recent vapers were more than four times more likely to move away from the perception of cigarettes as posing a 'great risk' of harm, a finding consistent with a desensitisation process.[51] These findings are concerning, as they highlight the risk that e-cigarettes, and subsequently cigarettes, may be introduced to a population who otherwise would never have used e-cigarettes.[2] It also highlights that propensity for risk may not be driving the association between e-cigarettes and subsequent smoking.[37]

Recently, however, some authors have proposed that the gateway theory and the common liability theory are not, as some say, opposing, but rather are complementary.[1 2] They state that use of drugs in general will be explained by common factors, whereas specific factors will explain why young people use drugs in a specific sequence.[1]

4.3.1 Catalyst model

In a 2016 paper, Schneider and Diehl proposed an alternative model for the path from e-cigarette use to conventional cigarette use, considering numerous hypotheses and pathways. They separate the process into two stages, from no consumption to e-cigarette consumption, and then from e-cigarette use to conventional cigarette use (Figure 4).[62(p651)] Factors such as flavour, health, price, role model, concealment, and acceptance play a role in the first stage by easing the process of initiation, as they appear healthier and more acceptable to some, while the flavours attract others. In the second stage (i.e. the transition from e-cigarettes to cigarettes), the authors hypothesise that addiction, accessibility, and experience may drive the subsequent move to conventional cigarette use.[62]

The addiction element of this model hypothesises that the addictive nature of nicotine will potentially encourage young people who have developed a tolerance to the nicotine provided by e-cigarettes to transition to conventional cigarettes due to a desire to increase the nicotine dose. This hypothesis is particularly relevant in relation to adolescents, due to the believed sensitivity of the developing brain to the effects of nicotine. The experience element hypothesises that familiarising young people with the habitual rituals associated with e-cigarettes could familiarise and ingratiate them with the similar processes associated with conventional cigarettes. Finally, the accessibility and proximity of both e-cigarettes and cigarettes may work to promote conventional cigarettes to e-cigarette users. For young people, the proximity to smokers, as an e-cigarette user, may be particularly important. This model demonstrates that there are a number of paths whereby e-cigarette use might encourage smoking uptake.

Two factors which exist outside the model but are nevertheless influential are the liability hypothesis and the renormalisation hypothesis. The liability hypothesis states that "individual predisposition and specific socialization make the initiation of e-cigarette and tobacco use more likely, especially among adolescents"[62(p650)] and the renormalisation hypothesis states that "the increasing rate of e-cigarette use leads to the renormalization of smoking and to more people initiating tobacco smoking, especially among adolescents."[62(p650)]

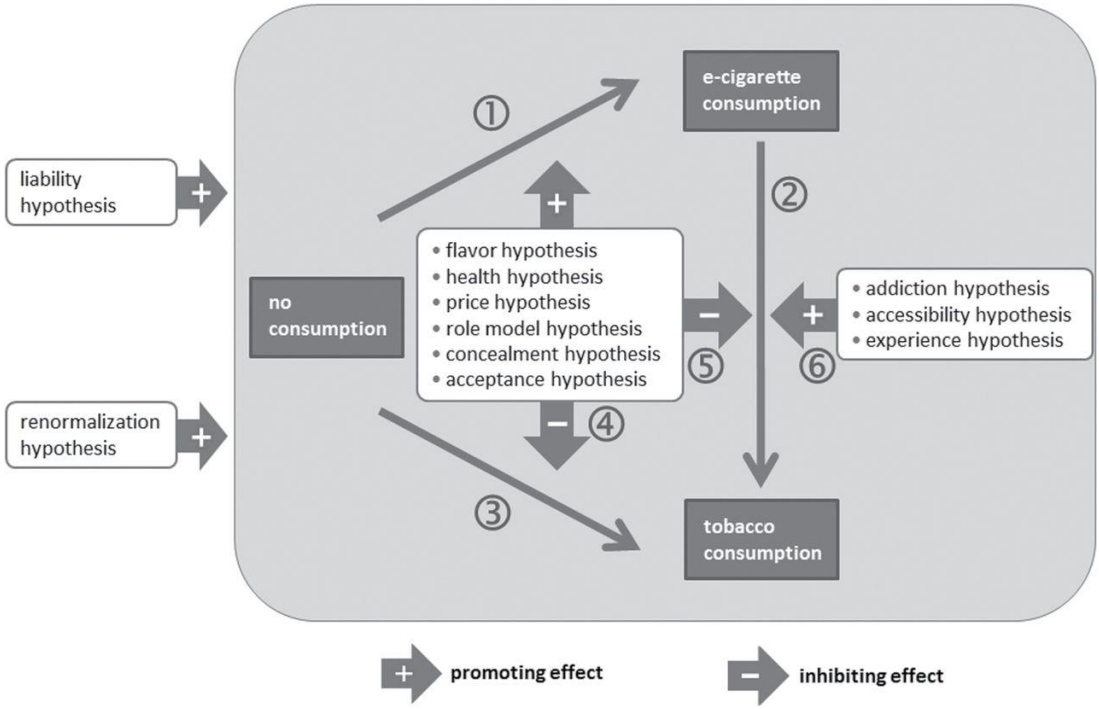


Figure 4 Schneider and Diehl's illustration of the possible catalyst function of e-cigarettes, along with possible reasons for potential transitions

Used with permission. © The Author 2015. Published by Oxford University Press on behalf of the Society for Research on Nicotine and Tobacco. Source: Schneider and Diehl,[62(p651)]

4.4 Limitations

As with any research study, there are some limitations to this systematic review, with regard to both the overall review and the included studies.

4.4.1 E-cigarettes as standard exposure

One limitation of the research in this area is the lack of specificity of the exposure (e-cigarette) in terms of generation, product type, e-liquid and its nicotine content, etc. None of the included studies asked specific questions, and only two[44 49] of the 21 studies measured the differences between nicotine and non-nicotine e-cigarettes. This is particularly pertinent as the world of e-cigarettes is fast-moving, with new products developing rapidly. As the data in this review were collected between 2013 and 2016, it is possible that the collected data refer to e-cigarette products which are no longer in widespread use. Future cohort studies will need to collect more detailed information on young people's e-cigarette use in order to increase our knowledge in this area.

In addition, given that the baseline data of many of these studies were collected in locations and at times when there were no age restrictions on e-cigarettes, it is possible that the e-cigarette use pattern may already have changed.[68 69]

4.4.2 Exposure and outcome measures

The most common measure of both e-cigarette and cigarette use was 'ever use' of either product, a measure which has been criticised by commentators.[63] 'Past-30-day use' has received the same criticism, as it does not identify whether people used the product once in the past 30 days, or if they used it regularly. However, the use of these measures has been justified by a number of publications, with a recent study by Birge *et al*. reporting that more than two-thirds of smokers who tried as little as a single puff during adolescence became, for a time, regular smokers.[70] In adolescents specifically, Dierker *et al.* (2012) report that a usual trajectory of smoking proceeds from experimentation to non-daily smoking and then to daily smoking.[71]

Furthermore, one of the studies included in this review, East *et al.*, used a causal mediation analysis, finding that e-cigarette escalation did not act as a mediator between ever use of cigarettes and subsequent smoking, which suggests that it is primarily ever use of e-cigarettes that contributes to initiation of use of cigarettes.[40]

Given the limited data collection points in these studies, it is possible that a proportion of e-cigarette non-users at baseline may have initiated e-cigarette use during the follow-up periods of the studies, but will continue to be labelled as non-users, thereby underestimating the exposure. Secondly, as pointed out by Berry *et al.*, by examining an exposure that is already established at baseline and adjusting for alcohol and marijuana use at that time point, studies may fail to account for variables that fall in the pathway between exposure and outcome.[37] Evidence from Wills *et al.* demonstrates that the temporal sequence of confounders can have an impact.[45] Future research should focus on following young people for longer, collecting more detailed data at multiple points in order to assess the patterns of use.

Finally, in all the studies in this area, it must be noted that self-reporting of smoking may result in under-reporting of smoking levels by young people.[72]

4.4.3 The issue of confounding and causality

It should be noted that all of the studies included in this review are observational prospective cohort studies with one or two follow-up points. As such, these studies are good for testing the sequence of events but cannot explain why this association is happening.[1] Many of these studies included the known potential confounding variables (e.g. social status, smoking susceptibility, peers who smoke), but of course, there could be other underlying characteristics which have not been accounted for in these models. One study, funded by the tobacco industry, conducted many exploratory analyses of the USA PATH Study data in order to better understand the impact of confounding variables in general, with a particular focus on propensity-to-smoke scores. They concluded that reported estimates of the gateway effect are too high and argued that the effect may not be seen if all confounding variables are fully accounted for.[73] Furthermore, it has been noted that although several studies ask questions assessing the respondents' sensation seeking, impulsivity, or rebelliousness, their actual illicit substance use (which was less frequently included) may be a better, more tangible measure.[74]

As it is unlikely that RCTs would be possible in this area (due to the ethical conundrum of providing young people with e-cigarettes), causality will be difficult to prove;[63] however, autoregressive and causal mediation analyses, such as those carried out by Wills *et al*.[45] and East *et al.*,[40] may help us to unpick the underlying factors which drive the association between use of e-cigarettes and subsequent smoking. These may help to further the case for causality.

4.4.4 Limitations of specific studies

Four studies that measured use of e-cigarettes at baseline and ever smoking between baseline and follow-up were considered to be of high quality,[37 43 47 48] and were included in our sensitivity analysis.

A recurring issue across our studies was the use of convenience, matched, or quota samples, which restricts the representativeness of the findings. [33-35 39 40 50 52] A further common limitation was the high loss to follow-up rates in the included studies, with only five papers retaining more than 80% of their sample at follow-up. [33 37 38 42 52]

In addition to the more common issues, some studies had specific problems which may inhibit interpretation of their findings. One study, conducted in the Netherlands, carried out its longitudinal analysis on a subset of its sample (less than one-third). However, although the authors provided demographic information on the overall sample, they did not provide information on this subset. This is problematic for assessing the study's representativeness.[44] Finally, one USA study, conducted by Spindle *et al.,* presented incorrect data in the Table 2 presented in their paper.[43]

4.5 Future research

4.5.1 Cigarette escalation

In this review, we specifically investigated cigarette-naive young people at baseline. However, interesting studies, such as those conducted by Bold *et al*.[75] Conner *et al*.,[39] and Chaffee *et al*.,[76] have investigated escalation of cigarette use among young e-cigarette users. For example, Chaffee *et al*. (2018) found that e-cigarette use was associated with progression from experimental smoking to established cigarette smoking among adolescent cigarette experimenters, demonstrating that this area needs further exploration.[76]

4.5.2 Future patterns of smoking

As outlined by Etter, one of Hill's requirements for ascertaining causality is the investigation of the dose-frequency response.[63] Kinnunen *et al*. state that in order to test the gateway theory, initiation, ever use, and regular use need to be explored.[49] They found that nicotine e-cigarette experimentation or use, but not non-nicotine e-cigarette experimentation or use, predicts the onset of daily cigarette smoking, and that nicotine e-cigarette experimentation predicts the daily use of nicotine e-cigarettes.

