Australian National University

Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation

Final report prepared for the National Health and Medical Research Council

June 2021

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DECLARATIONS OF INTEREST

The authors of this report have no affiliations with or involvement in any organisations or entities with any financial or non-financial interest in e-cigarettes. One of the authors (MM) has previously worked in Tobacco Control in New Zealand and another (EB) has published research on the health effects of smoking; all authors have authored papers based on the e-cigarettes program of work.

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Background

E-cigarettes are a diverse group of battery-powered devices that create an aerosol from a liquid (e-liquid). Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol – mainly used in e-cigarettes as a solvent to produce visible aerosol – glycerine and flavouring agents, and commonly contains nicotine. E-liquids containing nicotine salt compounds are increasingly common.

This document provides supplementary material to the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* from February 2021. The *Review* presented the findings of three separate reviews; *Review one: Patterns of e-cigarette use* (*Patterns Review*), *Review two: E-cigarette use and smoking uptake* (*Uptake Review*) and *Review three: E-cigarette use and smoking cessation* (*Cessation Review*).

Aim and Methods

This report responds to a request for additional evidence and analyses from the AustralianNational Health and Medical Research Council's Electronic Cigarette Working Committee by supplementing the material presented in the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* on patterns of e-cigarette use and smoking uptake and cessation associated with e-cigarette use, using the studies identified in the *Review* as well as additional evidence as applicable. The specific areas addressed are to:

- Include the latest Australian evidence in the *Patterns Review*;
- Conduct additional analyses relating to conflict of interest for the *Cessation Review* and the *Uptake Review*;
- Consider risk of bias in non-randomised studies using the ROBINS-I tool, a breakdown of available demographic information from included studies, the likelihood that e-cigarettes will increase the number of young people using nicotine and smoking, and high concentration nicotine salt products for the *Uptake Review*.

For detailed methods, see individual reviews in the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*. Where applicable, methods were an extension of those from the main reviews. Where additional methods were adopted, they are outlined in the relevant section.

Key Summary Points

Patterns Review – findings update

- The percentage of people in Australia aged 14 years and over who had ever used e-cigarettes increased significantly between 2013 (4.5%) and 2016 (8.8%), and 2016 and 2019 (11.3%). Among adults, ever-use increases with decreasing age, such that 26.1% of people aged 18-24 reported ever-use of e-cigarettes in 2019.
- The percentage of people in Australia aged 14 years and over reporting current use increased significantly between 2016 (1.2%) and 2019 (2.5%). Current use is greatest in younger adults aged less than 30 years and decreases with increasing age.
- The percentage of smokers in Australia aged 14 years and over who had ever used an e-cigarette increased significantly from 18.8% in 2013 to 31.0% in 2016, and increased further to 38.7% in 2019. Among non-smokers, 1.8% reported ever-use of e-cigarettes in 2013; this proportion increased significantly to 4.9% in 2016 and 6.8% in 2019.
- The percentage of smokers in Australia aged 14 years and over who were current users of e-cigarettes increased significantly between 2016 (4.4%) and 2019 (9.7%),and among non-smokers between 2016 (0.6%) and 2019 (1.4%).
- In 2019, current daily use of e-cigarettes was reported by 3.2% of current smokers, 2.2% of ex-smokers and 0.2% of never smokers, a significant increase for current and ex-smokers compared to 2016 (1.5% and 0.8% respectively).
- Analyses using 2019 data from the National Drug Strategy Household Survey show that among people aged 14 years and over reporting current use of e-cigarettes (i.e., those reporting daily, weekly or at least monthly use of e-cigarettes):
    - 54.1% ± 95% Margin of Error 5.6% report being current smokers (daily, weekly or less than weekly);
    - 32.2% ± 5.5% report being ex-smokers;
    - 15.8% ± 4.4% report being never smokers.

Uptake and *Cessation Reviews* – sensitivity analysis

- There were no potentially competing interests identified among studies included in the *Uptake Review*. Hence, the main results are not changed when competing interests are considered: that non-smokers who use e-cigarettes are on average three times as likely to become smokers of combustible cigarettes as non-smokers who do not use e-cigarettes.
- The results of the *Cessation Review* did not differ materially when potential conflicts of interest were considered, although the available evidence base was reduced. These results were that the evidence is currently insufficient to conclude that e-cigarettes are efficacious as an aid to smoking cessation

compared to no intervention/usual care, non-nicotine e-cigarettes and standard nicotine replacement therapy, although early signs are that they may be useful in highly controlled clinical settings.

Uptake Review – quality assessment

- Of the 12 newly identified studies included in the *Uptake Review*, three were considered to be at a serious risk of bias and nine at a moderate risk of bias, using the ROBINS-I tool.

Uptake Review – discussion update

Distribution of demographic factors

- Demographic factors reported in the studies in the *Uptake Review* included age, sex, ethnicity, education, affluence, urbanisation, SES, and family structure.
- Participants with a range of demographic characteristics were included although most studies were of people aged between 11 and 18 years.
- Analysis according to demographic subgroups was scant. There was no specific evidence available of any variation in the relationship of e-cigarette use to smoking uptake according to demographic factors. Where assessed, no statistically significant difference in the likelihood of smoking relapse was identified for sex, age, income or non-Hispanic white compared to Hispanic white ethnic/cultural groups.

Uptake of nicotine and combustible cigarette smoking among young people

- Based on the current evidence, young people, whether school-aged or aged up to 30 years, who used e-cigarettes had a risk of initiating smoking of combustible cigarettes that was approximately three-fold that of those who did not use e-cigarettes. There was substantial variation in the results between studies.
- Based on the current evidence, young people, whether school-aged or aged up to 30 years, who use e-cigarettes had an approximate three-fold risk of transitioning from being a non-smoker to a current smoker compared to those who did not use e-cigarettes. There was substantial variation in the results between studies.
- Based on evidence from three studies, the risk of transitioning from being a non-smoker to a current regular smoker is elevated for young people aged ≤18 years who had used e-cigarettes compared to those who had not, and this risk may be impacted by nicotine content, however evidence is limited.
- E-cigarettes commonly deliver nicotine, so use of e-cigarettes will generally result in increased use of nicotine by young people.

High concentration nicotine salt products

- Information on the nicotine content and delivery devices used by participants in the studies including in the *Uptake Review* was extremely limited.
- No research specifically investigating the relationship of the use of nicotine salt products to combustible cigarette uptake was located.

