A review of systematic reviews on the health effects of e-cigarette use in children and adolescents

Institute of Public Health

A review of systematic reviews on the health effects of e-cigarette use in children and adolescents

Developed by the Institute of Public Health for the Department of Health in Northern Ireland

To be cited as: Reynolds CME, Mack JB, O'Connor L, McAvoy H (2024). A review of systematic reviews on the health effects of e-cigarette use in children and adolescents. Institute of Public Health: Dublin and Belfast.

Published May 2024

ISBN: 978-1-913829-42-1
DOI: 10.14655/11971-1084920

Acknowledgements:

We would like to thank the Department of Health in Northern Ireland for their support with this work. We would also like to thank Mary Scarlett, Public Health Information & Research Branch, Information Analysis Directorate for reviewing the statistical elements of this review.

Declaration of interests:

CMER, JBM, LOC, and HMA have no conflicts of interest to declare.

Funding:

This report was produced within the Institute of Public Health annual budget. No additional funding was received.

Table of contents

List of Figures 5
List of Tables 5
Glossary 5
1. Executive Summary 8
2. Background 10
3. Aims and Objectives 14
4. Methodology 15
5. Results 21
6. Discussion 40
7. Conclusion 48
8. References 50
9. Appendix 54

List of Figures

Figure 1. Proportion of young people that reported ever having used e-cigarettes 12

Figure 2. Proportion of young people that regularly use e-cigarettes 12

Figure 3. PRISMA flow diagram of studies identified, screened, included, and excluded in this review of systematic reviews 21

List of Tables

Table 1. PECO Framework 16

Table 2. AMSTAR-2: Rating overall confidence in the results of the review 18

Table 3. Summary of findings 30

Table 4. Theories and models relating to e-cigarette initiation in children 42

Glossary

aOR	Adjusted odds ratio
ARR	Absolute risk reduction
CI	Confidence interval
COI	Conflict of interest
E-cigarette	Electronic cigarettes
ENDS	Electronic nicotine delivery system
ENNDS	Electronic non-nicotine delivery system
NIHR	National Institute for Health and Care Research
NHS	National Health Service
OR	Odds ratio
PECO	Population Exposure Comparator Outcome
PI	Prediction interval
RR	Risk reduction
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
YPBAS	Young Persons' Behaviours and Attitudes Survey

1 Executive Summary

1. Executive Summary

This review was undertaken to provide evidence to inform the development of policy and regulation on e-cigarettes in Northern Ireland. E-cigarette use among children and young people is rising in Northern Ireland. In 2022, one-fifth (21%) of 11–16-year-old children reported ever having used an e-cigarette, an increase of two percentage points from 2016. The proportion of children using e-cigarettes at least once a week doubled from 3% to 6% over the same period.

The methodology was agreed in advance with the Department of Health. In order to meet policy cycle timelines, a rapid review of systematic reviews published in the last ten years was conducted using strict eligibility criteria. Quality assessment was conducted using the validated AMSTAR-2 tool. Research overlap was also assessed.

We report on a review of 12 systematic reviews investigating the public health effects of e-cigarette use among children and adolescents. The outcomes found in our generalised search included tobacco cigarette smoking initiation, respiratory outcomes, mental health, drug use, and alcohol use.

This report found strong, high-quality evidence of an association between e-cigarette use and subsequent tobacco cigarette use based on longitudinal data. The reviews included found that those who had ever used e-cigarettes in their lifetime had over three times the risk of ever tobacco cigarette use at follow up. These results support a gateway effect of these products. However, although the main systematic review and meta-analysis on this topic was published in the last two years, the baseline data in the primary studies included were collected between 2013 and 2016 and device types (i.e. disposable, pods, etc.) and nicotine strengths were not reported. Although the majority of studies within the review were based in the USA, subgroup analysis found no difference in the adjusted odds ratios for the USA vs UK studies.

This review of systematic reviews also found some evidence to support the association between e-cigarette use and having asthma, increased coughing, poor mental health, marijuana use, and alcohol use including binge drinking. The quantity and quality of this evidence was mixed. Furthermore, many existing studies are cross-sectional in nature and so directionality of these relationships (i.e. which came first - e-cigarette use or asthma/ poor mental health/drug or alcohol use) remains unclear. Well-designed longitudinal studies investigating the long-term effects of these, and other potential health implications, of e-cigarette use are needed.

2 Background

2. Background

2.1 Policy context

The Ten-Year Tobacco Control Strategy for Northern Ireland was launched in 2012 and is due to expire in 2024 (1). The aim of this Strategy was to create a tobacco-free society, and significant progress was made during its implementation, with a decline in smoking prevalence seen at a population level in Northern Ireland (2).

Whilst the current Strategy focused primarily on tobacco use, there is increasing urgency to address the issue of e-cigarette use in children and young people. In recognition of the need for timely information, the Department of Health requested the Institute of Public Health to conduct a review of the evidence relating to health effects of e-cigarettes in children and adolescents. The findings of this review may help to inform the development of a new Tobacco Control Strategy in Northern Ireland.

2.2 Market context

Electronic nicotine-delivery systems (ENDS), specifically electronic cigarettes (also known as e-cigarettes, vaping devices, or vape pens), were first introduced to Europe in 2006 and have since become increasingly popular. E-cigarettes are devices that allow users to inhale or 'vape' an aerosol containing nicotine, flavourings, and/or other substances, including cannabis. Unlike traditional cigarettes, e-cigarettes are typically battery-operated and use a heating element to heat e-liquid from a cartridge, releasing an aerosol. There are four main e-cigarette devices used: disposable, tank, modified or modular ('mod'), and pod.

1. Disposable: these are non-rechargeable devices that typically come ready-filled with e-liquid. They are discarded after use.
2. Tank/Vape pens: these have a rechargeable battery and a tank that can be replenished with bottled e-liquid.
3. Modified/Modular/Mod: these are modifiable devices, allowing users to customise the substances in the device.
4. Pod: these have a prefilled or refillable "pod" or pod cartridge. They typically use nicotine salts rather than the freebase nicotine used in most other e-cigarette products. Nicotine salts allow particularly high levels of nicotine to be inhaled more easily and with less irritation to the throat than freebase nicotine.

Since 2021, a new type of disposable e-cigarettes came on the market, which is easy to use, attractive and widely available at prices children can easily afford (3). Prior to their emergence in 2021, significantly fewer children used e-cigarettes, and when they did, they mainly used rechargeable, reusable devices, which are in theory more expensive to buy. A disposable e-cigarette can be purchased for as little as £2.99, which is of concern as this may increase the accessibility of this product to children (4). However, a study set in England also found that disposable e-cigarettes have a higher average cost compared with e-liquid refills and that e-cigarette users who mainly used disposable devices spent around 40% more per week than those who used refillable devices (£8.41 vs. £5.93) (5).

2.3 Regulatory context

In October 2023, the Department of Health and Social Care (DHSC) published a command paper 'Stopping the start: our new plan to create a smokefree generation' which sets out proposed action to protect future generations from the harms of smoking and vaping. The UK Government and devolved administrations then launched a consultation on these actions. In terms of vaping products only, these included:

- restricting flavours
- regulating point of sale displays
- regulating packaging and presentation
- considering restricting the supply and sale of disposable vapes
- whether regulations should extend to non-nicotine vapes
- taking action on the affordability of vapes

Currently in Northern Ireland, it is illegal for a retailer to sell either tobacco products or nicotine inhaling products (including e-cigarettes/ vapes) to anyone under the age of 18 (6). This includes cigarette papers or e-cigarette/ vaping device refill containers. It is also an offence for an adult to buy, or try to buy, any tobacco products or nicotine inhaling products (including e-cigarettes/ vapes) on behalf of someone under the age of 18 (known as proxy purchasing). From the research outlined in this report, it is clear that the use of e-cigarette devices is linked to negative public health effects among children and adolescents. This report also describes regulatory measures that have been implemented in other countries to try curb the continuous rise in e-cigarette use among younger generations. These include, but are not limited to, banning point of sale displays, flavour restrictions, reducing affordability, restrictions on the descriptions and names of e-cigarettes and flavours, restricting sales to pharmacies, and disposable e-cigarette bans.

2.4 Use of e-cigarettes in Northern Ireland

Despite the current legislation, use of e-cigarettes remains high among children and adolescents in Northern Ireland. Health Survey Northern Ireland data found that in 2022/23, 20% (N = 132, 95% CI 13.3-27.0) of 16-24-year-olds were using e-cigarettes (7). According to the 2022 Young Persons' Behaviours and Attitudes Survey (YPBAS), e-cigarette use among children and young people is rising in Northern Ireland. In 2022, one-fifth (21%) of 11-16 year old children reported ever having used an e-cigarette, an increase of 2 percentage points from 2016 (8). The proportion of children using e-cigarettes at least once a week doubled from 3% to 6% over the same period. The 2022 YPBAS survey found that 86% of 11- to 16-year-olds in Northern Ireland who currently used e-cigarettes used a disposable type device (9).