This study provides evidence towards establishing the link between e-cigarette use and the onset of smoking. The next stage of this association is to consider whether e-cigarette use at a young age has any impact on the subsequent frequency of, and dependency on, cigarette smoking. Some studies have already investigated this, but further work needs to be done in order to synthesise these results, facilitating a deeper and more robust examination of this relationship.

The studies which examined different frequencies of the exposure (e-cigarette vaping) and the outcome (cigarette smoking) found significant positive associations, but further research is needed in order to build a body of knowledge. Furthermore, exploration of whether smoking during the follow-up period is associated with later dependent smoking is warranted.[74]

4.5.3 Vaping and smoking in different contexts

Given differences between USA and Europe results, future research should consider the impact of context. European adolescents who appear to have a higher incidence of smoking initiation following e-cigarette use than adolescents in the USA.

Recent research has found that adolescent e-cigarette users, which are generally considered less susceptible and at lower risk potentially, demonstrates the strongest association between e-cigarette use and subsequent smoking such as that reported by four of our included studies.[37 39 46 51]. Consequently, we can see that this may result in a generation of vapers and smokers who would otherwise not have ever used cigarettes – something which needs careful consideration at a public health level. That said, some authors note the need to take a population health approach when examining the potential impact, pointing out that even if the gateway theory is true, there are such low numbers of vapers among never users of cigarettes that the aggregate risk is small, and questioning whether it is ethical to restrict e-cigarette use. [54 63] However, in response, Chapman *et al*. warn that even if the numbers of e-cigarette users are currently low, this may change in response to the industry's marketing efforts.[2] They state:

> "The public health test of the importance of this if it occurs will be the absolute numbers involved. The current evidence about this issue is limited by the short time frame of the introduction of e-cigarettes into a market that has other nicotine-based products, to fully understand their effects on these products and their users. It is also limited by the fast evolution of e-liquids, and their delivery technology, as well as the scarcity of evidence regarding the potential effects of regulations on the role of these products in the marketplace for nicotine. Notwithstanding, the available evidence provides an unequivocal cause for caution about e-cigarettes' role as a harm reduction product given the emerging evidence in support of their gateway potential for cigarette smoking."[2(p697)]

4.5.4 What is causing the association?

It is very clear that there is a positive association between use of e-cigarettes and use of cigarettes. However, there is a need to better understand the roots of this association – is there a gateway, or a common liability hypothesis, or is it explained by the catalyst model or combinations of these theories? Despite fierce debates on the merits of different theories, no consensus has been reached on the most likely explanation. Future research should focus on designing studies which specifically set out to test these theories (or elements thereof). It would be beneficial for future research to attempt to isolate and unpick elements of Schneider and Diehl's model in order to test them and further our understanding of this association.[62]

Wills *et al*. (2016) used structural equation modelling analysis to unpick social and cognitive factors in the relationship between e-cigarette use and subsequent cigarette use.[45] They found that there was no significant direct effect of e-cigarette use on subsequent smoking, with marijuana use and smoking expectancies accounting for much of the variance, potentially supporting the common liability model. However, others, such as Berry *et al*. (2019), demonstrated that propensity for risk is unlikely to be the sole reason for initiation in this gateway, as association was especially pronounced in the low-risk group, and East *et al.* used a causal mediation analysis to suggest that it is primarily ever use of e-cigarettes that contributes to the initiation of cigarette smoking.[37 40] Chapman *et al*. report that there is both discordance and disagreement in this field, with authors engaged in a debate as to whether the gateway theory applies to e-cigarette users who go on to initiate smoking cigarettes, if it is possible to test, or if there are other theories which would better explain the relationship between e-cigarette use and subsequent smoking.[2]

Unfortunately for policy-makers, we need to conduct more research which attempts to unpick the specific social and cognitive covariates which contribute to (or drive) the relationship between e-cigarette use and subsequent smoking, such as the structural equation modelling conducted by Wills (2016).[45] In order for policy-makers to make decisions about the impact of e-cigarettes, they need to understand why e-cigarettes are associated with smoking. We suggest exploring the association using both explorative quantitative and qualitative research approaches.

What do we know and what do we need to do now?

We know that there is an association between using e-cigarette and initiating smoking cigarettes among adolescents, but we need to:

- Understand what drives the association or relationship between e-cigarette and cigarettes
- Explore the frequency and patterns of use of e-cigarettes and explain their relationship with subsequent smoking cigarette
- Explore the role of e-cigarettes and illicit substance use
- Examine what works to reduce ever e-cigarette use for previously never-smokers

Conclusions

We found a four-fold association between ever using e-cigarettes and initiating smoking tobacco cigarettes in adolescents in a combined analysis of nine cohort studies conducted with follow-up periods between 4 and 24 months. Sensitivity and subgroup analysis support the association between ever using e-cigarettes and initiating smoking tobacco cigarettes. The study design used to assess the relationship between e-cigarette use and initiation of cigarette smoking does not allow us to say there is a definitive causal relationship, but it does allow us to say that the findings builds a case towards a causal relationship as the findings are consistent across all studies included in the meta-analysis. Furthermore, the strength of association is statistically significant across all primary research studies in the meta-analysis. In addition, there use of e-cigarettes occurred before initiating smoking fulfilling the criteria for a temporal relationship and two studies have examined the dose response relationship. Moreover, the results of this systematic review are in line with the previous systematic reviews and meta-analyses. Whether there are other additional explanatory factors or not, we need to understand what drives the relationship between e-cigarette and tobacco cigarette use and if the effect is definitively causal. One author recommends large longitudinal epidemiological studies which measure smoking onset, control for confounders, and include a propensity score measure of liability to smoking. Other authors suggest exploring the association using qualitative research approaches.

We identified three theories that attempt to explain the move from using e-cigarette use to smoking tobacco cigarettes, and these are: the gateway theory, the common liability theory, and the catalyst model. The gateway theory was developed to explain the observed phenomenon of young people's use of alcohol and drugs in specific stages and sequences, and intimates that e-cigarette use leads to conventional cigarette use. The common liability theory states that there is an underlying common liability within people which increases their propensity to use

drugs and other illicit substances and that the move from e-cigarettes to conventional cigarettes or other drugs is part of their risk behaviours. Recently, however, some authors have proposed that the gateway theory and the common liability theory are not, as some say, opposing, but rather are complementary. They state that use of drugs in general will be explained by common factors, whereas specific factors will explain why young people use drugs in a specific sequence. In a 2016 paper, two authors proposed an alternative model, the catalyst model, to explain the path from e-cigarette use to conventional cigarette use, considering numerous hypotheses and pathways. They separate the process into two stages, from no consumption to e-cigarette consumption, and then from e-cigarette use to conventional cigarette use. Factors such as flavour, health, price, role model, concealment, and acceptance play a role in the first stage by easing the process of initiation, as they appear healthier and more acceptable to some, while the flavours attract others. In the second stage (i.e. the transition from e-cigarettes to cigarettes), the authors hypothesise that addiction, accessibility, and experience may drive the subsequent move to conventional cigarette use. Two factors which exist outside the model but are nevertheless influential are the [common] liability hypothesis and the renormalisation [of smoking] hypothesis. Despite fierce debates on the merits of different theories, no consensus has been reached on the most likely explanation. Future research should focus on designing studies which specifically set out to test these theories (or elements thereof). It would be beneficial for future research to attempt to isolate and unpick elements of Schneider and Diehl's Catalyst model that describes e-cigarette initiation and subsequent cigarette use in order to further our understanding of this relationship.

The EU has developed regulations to address e-cigarette manufacture, presentation, and sales under the Tobacco Products Directive (2014/40/EU). Ireland are in the process of implementing the European regulations. A population health approach, similar to that successfully used in Ireland to address tobacco, alcohol and psychoactive drug issues may need to be extended to tackle use of e-cigarettes; a population health approach to psychoactive substances usually involves addressing price, availability, and marketing to limit use among young and other vulnerable populations.