- From a safety perspective, at this stage, the findings regarding e-cigarettes and smoking uptake should be considered to apply to the range of devices in use by participants in the studies that have been summarised. Furthermore, nicotine e-cigarettes which have not been the subject of studies regarding their impact on smoking – such as nicotine salt products – should be assumed to increase the uptake of combustible smoking, unless specific evidence to the contrary is available.
- Since high concentration nicotine salt products have been identified as key drivers of increased youth e-cigarette use in North America, they may be particularly hazardous for increasing youth smoking uptake, through increasing prevalence of e-cigarette use.

Purpose and scope

This document provides supplementary material to the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*, as was commissioned by the Australian Government Department of Health. The document includes:

- Updated results of the *Patterns Review* with inclusion of data from the 2019 National Drug Strategy Household Survey (NDSHS);
- Results of a sensitivity analysis assessing differences between industry and non-industry funded studies included in the *Uptake Review* and *Cessation Review*;
- Results of an assessment of risk of bias using the ROBINS-I tool on newly identified primary research articles in the *Uptake Review*; and
- Additional discussion on the outcomes from the *Uptake Review*, including a breakdown of demographic factors from included studies, the likelihood that e-cigarettes will increase the number of young people using nicotine and smoking combustible cigarettes, and high concentration nicotine salt products.

This report was commissioned by the National Health and Medical Research Council of Australia (NHMRC) to supplement evidence reported as part of a program of work on e-cigarettes for the Australian Government Department of Health, to inform the update of the NHMRC CEO Statement on electronic cigarettes. The work was undertaken independently by researchers from the National Centre for Epidemiology and Population Health, Research School of Population Health, the Australian National University.

Background

E-cigarettes are a diverse group of battery-powered devices that create an aerosol from a liquid (e-liquid).[1, 2] Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol – mainly used in e-cigarettes as a solvent to produce visible aerosol – glycerine and flavouring agents, and commonly contains nicotine.[1]

The *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* considered the current evidence regarding the effects of e-cigarettes on smoking behaviour. This included a summary of evidence from peer-reviewed and grey literature on the prevalence and patterns of e-cigarette use, as well as peer-reviewed published evidence on the relationship of e-cigarettes use to combustible smoking uptake and cessation. The report presented the findings of three separate reviews; *Review one: Patterns of e-cigarette use* (*Patterns Review*), *Review two: e-cigarette use and smoking uptake* (*Uptake Review*) and *Review three: e-cigarette use and smoking cessation* (*Cessation Review*). See the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* for more detail on the background.

Aims

This report aims to supplement the material presented in the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* on patterns of e-cigarette use and smoking uptake associated with e-cigarette use. It usesstudies identified in the *Review* as well as additional evidence as applicable, to support the development of the NHMRC CEO Statement on electronic cigarettes.

This report is comprised of four main parts:

1. Incorporation of data from the NDSHS 2019 into an update of the *Patterns Review*;
2. Sensitivity analysis of studies included in the *Uptake Review* and the *Cessation Review*;
3. Quality assessment of newly identified primary research studies from the *Uptake Review*; and
4. Additional discussion points on the findings of the *Uptake Review*.

Methods

For detailed methods, see individual reviews in the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*. Where applicable, methods were an extension of those from the main reviews. Where additional methods were adopted, they are outlined in the relevant section.

Patterns Review – Findings update

Background

The narrative *Patterns Review* from the *Review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation* included results specific to the Australian context using data from the Australian Institute of Health and Welfare's (AIHW) NDSHS, published in 2013[3] and 2016.[4]

The main findings from the *Patterns Review* included that:

- In 2016, current use of e-cigarettes was relatively uncommon in Australia, as was dual use of e-cigarettes and combustible cigarettes.
    - Around 9% of people aged 14 years and over in Australia ever used e-cigarettes;
    - 0.5% of people aged 14 years and over reported daily e-cigarette use, and 1.2% reported current use;
    - 0.2% of people aged 14 years and over were estimated to be dual daily e-cigarette and combustible cigarette users, and 0.5% were estimated to be dual users.[4]
- In the general Australian population, the majority of people using e-cigarettes were either current or former users of combustible tobacco.[4]

Aims and Methods

This section provides an updated narrative review of NDSHS findings. Data from the newly published 2019 NDSHS were incorporated into the synthesis of findings from the 2013 and 2016 NDSHS surveys. The population sample sizes for the surveys were 22,274 (2019), 23,722 (2016) and 23,855 (2013).

Findings

Prevalence of lifetime e-cigarette use in Australia

National data on ever-use of e-cigarettes in Australia were first collected in the 2013 NDSHS,[3] with data on frequency of use collected in the 2016[4] and 2019[5] NDSHS surveys. Data are not available on whether or not these e-cigarettes delivered nicotine. In 2013, 4.5% of people in Australia aged 14 years and over were estimated to have ever used e-cigarettes,[3] increasing significantly to 8.8% in 2016[4] and increasing significantly again to 11.3% in 2019 (Table 1).[5] The prevalence of ever-use increased between 2016 and 2019 for all age groups other than for individuals aged 70 years and older, among whom use was low and did not change materially (1.0% in 2016 and 0.9% in 2019).[4, 5] The greatest absolute increases in the prevalence of ever-use between 2016 and 2019 were for 18–24-year-olds (19.2% to 26.1%; 6.9% absolute increase, 35.9% relative increase) and for 25–29-year-olds (14.8% to 20.4%; 5.6% absolute increase, 37.8% relative increase).[4, 5]

Prevalence of current e-cigarette use in Australia

In 2016, current use of e-cigarettes (defined as daily, weekly, monthly or less than monthly use) was reported by 1.2% of people in Australia aged 14 years and over (Table 2).[4] This figure rose significantly to 2.5% in 2019.[5] Across all age groups, current use increased between 2016 and 2019.[4, 5] The increase was greatest in younger age groups, with the exception of ages 14–17 years, where both 2016 and 2019 estimates should be treated with caution (relative standard error (RSE) of 25% to 50%). Among 18–24-year-olds it increased from 2.8% in 2016 to 5.3% in 2019 (89.3% relative increase).[4, 5] The 25–29 year age group showed a statistically significant four-fold increase from 1.2% to 4.8%, although the former estimate should be used with caution (RSE 25% to 50%).[4, 5] Similar to ever-use statistics, current use of e-cigarettes, according to the 2019 NDSHS, was greatest in younger age groups (18–24 years; 5.3%, 25–29 years; 4.8%, 30–39 years; 2.8%).[5] Across older age groups, there was an increase between 2016 and 2019 estimates in current usage for all age groups, with significant increases among 40–49-year-olds (1.5% to 2.6%) and 50–59-year-olds (0.8% to 2.0%).[5]