Figure 1. Proportion of young people that reported ever having used e-cigarettes

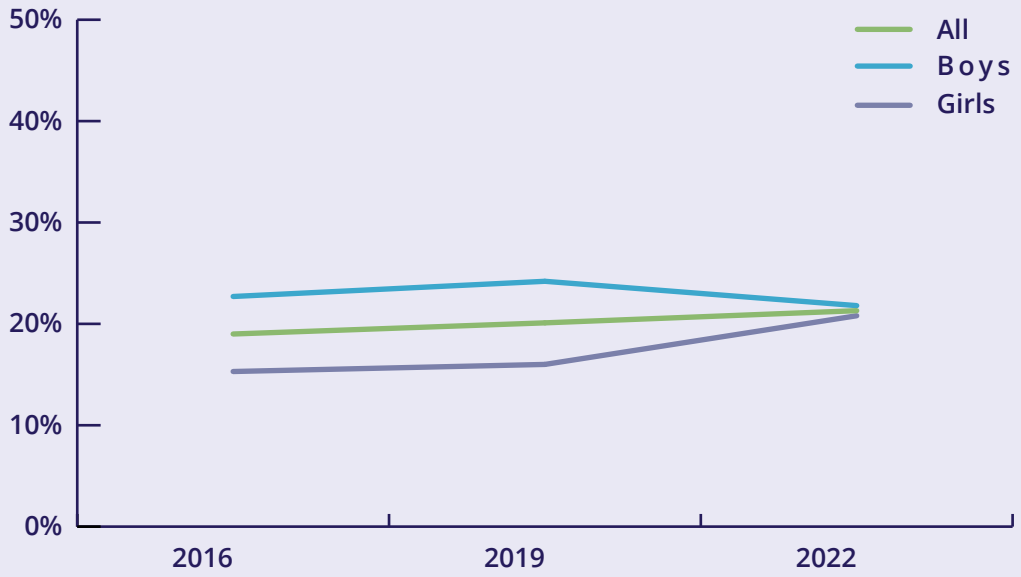
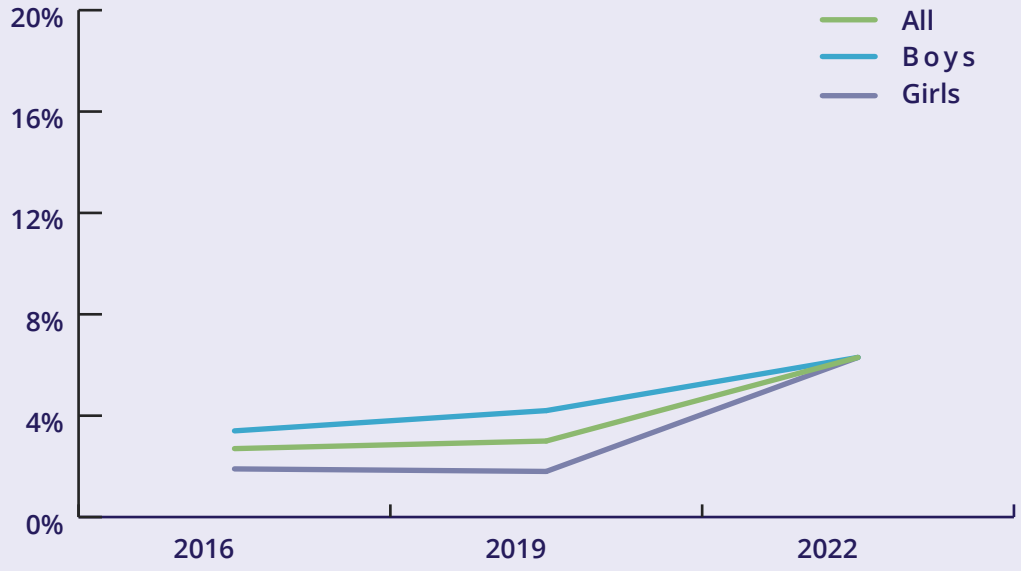


Figure 2. Proportion of young people that regularly use e-cigarettes



* Regular use is defined as at least once a week

Source: Young Persons' Behaviour and Attitudes Survey 2022 - Substance Use - (Smoking, Alcohol & Drugs. Available at: https://www.health-ni.gov.uk/sites/default/files/publications/health/infographic-22-ypbas.pdf)

In 2022, one-fifth (21%) of young people reported ever having used an e-cigarette, a small increase from 2016 (19%). The proportion indicating that they regularly used e-cigarettes showed an increase from 3% in 2016 to 6% in 2022.

The increasing incidence of e-cigarette use in young people and the need for a new Tobacco Control Strategy in Northern Ireland presents an opportune time to explore the effect of e-cigarettes on health outcomes in children and adolescents.

3 Aims and Objectives

3. Aims and Objectives

This report aims to support policy makers with evidence to inform the development of a new Tobacco Control Strategy in Northern Ireland and provide evidence to inform decisions on regulation.

The objective of this report was to conduct a rapid review of systematic reviews on the health effects of e-cigarette use in children and adolescents.

4 Methodology

4. Methodology

This section outlines the methodology employed for this report. The methodology was agreed in advance with the Department of Health and documented in a project initiation document. In order to meet policy cycle timelines, a rapid review of systematic reviews published in the last ten years was conducted using strict eligibility criteria. Quality assessment was conducted using the validated AMSTAR-2 tool[1] (Section 4.8). Research overlap (Section 4.9) was also assessed. Results were presented in a summary of findings table.

4.1 Eligibility criteria

The following eligibility criteria were agreed with the Department of Health:

Inclusion criteria

- Systematic review level evidence
- Published in the English language
- Published in the last ten years
- Human and in-vivo studies only
- Access to full-text article available
- No conflicts of interest declared from the tobacco or e-cigarette industry

Exclusion criteria

- Other nicotine products including heat-not-burn, novel tobacco products and oral nicotine products
- Pregnancy, birth, and postnatal outcomes (which may indirectly affect child health)
- Second-hand and third-hand vapour from e-cigarettes
- In-vitro studies
- Systematic reviews of three studies or less

4.2 Database

Only one database was searched to ensure policy timescales were adhered to. MedLine (PubMed) was selected as it is one of the largest databases of references and abstracts on life sciences and biomedical topics.

4.3 Dates of search

The data search included all published articles between January 2013 and February 2023.

4.4 Search strategy

The search strategy was refined in line with the needs and preferences of policy leads in the Department of Health. The Population Exposure Comparator Outcome (PECO) framework was used to structure the search string. Table 1 details the search terms used under the PECO framework:

[1] A MeaSurement Tool to Assess systematic Reviews (AMSTAR). Available at: *https://amstar.ca/About_Amstar.php*

Search string:

(Adolescen* OR Child* OR Infan* OR Teen* OR Young person OR Young people OR Young adult* OR Youth*) AND (E-cigarette OR Ecigarette OR E cigarette OR Electronic cigarette OR Nicotine inhaling product OR Vape OR Vaping OR Nicotine OR Electronic Nicotine Delivery Systems) AND (Harm OR Risk OR Negative OR Health OR Impact OR Effect OR Develop* OR Safety)

Table 1. PECO Framework

Population	Exposure	Comparator	Outcome
Adolescent*	E-cigarette	Non-user/Non-smoker	Harm
Child* (<18 years)	Ecigarette	Tobacco cigarette user	Risk
Infant*	E cigarette		Negative
Young people	Electronic cigarette		Health
Young person	Nicotine inhaling product		Impact
Young adult*	Vape		Effect
Youth	Vaping		Develop*
Teen*	Nicotine		Safety
	Electronic Nicotine Delivery Systems		

4.5 Study selection

All studies identified were independently assessed by two researchers (CMER and JBM) for inclusion in the review based on eligibility criteria in a two-stage process:

Stage 1: Titles and/or abstract review

Stage 2: Full text review

Any disagreements were resolved through mutual discussion. A third reviewer was available if required.

4.6 Data synthesis

Data extraction was completed by two researchers (CMER and JBM) independently. Any disagreements were resolved through mutual discussion. A third reviewer was available if required.

The results were presented in a summary of findings table and in the narrative of the results section. No additional analyses such as meta-analyses were conducted. The summary of findings table was developed using the PECO framework and examples of best practice e.g. from high impact factor journal articles.

4.7 Ethical considerations

As this study was a review of published/publicly available data, there were no ethical concerns.

4.8 Quality assessment methods

The methodological quality of reviews was manually assessed using AMSTAR-2, which is a validated instrument used to evaluate systematic reviews (10). This was completed by two researchers (CMER and JBM) independently with assistance from a third researcher (LOC). Any disagreements were resolved through mutual discussion. The interpretation of AMSTAR-2 results is given in Table 2.

Table 2. AMSTAR-2: Rating overall confidence in the results of the review

High
No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
Moderate
More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
Low
One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
Critically low
More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies
*Multiple non-critical weaknesses may diminish confidence in the review, and it may be appropriate to move the overall appraisal down from moderate to low confidence

4.9 Quality assessment methods

An assessment of research overlap was also conducted to identify the degree of overlap of studies used between all identified reviews. This was completed by two researchers (CMER and JBM). Research 'overlap' (using a primary study result multiple times in the same analysis) can be a challenge in reviews of systematic reviews, as it can result in discordance due to conflicting outcomes from the same research question (11).

The inclusion of the same primary study in more than one systematic review gives undue weight to that study. Using a primary study multiple times in the same analysis overstates its sample size and number of events, falsely leading to greater precision in the analysis, this is known as 'research overlap.' There are several ways to manage overlapping studies (11). These include choosing:

1. The review with the greatest number of trials/studies,
2. The highest quality review
3. The most recent review

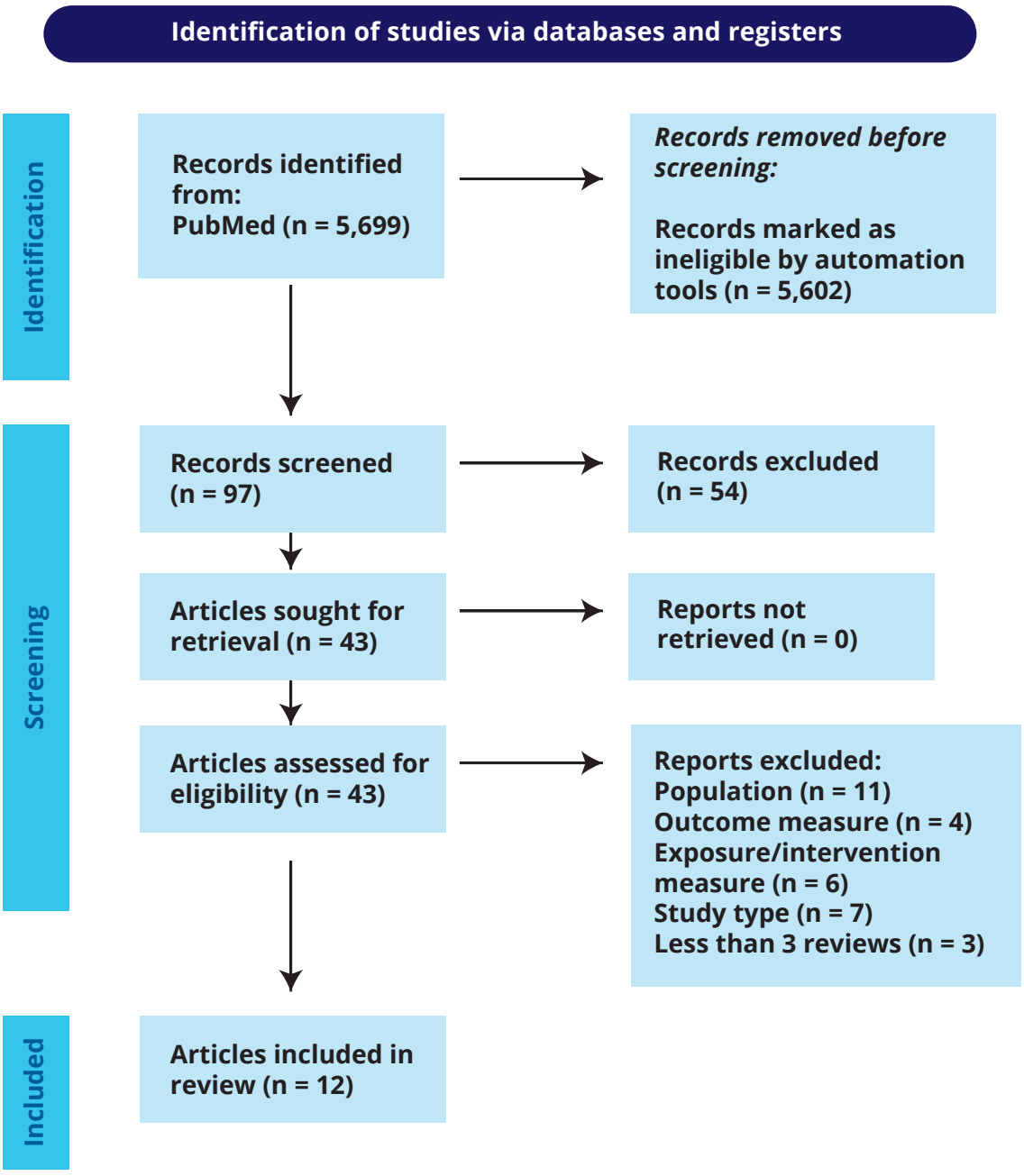
5 Results

5. Results

5.1 Selection process

Overall, 97 papers were title/abstract screened, and 43 papers were full text screened for eligibility (Figure 3). All were in English. A total of 12 papers were included in the final report. Two researchers completed all screening stages independently (CMER and JBM).