5 References

1. Kandel ER, Kandel DB. A molecular basis for nicotine as a gateway drug. *New Engl J Med* 2014;371(10):932-43. doi: 10.1056/NEJMsa1405092
2. Chapman S, Bareham D, Maziak W. The gateway effect of e-cigarettes: Reflections on main criticisms. *Nicotine Tob Res* 2018;21(5):695-98. doi: 10.1093/ntr/nty067
3. Department of Health, Ireland,. Tobacco Free Ireland. Report of the Tobacco Policy Review Group Dublin, Ireland: Department of Health,; 2013 [Available from: https://assets.gov.ie/19465/0c99a96e05c54b249c7d53b93b17437c.pdf.
4. Department of Health, Ireland,. Healthy Ireland. Summary report 2019 Dublin, Ireland: Government Publications,; 2019 [Available from: https://assets.gov.ie/41141/e5d6fea3a59a4720b081893e11fe299e.pdf.
5. Taylor K, Babineau K, Keogan S, et al. ESPAD 2015: European school survey project on alcohol & other drugs in Ireland Dublin, Ireland: TobaccoFree Research Institute Ireland; 2016 [180pp]. Available from: http://www.tri.ie/uploads/5/2/7/3/52736649/espad_2015_ireland_final.pdf.
6. Department of Health, Ireland,. Healthy Ireland survey 2018. Summary of findings Dublin, Ireland: Department of Health; 2019 [Available from: https://assets.gov.ie/41139/80328fcb555d4ed0ac6c4b2ddcd7b677.pdf.
7. National Advisory Committee on Drugs and Alcohol, Northern Ireland Department of Health. Prevalence of drug use and gambling in Ireland & drug use in Northern Ireland: Bulletin 1. Dublin, Ireland: National Advisory Committee on Drugs and Alcohol, 2016:48pp.
8. Költő A, Gavin A, Molcho M, et al. The Irish Health Behaviour in School-aged Children (HBSC) Study 2018 Dublin, Ireland: Department of Health & Galway Health Promotion Research Centre, National University of Ireland, Galway; 2020 [Available from: https://doi.org/10.13025/zvwm-rp65 accessed 02 Mar 2020.
9. Laverty AA, Filippidis FT, Vardavas CI. Patterns, trends and determinants of e-cigarette use in 28 European Union Member States 2014–2017. *Prev Med* 2018;116:13-18. doi: 10.1016/j.ypmed.2018.08.028
10. Farsalinos KE, Poulas K, Voudris V, et al. Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries. *Addiction* 2016;111(11):2032-40. doi: 10.1111/add.13506
11. Bauld L, MacKintosh AM, Eastwood B, et al. Young people's use of e-cigarettes across the United Kingdom: Findings from five surveys 2015–2017. *Int J Environ Res Public Health* 2017;14(9):E973. doi: 10.3390/ijerph14090973
12. Cullen KA, Ambrose BK, Gentzke AS, et al. Notes from the field: Use of electronic cigarettes and any tobacco product among middle and high school students — United States, 2011–2018. *MMWR Morb Mortal Wkly Rep* 2018;67:1276-77. doi: 10.15585/mmwr.mm6745a5
13. TNS opinion & social. Special Eurobarometer 458. Report: Attitudes of Europeans towards tobacco and electronic cigarettes Brussels, Belgium: European Commission; 2017 [205pp]. Available from: https://dx.doi.org/10.2875/804491.
14. Cochrane Effective Practice and Organisation of Care (EPOC). Data collection form. EPOC resources for review authors 2017 [Available from: https://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/Resources-for-authors2017/good_practice_data_extraction_form.doc accessed 20 Jan 2020.
15. EPPI-Reviewer 4.0: software for research synthesis. EPPI-Centre Software. [program]. London: Social Science Research Unit, Institute of Education, University of London., 2010.
16. McGowan J, Sampson M, Salzwedel DM, et al. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;75:40-46. doi: 10.1016/j.jclinepi.2016.01.021
17. Koster J. Pubmed PubReminer. Amsterdam, Netherlands: Academisch Medisch Centrum, Universiteitvan Amsterdam; 2019 [Available from: https://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi.
18. National Heart, Lung, and Blood Institute,. Study quality assessment tools. Quality assessment of controlled intervention studies. Bethesda, Maryland.: National Heart, Lung, and Blood Institute, National Institutes of Health,; [No date] [Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools accessed 15 Oct 2019.
19. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses: Cochrane Collaboration; 2019 [Available from: https://training.cochrane.org/handbook/current/chapter-10.

20. McKenzie JE, Brennan SE, Ryan RE, et al. Summarizing study characteristics and preparing for synthesis. *Cochrane Handbook for Systematic Reviews of Interventions* 2019:229-40.
21. Quigley JM, Woods B, Thompson J, et al. PRM209 - Confronting heterogeneity: Using systematic review effectively for meta-analysis. *Value Health* 2013;16(7):A612. doi: 10.1016/j.jval.2013.08.1763
22. Cope S, Zhang J, Saletan S, et al. A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for advanced breast cancer. *BMC medicine* 2014;12:93. doi: 10.1186/1741-7015-12-93
23. Schwarzer G. General package for meta-analysis [program]: Schwarzer, G.; 2019a [Available from: https://github.com/guido-s/meta.
24. Schwarzer G, Carpenter J, Rücker G. Meta-analysis with R Freiburg, Germany: Institut fur Medizinische Biometrie und Statistik (IMBI) 2019b [Available from: http://www.imbi.uni-freiburg.de/lehre/lehrbuecher/meta-analysis-with-r2020.
25. Glasser A, Abudayyeh H, Cantrell J, et al. Patterns of e-cigarette use among youth and young adults: Review of the impact of e-cigarettes on cigarette smoking. *Nicotine Tob Res* 2019;21(10):1320-30. doi: 10.1093/ntr/nty103
26. Mansournia MA, Altman DG. Population attributable fraction. *BMJ* 2018;360:k757. doi: 10.1136/bmj.k757 [published Online First: 22 Feb 2018]
27. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280(19):1690-91. doi: 10.1001/jama.280.19.1690
28. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. *Am J Epidemiol* 1974;99(5):325-32. doi: 10.1093/oxfordjournals.aje.a121617
29. Cummings P. Methods for estimating adjusted risk ratios. *Stata J* 2009;9(2):175-96. doi: 10.1177/1536867x0900900201
30. Cummings P. Rapid response: Re: Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ* 2014;348:f7450.
31. Murad MH, Asi N, Alsawas M, et al. New evidence pyramid. *Evid Based Med* 2016;21(4):125-27. doi: 10.1136/ebmed-2016-110401
32. Schünemann He, Brożek Je, Guyatt Ge, et al. GRADE handbook for grading quality of evidence and strength of recommendations (Updated October 2013): GRADE Working Group; 2013 [updated 2013. Available from: https://gdt.gradepro.org/app/handbook/handbook.html#h.u1371quprl84.
33. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA* 2015;314(7):700-07. doi: 10.1001/jama.2015.8950
34. Barrington-Trimis JL, Urman R, Berhane K, et al. E-cigarettes and future cigarette use. *Pediatrics* 2016;138(1):e20160379. doi: 10.1542/peds.2016-0379
35. Barrington-Trimis JL, Kong G, Leventhal AM, et al. E-cigarette use and subsequent smoking frequency among adolescents. *Pediatrics* 2018a;142(6):e20180486. doi: 10.1542/peds.2018-0486
36. Barrington-Trimis JL, Leventhal AM, Alonzo TA, et al. Performance of cigarette susceptibility index among e-cigarette and hookah users. *Drug Alcohol Depend* 2018b;183:43-50. doi: 10.1016/j.drugalcdep.2017.08.005
37. Berry KM, Fetterman JL, Benjamin EJ, et al. Association of electronic cigarette use with subsequent initiation of tobacco cigarettes in US youths. *JAMA Netw Open* 2019;2(2):e187794. doi: 10.1001/jamanetworkopen.2018.7794
38. Watkins SL, Glantz SA, Chaffee BW. Association of noncigarette tobacco product use with future cigarette smoking among youth in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2015. *JAMA Pediatrics* 2018;172(2):181-87. doi: 10.1001/jamapediatrics.2017.4173
39. Conner M, Grogan S, Simms-Ellis R, et al. Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study. *Tob Control* 2018;27(4):365-72. doi: 10.1136/tobaccocontrol-2016-053539
40. East K, Hitchman SC, Bakolis I, et al. The association between smoking and electronic cigarette use in a cohort of young people. *J Adolesc Health* 2018;62(5):539-47. doi: 10.1016/j.jadohealth.2017.11.301
41. Lozano P, Barrientos-Gutierrez I, Arillo-Santillan E, et al. A longitudinal study of electronic cigarette use and onset of conventional cigarette smoking and marijuana use among Mexican adolescents. *Drug Alcohol Depend* 2017;180:427-30. doi: 10.1016/j.drugalcdep.2017.09.001
42. Morgenstern M, Nies A, Goecke M, et al. E-cigarettes and the use of conventional cigarettes. *Dtsch Arztebl International* 2018;115(14):243-48. doi: 10.3238/arztebl.2018.0243

43. Spindle TR, Hiler MM, Cooke ME, et al. Electronic cigarette use and uptake of cigarette smoking: A longitudinal examination of U.S. college students. *Addict Behav* 2017;67:66-72. doi: 10.1016/j.addbeh.2016.12.009
44. Treur JL, Rozema AD, Mathijssen JJP, et al. E-cigarette and waterpipe use in two adolescent cohorts: Cross-sectional and longitudinal associations with conventional cigarette smoking. *Eur J Epidemiol* 2018;33(3):323-34. doi: 10.1007/s10654-017-0345-9
45. Wills TA, Gibbons FX, Sargent JD, et al. How is the effect of adolescent e-cigarette use on smoking onset mediated: A longitudinal analysis. *Psychol Addict Behav* 2016;30(8):876-86. doi: 10.1037/adb0000213
46. Wills TA, Sargent JD, Gibbons FX, et al. E-cigarette use is differentially related to smoking onset among lower risk adolescents. *Tobacco Control* 2017a;26(5):534-39. doi: 10.1136/tobaccocontrol-2016-053116
47. Wills TA, Knight R, Sargent JD, et al. Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii. *Tob Control* 2017b;26(1):34-39. doi: 10.1136/tobaccocontrol-2015-052705
48. Best C, Haseen F, Currie D, et al. Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: A cohort study. *Tob Control* 2018;27(4):373-78. doi: 10.1136/tobaccocontrol-2017-053691
49. Kinnunen JM, Ollila H, Minkkinen J, et al. Nicotine matters in predicting subsequent smoking after e-cigarette experimentation: A longitudinal study among Finnish adolescents. *Drug Alcohol Depend* 2019;201:182-87. doi: 10.1016/j.drugalcdep.2019.04.019
50. Hammond D, Reid JL, Cole AG, et al. Electronic cigarette use and smoking initiation among youth: A longitudinal cohort study. *CMAJ* 2017;189(43):E1328-36. doi: 10.1503/cmaj.161002
51. Miech R, Patrick ME, O'Malley PM, et al. E-cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students. *Tob Control* 2017;26(e2):e106-11. doi: 10.1136/tobaccocontrol-2016-053291
52. Leventhal AM, Stone MD, Andrabi N, et al. Association of e-cigarette vaping and progression to heavier patterns of cigarette smoking. *JAMA* 2016;316(18):1918-20. doi: 10.1001/jama.2016.14649
53. Aleyan S, Cole A, Qian W, et al. Risky business: A longitudinal study examining cigarette smoking initiation among susceptible and non-susceptible e-cigarette users in Canada. *BMJ Open* 2018;8(5):e021080. doi: 10.1136/bmjopen-2017-021080
54. Kozlowski LT, Warner KE. Adolescents and e-cigarettes: Objects of concern may appear larger than they are. *Drug Alcohol Depend* 2017;174:209-14. doi: 10.1016/j.drugalcdep.2017.01.001
55. Singh T, Arrazola RA, Corey CG, et al. Tobacco use among middle and high school students: United States, 2011-2015. *MMWR Morb Mortal Wkly Rep* 2016;65(14):361-67. doi: 10.15585/mmwr.mm6514a1
56. Soneji S, Barrington-Trimis JL, Wills TA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: A systematic review and meta-analysis. *JAMA Pediatr* 2017;171(8):788-97. doi: 10.1001/jamapediatrics.2017.1488
57. Aladeokin A, Haighton C. Is adolescent e-cigarette use associated with smoking in the United Kingdom? A systematic review with meta-analysis. *Tob Prev Cessat* 2019;5(April):15. doi: 10.18332/tpc/108553
58. Peruga A, World Health Organization Regional Office for Europe. Electronic nicotine and non-nicotine delivery systems: a brief Copenhagan: WHO Regional Office for Europe. ; 2020 [20pp]. Available from: http://www.euro.who.int/en/health-topics/disease-prevention/tobacco/publications/2020/electronic-nicotine-and-non-nicotine-delivery-systems-a-brief-2020 accessed 04 Jun 2020.
59. European Union. Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC. *Official Journal of the European Union* 2014;57(L127):1-38.
60. Kennedy RD, Awopegba A, De León E, et al. Global approaches to regulating electronic cigarettes. *Tob Control* 2017;26(4):440-45. doi: 10.1136/tobaccocontrol-2016-053179
61. Kandel D. Stages in adolescent involvement in drug use. *Science* 1975;190(4217):912-14. doi: 10.1126/science.1188374
62. Schneider S, Diehl K. Vaping as a catalyst for smoking? An initial model on the initiation of electronic cigarette use and the transition to tobacco smoking among adolescents. *Nicotine Tob Res* 2015;18(5):647-53. doi: 10.1093/ntr/ntv193
63. Etter JF. Gateway effects and electronic cigarettes. *Addiction* 2018;113(10):1776-83. doi: 10.1111/add.13924
64. Rhee SH, Hewitt JK, Young SE, et al. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Arch Gen Psychiatry* 2003;60:1256-64. doi: 10.1001/archpsyc.60.12.1256