Patterns of dual use in Australia

Dual users comprise individuals with varying frequencies and intensities of e-cigarette and combustible cigarette use concurrently. In 2013, 18.8% of current smokers and 1.8% of non-smokers (never or no current use) aged 14 years and over had ever used e-cigarettes in the NDSHS;[3] these figures increased significantly to 31.0% of smokers and 4.9% of non-smokers in 2016 (Table 1).[4] In the 2019 NDSHS, 38.7% of smokers and 6.9% of non-smokers aged 14 years and over had ever used an e-cigarette, a further significant increase for both groups compared to the 2016 survey results.[4, 5] There were no clear trends in relative changes of ever-use of e-cigarettes for smokers and non-smokers across different age groups between 2016 and 2019, although a result of note was the stagnation of prevalence amongst smokers aged 30–39 years (0.5% relative increase), and the significant increase for non-smokers of the same age (42.9% relative increase).[4, 5]

The proportion of male and female smokers aged 14 years and over ever using e-cigarettes was similar in 2016 (31.5% and 30.3% respectively) (Table 3).[4] The corresponding figures in 2019 highlighted a significant increase for both sexes (39.7% for male smokers and 37.5% for female smokers).[4, 5] Among current smokers in 2019, ever-use of e-cigarettes decreased consistently across older age groups, from 63.9% for 18–24-year-olds to 10.7% for individuals aged 70 years or over.[5] When stratifying by sex, the same relationship was seen among current male smokers. Among female smokers, this pattern was disrupted among older age groups from 40–49 years.[5]

Current (daily, weekly, monthly or less than monthly) use of e-cigarettes increased significantly for both current smokers (daily, weekly or less than weekly smoking) (4.4% to 9.7%; 5.3% absolute increase, 120.5% relative increase) and non-smokers (never or no current use) (0.6% to 1.4%; 0.8% absolute increase, 133.3% relative increase) between 2016 and 2019 among NDSHS participants aged 14 years and over (Table 2).[4, 5] Between 2016 and 2019, current use of e-cigarettes among current smokers increased across all age categories. The absolute increase was largest for age groups 14–17-year-olds (4.3% to 17.5%; 13.2% absolute

increase, 307.0% relative increase) (RSE 51% to 90% for both estimates), followed by 18–24 years (6.8% to 18.7%; 11.9% absolute increase, 175.0% relative increase) and 25–29 years (3.6% to 13.7%; 10.1% absolute increase, 280.6% relative increase).[4, 5] For non-smokers, there was a significant 2.7% absolute and 540.0% relative increase among 25–29-year-olds, from 0.5% in 2016 (RSE 25% to 50%) to 3.2% in 2019.[4, 5] A significant increase was also evident between 2016 and 2019 among 30–39-year-olds (0.5% to 1.7%; 1.2% absolute increase, 240.0% relative increase).

Stratifying by sex, the greatest absolute and relative increases in current e-cigarette use among male smokers was for 18–24-year-olds, from 7.4% (RSE 25% to 50%) in 2016 to 20.9% in 2019 (13.5% absolute increase, 182.4% relative increase) and 25–29-year-olds, with a 12.5% absolute increase and more than three-fold relative increase from 3.5% (RSE 25% to 50%) in 2016 to 16.0% (RSE 25% to 50%) in 2019 (Table 4). Among female smokers, the greatest absolute increases between 2016 and 2019 were also seen among the youngest age groups; for 18–24-year-olds (5.9% (RSE 25% to 50%) to 15.4% (RSE 25% to 50%); 9.5% absolute increase, 161.0% relative increase) and 25–29-year-olds (3.9% (RSE 51% to 90%) to 11.1% (RSE 25% to 50%); 7.2% absolute increase, 184.6% relative increase). Statistically significant increases were seen among 40–49-year-olds, with a 5.9% absolute increase and close to four-fold relative increase from 2.2% (RSE 25% to 50%) in 2016 to 8.1% in 2019, and 50–59-year-olds, from 3.0% (RSE 25% to 50%) in 2016 to 8.3% in 2019 (5.3% absolute increase, 176.7% relative increase).[4, 5]

Frequency of e-cigarette use in Australia according to smoking status

In 2016, current daily use of e-cigarettes was reported by 1.5% of current (daily, weekly or less than weekly) smokers, 0.8% of ex-smokers and 0.2% (RSE 51% to 90%) of never smokers (Table 5).[4] In 2019, current daily use of e-cigarettes was reported by 3.2% of current smokers, 2.2% of ex-smokers and 0.2% (RSE 25% to 50%) of never smokers, a significant increase for current and ex-smokers compared to 2016.[4, 5] In 2016, 6.8% of current smokers, 1.7% of ex-smokers and 0.3% of never smokers reported previous use of e-cigarettes.[4] In 2019, 10.2% of current smokers, 1.9% of ex-smokers and 0.3% of never smokers reported previous use of e-cigarettes.[5] The proportion of current smokers reporting trying e-cigarettes ‘only once or twice’ decreased from 19.9% to 18.8%, whilst never-use significantly decreased from 69.0% to 61.3%.[4, 5] There was little change across each frequency category for never smokers between 2016 and 2019.[4, 5]

Stratifying by sex, between 2016 and 2019, there was a greater absolute increase in daily use for males (7.4% to 11.3%; 3.9% absolute increase) compared to females (3.6% to 7.0%; 3.4% absolute increase), and in at least weekly (but not daily) use for females (2.2% to 5.0%; 2.8% absolute increase) compared to males (3.2% to 5.3%; 2.1% absolute increase) (Table 6).[4, 5] These increases were statistically significant.

Proportion of e-cigarette users who are current smokers, ex-smokers and never smokers

The prevalence ± margin of error (MOE) of at least monthly e-cigarette use in the 2019 NDSHS was 2% ± 0.24% (Table 5). Applying these to the Australian Bureau of Statistics (ABS) population estimates according to smoking status (total = 20.9M; Table 7), the number of current daily, weekly or at least monthly e-cigarette users aged 14 years and over were estimated to be 418,000 ± 50,671 overall. From NDSHS 2019 data on estimated numbers of smokers (Table 7) and data on e-cigarette use according to smoking status (Table 5), among people aged 14 years and over reporting current use of e-cigarettes (classified as those using e-cigarettes, daily, weekly or at least monthly) it is estimated that:

- 54.1% ± 95% MOE 5.6% report being current smokers (daily, weekly or less than weekly);
- 32.2% ± 5.5% report being ex-smokers;
- 15.8% ± 4.4% report being never smokers.