Figure 3. PRISMA flow diagram of studies identified, screened, included, and excluded in this review of systematic reviews



Source: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

5.2 Study design

All 12 of the included studies were systematic reviews that included at least three primary studies. Eight of the 12 articles also included meta-analyses.

5.3 Populations

The majority of studies focussed solely on children and adolescents, however some also included adults. Where possible, results for children only (<18 years) were extracted from these studies. Five studies included young people up to the age of 19 years (12-16). One study included young people up to 20 years (17). Two studies based their eligibility criteria of primary studies on mean and median ages, one set this at less than 18 years (18), the other at less than 20 years (19). One study included young, non-smokers up to 30 years (20). However, participants were mostly under the age of 18 years and many of the studies included were school-based (20).

The majority of the primary studies included in the systematic reviews were based in the USA. Other countries in which the primary studies took place included: East Asia, Canada, South Korea, Europe, North America, the UK, Taiwan, Mexico, Germany, the Netherlands, Switzerland, Hong Kong, Finland, Romania, France, Greece, Australia, New Zealand, Russia, Poland, and Iceland. Where studies included meta-analyses of subgroups by geographical location (i.e. USA vs UK), these results were presented in the narrative of the results section.

5.4 Definitions of e-cigarette use

The majority of studies focussed on e-cigarette use generally and did not break down the consumer product into e-cigarette types (mod, tank, disposable etc.) or flavours. Just one review by Meernik et al. 2019 investigated the use of flavours within e-cigarettes and focussed solely on 'non-menthol flavoured e-cigarettes' (15). One other review commented that two primary studies included specifically assessed the use of non-nicotine e-cigarettes while one other primary study compared flavoured and non-flavoured e-cigarettes (19). The remainder of the reviews described the devices as 'e-cigarettes' or 'electronic nicotine delivery systems (ENDS).'

In terms of measures of use, the majority of studies focussed on 'ever,' 'current' and '30-day use'. Some reviews also included past use. The majority used the comparator group 'non-users of e-cigarettes.' Just one study compared their results with never, trial or not recent e-cigarette and smokers (20). All measures of e-cigarette use are described in the summary of findings tables and outlined in the narrative of the results sections below.

5.5 Declarations of interest

Declarations of interest were assessed by both researchers (CMER and JBM). Reviews that declared conflicts of interest due to affiliations with the tobacco or e-cigarette industry were excluded from this report. One review did not include a declaration of interest statement and one did not report any conflicts of interest however two authors reported grants from Pfizer outside the submitted work (20, 21).

5.6 Quality assessment

The quality of the included reviews was manually assessed using AMSTAR-2 (10). Of the 12 reviews included, four were rated 'critically low' (15-17, 22), four were rated 'low' (12, 13, 21, 23), three were rated 'moderate' (14, 18, 20) and just one was rated 'high' (19). Heterogeneity was reported for all studies that reported it in their meta-analyses. $I^2 < 40\%$ was considered low heterogeneity, 30–60% moderate, 50% to 90% substantial, and 75% to 100% considerable (24).

5.7 Tobacco cigarette smoking initiation

We found significant overlap between all five out of the six systematic reviews that contained meta-analyses investigating the association between e-cigarette use at baseline and tobacco cigarette smoking at follow up (Appendix Table 1). Due to this, the most recent and largest systematic review of the highest quality by Yoong et al. 2021 was chosen for full discussion in this section. The remaining four other systematic reviews had over 85% of the same studies included in their meta-analysis. These are presented in the summary of findings table but will be discussed only briefly here. Meernik et al. 2019 conducted a systematic review, but it did not include a meta-analysis and therefore, was not included in the overlap assessment. The findings from Meernik et al. 2019 will also be discussed in the narrative of the results section.

Yoong et al. 2021 investigated the association between electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS) use among non-smoking children and adolescents aged <20 years with subsequent tobacco use. Twenty-five prospective longitudinal studies were included in the systematic review and 23 in the meta-analysis (after exclusion of overlapping studies). No industry-funded studies were included in the meta-analysis and where multiple follow-up points were available, the furthest timepoint from baseline was included.

The majority of studies were conducted in the USA (n = 13), as well as Germany (n = 3), the UK (n = 2), Scotland (n = 1), Canada (n = 1), Finland (n = 1), Mexico (n = 1), Taiwan (n = 1), Netherlands (n = 1) and Romania (n = 1). Data collection occurred from 2013–2016 at baseline and the follow-up period was between six and 24 months. All studies used self-reported measures to assess cigarette (and/or tobacco) use at follow up. Overall, 21 studies assessed cigarette smoking only as an outcome, three assessed cigarettes and other tobacco and one assessed other tobacco only. Two studies specifically assessed the use of non-nicotine e-cigarettes while one study compared flavoured and non-flavoured e-cigarettes.

The primary outcome variable was ever and current cigarette smoking. For 'ever' cigarette smoking, this included 'lifetime ever use.' For 'current' cigarette use, this included 'use in the past 30 days', 'frequent' and 'daily' cigarette use. The exposure variable was 'ever' and 'current' ENDS/ENNDS use. For 'ever' use of ENDS and/or ENNDS, this was defined as 'lifetime ever use.' For 'current' use of ENDS and/or ENNDS, this included 'use in the past 30 days', 'recent use' and self-defined 'current use'.

Seventeen studies assessed the association between ever ENDS/ENNDS use and subsequent ever cigarette use. Ever users of ENDS/ENNDS had over three times the risk of ever cigarette use at follow up (adjusted risk ratios (ARR), also known as risk difference, 3.01, 95% CI 2.37-3.82, p<0.001, I^2=82.3%). Most of the primary studies adjusted for covariates including sex and age or school grade, with the majority also adjusting for additional variables including susceptibility to smoking, influence by friends and family, psychological constructs and status, and exposure to advertising.

Six studies assessed the association between ever ENDS/ENNDS use at baseline and subsequent current cigarette use at follow-up. Ever users of ENDS/ENNDS had two and a half times the risk of current use at follow up (ARR 2.56, 95% CI 1.61-4.07, p<0.001, I^2=77.3%) at follow up.

Among current ENDS/ENNDS users, there was a significant association with ever (risk ratio (RR) 2.63, 95% CI 1.94-3.57, p<0.001, I^2=21.2% from four studies) but not current cigarette use at follow up (RR 1.88, 95% CI 0.34-10.30, p=0.467, I^2=0% from two studies), although

a positive relationship was found. A positive association was found between ENNDS use at baseline and later cigarette use (RR 2.56, 95% CI 0.47-13.94, p>0.05, I^2=77.5% from two studies). However, this was not statistically significant potentially due to the small number of studies included.

The ARRs for baseline ever ENDS/ENNDS use, and current cigarette use at follow-up were similar by geographic location, year of publication, length of follow up and study quality. For example, when the eight studies from the USA were pooled in analysis the adjusted risk ratios assessing the association between ever e-cigarette use at baseline and ever tobacco use at follow-up was 3.22 (95% CI 2.20-4.74, p-value not reported[1], I^2=84.9%). This was similar[2] to the ARR for the three UK studies at 4.14 (95% CI 2.34-7.31, p-value not reported[1], I^2=72.3%) and the 'other' countries at 2.27 (95% CI 1.71-3.02, p-value not reported[1], I^2=67.7%). The authors reported high heterogeneity in the meta-analysis, unexplained by the subgroup analysis, indicating that the reason for the variation remains unknown.

Using AMSTAR-2, Yoong et al. 2021 was rated 'high'.

As discussed, four systematic reviews found on this topic had high primary study overlap within their meta-analysis with Yoong et al. 2021. These included Khouja et al. 2020 at 88%, Aladeokin and Haighton 2019 at 100%, Chan et al. 2021 at 100%, and O'Brien et al. 2021 also at 100% (Appendix Table 1).

Chan et al. 2021 and Khouja et al. 2020 both found a three times higher adjusted odds of commencing tobacco cigarette smoking for teenagers who had ever used e-cigarettes at baseline. Similarly, O'Brien et al. 2021 found a four times higher adjusted odds, while Aladeokin and Haighton 2019 found an almost six times unadjusted odds of subsequent cigarette smoking at follow up.

Moderate to high heterogeneity was reported in the majority of the meta-analyses, apart from Aladeokin and Haighton 2019 who reported that the presence and extent of heterogeneity (I^2=52%) as well as the risk of bias were relatively low. The meta analysis by Aladeokin and Haighton 2019 was based on three longitudinal studies from the UK only. Results from four of the cross-sectional studies also included in the review found that in adolescents who have ever used e-cigarettes, current regular smokers were more likely to use e-cigarettes than other groups such as light smokers or ex-smokers, showing an association of use. Results also showed that traditional cigarette smoking can also precede e-cigarette use in adolescents, and there was increased likelihood of an increase in initial product use (e-cigarette or traditional cigarette) when the alternate product was initiated.

Using AMSTAR-2, Khouja et al. 2020 and Aladeokin and Haighton 2019 were rated 'moderate', whilst Chan et al. 2021 and O'Brien et al. 2021 were rated 'low'.

[1] Data extracted from supplementary files - forest plot did not provide p-values, but 95% CI do not cross the null therefore indicating all reported ARRs are statistically significant in the between-country analysis.

[2] Overlapping 95% CI confidence intervals indicate that these ARRs are not statistically different from each other.

Meernik et al. 2019 conducted a systematic review of 51 articles. However, just six were of note to the outcome of interest within this review. It did not include a meta-analysis. The six studies showed consistent positive associations between availability of non-menthol flavoured e-cigarettes and intention to use e-cigarettes, however one did not. Flavoured e-cigarette use among non-smoking youth was associated with increased intention to initiate cigarette use. One study reported that students who reported using flavoured e-cigarettes were less likely to quit tobacco use compared with those who reported not using e-cigarettes or with those who had used non-flavoured e-cigarettes.

Using AMSTAR-2, Meernik et al. 2019 was rated 'critically low'.