65. Kendler KS, Myers J, Prescott CA. Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. *Arch Gen Psychiatry* 2007;64:1313-20. doi: 10.1001/archpsyc.64.11.1313
66. Vanyukov MM, Tarter RE, Kirillova GP, et al. Common liability to addiction and "gateway hypothesis": Theoretical, empirical and evolutionary perspective. *Drug Alcohol Depend* 2012;123 S3-S17. doi: 10.1016/j.drugalcdep.2011.12.018 [published Online First: 17 Jan 2012]
67. Palmer RHC, Young SE, Hopfer CJ, et al. Developmental epidemiology of drug use and abuse in adolescence and young adulthood: Evidence of generalized risk. *Drug Alcohol Depend* 2009;102(1-3):78-87. doi: 10.1016/j.drugalcdep.2009.01.012 [published Online First: 27 Feb 2009]
68. Gartner C. How can we protect youth from putative vaping gateway effects without denying smokers a less harmful option? *Addiction* 2018;113(10):1784-85. doi: 10.1111/add.14126
69. Gartner CE. E-cigarettes and youth smoking: Be alert but not alarmed. *Tob Control* 2018;27(4):359. doi: 10.1136/tobaccocontrol-2017-054002 [published Online First: 08 Sep 2017]
70. Birge M, Duffy S, Miler JA, et al. What proportion of people who try one cigarette become daily smokers? A meta-analysis of representative surveys. *Nicotine Tob Res* 2017;20(12):1427-33. doi: 10.1093/ntr/ntx243
71. Dierker L, Swendsen J, Rose J, et al. Transitions to regular smoking and nicotine dependence in the Adolescent National Comorbidity Survey (NCS-A). *Ann Behav Med* 2011;43(3):394-401. doi: 10.1007/s12160-011-9330-9
72. Brener ND, Billy JOG, Grady WR. Assessment of factors affecting the validity of self-reported health-risk behavior among adolescents: Evidence from the scientific literature. *J Adolesc Health* 2003;33(6):436-57. doi: 10.1016/S1054-139X(03)00052-1
73. Lee P, Fry J. Investigating gateway effects using the PATH study [version 2; peer review: 2 approved]. *F1000Research* 2019;8:264. doi: 10.12688/f1000research.18354.2
74. Warner KE. How to think—not feel—about tobacco harm reduction. *Nicotine Tob Res* 2018;21(10):1299-309. doi: 10.1093/ntr/nty084
75. Bold KW, Kong G, Camenga DR, et al. Trajectories of e-cigarette and conventional cigarette use among youth. *Pediatrics* 2018;141(1):e20171832. doi: 10.1542/peds.2017-1832 [published Online First: 01 Jan 2018]
76. Chaffee BW, Watkins SL, Glantz SA. Electronic cigarette use and progression from experimentation to established smoking. *Pediatrics* 2018;141(4):e20173594. doi: 10.1542/peds.2017-3594
77. El Dib R, Suzumura EA, Akl EA, et al. Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: A systematic review and meta-analysis. *BMJ Open* 2017;7(2):e012680. doi: 10.1136/bmjopen-2016-012680
78. Evans SE, Hoffman AC. Electronic cigarettes: Abuse liability, topography and subjective effects. *Tob Control* 2014;23 Suppl 2:ii23-29. doi: 10.1136/tobaccocontrol-2013-051489
79. Glasser AM, Collins L, Pearson JL, et al. Overview of electronic nicotine delivery systems: A systematic review. *Am J Prev Med* 2017;52(2):e33-e66. doi: 10.1016/j.amepre.2016.10.036
80. Hartmann-Boyce J, McRobbie H, Bullen C, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2016;9:CD010216. doi: 10.1002/14651858.CD010216.pub3
81. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: A systematic review and meta-analysis. *Lancet Respir Med* 2016;4(2):116-28. doi: 10.1016/s2213-2600(15)00521-4
82. Khoudigian S, Devji T, Lytvyn L, et al. The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: A systematic review and a meta-analysis. *Int J Public Health* 2016;61(2):257-67. doi: 10.1007/s00038-016-0786-z
83. Knight-West O, Bullen C. E-cigarettes for the management of nicotine addiction. *Subst Abuse Rehabil* 2016;7:111-18. doi: 10.2147/sar.S94264
84. Liu X, Lu W, Liao S, et al. Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). *Medicine (Baltimore)* 2018;97(19):e0324. doi: 10.1097/md.0000000000010324
85. Livingston CJ, Freeman RJ, Costales VC, et al. Electronic nicotine delivery systems or e-cigarettes: American College of Preventive Medicine's practice statement. *Am J Prev Med* 2019;56(1):167-78. doi: 10.1016/j.amepre.2018.09.010
86. Malas M, van der Tempel J, Schwartz R, et al. Electronic cigarettes for smoking cessation: A systematic review. *Nicotine Tob Res* 2016;18(10):1926-36. doi: 10.1093/ntr/ntw119

87. O'Leary R, MacDonald M, Stockwell T, et al. Clearing the air: A systematic review on the harms and benefits of e-cigarettes and vapour devices Victoria, Canada: Canadian Institute for Substance Use Research, University of Victoria, 2017.
88. Rahman MA, Hann N, Wilson A, et al. E-cigarettes and smoking cessation: Evidence from a systematic review and meta-analysis. *PloS One* 2015;10(3):e0122544. doi: 10.1371/journal.pone.0122544
89. Bals R, Boyd J, Esposito S, et al. Electronic cigarettes: A task force report from the European Respiratory Society. *Eur Resp J* 2019;53(2):1801151. doi: 10.1183/13993003.01151-2018
90. Health Information and Quality Authority, (HIQA). Health technology assessment (HTA) of smoking cessation interventions Dublin, Ireland: Health Information and Quality Authority (HIQA); 2017 [Available from: https://www.hiqa.ie/sites/default/files/2017-04/Smoking%20Cessation%20HTA.pdf.
91. McNeill A, Brose LS, Calder R, et al. Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England London, England: Public Health England; 2018 [Available from: https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review.
92. National Academies of Sciences, Engineering, Medicine. Public health consequences of e-cigarettes. Washington DC, USA: The National Academies Press; 2018 [774pp]. Available from: https://dx.doi.org/10.17226/24952.
93. Wells C, Farrah K. Electronic cigarettes for the reduction or cessation of smoking: clinical utility, safety, and guidelines [Rapid Response]. Ottowa, Canada: Canadian Agency for Drugs and Technologes in Health (CADTH); 2017 [Available from: https://www.cadth.ca/electronic-cigarettes-reduction-or-cessation-smoking-clinical-utility-safety-and-guidelines-0.

Appendix 1: Literature search strategies and results

List of databases and resources used

1. Ovid Medline
2. Cochrane Library
3. Ovid PsycInfo
4. Elsevier Embase
5. NHS NIHR PROSPERO
6. LILACS
7. Google Scholar
8. CORE.ac.uk
9. List of reviews and reports used for citation searching

Results from each database			
Database	**Articles before deduplication**	**Articles after de-duplication**	**Duplicates excluded from each database**
Total	14676	6510	8166
Ovid Medline	3874	3690	184
Cochrane Central	527	274	253
Cochrane Systematic Reviews Database	14	12	2
PsycInfo	1519	369	1150
Embase	4212	1391	2821
PROSPERO	93	93	0
LILACS	4042	558	3506
Google Scholar	200	43	157
CORE	192	80	112

1. Ovid Medline search strategy and results

Ovid Medline: E-cigarettes and heat-not-burn products	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 12, 2019
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and heat-not-burn products (approximately 1988 in their current forms)
Study types	Exclude animal models, cell lines
Publication types	Exclude commentary, editorials, replies. Letters are not outright excluded as research letters are in scope.