The number of current e-cigarette users who report being never smokers would be 66,000 ± 20,228 noting the following assumptions/limitations:

1. MOEs for smoking prevalence estimates have been incorporated into the MOE for proportions of e-cigarette use;
2. Rounding of numbers in ABS estimates;
3. Approximations used in the equations.

Summary

- The percentage of people in Australia aged 14 years and over who had ever used e-cigarettes increased significantly between 2013 (4.5%) and 2016 (8.8%), and 2016 and 2019 (11.3%). Among adults, ever-use increases with decreasing age, such that 26.1% of people aged 18-24 reported ever-use of e-cigarettes in 2019.
- The percentage of people in Australia aged 14 years and over reporting current use increased significantly between 2016 (1.2%) and 2019 (2.5%). Current use is greatest in younger adults aged less than 30 years and decreases with increasing age.
- The percentage of smokers in Australia aged 14 years and over who had ever used an e-cigarette increased significantly from 18.8% in 2013 to 31.0% in 2016, and increased further to 38.7% in 2019. Among non-smokers, 1.8% reported ever-use of e-cigarettes in 2013; this proportion increased significantly to 4.9% in 2016 and 6.9% in 2019.
- The percentage of smokers in Australia aged 14 years and over who were current users of e-cigarettes increased significantly between 2016 (4.4%) and 2019 (9.7%); and among non-smokers between 2016 (0.6%) and 2019 (1.4%).
- In 2019, current daily use of e-cigarettes was reported by 3.2% of current smokers, 2.2% of ex-smokers and 0.2% of never smokers, a significant increase for current and ex-smokers compared to 2016 (1.5% and 0.8% respectively).

- Analyses using 2019 data from the NDSHS show that among people aged 14 years and over reporting current use of e-cigarettes (i.e., those reporting daily, weekly or at least monthly use of e-cigarettes):
    - 54.1% ± 95% Margin of Error 5.6% report being current smokers (daily, weekly or less than weekly);
    - 32.2% ± 5.5% report being ex-smokers;
    - 15.8% ± 4.4% report being never smokers.

Table 1: Ever-use of electronic cigarettes (e-cigarettes), by age and smoking status, 2013 to 2019 (per cent)

Age group (years)	Proportion								
	Smokers[a]			Non-smokers[b]			Persons		
	2013	2016	2019	2013	2016	2019	2013	2016	2019
14-17[c]	‡	50.8	63.6	‡	8.0	7.8	‡	9.2	9.6
18-24	30.8	49.1#	63.9†	4.9	13.6#	19.6†	9.5	19.2#	26.1†
25-29	26.0	37.6#	53.5†	3.0	9.0#	14.2†	7.9	14.8#	20.4†
30-39	19.3	39.0#	39.2	1.9	6.3#	9.0†	5.1	12.2#	13.9
40-49	13.8	26.2#	35.6†	0.9	3.3#	4.2	3.3	7.8#	10.3†
50-59	11.4	20.9#	30.6†	1.2	2.1#	3.3†	2.9	5.2#	8.3†
60-69	8.6	18.7#	25.8†	1.0	1.0	1.4	1.9	3.0#	4.3†
70+	9.5	11.6	10.7	*0.3	*0.3	*0.3	0.9	1.0	0.9
14+	18.8	31.0#	38.7†	1.8	4.9#	6.9†	4.5	8.8#	11.3†
18+	17.9	30.8#	38.4†	1.8	4.7#	6.8†	4.4	8.8#	11.4†

* Estimate has a relative standard error of 25% to 50% and should be used with caution.

Statistically significant change between 2013 and 2016.

† Statistically significant change between 2016 and 2019.

‡ NDSHS 2013 included individuals 12-17 years of age, and not 14-17 years of age.

(a) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

(b) Includes those who have never smoked more than 100 combustible cigarettes (manufactured and/or roll-your-own), and those who have smoked this amount of combustible tobacco and report no longer smoking.

(c) Due to the small sample size, estimates should be interpreted with caution.

Note: A number of changes were made to the questionnaire to better capture the use of electronic cigarettes in 2016, including modifying the question about lifetime use and current use of electronic cigarettes (see questionnaire changes for more information). These changes mean that 2016 and 2013 data are not fully comparable. However, data may still be used to give an indication of the change in use of electronic cigarettes between 2013 and 2016.

Source: NDSHS 2019 (Table 2.19), NDSHS 2016 (Table 3.16)

Table 2: Current use(a) of electronic cigarettes (e-cigarettes), by age and smoking status, 2016 and 2019 (per cent)

	Proportion					
	Smokers[(b)]		Non-smokers[(c)]		Persons	
Age group (years)	2016	2019	2016	2019	2016	2019
14-17[(d)]	**4.3	**17.5	*0.8	*1.3	*0.9	*1.8
18-24	6.8	18.7†	*2.0	2.9	2.8	5.3†
25-29	*3.6	13.7†	*0.5	3.2†	*1.2	4.8†
30-39	5.9	8.6	0.5	1.7†	1.5	2.8†
40-49	4.3	9.4†	0.8	1.0	1.5	2.6†
50-59	3.3	6.4†	*0.3	1.0†	0.8	2.0†
60-69	*2.9	7.0†	*0.4	*0.4	0.7	1.2
70+	**0.8	*2.5	**<0.1	*0.1	*0.1	*0.2
14+	4.4	9.7†	0.6	1.4†	1.2	2.5†
18+	4.4	9.6†	0.6	1.4†	1.2	2.6†

* Estimate has a relative standard error of 25% to 50% and should be used with caution.

** Estimate has a high level of sampling error (relative standard error 51% to 90%), meaning that it is unsuitable for most uses.

† Statistically significant change between 2016 and 2019.

(a) Includes people who reported smoking electronic cigarettes daily, weekly, monthly, or less than monthly.

(b) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

(c) Includes those who have never smoked more than 100 combustible cigarettes (manufactured and/or roll-your-own), and those who have smoked this amount of combustible tobacco and report no longer smoking.

(d) Due to the small sample size, estimates should be interpreted with caution.