Conclusion:
Overall, meta-analyses showed consistent evidence that e-cigarette use at baseline resulted in a higher odds of subsequent tobacco cigarette smoking at follow up. All five of the six systematic reviews containing meta-analysis had significant primary study overlap. Just one study was rated 'high' based on the AMSTAR-2 appraisal tool for systematic reviews.

One systematic review reported evidence of positive associations between availability of non-menthol flavoured e-cigarettes and intention to use e-cigarettes and tobacco cigarettes among non-smoking youth and reduced likelihood of quitting tobacco cigarettes.

5.8 Respiratory outcomes

A total of three systematic reviews investigated respiratory outcomes including asthma and respiratory symptoms, predominantly coughing (Table 3). Two out of the three also included meta-analyses (21, 22). All three reviews included studies from the USA and Canada. Other countries/regions where the primary studies took place included East Asia, South Korea, Switzerland, and Hong Kong.

An investigation of research overlap (Appendix Table 2) by the current report's authors found that eight studies (72.7%) were common to both Li et al. 2022 and Wills et al. 2021. Due to this, Li et al. 2022 was chosen to be discussed in full in this section as it was the most recent article and had a higher AMSTAR-2 rating than Wills et al. 2021. Wills et al. 2021 is presented in the summary of findings table but will only be briefly discussed in this section. Bourke et al. 2021 was not included in the overlap assessment as it did not contain a meta-analysis.

Li et al. 2022 examined the association between e-cigarettes and asthma among a similar population of middle- and high-school students with a mean age of 15 to 16 years. Ten cross-sectional studies were included of which five studies were conducted in the USA, four were conducted in South Korea, and one study was conducted in Canada. E-cigarette use was defined in the majority of the primary studies as 'ever' or 'current use' and compared to 'never use.' The review found that on meta-analysis, any e-cigarette use (current or ever use) was associated with significantly higher odds of having asthma (pooled odds ratio (OR) 1.31, 95% CI 1.22-1.42, $p<0.001$, I^2 =80%) than non-use, with both current use (OR 1.36, 95% CI 1.26, 1.48, $p<0.001$, I^2 =61%) and ever use (OR 1.20, 95% CI 1.12-1.28, $p<0.001$,

I^2=19%) showing similar associations. Pooled ORs were 1.22 (95% CI 1.12-1.33, p<0.001, I^2 =30%) in studies based on exclusive e-cigarette use and 1.34 (95% CI 1.22-1.48, p<0.001, I^2 =90%) in studies where it was not clearly defined whether smoking was also present or not. Several other subgroup analyses were conducted, including Asian versus North American studies, each of which found no significant differences in effect estimates. The authors also reported that no significant publication bias was present based on two statistical tests.

Using AMSTAR-2, Li et al. 2022 was rated 'low'.

Wills et al. 2021 also reviewed the association of e-cigarette use with asthma and with COPD. For the current report, only the results for asthma were reported as the primary COPD studies were conducted in adults. The studies included had similar measures, age groups and outcomes as Li et al 2022. Most of the studies controlled for cigarette smoking, indicating that observed effects for e-cigarettes are not attributable to confounding with smoking. The meta-analysis for asthma was based on 11 studies of adolescents and four studies of adults. A random effects meta-analysis indicated the pooled adjusted odds ratio (aOR) for asthma was 1.39 (95% CI 1.28-1.51, p-value not reported[4], I^3=50%) for e-cigarette users compared to non-e-cigarette users. There was moderate heterogeneity in the results with international studies exhibiting greater heterogeneity than US-based studies. A separate meta-analysis of the four adult studies only reported a significant aOR of 1.40 (95% CI 1.23–1.58, p-value not reported[3], I^2 percentage not reported) and it was therefore deemed appropriate by the authors to include these within the adolescent studies analysis. A separate meta-analysis was therefore not conducted for adolescent studies only.

Using AMSTAR-2, Wills et al. 2021 was rated 'critically low'.

Bourke et al. 2021 investigated the association between e-cigarette use in children and adolescents under the age of 20 years and coughing. The systematic review included seven studies, six of which were cross-sectional and one was a retrospective medical chart review. No meta-analysis was included. The majority of primary studies were conducted in the USA. The measures of e-cigarette use in the primary studies included current use, past use, and ever use. Three studies compared e-cigarette users to non-users and four studies had no comparator group. The systematic review showed a strong association between e-cigarette use and coughing. Three of the seven primary studies showed an increased rate of coughing among e-cigarette users compared to non-users. Bourke and colleagues also found associations between e-cigarette use and other respiratory symptoms such as wheeze, asthma, dyspnoea, rhinitis, dry mouth, and headaches. However, these were not main outcome variables of the review and some of these symptoms were found in singular primary studies.The authors noted that smoking was not taken into account in the analyses of six of the seven studies included.

Using AMSTAR-2, Bourke et al. 2021 was rated 'critically low'.

[3] Did not provide p-values, but 95% CI do not cross the null therefore indicating statistical significance.

Conclusion:
Overall, meta-analyses showed consistent evidence that any frequency of e-cigarette use was associated with a significantly higher odds of having asthma. The two systematic reviews containing meta-analyses had significant primary study overlap and were rated 'low' and 'critically low' based on the AMSTAR-2 appraisal tool for systematic reviews.

One systematic review study reported a strong association between e-cigarette use and coughing. No reviews included evidence on severity of asthma, respiratory infections, health service use or hospitalisations due to respiratory issues.

5.9 Mental health

One systematic review by Becker et al. 2021 explored the effect of e-cigarettes on mental health in adolescents and young adults between the ages of 12- and 26-years-old. The included studies were mostly conducted in the USA, but also included studies carried out in South Korea, the UK, and Taiwan. Forty studies (16 longitudinal, 23 cross-sectional and one case study) were included in this review. Of these, 24 studies focused on adolescents, and 16 focused on young adults. For the purpose of this report, data was not extracted for young adults.

Methods of measuring e-cigarette use varied across assessment of lifetime use, current use, age of use onset, and frequency of use.

Mental health outcomes were grouped under three main categories: internalising disorders, externalising disorders, and transdiagnostic concepts. The 24 studies that focused on adolescents found that e-cigarette use is associated with internalising problems (including depression, anxiety (limited evidence), suicidality and eating disorders), externalising problems (including attention-deficit/hyperactivity disorder and conduct disorder), and transdiagnostic concepts (impulsivity and perceived stress), when compared with non-use. The authors noted that most studies were cross-sectional, or longitudinal studies with short-term follow-up, and therefore, directionality remains uncertain.

Using AMSTAR-2, Becker et al. 2021 was rated 'critically low'.

Conclusion:
Conclusion box: One systematic review reported that child e-cigarette use correlates with several domains of mental health problems.

5.10 Drug use

One systematic review by Chadi et al. 2019 examined the association between e-cigarettes and drug use. The majority of the studies included in this review were conducted in the USA. Other countries included France, Greece, Australia, New Zealand, Russia, and Canada. Of the 21 independent observational studies included in this review, 14 studies focused only on the youth population and were therefore, included in a separate meta-analysis.

The measures of e-cigarette use included current use (in the past month) and/or ever use. The meta-analysis included 3 longitudinal and 18 cross-sectional studies that included 128 227 participants aged up to 24 years. Overall, the odds of marijuana use were higher in those who had an e-cigarette use history vs those who did not (aOR 3.47, 95%CI 2.63-4.59, I^2=94%). This association remained the same regardless of which study type was investigated (longitudinal versus cross-sectional). Subgroup analysis by single use of e-cigarettes vs dual use of both e-cigarettes and cigarettes or other tobacco products showed a stronger association with marijuana use in studies with youths (up to age 24 years) with dual use (4 studies; aOR 5.39, 95% CI 3.53-8.24, I^2=87.6%) than in studies with youths with e-cigarette use only (17 studies; aOR, 3.10, 95% CI 2.22-4.34, I^2=94.6%) however 95% confidence intervals were overlapping.

A further subgroup analysis, and the one most relevant to the current report, was based on the 14 studies that included participants with a mean or median age younger than 18 years. This analysis showed a strong association between e-cigarette use and marijuana use (aOR 4.29, 95% CI 3.14-5.87, p-value not reported[4], I^2=94%). Observed heterogeneity was high.

An analysis that compared European and North American studies (included some studies with participants over 18 years) found that the pooled aOR for the association between e-cigarette use and marijuana use was higher for North American studies (15 studies aOR, 4.03, 95% CI 2.97-5.49, p-value not reported[4]) than for European studies (4 studies aOR, 2.12, 95% CI 1.70-2.65, p-value not reported[4]).

Using AMSTAR-2, Chadi et al. 2019 was rated 'moderate'.

Conclusion box:
One systematic review found a significant increase in the odds of past or current and subsequent marijuana use was found in adolescents who used e-cigarettes.

5.11 Alcohol use

One systematic review by Rothrock et al. 2020 investigated the association between e-cigarettes and alcohol use in children aged 10 to 19 years or high school age or younger. The majority of the 28 studies were conducted in the USA, but also included studies from Taiwan, France, the UK, Hong Kong, Poland, Russia, Iceland, South Korea, Canada, Switzerland, Mexico, and Australia. Of the 28 articles included in the meta-analysis, 25 studies were cross-sectional and three were retrospective cohort studies. Measures of e-cigarette use was defined as ever (lifetime) use or current use (use in the past 30 days). Binge drinking definitions differed between studies with the use of the term drunkenness or having ≥4, ≥5, or ≥6 drinks at a time. While individuals with binge drinking and drunkenness do not comprise the same population, the authors combined the studies and subsets of studies that evaluated binge drinking and drunkenness into a composite outcome of binge drinking/drunkenness.

Rothrock et al. 2020 found that adolescents who used e-cigarettes were six and a half times more likely to use any alcohol (OR 6.62, 95% CI 5.67–7.72, p-value not reported[4], I^2=96%) and meet the composite definition of binge drinking/drunkenness (OR 6.73, 95% CI

[4] did not provide p-values, but 95% CI do not cross the null therefore indicating statistical significance.

4.5–10.07, p-value not reported[5], I^2=99%) compared to those who did not use e-cigarettes. Studies included in the meta-analysis were cross-sectional and retrospective cohort surveys and did not adjust for other confounders that might affect e-cigarette and alcohol use including education, gender, genetics, family, environment, local laws, availability of alcohol and e-cigarettes, social settings, and cultural factors. Therefore, crude odds ratios and not adjusted odds ratios were used to analyse the associations.

Heterogeneity was high across all studies evaluating any alcohol use, all studies evaluating binge drinking/drunkenness, and all subgroups. Univariate meta-regression found no moderators that had a significant effect on heterogeneity. Egger regression found no publication bias in studies of any alcohol use or binge drinking/drunkenness.

Using AMSTAR-2, Rothrock et al. 2020 was rated 'low'.

Conclusion:
One systematic review found that e-cigarette users had a higher risk of alcohol use and binge drinking/drunkenness compared to non-e-cigarette users.