Concept	Search number	Search term	Results
E-cigarettes	1	Vaping/	291
	2	Electronic Nicotine Delivery Systems/	2293
	3	"Nebulizers and Vaporizers"/ and (nicotine or tobacco).mp.	155
	4	e-cig$.mp.	3087
	5	Ecig$.mp.	80
	6	(Vape or vaping or vaper or vapers).mp.	853
	7	(Vapori#e$ adj3 (cigarette$ or nicotine)).mp.	77
	8	((electric or electronic) adj2 (cig$ or nicotine or tobacco or smoking)).mp.	3496
	9	(e-sigaret$ or "e-sígarett$" or een sigaret$ or E-Zigarette$ or "cigarette$ électronique$" or "L'e-cigarette" or vapoteuse$ or "cigarrill$ electrónico$" or sigarett$ elettronic$ or sigarett$ elettronik$ or sigarett$ elettroniche$ or elektronik$ sigar$ or e-savuke$ or e-rokok$ or rokok$ elektronik$ or e-papieros$ or e-ugwayi).mp.	55
	10	(mods adj5 (tobacco or nicotine)).mp.	2
	11	Juul$.mp.	40
	12	(e-juice$ or e-liquid$).mp.	392
	13	(cig-a-like$ or cigalike$ or ciga-like$).mp.	36
	14	(e-hookah$ or electronic hookah$ or "hookah pens").mp.	19
	15	(ENNDS or electronic non-nicotine delivery).mp.	3
	16	((NMNDS and nicotin$) or non-medicinal nicotine delivery system$).mp.	0
	17	or/1-16	4520
Heat-not-burn products	18	(Heated tobacco product$ or tobacco heating product$ or tobacco heating system$).mp.	118
	19	("heat-not-burn" or "heat not burn" or "heat notburn" or "heatnot burn").mp.	83
	20	(Heatsticks or heat-sticks or tobacco sticks or Neosticks).mp.	13
	21	((HEETS or Fiit or glo) adj3 (tobacco or nicotine or smok$)).mp.	2
	22	(IQOS or iFuse or Ploom).mp.	70
	23	(electrically-heated smoking system and (nicotin$ or tobacco$)).mp.	1
	24	(Vapotage or "tabac chauffé" or "verhitte tabak" or "riscaldatori di tabacco" or "tabacco riscaldato" or "erhitzter Tabak" or "verhit tabak" or "zahřátý tabák" or "opvarmet tobak" or "oppvarmet tobakk" or "uppvärmd tobak" or "kuumutatud tubakas" or "pinainit na tabako" or "lämmitetty tupakka" or "shan taba mai tsanani" or "hitað tóbak" or "apsildāmā tabaka" or "tembakau dipanaskan" or "šildomas tabakas" or "tembakau yang dipanaskan" or "te taakapa" or "podgrzewany tytoń" or "tabaco aquecido" or "încălzit tutunul" or "zahriaty tabak" or "ogrevani tobak" or "tabaco caliente" or "ısıtılmış tütün" or "ugwayi ovuthayo" or "thuốc lá nóng").mp.	11
	25	or/18-24	218
E-cigarettes or heat-not-burn products	26	17 or 25	4645
Basic animal and cell studies search	27	animals/ not humans.sh.	4536484
	28	exp animals, laboratory/ or exp Animal experimentation/ or exp Models, animal/ or Disease Models, Animal/ or exp Animal Diseases/	1563266

	29	(animal adj2 (model$ or stud$ or experiment$ or laboratory)).ti,ab,kf.	231870
	30	(Cat or cats or feline or dog or dogs or canine or rat or rats or Wistar or Sprague-Dawley or rodent$ or mouse or mice or murine or zebrafish or fish or chicken$ or horse$ or rabbit$ or "C. elegans" or caenorhabditis elegans or nematod$ or Xenopus or bird or birds or reptil$ or livestock or larva$).ti,ab,kf.	3615741
	31	exp In Vitro Techniques/ or exp Biological Assays/ or exp cells, cultured/ or exp clinical laboratory techniques/ or Chemistry techniques, analytical/ or chemistry techniques, synthetic/	4144439
	32	("in vitro" or biological assay$ or cell culture or cultured cells or cell lines or cell transformation assay$).ti,ab,kf.	1414252
	33	27 or 28 or 29 or 30 or 31 or 32	8519746
(E-cigarettes or heat-not-burn products) NOT cell or animal studies	34	26 not 33	4284
Publication type	35	(comment or editorial or note).pt.	1105825
	36	(reply or commentary or comment or editorial).ti.	135049
	37	35 or 36	1158642
(((E-cigarettes or heat-not-burn products**) NOT cell or animal studies) NOT letters, commentary)**	**38**	**34 not 37**	**3874**

2. Cochrane Systematic Reviews and Cochrane Central search strategy and results

Cochrane Library: E-cigarettes and HeatNotBurn devices	
Database	John Wiley & Sons Cochrane Library
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)

Concept	Search number	Search terms	Results
E-cigarettes	#1	MeSH descriptor: [Vaping] explode all trees	10
	#2	MeSH descriptor: [Electronic Nicotine Delivery Systems] explode all trees	72
	#3	MeSH descriptor: [Nebulizers and Vaporizers] explode all trees	2218
	#4	((nicotine OR tobacco)):ti,ab,kw	10856
	#5	#3 AND #4	31
	#6	(e-cig*):ti,ab,kw	309
	#7	(ecig*):ti,ab,kw	309
	#8	((vape OR vaping OR vaper OR vapers)):ti,ab,kw	66
	#9	(((vaporise OR vaporised OR vaporiser OR vaporize OR vaporized OR vaporizer) NEAR/3 (cigarette* OR nicotine))):ti,ab,kw	18
	#10	(((electric or electronic) NEAR/2 (nicotine or tobacco or smoking or cig*))):ti,ab,kw	321
	#11	((e-sigaret* OR "e-sígarett*" OR E-Zigarette* OR "cigarette* électronique*" OR "L'e-cigarette" OR vapoteuse* OR "cigarrill* electrónico*" OR sigarett* elettronic* OR sigarett* elettronik* OR sigarett* elettroniche* OR elektronik* sigar* OR e-savuke* OR e-rokok* OR rokok* elektronik* OR e-papieros* OR e-ugwayi)):ti,ab,kw	9
	#12	((mods NEAR/5 (nicotine OR tobacco))):ti,ab,kw	0
	#13	(Juul*):ti,ab,kw	11
	#14	(e-juic* OR e-liquid*):ti,ab,kw	48
	#15	((cig-a-like* OR cigalike* OR ciga-like*)):ti,ab,kw	4
	#16	(e-hookah* OR "electronic hookah" OR "electronic hookahs" OR "hookah pen" OR "hookah pens"):ti,ab,kw	2
	#17	(ENNDS OR "electronic non-nicotine delivery"):ti,ab,kw	0
	#18	((NMNDS AND nicotin*)):ti,ab,kw	0
	#19	(non-medicinal nicotine delivery system*):ti,ab,kw	0
	#20	#1 OR #2 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	463
Heat-not-burn products	#21	("heated tobacco" OR "tobacco heating"):ti,ab,kw	43
	#22	(Heated tobacco product* OR tobacco heating product* OR tobacco heating system*):ti,ab,kw	70
	#23	("heat-not-burn" OR "heat not burn" OR "heat notburn" OR "heatnot burn" OR "heatnotburn"):ti,ab,kw	6
	#24	(Heatsticks OR heat-sticks OR "heat sticks" OR tobacco sticks OR Neosticks):ti,ab,kw	9
	#25	(IQOS or iFuse or Ploom):ti,ab,kw	17
	#26	((Vapotage OR "tabac chauffé" OR "verhitte tabak" OR "riscaldatori di tabacco" OR "tabacco riscaldato" OR "erhitzter Tabak" OR "verhit tabak" OR "zahřátý tabák" OR "opvarmet tobak" OR "oppvarmet tobakk" OR "uppvärmd tobak" OR "kuumutatud tubakas" OR "pinainit na tabako" OR "lämmitetty tupakka" OR "shan taba mai tsanani" OR "hitað tóbak" OR "apsildāmā tabaka" OR "tembakau dipanaskan" OR "šildomas tabakas" OR "tembakau yang dipanaskan" OR "te taakapa" OR "podgrzewany tytoń" OR "tabaco aquecido" OR "încălzit tutunul" or "zahriaty tabak" OR "ogrevani tobak" OR "tabaco caliente" OR "ısıtılmış tütün" OR "ugwayi ovuthayo" OR "thuốc lá nóng")):ti,ab,kw	7
	#27	((HEETS or Fiit or glo) NEAR/3 (tobacco or nicotine or smok*)):ti,ab,kw	1
	#28	(("electrically-heated smoking system" AND (nicotin* OR tobacco*))):ti,ab,kw	1
	#29	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	103
E-cigarettes OR heat-not-burn products	#30	#20 OR #29	541 (of which 14 reviews, 527 central)

3. Ovid PsycInfo search strategy and results

Ovid Medline: E-cigarettes and HeatNotBurn devices	
Database	Ovid PsycInfo
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)
Study types	NOTE: did not remove animal or publication type items from Psycinfo as after testing, very few animal studies, and publication types filter removed useful items also.
Publication types	Exclude commentary, editorials, replies. Letters are not outright excluded as research letters are in scope.

Concept	Search number	Search terms	Results
E-cigarettes	1	exp Electronic cigarettes/	897
	2	((Nebulizer$ or Vaporizer$) adj5 (nicotine or tobacco)).mp.	14
	3	e-cig$.mp.	1188
	4	Ecig$.mp.	59
	5	(Vape or vaping or vaper or vapers).mp.	252
	6	(Vapori#e$ adj3 (cigarette$ or nicotine)).mp.	33
	7	((electric or electronic) adj2 (cig$ or nicotine or tobacco or smoking)).mp.	1215
	8	(e-sigaret$ or "e-sígarett$" or een sigaret$ or E-Zigarette$ or "cigarette$ électronique$" or "L'e-cigarette" or vapoteuse$ or "cigarrill$ electrónico$" or sigarett$ elettronic$ or sigarett$ elettronik$ or sigarett$ elettroniche$ or elektronik$ sigar$ or e-savuke$ or e-rokok$ or rokok$ elektronik$ or e-papieros$ or e-ugwayi).mp.	1
	9	(mods adj5 (tobacco or nicotine)).mp.	1
	10	Juul$.mp.	27
	11	(e-juice$ or e-liquid$).mp.	76
	12	(cig-a-like$ or cigalike$ or ciga-like$).mp.	21
	13	(e-hookah$ or electronic hookah$ or "hookah pens").mp.	6
	14	(ENNDS or electronic non-nicotine delivery).mp.	0
	15	((NMNDS and nicotin$) or non-medicinal nicotine delivery system$).mp.	0
	16	or/1-15	1510
Heat-not-burn products	17	(Heated tobacco product$ or tobacco heating product$ or tobacco heating system$).mp.	6
	18	("heat-not-burn" or "heat not burn" or "heat notburn" or "heatnot burn").mp.	14
	19	(Heatsticks or heat-sticks or tobacco sticks or Neosticks).mp.	2
	20	((HEETS or Fiit or glo) adj3 (tobacco or nicotine or smok$)).mp.	0
	21	(IQOS or iFuse or Ploom).mp.	6
	22	(electrically-heated smoking system and (nicotin$ or tobacco$)).mp.	0
	23	(Vapotage or "tabac chauffé" or "verhitte tabak" or "riscaldatori di tabacco" or "tabacco riscaldato" or "erhitzter Tabak" or "verhit tabak" or "zahřátý tabák" or "opvarmet tobak" or "oppvarmet tobakk" or "uppvärmd tobak" or "tabaco aquecido" or "kuumutatud tubakas" or "pinainit na tabako" or "lämmitetty tupakka" or "shan taba mai tsanani" or "hitað tóbak" or	2

		"apsildāmā tabaka" or "tembakau dipanaskan" or "šildomas tabakas" or "tembakau yang dipanaskan" or "te taakapa" or "podgrzewany tytoń" or "tabaco aquecido" or "încălzit tutunul" or "zahriaty tabak" or "ogrevani tobak" or "tabaco caliente" or "ısıtılmış tütün" or "ugwayi ovuthayo" or "thuốc lá nóng").mp.	
	24	or/17-23	20
E-cigarettes OR heat-not-burn products	25	16 or 24	1518

4. Elsevier Embase search strategy and results

Elsevier Embase: E-cigarettes and HeatNotBurn devices	
Database	Elsevier Embase
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)
Study types	Exclude animal models, cell lines
Publication types	Exclude commentary, editorials, replies. Letters are not outright excluded as research letters are in scope.