Source: NDSHS 2019 (Table 2.24)

Table 3: Ever-use of electronic cigarettes (e-cigarettes), current smokers(a) by age and sex, 2013 to 2019 (per cent)

Age group (years)	Proportion								
	Males			Females			Persons		
	2013	2016	2019	2013	2016	2019	2013	2016	2019
12-17	53.7	*46.0	‡	43.4	*52.1	‡	50.1	50.8	‡
18-24	36.2	47.9	63.4†	24.1	50.4#	64.2	30.8	49.1#	63.9†
25-29	26.6	41.8#	52.5	25.4	32.5	54.9†	26.0	37.6#	53.5†
30-39	21.1	39.0#	42.9	16.3	39.1#	34.8	19.3	39.0#	39.2
40-49	13.4	29.3#	35.8	14.2	22.2#	35.2†	13.8	26.2#	35.6†
50-59	8.4	19.4#	32.2†	15.1	22.5#	28.9	11.4	20.9#	30.6†
60-69	*7.4	15.6#	22.7	10.1	22.6#	29.8	8.6	18.7#	25.8†
70+	*7.4	*8.8	*10.5	*11.8	15.3	*11.2	9.5	11.6	10.7
14+	19.7	31.5#	39.7†	17.6	30.3#	37.5†	18.8	31.0#	38.7†
18+	18.5	31.4#	39.5†	17.1	30.0#	37.1†	17.9	30.8#	38.4†

* Estimate has a relative standard error of 25% to 50% and should be used with caution.

Statistically significant change between 2013 and 2016.

† Statistically significant change between 2016 and 2019.

‡ NDSHS 2019 did not include data on individuals 12-17 years of age.

(a) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

Note: A number of changes were made to the questionnaire to better capture the use of electronic cigarettes in 2016, including modifying the question about lifetime use and current use of electronic cigarettes (see questionnaire changes for more information). These changes mean that 2016 and 2013 data are not fully comparable. However, data may still be used to give an indication of the change in use of electronic cigarettes between 2013 and 2016.

Source: NDSHS 2019 (Table 2.20), NDSHS 2016 (Table 3.17)

Table 4: Current use(a) of electronic cigarettes (e-cigarettes), smokers(b), by age and sex, 2016 and 2019 (per cent)

	Proportion					
	Males		Females		Persons	
Age group (years)	2016	2019	2016	2019	2016	2019
18-24	*7.4	20.9†	*5.9	*15.4	6.8	18.7†
25-29	*3.5	*16.0†	**3.9	*11.1	*3.6	13.7†
30-39	7.1	9.7	*3.9	7.5	5.9	8.6
40-49	*6.0	10.4	*2.2	8.1†	4.3	9.4†
50-59	*3.7	*4.4	*3.0	8.3†	3.3	6.4†
60-69	*1.9	*7.1#	*4.3	*7.0	*2.9	7.0†
70+	n.p.	**2.6	**1.8	**2.4	**0.8	*2.5
14+	5.0	10.6†	3.5	8.7†	4.4	9.7†
18+	5.0	10.4†	3.5	8.7†	4.4	9.6†

* Estimate has a relative standard error of 25% to 50% and should be used with caution.

** Estimate has a high level of sampling error (relative standard error 51% to 90%), meaning that it is unsuitable for most uses.

† Statistically significant change between 2016 and 2019.

n.p. not published because of small numbers, confidentiality, or other concerns about the quality of the data.

(a) Includes people who reported smoking electronic cigarettes daily, weekly, monthly, or less than monthly.

(b) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

Source: NDSHS 2019 (Table 2.25)

Table 5: Frequency of electronic cigarette (e-cigarette) use by smoking status, people aged 14 and over, 2016 and 2019 (col per cent)

Frequency of e-cigarette use	Proportion							
	Smokers[(a)]		Ex-smokers[(b)]		Never smoked[(c)]		Total	
	2016	2019	2016	2019	2016	2019	2016	2019
Daily	1.5	3.2†	0.8	2.2†	**0.2	*0.2	0.5	1.1†
At least weekly (but not daily)	1.2	3.0†	*0.1	*0.5†	*<0.1	*<0.1	0.3	0.6†
At least monthly (but not weekly)	0.7	1.6†	**<0.1	**<0.1	*<0.1	*0.2†	0.1	0.4†
At least monthly	*3.4*	*7.8†*	*1.0*	*2.8†*	**0.3*	*0.5*	*0.9*	*2.0†*
Less than monthly	1.0	1.9†	*0.2	*0.4	*0.2	0.2	0.3	0.5†
I used to use them, but no longer use	6.8	10.2†	1.7	1.9	0.3	0.3	1.6	2.0†
I only tried them once or twice	19.9	18.8	4.7	6.4†	3.2	4.2†	6.0	6.7†
Never used	69.0	61.3†	92.5	88.6†	96.1	94.8†	91.2	88.7†

* Estimate has a relative standard error of 25% to 50% and should be used with caution.

** Estimate has a high level of sampling error (relative standard error 51% to 90%), meaning that it is unsuitable for most uses.

† Statistically significant change between 2016 and 2019.

(a) Includes people who reported smoking combustible cigarettes (manufactured and/or roll-your-own) daily, weekly, or less than weekly.

(b) Smoked at least 100 combustible cigarettes (manufactured and/or roll-your-own) or the equivalent amount of tobacco in their life, and reported no longer smoking.

(c) Never smoked 100 combustible cigarettes (manufactured and/or roll-your-own) or the equivalent amount of combustible tobacco products.

Source: NDSHS 2019 (Table 2.22)

Table 6: Frequency of electronic cigarette (e-cigarette) use by sex, people aged 14 and over who have used an e-cigarette in their lifetime, 2016 and 2019 (per cent)

Frequency of e-cigarette use	Proportion					
	Males		Females		Persons	
	2016	2019	2016	2019	2016	2019
Daily	7.4	11.3†	3.6	7.0†	5.8	9.4†
At least weekly (but not daily)	3.2	5.3	2.2	5.0†	2.9	5.1†
At least monthly (but not weekly)	*1.4	3.4†	*2.0	3.3	1.6	3.4†
At least monthly	*12.0*	*19.9*†	*7.8*	*15.3*†	*10.3*	*17.9*†
Less than monthly	4.0	4.4	2.7	4.1	3.4	4.4
I used to use them, but no longer use	19.1	19.2	16.5	16.9	18.0	18.1
I only tried them once or twice	64.9	56.5†	73.0	63.7†	68.3	59.6†

* Estimate has a relative standard error of 25% to 50% and should be used with caution.

† Statistically significant change between 2016 and 2019.

Note: Base is people who had used electronic cigarettes in their lifetime.