[5] Did not provide p-values, but 95% CI do not cross the null therefore indicating statistical significance.

Table 3. Summary of findings

Author	Topic	Country	Study design	Population	Device type	E-cigarette measure	Comparator	Outcome	Conflict of Interest (COI)	AMSTAR-2
Yoong et al. 2021	Tobacco cigarette smoking initiation	Majority US: others included Germany, UK, Scotland, Canada, Finland, Mexico, Taiwan, Netherlands, and Romania	25 studies prospective longitudinal studies were included in the systematic review, with 23 of these studies included in the meta-analysis	Children and adolescents aged less than 20 years who were non-tobacco users at baseline. However, participants were aged between 11 to 26 years (as studies were eligible for inclusion if they had a mean age of <20)	All studies referred to electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) as e-cigarettes. Two studies specifically assessed the use of non-nicotine e-cigarettes while one study compared flavoured and non-flavoured e-cigarettes.	Ever and current ENDS/ ENNDS use. For ever use of ENDS and/or ENNDS, this was defined as lifetime ever use. For current use of ENDS and/ or ENNDS, this included use in the past 30 days, recent use, and self-defined current use.	Not provided	This systematic review described the association between electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ ENNDS) use among non-smoking children and adolescents aged <20 years with subsequent tobacco use. Ever users of ENDS/ENNDS had over three times the risk of ever cigarette use (adjusted risk ratios (ARR) 3.01, 95% CI 2.37-3.82, p<0.001, I^2=82.3%), and current cigarette use had over two times the risk (ARR 2.56, 95% CI 1.61-4.07, p<0.001, I^2=77.3%) at follow up. Among current ENDS/ ENNDS users, there was a significant association with ever, but not current cigarette use at follow up. A positive association was found between ENNDS use at baseline and later cigarette use (risk ratio (RR) 2.56, 95% CI 0.47-13.94, p>0.05, I^2=77.5%). However, this was not statistically significant potentially due to the small number	None	High

								of studies included. The authors reported high heterogeneity in the meta-analysis, unexplained by the subgroup analysis, indicating that the reason for the variation remains unknown. This review found evidence of a longitudinal association between ENDS/ENNDS use at baseline and subsequent tobacco use in those aged <20 years.		
O'Brien et al. 2021	Tobacco cigarette smoking initiation	Europe and North America	21 longitudinal cohort prospective studies based on data from 14 one-off primary studies were included, 9 of which were included in the meta-analysis.	16,808 participants included within the 9 studies in meta-analysis. All adolescents aged 13-19 years at baseline.	E-cigarettes	Mostly ever use and some 30-day use	Non-users of e-cigarettes	Based on primary study aORs, meta-analysis calculated a 4.06 (95% CI 3.00–5.48, I2 68%, 9 primary studies) times higher odds of commencing tobacco cigarette smoking for teenagers who had ever used e-cigarettes at baseline, though the odds ratio were marginally lower (OR 3.71, 95%CI 2.83–4. 86, I2 35%, 4 primary studies) when only the four high-quality studies were analysed. The geographical, regulatory, and cultural context of these studies were considered, and European studies were compared with those from the USA. The combined OR was higher in the European studies (OR 6.22, 95%CI 3.73–10.38, I2 54%) compared with the USA studies (OR 3.18, 95%CI 2.26–4.47 I2 65%). However, the CIs overlap indicating that they are not statistically different.	None	Low

Khouja et al. 2020	Tobacco cigarette smoking initiation	Mainly USA: others included the UK, Canada, Mexico, Germany, and the Netherlands	Systematic review and meta-analysis of 17 observational studies, of which 14 included children only (under 18 years)	Young, non-smokers (up to 30 years). Participants were mostly under the age of 18 years and many of the studies were school-based	E-cigarettes	Baseline or retrospective measure of e-cigarette use (including but not limited to ever, occasional, heavy, recent, regular, or frequent use) prior to initiating smoking	Young people who were never, trial or not recent e-cigarette users or smokers	When pooled in a random-effects meta-analysis, e-cigarette use in non-smoking young people was associated with a four-and-a-half-fold increase in the odds of subsequent smoking (OR 4.59, 95% CI 3.60-5.85). Pooling the adjusted estimates, the association was still strong but somewhat weaker (aOR 2.92, 95% CI 2.30-3.71). However, there was high heterogeneity in both analysis (I^2=88% and (I^2=85%). When the unadjusted main analyses were stratified by age (including versus excluding under the age of 18 years) the pooled OR among studies including those under the age of 18 years was slightly higher (OR 4.87, 95% CI 3.73-6.35) than the pooled OR of studies excluding those under the age of 18 years (OR 3.17, 95% CI 2.37-4.25). Heterogeneity estimates indicated that there was low heterogeneity between studies excluding those under the age of 18 years (I^2=32%) but high heterogeneity between studies including those under the age of 18 years (I^2=88%). Stratification by location indicated stronger associations in the UK compared with the USA and other countries. The results provide some support for a causal relationship between e-cigarette use and later smoking.	None however two authors reported grants from Pfizer outside the submitted work.	Moderate

Chan et al. 2021	Tobacco cigarette smoking initiation	Majority USA: others included UK, Canada, Taiwan, Mexico	Systematic review and meta-analysis of 11 longitudinal studies	General population of adolescents (aged 18 years and below) who have never smoked at baseline. Sample sizes ranged from 246 to 17318.	E-cigarettes	Lifetime e-cigarette use, past month e-cigarette use	Seven studies examined the association between life-time e-cigarette use at baseline and smoking initiation at follow up, two examined past month e-cigarette use and smoking initiation and one examined life-time e-cigarette use, and past 6-month smoking and one examined past month e-cigarette use and smoking initiation.	Those who initiated e-cigarette use during adolescence had a 2.93 (95% CI 2.22-3.87, p<0.001) times higher adjusted odds of future smoking initiation. All but one study were rated as having critical or serious risk of bias. Overall, the attrition rate was very high (median = 30%). Overall, there was a longitudinal association between adolescent e-cigarette use and smoking initiation; however, the evidence is limited by publication bias, high sample attrition, significant heterogeneity, and inadequate adjustment for potential confounders.	None	Low

Aladeokin and Haighton 2019	Tobacco cigarette smoking initiation	UK	8 studies (5 cross-sectional, 3 longitudinal) included in systematic review of which three (longitudinal) were included in a meta-analysis	Adolescents 10-19 years. Population size of 73,076.	E-cigarettes	Ever-use, tried or regular use	Adolescents who had never used e-cigarettes (amongst the 3 longitudinal studies included in the meta-analysis)	The three longitudinal studies included in the meta-analysis showed that non-smoking adolescents who use e-cigarettes are up to six times more likely to smoke traditional cigarettes. The unadjusted odds ratio was 5.55 (95% CI 3.94–7.82, I2=52%). Furthermore, results showed that traditional cigarette smoking can also precede e-cigarette use in adolescents and there was increased likelihood of an increase in initial product use (e-cigarette or traditional cigarette) when the alternate product was initiated. The remaining included studies employed cross-sectional surveys and therefore were only able to show an association between e-cigarette use and traditional cigarette smoking in British adolescents.	None	Moderate
Meernik et al. 2019	Tobacco cigarette smoking initiation	Majority US: others included UK and South Korea	Systematic review of 51 studies (cross-sectional and longitudinal). 13 studies focused on youth only. The remainder focused on adults or adults and youth, and so were not included in the data extraction	Majority <18 years, some went up to 19 years	Non-menthol flavoured e-cigarettes	E-cigarette use in last 30 days, ever use	Non-users of e-cigarettes, non-flavoured e-cigarette user	Six studies showed consistent positive associations between flavours and intention to use e-cigarettes, however one did not. Flavoured e-cigarette use among non-smoking youth was associated with increased intention to initiate cigarette use. One study reported that students who reported using flavoured e-cigarettes were less likely to quit tobacco use compared with those who reported not using e-cigarettes or with those who had used non-flavoured e-cigarettes.	None	Critically low

Li et al. 2022	Asthma	USA, South Korea, and Canada	Meta-analysis of 10 cross-sectional studies. Two separate pooled analyses were conducted. The first investigated current use (n=8 studies) and the second investigated ever use (n= 7 studies) of e-cigarettes.	483,948 middle- and high-school students with a mean age of 15 −16 years	E-cigarettes	Mostly ever and 30-day use	Never-use of e-cigarettes	Overall, any e-cigarette use (current or ever use) was associated with significantly higher odds of having asthma (pooled OR 1.31, 95% CI 1.22-1.42, I2=80%, p<0.001) than non-use, and both current use (OR 1.36, 95% CI 1.26-1.48, I2=61% p<0.001) and ever use (OR 1.20, 95% CI 1.12-1.28, I2=19%, p<0.001) showed similar associations.	COI statement not reported	Low
*Wills et al. 2021**	Asthma	USA, East Asia, Canada	Meta-analysis of 11 epidemiological studies focused on asthma.	Adolescents, mostly high school (15-18 years).	E-cigarettes	Mostly ever and 30-day use	Non-users of e-cigarettes	Overall, the studies showed higher adjusted odds ratios (aOR 1.39, 95% CI 1.28–1.51, I2=50%, p<0.01) – includes 11 studies of children and 4 adult studies) for asthma among e-cigarette users compared to non-e-cigarette users following adjustment for smoking.	None	Critically low

Bourke et al. 2021	Coughing	Majority USA: others included Canada, Switzerland, and Hong Kong.	Systematic review of 7 studies (6 cross-sectional studies, one retrospective medical chart review)	Participants were under the age of 20.	E-cigarettes	Current users, past users, ever users	Three studies compared e-cigarette users to non-users, four studies had no comparator group	This systematic review showed a strong association between e-cigarette use and coughing, three of the seven showed an increased rate of coughing among e-cigarette users compared to non-users.	None	Critically low
Becker at al. 2021	Mental Health	Mainly USA: others included South Korea, UK, and Taiwan	Systematic review of 40 studies (16 longitudinal, 23 cross-sectional and 1 case study).	24 studies focused on adolescents (aged 12-19 years), 16 on young adults. Data not extracted for young adults.	E-cigarettes	Measures varied in assessing lifetime use, current use, age of use onset, and frequency of use	Non-users of e-cigarettes	Youth e-cigarette use is associated with greater mental health problems (compared with non-use) across several domains, particularly among adolescents. Among adolescent studies, e-cigarette use is associated with internalising problems, depression, suicidality, disordered eating, externalising problems, ADHD, conduct disorder, impulsivity, and perceived stress, with additional limited evidence for an association with anxiety.	None	Critically low