Concept	Search number	Search terms	Results
E-cigarettes	#1	'vaping'/exp OR 'vaping'	1,014
	#2	'electronic cigarette'/exp	4,468
	#3	'e cig*':ti,ab,kw	3,604
	#4	ecig*:ti,ab,kw	212
	#5	vape:ti,ab,kw OR vaping:ti,ab,kw OR vaper:ti,ab,kw OR vapers:ti,ab,kw	803
	#6	vapori?e$ NEAR/3 (cigarette* OR nicotine)	79
	#7	((electric OR electronic) NEAR/2 (cig* OR nicotine OR tobacco OR smoking)):ti,ab,kw	3,046
	#8	'e sigaret*':ti,ab,kw OR 'e sígarett*':ti,ab,kw OR 'e zigarette*':ti,ab,kw OR 'cigarette* électronique*':ti,ab,kw OR 'l e cigarette':ti,ab,kw OR vapoteuse*:ti,ab,kw OR 'cigarrill* electrónico*':ti,ab,kw OR 'sigarett* elettronic*':ti,ab,kw OR 'sigarett* elettronik*':ti,ab,kw OR 'sigarett* elettroniche*':ti,ab,kw OR 'elektronik* sigar*':ti,ab,kw OR 'e savuke*':ti,ab,kw OR 'e rokok*':ti,ab,kw OR 'rokok* elektronik*':ti,ab,kw OR 'e papieros*':ti,ab,kw OR 'e ugwayi':ti,ab,kw	9
	#9	(mods NEAR/5 (tobacco OR nicotin* OR smoking OR cigarette)):ti,ab,kw	2
	#10	'juul*':ti,ab,kw	42
	#11	'e juice*':ti,ab,kw OR 'e liquid*':ti,ab,kw	548

	#12	'cig-a-like*':ti,ab,kw OR 'cigalike*':ti,ab,kw OR 'ciga-like*':ti,ab,kw OR 'cig-alike':ti,ab,kw	86
	#13	'e hookah*':ti,ab,kw OR 'electronic hookah*':ti,ab,kw OR 'electric hookah*':ti,ab,kw OR 'hookah pen*':ti,ab,kw OR 'e-shisha':ti,ab,kw OR 'electronic shisha':ti,ab,kw OR 'electric shisha':ti,ab,kw	17
	#14	'ennds':ti,ab,kw OR 'electronic non-nicotine delivery':ti,ab,kw	6
	#15	nmnds:ti,ab,kw AND nicotine:ti,ab,kw	0
		#16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	5,675
Hurn products	#17	'heated tobacco':ti,ab,kw OR 'tobacco heating':ti,ab,kw	183
	#18	'heat-not-burn':ti,ab,kw OR 'heat not burn':ti,ab,kw OR 'heat notburn':ti,ab,kw OR 'heatnot burn':ti,ab,kw	104
	#19	'heatsticks':ti,ab,kw OR 'heatstick':ti,ab,kw OR 'heat-stick':ti,ab,kw OR 'heat-sticks':ti,ab,kw OR 'tobacco sticks':ti,ab,kw OR 'tobacco stick':ti,ab,kw OR 'neostick':ti,ab,kw OR neosticks:ti,ab,kw	17
	#20	((heets OR fiit OR glo OR ifuse) NEAR/3 (tobacco OR nicotine OR smok*)):ti,ab,kw	5
	#21	iqos:ti,ab,kw OR ploom:ti,ab,kw	55
	#22	'electrically-heated smoking system':ti,ab,kw AND (nicotin*:ti,ab,kw OR tobacco*:ti,ab,kw)	1
	#23	vapotage:ti,ab,kw OR 'tabac chauffé':ti,ab,kw OR 'verhitte tabak':ti,ab,kw OR 'riscaldatori di tabacco':ti,ab,kw OR 'tabacco riscaldato':ti,ab,kw OR 'erhitzter tabak':ti,ab,kw OR 'verhit tabak':ti,ab,kw OR 'zahřátý tabák':ti,ab,kw OR 'opvarmet tobak':ti,ab,kw OR 'oppvarmet tobakk':ti,ab,kw OR 'uppvärmd tobak':ti,ab,kw OR 'kuumutatud tubakas':ti,ab,kw OR 'pinainit na tabako':ti,ab,kw OR 'lämmitetty tupakka':ti,ab,kw OR 'shan taba mai tsanani':ti,ab,kw OR 'hitað tóbak':ti,ab,kw OR 'apsildāmā tabaka':ti,ab,kw OR 'tembakau dipanaskan':ti,ab,kw OR 'šildomas tabakas':ti,ab,kw OR 'tembakau yang dipanaskan':ti,ab,kw OR 'te taakapa':ti,ab,kw OR 'podgrzewany tytoń':ti,ab,kw OR 'tabaco aquecido':ti,ab,kw OR 'încălzit tutunul':ti,ab,kw OR 'zahriaty tabak':ti,ab,kw OR 'ogrevani tobak':ti,ab,kw OR 'tabaco caliente':ti,ab,kw OR 'ısıtılmış tütün':ti,ab,kw OR 'ugwayi ovuthayo':ti,ab,kw OR 'thuốc lá nóng':ti,ab,kw	1
	#24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	263
E-cigarettes OR heat-not-burn products	#25	#16 OR #24	5,850
Animal, in vitro or cell line studies	#26	'animal'/exp NOT 'human'/exp	5,227,728
	#27	'experimental animal'/exp	623,633
	#28	'animal experiment'/exp	2,359,962
	#29	'nonhuman'/exp	5,756,936
	#30	'animal model'/exp	1,244,803
	#31	'animal tissue, cells or cell components'/exp	3,618,529

	#32	'veterinary clinical trial'/exp	2
	#33	animal NEAR/2 (model* OR stud* OR experiment* OR laboratory)	2,716,111
	#34	cat:ti,ab,kw OR cats:ti,ab,kw OR feline:ti,ab,kw OR dog:ti,ab,kw OR dogs:ti,ab,kw OR canine:ti,ab,kw OR rat:ti,ab,kw OR rats:ti,ab,kw OR wistar:ti,ab,kw OR 'sprague dawley':ti,ab,kw OR rodent*:ti,ab,kw OR mouse:ti,ab,kw OR mice:ti,ab,kw OR murine:ti,ab,kw OR zebrafish:ti,ab,kw OR fish:ti,ab,kw OR chicken*:ti,ab,kw OR horse*:ti,ab,kw OR rabbit*:ti,ab,kw OR 'c. elegans':ti,ab,kw OR 'caenorhabditis elegans':ti,ab,kw OR nematod*:ti,ab,kw OR xenopus:ti,ab,kw OR bird:ti,ab,kw OR birds:ti,ab,kw OR reptil*:ti,ab,kw OR livestock:ti,ab,kw OR larva*:ti,ab,kw	4,327,895
	#35	'human tissue, cells or cell components'/exp	2,434,643
	#36	'bioassay'/exp	250,786
	#37	'in vitro study'/exp	5,605,074
	#38	'in vitro':ti,ab,kw OR 'biological assay*':ti,ab,kw OR 'cell culture':ti,ab,kw OR 'cultured cells':ti,ab,kw OR 'cell lines':ti,ab,kw OR 'cell transformation assay*':ti,ab,kw	1,769,394
	#39	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	11,508,677
(E-cigarettes OR heat-not-burn products) NOT animal, in vitro or Cell lines	#40	#25 NOT #39	4,844
Editorials, replies, commentaries	#41	'editorial'/exp	603,392
		#42 'note'/exp	706,258
	#43	('editorial'/it OR 'note'/it) AND ([editorial]/lim OR [note]/lim)	1,337,186
	#44	'reply':ti	77,815
	#45	commentary:ti	51,142
	#46	editorial:ti	72,014
	#47	note:ti	28,805
	#48	#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47	1,506,914
((E-cigarettes OR HnB) NOT animal, in vitro or Cell lines) NOT Editorials, replies, commentaries	#49	#40 NOT #48	4,212

5. NHS NIHR PROSPERO

NHS NIHR PROSPERO E-cigarettes and **heat-not-burn products**	
Database	NHS NIHR PROSPERO https://www.crd.york.ac.uk/prospero/#searchadvanced
Date of Search	15.04.2019
Note	"All status reviews, All fields" used
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)
Study types	None
Publication types	None

Concept	Search number	Search terms	Search results
E-cigarettes	#1	e-cig*	62
	#2	ecig*	3
	#3	MeSH DESCRIPTOR Vaping EXPLODE ALL TREES	6
	#4	e-juic*	2
	#5	e-liquid*	4
	#6	cig-a-like OR cigalike OR cig-alike OR ciga-like	0
	#7	e-hookah	5
	#8	juul	26
	#9	vape	11
	#10	vaping	22
	#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	92
HnB	#12	"heated tobacco" OR "tobacco heating"	2
	#13	"heat-not-burn" OR "heat not burn" OR "heat notburn" OR "heatnot burn"	2
	#14	heatsticks OR "heat-sticks" OR "tobacco sticks" OR neosticks	0
	#15	iqos OR ploom OR iFuse	1
	#16	"electrically heated smoking system" AND tobacco	0
	#17	#16 OR #15 OR #14 OR #13 OR #12	4
E-cigarettes OR heat-not-burn products	#18	#17 OR #11	93

6. LILACS (Latin American and Caribbean Health Sciences Literature)

LILACS: E-cigarettes and **heat-not-burn products** devices	
Database	LILACS (Including databases: (LILACS, IBECS, CUMED, BDENF – Nursing, BBO – Dentistry, WHO IRIS, PAHO-IRIS, Index Psychology - Scientific journals, MedCarib)
Date of Search	15.04.2019
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and HeatNotBurn (approximately 1988 in their current forms)
Study types	Exclude animal models, cell lines
Publication types	Exclude commentary, editorials, replies. Letters are not outright excluded as research letters are in scope.