Source: NDSHS 2019 (Table 2.21)

Table 7: Tobacco smoking status, people aged 14 and over, by sex, 2019 (persons)

Smoking status	n	RSE	MOE
Daily smoker	2,300,000	2.7	100,000
Current occasional - weekly	300,000	7.6	40,000
Current occasional - less than weekly	300,000	6.9	50,000
Current smokers[(a)]	*2,900,000*	*2.3*	*100,000*
Ex-smoker[(b)]	4,800,000	1.6	100,000
Smoker in their lifetime[(c)]	*7,700,000*	*1.3*	*200,000*
Never smoked[(d)]	13,200,000	0.7	200,000

(a) Includes people who reported smoking daily, weekly, or less than weekly.

(b) Smoked at least 100 cigarettes (manufactured and/or roll-your-own) or the equivalent amount of tobacco in their life, and reported no longer smoking.

(c) Includes people who reported smoking daily, weekly or less than weekly and ex-smokers.

(d) Never smoked 100 cigarettes (manufactured and/or roll-your-own) or the equivalent amount of tobacco.

Source: NDSHS 2019 (Table 2.2)

Uptake and Cessation reviews – Sensitivity Analyses

Background

The *Uptake Review* assessed the relationship of e-cigarette use to smoking uptake. The *Cessation Review* assessed current published peer-reviewed Randomised Control Trial (RCT) evidence on the efficacy of e-cigarettes – with or without nicotine – for the sustained cessation of combustible tobacco cigarette smoking and for the cessation of ongoing exposure to nicotine.

For the *Uptake Review* and the *Cessation Review*, it was important to consider whether authors of the studies under review held any conflicts of interest that could potentially bias their findings, or whether the research was funded by an organisation with a financial interest in the outcomes. As part of the methods, research funding and author conflict of interest information was extracted from each study.

Aims and Methods

This section presents findings from the *Uptake Review* and the *Cessation Review* separately according to whether or not the research was funded by the tobacco or e-cigarette industry, to consider whether findings differ materially according to funding source and to consider evidence independent of industry, if differences are observed.

The methods used for this analysis are those detailed in the *Uptake Review* and *Cessation Review*. In short, details of research funding sources and author conflict of interest for each study were extracted. Studies were considered to have a conflict of interest if they were funded and/or received contributions in kind by the tobacco or e-cigarette industry, or if their authors currently or previously received funding from the tobacco or e-cigarette industry. No data requests were made of the authors of any papers to seek additional information. In RCTs that did not report risk ratios regarding cessation, risk ratios were calculated from number of events or percentages reported. Where applicable, sensitivity analyses were conducted using fixed-effects modelling restricted to studies without noted potential competing interests. All analyses were conducted using STATA version 16.1.

Findings

See the *Uptake Review* and *Cessation Review* for detailed reporting on the findings of the main reviews, including PRISMA flowchart, study characteristics, narrative summary of included studies, effect measures and missing data.

Uptake Review

There were 25 primary research studies in total included in the Uptake Review. There were 13 eligible primary research studies included from three systematic review papers identified in the umbrella review on the uptake of combustible cigarette smoking, involving sample sizes ranging from 298 to 17,318. Twelve studies were newly identified for the top-up systematic review, involving sample sizes ranging from 374 to 14,623.

Table 8 contains the conflict of interest and funding information extracted for each study included in the *Uptake Review*. No potentially competing interests were identified from the studies themselves, or the authors, among the systematic reviews in the umbrella review or the primary research studies in the top-up systematic review, based on the disclosure statements from the publications. One primary research study identified during screening in the top-up systematic review, Lee et al.,[6] was funded by the tobacco industry. This study was excluded from the review because there was a large overlap with data presented in a more recent paper by Berry et al.[7]

Cessation Review

Nine RCTs of ENDS were identified that examined smoking cessation as an outcome, involving the randomisation of a total of 5,445 smokers; 2,836 randomised to ENDS and 2,609 to comparison groups.

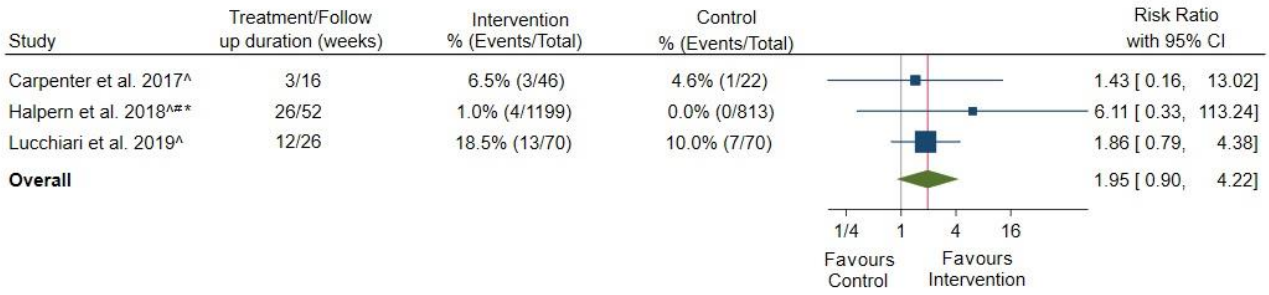
Four of the RCTs consisted of three arms. The study by Lucchiari et al. contained an ENDS, an ENNDS and a usual care arm[8] and Bullen et al. contained an ENDS, an ENNDS and a NRT arm[9]. As such, both were included in two separate meta-analyses according to the relevant comparator. There were two ENDS arms with differing nicotine concentrations in two RCTs.[10, 11] These arms were combined for the meta-analysis.

Nicotine-delivering e-cigarettes versus no intervention or usual care

Three of the RCTs included in the review compared ENDS to no intervention or usual care.[8, 11, 12] None were funded directly by the tobacco or e-cigarette industry, nor were there any reported potential competing interests for the authors of the studies. However, Halpern et al.[12] reported receiving e-cigarettes donated by an e-cigarette company. Sensitivity analysis was conducted excluding Halpern et al.[12]