Chadi et al. 2019	Drug use	Majority USA: others included France, Greece, Australia, New Zealand, Russia, Canada	Systematic review and meta-analysis of 21 observational studies. 14 studies only focused on the youth population and were included in a separate meta-analysis.	Participants with a mean or median age younger than 18 years	This study referred to electronic nicotine delivery systems (ENDS)	Current (in the past month) and/or ever	No history of ENDS use	ENDS use was significantly associated with marijuana use in a large sample of adolescents and young adults pooled from 21 independent observational studies. Subgroup analyses by age showed a stronger association between ENDS use and marijuana use in studies with participants with a mean or median age younger than 18 years (14 studies; aOR 4.29, 95% CI 3.14-5.87, I2=94%) vs studies with participants with a mean or median age 18 years and older (7 studies; aOR 2.30, 95% CI 1.40-3.79, I2=91%). A subgroup analysis that compared European and North American studies (included some studies with participants over 18 years) found that the	None	Moderate

								pooled aOR for the association between ENDS use and marijuana use was higher for North American studies (15 studies aOR, 4.03, 95% CI 2.97-5.49, I2 not reported) than for European studies (4 studies aOR, 2.12, 95% CI 1.70-2.65, I2 not reported).		
Rothrock et al. 2020	Alcohol use	Majority USA: others included Taiwan, France, UK, Hong Kong, Poland, Russia, Iceland, South Korea, Canada, Switzerland, Mexico, Australia	Systematic review and meta-analysis of 28 studies (25 were cross-sectional and 3 were retrospective cohort studies)	Adolescents aged 10 to 19 years or high school age or younger. Total participants-458,357.	E-cigarettes	E-cigarette use was defined as ever (lifetime) or current use (use in the past 30 days)	Non-users of e-cigarettes	Meta-analysis showed that adolescents who used e-cigarettes were six and a half times more likely to use any alcohol (OR 6.62, 95% CI 5.67–7.72, I2=96%) and meet the composite definition of binge drinking/drunkenness (OR 6.73, 95% CI 4.5–10.07, I2=99%) compared to those who did not use e-cigarettes.	None	Low

*After the author and year indicates the review included adults but children's data were extracted where possible unless otherwise indicated in the table.

6 Discussion

6. Discussion

6.1 Overall findings

We report on a review of 12 systematic reviews investigating the public health effects of e-cigarette use among children and adolescents. The outcomes found in our generalised search included tobacco cigarette smoking initiation, respiratory outcomes, mental health, drug use, and alcohol use.

This report found strong evidence of an association between ever e-cigarette use and subsequent ever or current cigarette use at follow up based on longitudinal data. These results support a gateway effect of these products. However, although the main systematic review and meta-analysis on this topic was published in the last two years, the baseline data in the primary studies included were collected between 2013 and 2016 and device types (i.e. disposable, pods, etc.) and nicotine strengths were not reported (19). Although the majority of studies within the review were based in the USA, subgroup analysis found no difference in the adjusted odds ratios for the USA vs UK studies.

This review of systematic reviews also found some evidence to support the association between e-cigarette use and having asthma, increased coughing, poor mental health, marijuana use, and alcohol use. The quantity and quality of this evidence was mixed. Furthermore, many existing studies are cross-sectional in nature and so directionality of these relationships remains unclear. Well-designed longitudinal studies investigating long-term effects of these, and other potential health implications, of e-cigarette use are needed.

6.2 Limitations

6.2.1 Limitations within the report

This review of systematic reviews has limitations. Firstly, just one database (PubMed) was used due to policy cycle timelines. Only systematic reviews published in the English language over the last 10 years were selected due to both time and resource constraints. Although a systematic approach was taken, this was not a full systematic review.

6.2.2 Limitations within the evidence base

The primary limitation of the research was the heterogeneity of the exposure (e-cigarette) in terms of device type, generation, nicotine content, and e-liquid including flavours. E-cigarettes and their e-liquids are not a standardised product/exposure but an umbrella term for a device that delivers nicotine, other chemicals and products, including flavourings. The regulation of e-cigarettes and e-liquids differs significantly across jurisdictions in terms of nicotine concentration limits, age of sale and enforcement (25). We did, however, provide any subgroup analyses on European or UK versus US or Asian studies which showed no statistically significant differences in results. None of the primary studies in the meta-analysis biochemically verified outcomes and they relied on self-report. However, the tried and tested questions about ever use, recent or last year use, and current or last 30 days use were used and as it is not human nature to over-estimate use of these types of products, it is likely that the strength of relationships would only increase if

biochemical measures were employed.

The primary studies included in the systematic reviews that investigated the association between e-cigarettes and respiratory symptoms, mental health, drug use and alcohol use were mostly cross-sectional and so directionality of these relationships remains unclear as does any dose response and causality cannot be inferred. Lastly, although the majority of the systematic reviews and meta-analysis included in this report were published in the last three years, the primary study data were collected several years earlier. In most cases, the primary data pre-dates the rise in popularity of new e-cigarette products, particularly disposable e-cigarettes, which are now, by far the most popular of all e-cigarette products among children in the UK (26). This review did not explore social, economic, educational, or behavioural outcomes.

6.3 Strengths

6.3.1 Strengths within the report

Only systematic review level evidence was included in this rapid review and there are strengths and limitations to this approach. Systematic reviews are considered the 'best evidence' for decision making, particularly in health-related topic areas, as they are based on the findings of multiple studies that were identified in comprehensive, systematic literature searches. On the other hand, systematic reviews may miss out on emerging evidence. Other study types, including non-systematic reviews and reports by leading health organisations and expert groups, have captured other health-related outcomes of e-cigarettes among children not included in this review. These outcomes include deleterious impacts on brain development, poisonings/severe toxicity from e-liquid ingestion, and acute injuries from burns and explosions of the devices (27-29).

A quality assessment with a validated tool, AMSTAR-2, was conducted by two researchers independently and results were discussed. An investigation of research overlap was also conducted. Research overlap prevents giving undue weight to one primary study. This was managed by providing the full results of the systematic review with the best balance of quality of studies, quality of review, and that was most recently published. In terms of bias, we excluded any research that was funded by, or affiliated with, the tobacco or e-cigarette industry.

6.3.2 Strengths within the evidence base

The strongest and highest quality review in this report was Yoong et al.2021 which investigated the relationship between e-cigarette use and subsequent tobacco cigarette smoking initiation (19). The longitudinal data permits researchers to start the process of establishing a causal relationship. Moreover, the use of e-cigarettes which occurred before initiating smoking, fulfils the criteria for a temporal relationship.

6.4 Tobacco cigarette smoking initiation

Substance use data from the 2022 wave of the YPBAS reported that 8% of all 11-16 year olds in Northern Ireland had ever reported smoking, however this rose to 21% when confined to Year 12 students only (30). Two percent of all 11–16-year-olds were current smokers but this tripled when confined to Year 12 only (7%). Based on the same data, just over one fifth (21%) of all 11–16-year-olds had ever tried an e-cigarette and when confined to Year 12 students, this rose to 48%. Approximately a quarter (26%) of students living

in the most deprived areas had ever used an e-cigarette. Just under one in 10 (9%) of all 11–16-year-olds were current e-cigarette users but when confined to Year 12 children, this rose to just under a quarter (24%). Of those who had both ever smoked and ever used e-cigarettes, 38% started using e-cigarettes before they started smoking cigarettes, 45% started using e-cigarettes after they started smoking and 17% started using e-cigarettes at the same time as they started smoking.

There are differing opinions on the relationship between e-cigarettes and traditional tobacco cigarettes. The three main theories or hypothesis are the 'gateway theory,' the 'common liability theory' and the 'catalyst model' (Table 4).

Table 4. Theories and models relating to e-cigarette initiation in children

Theory/Model	Description
Gateway theory	The use of e-cigarettes causes the subsequent use of conventional cigarettes.
Common liability theory	Those who use e-cigarettes and subsequently smoke traditional cigarettes would have tried cigarettes in the absence of e-cigarette use, since the use of either product reflect a common propensity for risky behaviour.
Catalyst model	Tobacco smoking among never users of e-cigarettes is associated with greater odds of later e-cigarette use.

The gateway hypothesis suggests that the use of e-cigarettes causes the subsequent use of conventional cigarettes whereas the common liability theory suggests that those who use e-cigarettes and subsequently smoke traditional cigarettes would have tried cigarettes in the absence of e-cigarette use, since the use of either product reflect a common propensity for risky behaviour (31). There is also some evidence for a 'reverse gateway theory' whereby tobacco smoking among never users of e-cigarettes is associated with greater odds of later e-cigarette use however this theory requires further investigation and may reflect a conscious transition to a potentially less harmful behaviour (32). Furthermore, the authors of the original gateway theory even describe nicotine as a gateway drug that primes the brain for other substance use, 'whether the exposures is from smoking tobacco, passive tobacco smoke, or e-cigarettes'. Lastly, the catalyst model separates 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 (12).

The authors of the largest and highest quality meta-analysis included in this report found strong evidence to support a causal relationship between ever e-cigarette use (with or without nicotine) and ever smoking (19). There were few studies assessing the impact of

non-nicotine and flavoured tobacco products. In Northern Ireland, e-cigarette use among youth is increasing and 77% of 11-18-year-olds agreed that the flavours and colourful packaging used for e-cigarettes make them appealing (33). Among 11- to 17-year-olds in Britain who use e-cigarettes, the most popular flavours are fruit (60%), followed by sweet or soft drink (25%) (26). E-cigarette products with flavours other than tobacco are perceived by youth to be less harmful (15). Flavours contribute to the appeal and palatability of e-cigarettes to non-smokers and children and there is no evidence that certain flavours enhance the ability of smokers to stop using tobacco (15, 34). Furthermore, emerging evidence shows that concentrations of flavour chemicals in e-liquid are high enough to be cytotoxic (35, 36). The cooling attributes of certain e-cigarette flavours such as menthol have been shown to play a role in initiating tobacco use among young people (37). Cooling flavours can suppress the irritable effects of nicotine, counterbalancing a barrier that may otherwise prevent young people from using e-cigarettes (35).

Many countries and regions across the world, including Finland, the Netherlands, and Australia have implemented restrictions on e-cigarette flavours and although it is too soon to evaluate the impact of these policy measures, the best available review level evidence concluded that restricting flavours is effective in reducing youth e-cigarette use (38).

6.5 Respiratory outcomes

Data from the Northern Ireland branch of Asthma + Lung UK reports that around 126,000 people are currently receiving treatment for asthma in Northern Ireland, including 36,000 children (39). It has long been established that tobacco cigarette smoking and second hand smoke exposure contributes to respiratory infections and asthma in children which can negatively affect the development of their lungs (40). However, the relationship between asthma and e-cigarette use is not as well understood.

Our report found two systematic reviews that investigated the association between asthma and e-cigarette use and one which reported on other respiratory symptoms. Our report found that based on observational data and adjusted for smoking use in the meta-analyses, e-cigarette use was associated with having asthma (21, 22). The reviews included in this report were not able to distinguish between active asthma and nonactive asthma, as these data were not reported in the included primary studies (21, 22). This is an important classification and should be considered in the data collection of future studies on this topic. Systematic review level evidence also found an increased rate of coughing associated with e-cigarette use (17).