Search number	Search terms	Search results
1	(tw:(("E-cigarette" OR "E-cigarettes" OR “ecigarette” or “ecigarettes” OR vaping OR vape OR "electronic nicotine" OR "cig-a-like" OR "e-hookah" OR "E-liquid" OR "E-juice")))	
2	“cigarrillo electrónico” OR “cigarrillo electrónico” OR OR “e-cigarros” OR “e-cigarro” OR "cigarette électronique" OR "cigarettes électroniques" OR “e-sigaretten” OR “een sigaret” OR “sigaretta elettronica” OR “sigarette elettroniche”	
3	"heated tobacco" OR "tobacco heating" OR "heat-not-burn" OR "heat not burn" OR IQOS OR heatsticks OR "heat-sticks" OR "tobacco sticks"	
4	Vapotage OR "tabac chauffé" OR "verhitte tabak" OR "riscaldatori di tabacco" OR "tabacco riscaldato" OR "erhitzter Tabak" OR "verwarmde tabak" OR "tabaco aquecido"	
		Database results Show in graphical form: total n=4061 MEDLINE (4019) IBECS (21) LILACS (14) DeCS - Descriptors in Health Sciences (2) WHO IRIS (2) BRISA/RedTESA (1) LIS -Health Information Locator (1) PAHO-IRIS (1)

7. Google scholar

Google Scholar: E-cigarettes and **heat-not-burn products**	
Search Engine and Browser	Google Scholar on Firefox 66
Date of Search	15.04.2019
Note	Due to the simple search interface, reduced searches were used for the two research concepts. Limitation of using Google Scholar include limited search faceting and the unknown algorithm sorting the results.
Age limits	None used in the search
Geographic limits	None
Language limits	None used in the search
Date limits	None, apart from the limits set by the invention of e-cigarettes (2003-4) and heat-not-burn products (approximately 1988 in their current forms)
Study types	Exclude animal models, cell lines
Publication types	Excluded patents

Concept	Search terms	Results	Results considered
E-cigarettes	(E-cigarette OR ecigarette OR Vape OR Vaping OR Vaper OR e-juice OR e-liquid OR e-hookah)	About 28,700 results (0.56 sec)	First 100 results (first 10 pages of results)
heat-not-burn products	"heated tobacco" OR "tobacco heating" OR "heat-not-burn" OR "heat not burn" OR "IQOS" OR "heatsticks" OR "heat-sticks" OR "tobacco sticks"	About 4,140 results (0.34 sec)	First 100 results (first 10 pages of results)

8. CORE.ac.uk

CORE.ac.uk E-cigarettes and **heat-not-burn products**			
Repository	CORE.ac.uk (The Open University and JISC)		
Date of Search	15.04.2019		
Note	Due to the simple search interface, reduced searches were used. Search terms were limited to e-cigarette and vaping terms.		
Age limits	None used in the search		
Geographic limits	None		
Language limits	None used in the search.		
Date limits	None		
Study types	None excluded in the search		
Publication types	None excluded in the search		
Search terms	Results	Selected	After deduplication

title:((E-cigarette OR ecigarette OR Vape OR Vaping OR Vaper))	Over 2 million results	First 100 (default sorting: relevance)	100
title:(("heat-not-burn" OR "tobacco heating" OR "heated tobacco" OR "heat not burn" OR IQOS OR heatnotburn)	158	100 (default sorting: relevance)	92

9. List of reviews and reports used for citation searching in supplemental searches

Reviews

1. El Dib R, Suzumura EA, Akl EA, et al.[77] Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: A systematic review and meta-analysis. *BMJ Open* 2017;7(2):e012680. doi: 10.1136/bmjopen-2016-012680 [published Online First: 23 Feb 2017]
2. Evans SE, Hoffman AC.[78] Electronic cigarettes: Abuse liability, topography and subjective effects. *Tob Control* 2014;23 Suppl 2:ii23-9. doi: 10.1136/tobaccocontrol-2013-051489 [published Online First: 14 Apr 2014]
3. Glasser A, Abudayyeh H, Cantrell J, et al.[25] Patterns of e-cigarette use among youth and young adults: Review of the impact of e-cigarettes on cigarette smoking. *Nicotine Tob Res* 2019;21(10):1320-30. doi: 10.1093/ntr/nty103 [published Online First: 17 May 2018]
4. Glasser AM, Collins L, Pearson JL, et al.[79] Overview of electronic nicotine delivery systems: A systematic review. *Am J Prev Med* 2017;52(2):e33-e66. doi: 10.1016/j.amepre.2016.10.036 [published Online First: 30 Nov 2015]
5. Hartmann-Boyce J, McRobbie H, Bullen C, et al.[80] Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2016;9:Cd010216. doi: 10.1002/14651858.CD010216.pub3 [published Online First: 13 Sep 2016]
6. Kalkhoran S, Glantz SA.[81] E-cigarettes and smoking cessation in real-world and clinical settings: A systematic review and meta-analysis. *Lancet Respir Med* 2016;4(2):116-28. doi: 10.1016/s2213-2600(15)00521-4 [published Online First: 14 Jan 2016]
7. Khoudigian S, Devji T, Lytvyn L, et al.[82] The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: A systematic review and a meta-analysis. *Int J Public Health* 2016;61(2):257-67. doi: 10.1007/s00038-016-0786-z [published Online First: 29 Jan 2016]
8. Knight-West O, Bullen C.[83] E-cigarettes for the management of nicotine addiction. *Subst Abuse Rehabil* 2016;7:111-8. doi: 10.2147/sar.S94264 [published Online First: 18 Aug 2016]
9. Liu X, Lu W, Liao S, et al.[84] Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). *Medicine (Baltimore)* 2018;97(19):e0324. doi: 10.1097/md.0000000000010324 [published Online First: 11 May 2018]
10. Livingston CJ, Freeman RJ, Costales VC, et al.[85] Electronic nicotine delivery systems or e-cigarettes: American College of Preventive Medicine's practice statement. *Am J Prev Med* 2019;56(1):167-78. doi: 10.1016/j.amepre.2018.09.010 [published Online First: 17 Dec 2018]
11. Malas M, van der Tempel J, Schwartz R, et al.[86] Electronic cigarettes for smoking cessation: A systematic review. *Nicotine Tob Res* 2016;18(10):1926-36. doi: 10.1093/ntr/ntw119 [published Online First: 25 Apr 2016]
12. O'Leary R, MacDonald M, Stockwell T, et al.[87] Clearing the air: A systematic review on the harms and benefits of e-cigarettes and vapour devices Victoria, Canada: Canadian Institute for Substance Use Research, University of Victoria, 2017.
13. Rahman MA, Hann N, Wilson A, et al.[88] E-cigarettes and smoking cessation: Evidence from a systematic review and meta-analysis. *PloS One* 2015;10(3):e0122544. doi: 10.1371/journal.pone.0122544 [published Online First: 30 Mar 2015]

Reports

1. Bals R, Boyd J, Esposito S, et al.[89] Electronic cigarettes: A task force report from the European Respiratory Society. *Eur Resp J* 2019;53(2):1801151. doi: 10.1183/13993003.01151-2018 [published Online First: 31 Jan 2019]
2. Health Information and Quality Authority, (HIQA).[90] Health technology assessment (HTA) of smoking cessation interventions Dublin, Ireland: Health Information and Quality Authority (HIQA); 2017 [Available from: https://www.hiqa.ie/sites/default/files/2017-04/Smoking%20Cessation%20HTA.pdf.

3. McNeill A, Brose L, Calder R, et al.[91] Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England London, England: Public Health England; 2018 [Available from: https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review.
4. National Academies of Sciences, Engineering, Medicine.[92] Public health consequences of e-cigarettes. Washington DC, USA: The National Academies Press; 2018 [774pp]. Available from: https://dx.doi.org/10.17226/24952
5. Wells C, Farrah K.[93] Electronic cigarettes for the reduction or cessation of smoking: clinical utility, safety, and guidelines [Rapid Response]. Ottowa, Canada: Canadian Agency for Drugs and Technologes in Health (CADTH); 2017 [Available from: https://www.cadth.ca/electronic-cigarettes-reduction-or-cessation-smoking-clinical-utility-safety-and-guidelines-0.