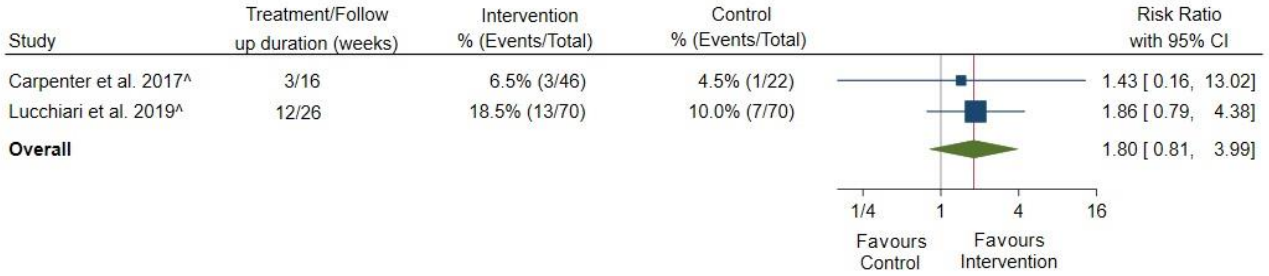
Findings showed that no individual study reported a significant difference in cessation outcomes between randomised groups (Figure 1). Halpern et al.[12] reported an RR of 6.11 (95% CI 0.33-113.24). Results from the random-effects meta-analysis found no significant difference between randomised groups when the random-effects meta-analysis was restricted to studies with no noted potential competing interests (RR 1.80; 95% CI 0.81-3.99; I^2 = 0.0%) (Figure 2).

Figure 1: Biochemically verified sustained smoking cessation in smokers randomised to nicotine-delivering e-cigarettes versus no intervention or usual care: random-effects meta-analysis.



^ RRs are calculated from number of events or percentages reported in the published study
# # RR is undefined due to zero events in the control group. RR estimated by applying the continuity correction (adding 0.5 to each cell of the 2x2 table)
Total cessation events: 20/1315 in intervention group, 8/905 in control group
Heterogeneity: Tau^2=0.00; Chi^2= 0.67, df=2, p = 0.71; I^2 =0.0%; Test for overall effect: Z=1.71, p=0.09

Figure 2: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine-delivering e-cigarettes versus no intervention or usual care in studies with no reported potential competing interests: random-effects meta-analysis.



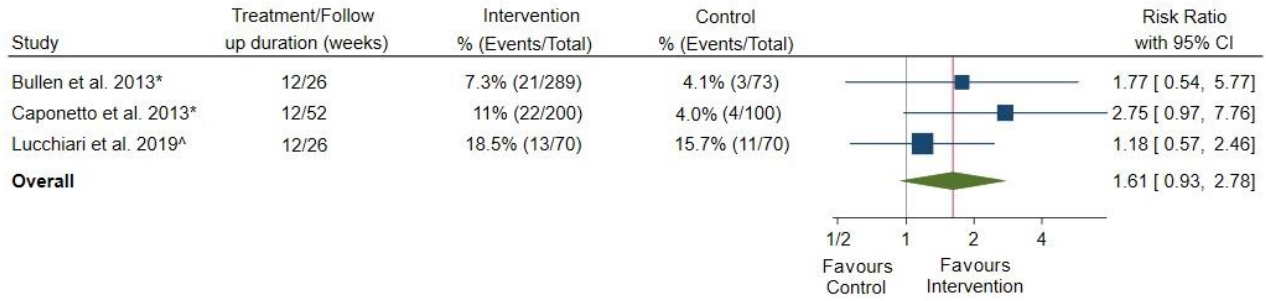
^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 16/116 in intervention group, 8/92 in control group
Heterogeneity: Tau^2=0.00; Chi^2= 0.05, df=1, p = 0.83; I^2 =0.0%; Test for overall effect: Z=1.44, p=0.15

Nicotine-delivering e-cigarettes versus e-cigarettes which do not deliver nicotine

Three RCTs compared smoking cessation outcomes in participants randomised to ENDS and ENNDS (considered a placebo).[8-10] No studies were directly funded by the tobacco or e-cigarette industry. Bullen et al.[9] had a study author who reported previously receiving research funding from an e-cigarette manufacturer and Caponnetto et al.[10] had a study author who had received funding from the tobacco industry. Both studies reported using e-cigarettes donated by an e-cigarette company.[9, 10] As only one paper did not have noted competing interests, sensitivity analysis was not conducted.

Findings were that no statistically significant difference between ENDS and ENNDS was found in any study (Figure 3). Restricting the evidence to that without known potential competing interests, one study remained with a RR of 1.18 (95% CI 0.57-2.46) for cessation in smokers randomised to ENDS versus ENNDS.[8]

Figure 3: Biochemically verified sustained smoking cessation in smokers randomised to nicotine-delivering e-cigarettes versus non-nicotine-e-cigarettes: random-effects meta-analysis.



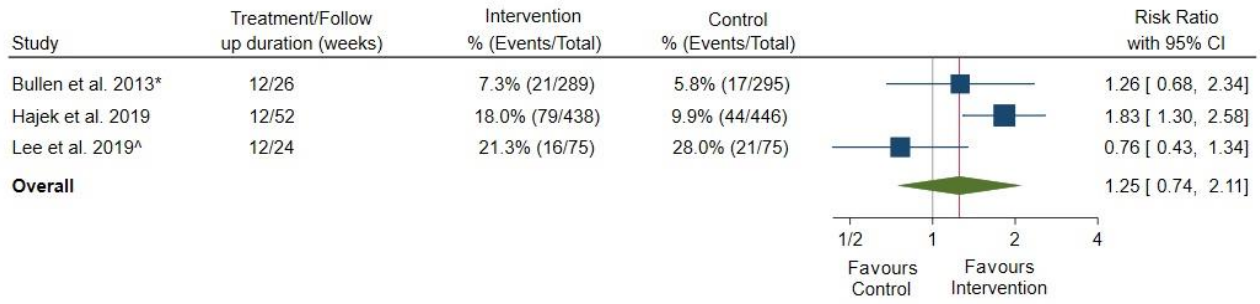
* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total events: 56/559 in intervention group, 18/243 in control group
Heterogeneity: Tau^2=0.01; Chi^2= 1.73, df=2, p = 0.42; I^2 =3.4%; Test for overall effect: Z=1.71, p=0.09

Nicotine-delivering e-cigarettes versus other nicotine replacement therapy

Three RCTs were identified that compared ENDS to approved NRT.[9, 13, 14] Bullen et al.[9] had the potential competing interests noted above; no other studies had reported competing interests. Sensitivity analysis was conducted.