At the time of writing, there is no available therapeutic regimens that can cure asthma. There are, however, associations between asthma and a wide range of environmental factors or 'asthma triggers' such as tobacco smoke, dust mites, and air pollution. Li et al. 2022 concluded that based on their results e-cigarette use appears to be a potential trigger for asthma in adolescents (21). It is still widely debated as to whether e-cigarettes should be promoted as a harm-reduction device for smokers, particularly for adolescents as subgroup analysis in this study indicated that exclusive use of e-cigarettes remained significantly associated with asthma in adolescents (pooled OR=1.22, 95% CI=1.12, 1.33).

Wills et al. 2021 included both a meta-analysis of the association between e-cigarette use and asthma as well as a summary of laboratory studies investigating the effects of e-cigarettes on four types of biological processes that are linked to respiratory outcomes (22). The authors reported that while other processes are possibly implicated, such as fine particulate matter, these are the areas where the most direct evidence is available. Although nicotine itself has adverse effects on pulmonary variables, in several studies the effects observed for e-cigarettes are independent of nicotine content, hence are attributable to other components of e-cigarette liquid or aerosol. The results of the meta-

analysis are included in the results section of this report however we now discuss the potential underlying mechanisms behind the relationship.

Wills et al. reported that epidemiological studies have consistently noted that dual users have significantly more respiratory symptomatology compared with exclusive e-cigarette users or exclusive smokers (22). Therefore, although e-cigarette use is correlated with smoking, they are not interchangeable, and they produce additive effects. The laboratory studies of genetic expression also show that effects of e-cigarettes occur in part through different biological pathways than cigarettes. E-cigarette use does not merely parallel effects of smoking but contributes independently to risk.

Laboratory studies have shown e-cigarettes to have effects on four biological processes that are relevant for respiratory disease (22). Evidence is found for exposure to e-cigarette liquid or aerosol producing cytotoxic effects and oxidative stress. Results for inflammation are less consistent, but effects on cytokines and other indices of inflammation have been found in several studies. Both cell studies and animal models indicate that bacterial virulence and indices of susceptibility to infection are increased by e-cigarette exposure and that bacteria- and virus-infected animals show higher morbidity and mortality when they are exposed to e-cigarette aerosol.

Finally, Wills et al reported that studies of genetic variables have found e-cigarettes to cause DNA damage and e-cigarette use to suppress genes involved in immune function, with pathways that can be distinct from those found for cigarettes (22). The finding of biological effects for e-cigarettes across four outcome domains in both cell cultures, animal models and human studies shows a replicable body of findings linking e-cigarettes to several biological processes involved in the pathogenesis of respiratory disease in humans.

6.6 Mental health

Mental health in children and adolescents in Northern Ireland was included as part of the YPBAS in 2022. In 2022, when asked whether they ever had concerns or worries about their mental health, 19% of respondents indicated they definitely have had concerns and a further 32% indicated to some extent (41). The corresponding findings from the previous survey in 2019 were 15% and 27% respectively (42).

One review investigated e-cigarette use and mental health among adolescents (16). It found that among adolescent studies, e-cigarette use was associated with internalising problems, depression, suicidality, disordered eating, externalising problems, ADHD, conduct disorder, impulsivity, and perceived stress, with additional limited evidence for an association with anxiety. Due to the study designs of the primary studies included, the review was not able to determine the directionality of the relationships and the evidence that was available was mixed. In addition, most studies relied on mental health screening measures, which were not designed to be diagnostic.

Some longitudinal evidence suggests that e-cigarette use is linked to subsequent psychopathology whereas others found bi-directional relationships, and some found no relationships at all. Additionally, most studies found high co-use of other substances as well as e-cigarette use however, those that included substance use as a covariate still found significant relationships between e-cigarette use and mental ill-health. Further longitudinal research is needed to better understand how mental illness influences the uptake, use patterns, and cessation of e-cigarettes.

6.7 Drug use

Data from the 2022 wave of YPBAS reported that four percent of all 11-16 year olds had used drugs at least once (9). This rose to one in ten when confined to Year 12 students only. The most recent national substance treatment statistics from 2021 and 2022 in England found that cannabis remained the most common substance that young people received treatment for at 87% (43). Around half of young people in treatment (46%) said they had problems with alcohol, 8% had problems with ecstasy and 8% reported powder cocaine problems. The most common vulnerability reported by young people starting treatment was early onset substance use (80%), which means the young person started using substances before the age of 15. This was followed by polydrug use (55%). It is well established that the younger the age at onset of substance use, the higher the likelihood of developing a substance use disorder later in life (44).

One review was found on the relationship between drugs and e-cigarette use (18). It found a significant increase in the odds of using marijuana in youths who had used e-cigarettes in both cross-sectional and longitudinal studies. Furthermore, the three longitudinal studies included in the review suggested that e-cigarettes use typically predates use of marijuana.

Adolescents and young adults, whose brains are still developing, are reported to be more vulnerable than older adults to the addictive properties of nicotine, alcohol, marijuana, and other drugs (45). Longitudinal studies have shown that marijuana use during adolescence is associated with reduced cognitive abilities, motivation, satisfaction with life, and life achievement, as well as significantly greater rates of mental health disorders, such as depression, anxiety, and schizophrenia (18).

6.8 Alcohol use

Substance use data from the 2022 wave of YPBAS reported that 31% of all 11-16 year olds report having ever taken an alcoholic drink, 46% of whom had ever been drunk (9). Over half (51%) of those who had ever been drunk reported being drunk in the last month. One review found in our search investigated the relationship between alcohol and e-cigarette use. It found that adolescents who used e-cigarettes were six and a half times more likely to use any alcohol and meet the composite definition of binge drinking/drunkenness compared to those who did not use e-cigarettes based on crude odds ratios.

There were differences in the drinking ages within the countries where the data originated from within the review. For example, the USA had a legal drinking age of 21 years old, seven countries had a legal drinking age of 18 years, one each had 19 or 20 years, and two countries had a range depending on the province and type of alcohol ingested. Despite having the highest drinking age, the US odds ratio for any alcohol use in e-cigarette users was still high, (OR 7.5, 95% CI, 6.4–8.4), indicating that many factors besides the legal drinking age play an important role in alcohol consumption in e-cigarette users.

6.9 International recommendations on e-cigarette regulation

The most recent update from the World Health Organization (WHO) reports that there remains a great deal of uncertainty surrounding the potential toxicity of ENDS (46). Although some have been shown to help smokers quit conventional smoking under certain conditions, when used as nicotine replacement therapies (NRTs) the scientific evidence is inconclusive. The update also reported that there have only been a limited number of randomized control trials and longitudinal studies investigating the role of ENDS as potential cessation aids offered to a population, and their conclusions are equivocal.

ENDS are currently banned in over 30 countries worldwide. In others, they are regulated as consumer products, as pharmaceutical products, as tobacco products, other categories or totally unregulated. Where they are not banned, the WHO recommends that ENDS are regulated to:

- Prevent initiation of ENDS use by non-smokers and children, such as by preventing or restricting advertising, promotion and sponsorship, and restricting flavours that appeal to children
- Minimise as far as possible potential health and/or risks to ENDS users, such as by regulating product characteristics
- Protect non-users from exposure to their emissions, such as by prohibiting ENDS use in indoor spaces where smoking is not permitted
- Prevent unproven health claims
- Protect public health policies from commercial and other vested interests.

An independent review into smokefree 2030 policies in England, "Making smoking obsolete", was conducted by Dr Javed Khan OBE and published in 2022 (47). This review emphasises that e-cigarette use should only be used as a tobacco smoking cessation tool. Conversely, Quigley et al (2020) found that e-cigarettes were no more effective than approved and regulated nicotine replacement therapies to help people stop smoking (48). E-cigarettes as a smoking cessation device are not regulated or approved, and their safety beyond 12 months is not yet known. However, there is agreement that young people and those who have never smoked should not use e-cigarettes. The recommendations outlined in Dr Khan's report included:

» Ban cartoon characters or images appealing to young people from e-cigarette products.

» Review the way flavours are described – or even the flavours themselves – to ensure e-cigarettes do not appeal to young people.

» Prohibit e-cigarette companies from giving away e-cigarettes for free.

» Make the use (or even the possession) of any age restricted products illegal on school and college premises.

» Update the school health education curriculum to talk about the risks of e-cigarette use and its age restrictions. This should include guidance on policies associated with cannabis vaping among young people.

» More research should be commissioned on how young people access e-cigarette products online, and an extension through an online ban of e-cigarette sales should be considered in the future.

7 Conclusion

7. Conclusion

This review of 12 systematic reviews investigating the health effects of e-cigarette use among children and adolescents found strong, high-quality evidence of an association between e-cigarette use at baseline and subsequent cigarette use at follow up supporting a gateway effect of these products. It also found some evidence to support the association between e-cigarette use and having asthma, increased coughing, marijuana use, alcohol use and mental ill-health. The quantity and quality of this evidence was mixed. Many existing studies are cross-sectional in nature and so directionality remains uncertain. Well-designed longitudinal studies to investigate long-term health implications of e-cigarette use are needed.

8 References

8. References

1. Department of Health, Social Services, and Public Safety. Ten-Year Tobacco Control Strategy For Northern Ireland. Belfast; 2012.
2. Department of Health Northern Ireland. The 10 Year Tobacco Control Strategy For Northern Ireland: Final Review. Belfast; 2023.
3. Action on Smoking and Health (ASH). Policy options to tackle the issue of disposable (single use) vapes. London; 2023.
4. Mahase E. Paediatricians call for ban on disposable e-cigarettes as child vaping rises. British Medical Journal Publishing Group; 2023.
5. Jackson SE, Tattan-Birch H, Shahab L, Brown J. How has expenditure on nicotine products changed in a fast-evolving marketplace? A representative population survey in England, 2018-2022. Nicotine & Tobacco Research. 2023.
6. NI Direct. Smoking and vaping regulations in Northern Ireland Belfast: nidirect; 2022 [Available from: ***https://www.nidirect.gov.uk/articles/smoking-and-vaping-regulations-northern-ireland#:~:text=prisons-,Restrictions%20on%20retailers,under%20the%20age%20of%2018***.
7. Corrigan D, O'Hagan C, Scarlett M, Stewart B. Health Survey (NI): First Results 2021/22. Belfast; 2022.
8. Northern Ireland Statistics and Research Agency. Young Persons Behaviours and Attitudes Survey: Key Findings 2022-2023. Belfast; 2023.
9. Foster C, Scarlett M, Stewart B. Young Persons' Behaviour and Attitudes Survey 2022 - Substance Use - (Smoking, Alcohol & Drugs). Belfast; 2023.
10. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. bmj. 2017;358.
11. Lunny C, Pieper D, Thabet P, Kanji S. Managing overlap of primary study results across systematic reviews: practical considerations for authors of overviews of reviews. BMC Medical Research Methodology. 2021;21(1):1-14.
12. O'Brien D, Long J, Quigley J, Lee C, McCarthy A, Kavanagh P. Association between electronic cigarette use and tobacco cigarette smoking initiation in adolescents: a systematic review and meta-analysis. BMC Public Health. 2021;21(1):954.
13. Rothrock AN, Andris H, Swetland SB, Chavez V, Isaak S, Pagane M, et al. Association of E-cigarettes with adolescent alcohol use and binge drinking-drunkenness: A systematic review and meta-analysis. Am J Drug Alcohol Abuse. 2020;46(6):684-98.
14. Aladeokin A, Haighton C. Corrigendum: Is adolescent e-cigarette use associated with smoking in the United Kingdom?: A systematic review with meta-analysis. Tob Prev Cessat. 2019;5:38.
15. Meernik C, Baker HM, Kowitt SD, Ranney LM, Goldstein AO. Impact of non-menthol flavours in e-cigarettes on perceptions and use: an updated systematic review. BMJ Open. 2019;9(10):e031598.
16. Becker TD, Arnold MK, Ro V, Martin L, Rice TR. Systematic Review of Electronic Cigarette Use (Vaping) and Mental Health Comorbidity Among Adolescents and Young Adults. Nicotine Tob Res. 2021;23(3):415-25.