Appendix 2: Quality assessment-tool and results

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Quality assessment

Study ID	QA1	QA2	QA3	QA4	QA5	QA6	QA7	QA8	QA9	QA10	QA11	QA12	QA13	QA14
Aleyan 2018[53]	Y	Y	Y	Y	NR	Y	Y	N	Y	N	Y	N/A (self-report)	N	N/A
Hammond 2017[50]	Y	Y	Y	Y	N [Variance cannot be used as this is a convenience sample]	Y	Y	N	Y	N	Y	N/A (self-report)	N	Partial
Barrington-Trimis 2018a[35]	Y	Y	CD	CD	N [Variance cannot be used as this is includes a convenience sample]	Y	CD	N	Y	Y	Y	N/A (self-report)	N	N
Barrington-Trimis 2018b[36]	Y	Y (no mean age)	NR	Y	NR	Y	Y	N	Y	N	Y	N/A (self-report)	N	N/a
Barrington-Trimis 2016[34]	Y	Y	Y	N	N [Justification for matched cases not provided - sample size restricted inappropriately]	Y	Y	N	Y	Y (but not reported)	Y	N/a (self- report)	N	Partial
Berry 2019[37]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y (but not reported)	Y	N/A (self-report)	Y	Y
Watkins 2018[38]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N/A (self-report)	Y	Y
Conner 2018[39]	Y	Y	CD	Y	N [Variance cannot be used as this is a sample of controls in an RCT]	Y	Y	Y	Y	N	Y	N/A (self-report)	N	Y
East 2018[40]	Y	Y	N	N - this was a non-probability sample	NR [Variance cannot be used as	Y	Y	N	Y	Y	Y	N/A (self- report)	N	Y

				- quotas set by age gender, GOR	this is a quota sample]									
Leventhal 2015[33]	Y	Y?	Y	Y	N [Variance cannot be used as this is a convenience sample]	Y	Y	N	Y	Y	Y	N/A (self- report)	Y	Y
Leventhal 2016[52]	Y	Y	Y	Y	N [Variance cannot be used as this is a convenience sample]	Y	Y	Y	Y	N	Y	N/A (self-report)	Y	Y
Lozano 2017[41]	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N/A (self- report)	N	Y
Miech 2017[51]	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N/A (self- report)	N	Partial
Morgenstern 2018[42]	Y	Y	y	Y	Y	Y	Y	N	Y	N	Y	N/A (self- report)	Y	Partial
Spindle 2017[43]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N/A (self- report)	N	Y
Treur 2018[44]	Y	N	N (schools rather than persons)	CD	Y	Y	Y	Y	Y	Y [but not reported]	Y	N/A (self- report)	N	Partial
Wills 2016[45]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y [but not reported]	Y	N/A (self- report)	N	Y
Wills 2017a[46]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y [but not reported]	Y	N/A (self- report)	N	Partial
Wills 2017b[47]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A (self- report)	N	Partial
Best 2018[48]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA (self-report)	N	Y
Kinnunen 2019[49]	Y	Partial	Y	Y	Y	Y	Y/Y	Y	Y	Y	Y	N/A (self-report)	N	Partial

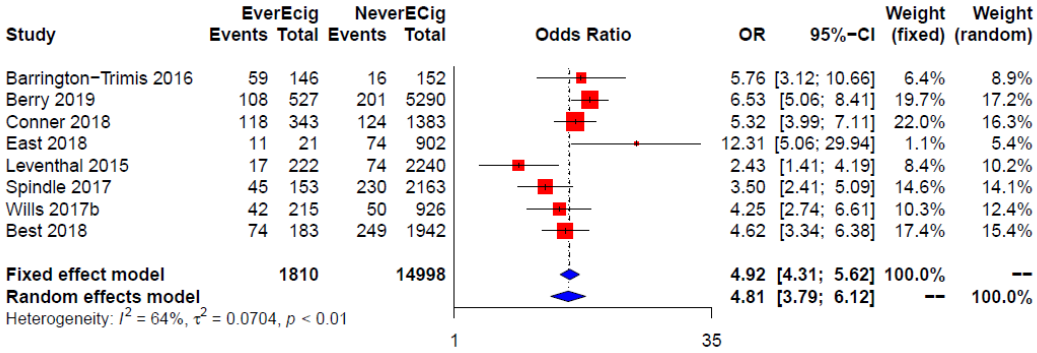
Appendix 3: Meta-analysis-feasibility

Feasibility analysis

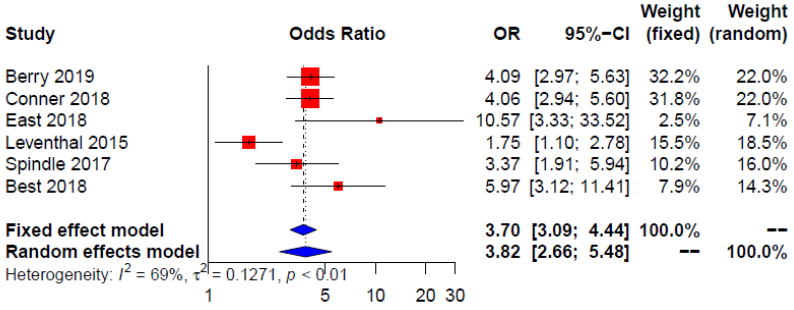
1. Collapsed duplicates – 14 unique studies
2. Separated studies by outcome and exposure
    a. Will look at ever smoked (outcome) and ever tried e-cigarette at baseline (exposure) as there is data to look at this
    b. Chose studies that report AOR
    c. Chose studies with longest follow up period
    d. Cannot look at past 30 day use of smoking as only Watkins/Spindle have complete data and have had to correct Table 2 in Spindle 2017[38 43]
3. Separated studies by length of follow up period
    a. Decided to include all time lengths as could not find evidence suggesting when effect should have taken place
    b. Will do subgroup analyses
4. Cannot separate studies by e-cigarette type as information is not available
    a. Will do subgroup of pre/post 2014- as this is the point at which e-cigarette use rapidly increased in US.
5. Separated studies by way measured
    a. Can calculate ORs for most
    b. Can only use those with AOR in main analyses (n=10)
6. All together will use 9: Barrington-Trimis (2016), Berry (2019), Conner (2018), East (2018), Leventhal (2015), Spindle (2017), Treur (2018), Wills (2017b), Best (2018). [34 37 39 40 33 43 44 47 48]

Meta-analysis results

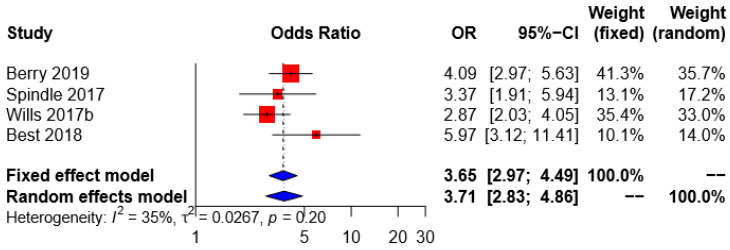
Unadjusted meta-analysis: ever e-cigarette use



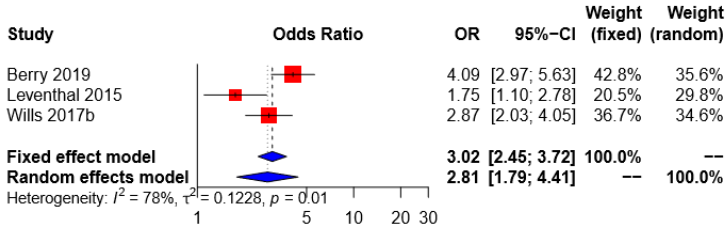
Sensitivity: only 3-domain covariate adjusted studies retained

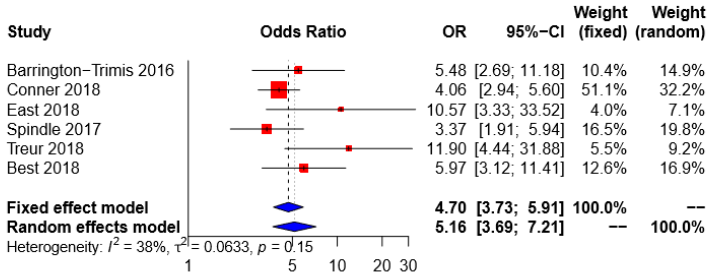


Sensitivity: only high-quality single time point studies retained

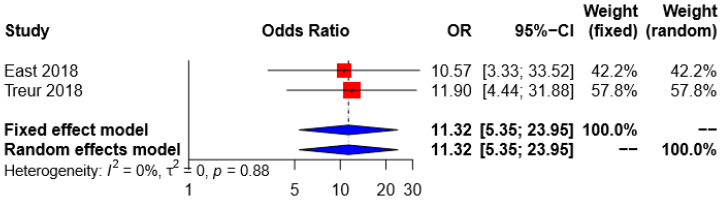


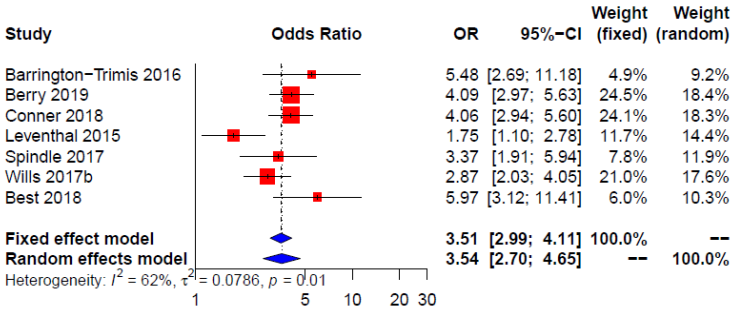
Subgroup: pre/post 2014





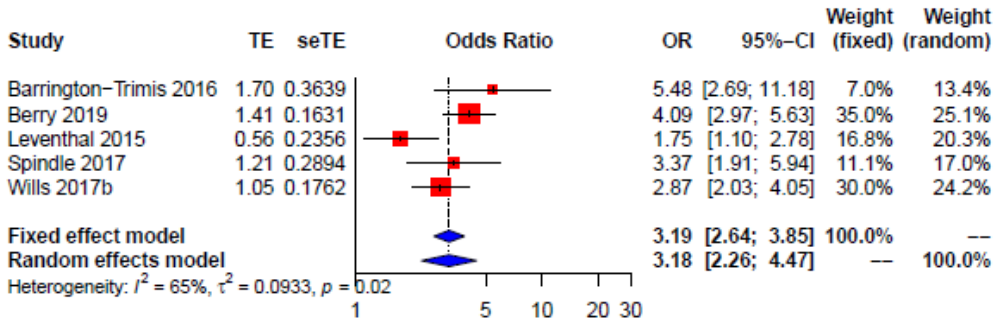
Subgroup: greater and less than 12 months follow up



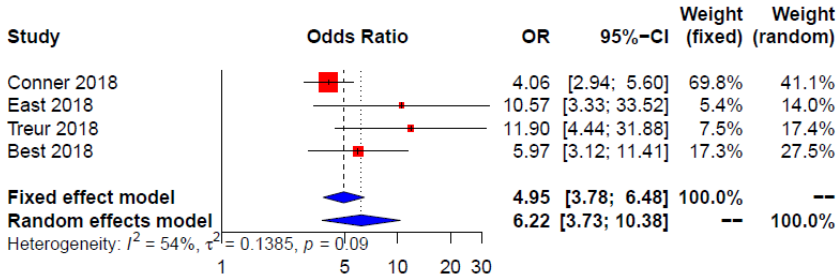


Subgroup: USA and Europe

USA



Europe



Meta-analysis: past 30 day e-cigarette use