17. Bourke M, Sharif N, Narayan O. Association between electronic cigarette use in children and adolescents and coughing a systematic review. Pediatr Pulmonol. 2021;56(10):3402-9.

18. Chadi N, Schroeder R, Jensen JW, Levy S. Association Between Electronic Cigarette Use and Marijuana Use Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. JAMA Pediatr. 2019;173(10):e192574.

19. Yoong SL, Hall A, Turon H, Stockings E, Leonard A, Grady A, et al. Association between electronic nicotine delivery systems and electronic non-nicotine delivery systems with initiation of tobacco use in individuals aged < 20 years. A systematic review and meta-analysis. PLoS One. 2021;16(9):e0256044.

20. Khouja JN, Suddell SF, Peters SE, Taylor AE, Munafò MR. Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis. Tob Control. 2020;30(1):8-15.

21. Li X, Zhang Y, Zhang R, Chen F, Shao L, Zhang L. Association Between E-Cigarettes and Asthma in Adolescents: A Systematic Review and Meta-Analysis. Am J Prev Med. 2022;62(6):953-60.

22. Wills TA, Soneji SS, Choi K, Jaspers I, Tam EK. E-cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. Eur Respir J. 2021;57(1).

23. Chan GCK, Stjepanović D, Lim C, Sun T, Shanmuga Anandan A, Connor JP, et al. Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. Addiction. 2021;116(4):743-56.

24. Deeks JJ, Higgins JP, Altman DG, Group obotCSM. Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 241-84.

25. Snell LM, Nicksic N, Panteli D, Burke S, Eissenberg T, Fattore G, et al. Emerging electronic cigarette policies in European member states, Canada, and the United States. Health Policy. 2021;125(4):425-35.

26. Action on Smoking and Health (ASH). Use of e-cigarettes (vapes) among young people in Great Britain. London; 2023.

27. World Health Organization. Technical note on the call to action on electronic cigarettes. Geneva; 2023.

28. Scientific Committee on Health, Environmental and Emerging Risks (SCHEER). Opinion on electronic cigarettes. Brussels; 2021.

29. McCarthy A, Lee C, O'Brien D, Long J. Harms and benefits of e-cigarettes and heat-not-burn tobacco products: A literature map. Dublin; 2021.

30. Department of Health. Young persons behaviour and attitudes survey 2022 - substance use data tables. Belfast2023.

31. Sun R, Mendez D, Warner KE. Is Adolescent E-Cigarette Use Associated With Subsequent Smoking? A New Look. Nicotine Tob Res. 2022;24(5):710-8.

32. Martinelli T, Candel M, de Vries H, Talhout R, Knapen V, van Schayck CP, et al. Exploring the gateway hypothesis of e-cigarettes and tobacco: a prospective replication study among adolescents in the Netherlands and Flanders. Tob Control. 2023;32(2):170-8.

33. Public Health Agency Health Intelligence Unit. Knowledge, Perceptions and Behaviours of Young People towards E-cigarettes/Vaping. Belfast; 2023.

34. Institute for Global Tobacco Control. State of the Evidence: Flavored Tobacco Product Bans or Restrictions. 2020.

35. Omaiye EE, McWhirter KJ, Luo W, Pankow JF, Talbot P. High-Nicotine Electronic Cigarette Products: Toxicity of JUUL Fluids and Aerosols Correlates Strongly with Nicotine and Some Flavor Chemical Concentrations. Chem Res Toxicol. 2019;32(6):1058-69.

36. Hua M, Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P. Identification of Cytotoxic Flavor Chemicals in Top-Selling Electronic Cigarette Refill Fluids. Sci Rep. 2019;9(1):2782.

37. Truth Initiative. Young e-cigarette users report widespread use of flavor blends and "concept" flavors like Iced Mango, Blue Dream, and OMG Washington DC2023 [Available from: ***https://truthinitiative.org/research-resources/emerging-tobacco-products/young-e-cigarette-users-report-widespread-use-flavor***.

38. Reiter A, Hébert-Losier A, Mylocopos G, Filion KB, Windle SB, O'Loughlin JL, et al. Regulatory Strategies for Preventing and Reducing Nicotine Vaping among Youth: A Systematic Review. American Journal of Preventive Medicine. 2023.

39. Asthma + Lung UK. Northern Ireland 2024 [Available from: ***https://www.asthmaandlung.org.uk/northern-ireland#:~:text=Key%20stats,Pulmonary%20Fibrosis%20in%20Northern%20Ireland.***

40. Semple S, O'Donnell R, Purdy J. An overview of progress on reducing second-hand smoke exposure in Northern Ireland and policy options for the future. Dublin and Belfast; 2023.

41. Scarlett M, Corrigan D, Stewart B. Young Persons' Behaviour and Attitudes Survey 2022: Mental Health & Wellbeing modules. Belfast; 2023.

42. Cooke K, Scarlett M, Stewart B. Young Persons' Behaviour and Attitudes Survey 2019: Mental Health & Wellbeing modules. Belfast; 2020.

43. Office for Health Improvement & Disparities. Young people's substance misuse treatment statistics 2021 to 2022: report: OHID; 2023 [Available from: ***https://www.gov.uk/government/statistics/substance-misuse-treatment-for-young-people-statistics-2021-to-2022/young-peoples-substance-misuse-treatment-statistics-2021-to-2022-report#:~:text=The%20most%20common%20vulnerability%20was,reporting%20polydrug%20use%20(55%25)***.

44. Hamidullah S, Thorpe HHA, Frie JA, McCurdy RD, Khokhar JY. Adolescent Substance Use and the Brain: Behavioral, Cognitive and Neuroimaging Correlates. Front Hum Neurosci. 2020;14:298.

45. Squeglia LM, Gray KM. Alcohol and Drug Use and the Developing Brain. Curr Psychiatry Rep. 2016;18(5):46.

46. World Health Organization. WHO report on the global tobacco epidemic, 2019: offer help to quit tobacco use. Geneva: World Health Organization; 2019 2019.

47. Khan J. The Khan review: making smoking obsolete. Office for Health Improvements and Disparities; 2022.

48. Quigley J, Kennelly H, Lee C, O'Brien D, Williams M, McCarthy A, et al. Electronic cigarettes and smoking cessation: An evidence review. Dublin; 2020.

9 Appendix

9. Appendix

Appendix Table 1. Tobacco cigarette smoking initiation research overlap assessment (meta-analysis studies only)

	Yoong et al. 2021 (n=23)	Khouja et al. 2020 (n=17)	Chan et al. 2021 (n=11)	O'Brien et al. 2021 (n=9)	Aladeokin and Haighton 2019 (n=3)
Barrington-Trimis et al. 2016	✓	✗	✓	✓	✗
Berry et al. 2019	✓	✗	✓	✓	✗
Conner et al. 2018	✓	✓	✓	✓	✓
East et al. 2018	✓	✓	✓	✓	✓
Leventhal et al. 2015	✓	✓	✓	✓	✗
Spindle et al. 2017*	✓	✓	✗	✓	✗
Treur et al. 2018	✓	✓	✗	✓	✗
Wills et al. 2017	✓	✓	✓	✓	✗
Best et al. 2018	✓	✓	✓	✓	✓
Barrington-Trimis et al. 2018	✓	✓	✗	✗	✗
Hammond et al. 2017	✓	✓	✓	✗	✗
Loukas et al. 2018*	✓	✓	✗	✗	✗
Lozano et al. 2017	✓	✓	✓	✗	✗
Miech et al. 2017	✓	✓	✓	✗	✗
Morgenstern et al. 2018	✓	✓	✗	✗	✗
Primack et al. 2015	✓	✓	✗	✗	✗
Watkins et al. 2018	✓	✓	✗	✗	✗
Chien et al. 2019	✓	✗	✓	✗	✗
Hansen et al. 2020	✓	✗	✗	✗	✗

Kinnunen et al. 2019	✓	✗	✗	✗	✗
Kong et al. 2019	✓	✗	✗	✗	✗
Osibogu et al. 2020	✓	✗	✗	✗	✗
Pénzes et al. 2018	✓	✗	✗	✗	✗
Auf et al. 2019	✗	✓	✗	✗	✗
Primack et al. 2018*	✗	✓	✗	✗	✗
Overlap percentage^	Reference	88.00%	100.00%	100.00%	100.00%

*Includes participants over 18 years

^Based on the reference group Yoong et al. 2021

Appendix Table 2. Asthma research overlap assessment (meta-analysis studies only

	Li et al. 2022 (n=10)	Wills et al. 2021 (n=11)
Cho and Paik 2016	✓	✓
Kim et al. 2017	✓	✓
Lee et al. 2019	✓	✓
Wang et al. 2016	✗	✓
Choi and Bernat 2016	✓	✓
Fedel et al. 2016	✓	✓
Bayly et al. 2019	✗	✓
Larsen et al. 2016	✓	✓
Schweitzer et al. 2017	✓	✓
Wills et al. 2020	✓	✓
McConnell et al. 2017	✗	✓
Chung et al. 2020	✓	✗
Han et al. 2020	✓	✗
Richmond et al. 2018	✗	✗
King et al. 2020	✗	✗
Mantey et al. 2017	✗	✗
Mozun et al. 2020	✗	✗
Rao et al. 2020	✗	✗
Overlap percentage^	Reference	72.7%

^Based on the reference group Li et al. 2022

Institute of Public Health

publichealth.ie

Dublin Office
700 South Circular Road
Dublin 8
DO8 NH90, Ireland
T: + 353 1 478 6300

Belfast Office
6th Floor, City Exchange
11-13 Gloucester Street
Belfast
BT1 4LS, Northern Ireland
T: + 44 28 90 648494

info@publichealth.ie
publichealth.ie