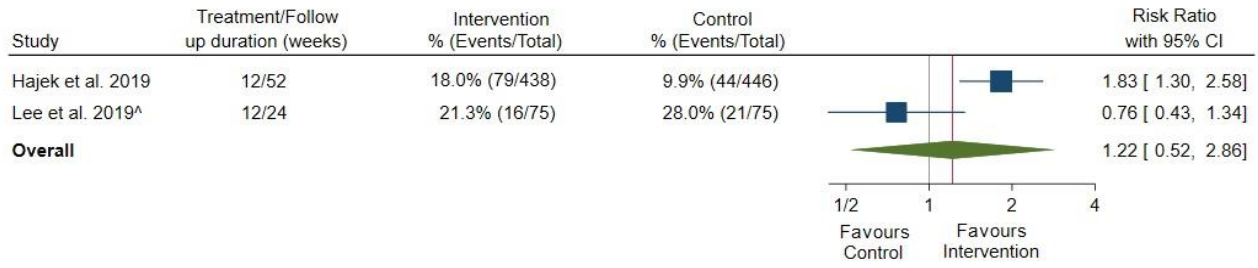
Findings showed that, of the three relevant studies, two reported no statistically significant difference between ENDS and approved NRT,[9, 15] and the other found significantly greater cessation in those randomised to ENDS (Figure 4).[13] Results from the random-effects meta-analysis found that the conclusion from the random-effects model did not substantially change when the meta-analysis was limited to studies with no noted potential competing interests (RR 1.22; 95% CI 0.52-2.86; I^2 = 85.1%) (Figure 5).

Figure 4: Biochemically verified sustained smoking cessation in smokers randomised to nicotine-delivering e-cigarettes versus other nicotine-replacement therapy: random-effects meta-analysis.



* Potential competing interests have been noted
^ RRs are calculated from number of events or percentages reported in the published study
Total events: 116/802 in intervention group, 82/816 in control group
Heterogeneity: Tau2=0.15; Chi2= 6.85, df=2, p = 0.03; I2 =69.0%; Test for overall effect: Z=0.85, p=0.40

Figure 5: Sensitivity analysis: verified smoking cessation in smokers randomised to nicotine-delivering e-cigarettes versus other nicotine-replacement therapy in studies with no reported potential competing interests: random-effects meta-analysis.



^ RRs are calculated from number of events or percentages reported in the published study
Total cessation events: 95/513 in intervention group, 65/521 in control group
Heterogeneity: Tau2=0.00; Chi2= 6.70, df=1, p = 0.01; I2 =85.1%; Test for overall effect: Z=0.45, p=0.65

Summary

- There were no potential competing interests identified among studies included in the *Uptake Review*. Hence, the main results are not changed when competing interests are considered: that non-smokers who use e-cigarettes are on average three times as likely to become smokers of combustible cigarettes as non-smokers who do not use e-cigarettes.
- The results of the *Cessation Review* did not differ materially when potential conflicts of interest were considered, although the available evidence base was reduced. These results were that the evidence is currently insufficient to conclude that e-cigarettes are efficacious as an aid to smoking cessation compared to no intervention/usual care, non-nicotine e-cigarettes and standard nicotine replacement therapy, although early signs are that they may be useful in highly controlled clinical settings.

Table 8: Competing interest information extracted from papers identified in the Uptake Review and conflict of interest assessment

Reference	Funding/ conflict of interest statement	Assessment
Newly identified studies		
Aleyan et al. 2019[16]	Funding: The COMPASS study has been supported by a bridge grant from the CIHR Institute of Nutrition, Metabolism and Diabetes (INMD) through the "Obesity – Interventions to Prevent or Treat" priority funding awards (OOP-110788; awarded to SL), an operating grant from the CIHR Institute of Population and Public Health (IPPH) (MOP-114875; awarded to SL), a CIHR project grant (PJT-148562; awarded to SL), a CIHR bridge grant (PJT-149092; awarded to KP/SL), a CIHR project grant (PJT-159693; awarded to KP), and by a research funding arrangement with Health Canada (#1617-HQ-000012; contract awarded to SL). Adam Cole was funded by the Canadian Institute of Health Research (CIHR) during the time of the study. The funding sources noted above had no involvement in the study design, collection, analysis, interpretation of data and writing of the report. Conflicts of Interest: The authors declare no conflict of interest.	None
Barrington-Trimis et al. 2019[17]	Funding sources: Research reported in this publication was supported by grant number P50CA180905 (J.B.T., A.M.L., F.L., T.B.C., R.M.) from the National Cancer Institute at the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) Center for Tobacco Products (CTP), and grant numbers R01DA033296 (A.M.L.), P50DA036151 (G.K., M.M., S.K.S.), K01DA042950 (J.B.T.) from the National Institute on Drug Abuse at NIH, and DGE- 1418060 (M.B.) from the National Science Foundation Graduate Research Fellowship Program. The funder had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the article. Conflicts of interest: The authors have no conflicts of interest to disclose.	None
Berry et al. 2019[7]	Conflict of interest disclosures/funding: Drs Fetterman, Benjamin, Bhatnagar, and Stokes and Ms Berry were supported by grants P50HL120163 and 2U54HL120163-06 from the National Heart, Lung, and Blood Institute of the National Institutes of Health and Center for Tobacco Products. Drs Barrington-Trimis and Leventhal were supported by grants P50CA180905 and U54CA180905 from the National Cancer Institute of the National Institutes of Health. Dr Stokes reported receiving research funding from Johnson & Johnson outside of the submitted work. No other disclosures were reported.	None
Bold et al. 2018[18]	Financial disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose. Funding: Supported in part by grants from the National Institute on Drug Abuse and the Food and Drug Administration Center for Tobacco Products (P50DA036151, P50DA009241, T32DA019426, and l40DA042454). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration. Funded by the National Institutes of Health (NIH). Potential conflict of interest: The authors have indicated they have no potential conflicts of interest to disclose.	None

Reference	Funding/ conflict of interest statement	Assessment
Brose et al. 2019[19]	Competing interests: The authors declare that they have no competing interests. Funding: This work was supported by Cancer Research UK (C52999/A21496; C57277/A23884).	None
Chien et al. 2019[20]	Funding: The work was supported by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan (Grant Number: MOHW105-HPA-H-114-133708), from the Health and Welfare Surcharge on Tobacco Products—Grant Number: 03724606—Project Code: 1051218-107), and grants R01DA043950 from the US National Institute of Drug Abuse and P50CA180890 from the National Cancer Institute, the Food and Drug Administration (FDA) Center for Tobacco Products. The content is solely the responsibility of the authors and does not necessarily represent the official views of Health Promotion Administration, NIH or the Food and Drug Administration. The funding agencies had no role in study design, data collection, analysis, and interpretation, or writing of this study. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication. Conflicts of interest: The authors declare no conflict of interest.	None
Conner et al. 2019[21]	Funding: The research was supported by a grant from the UK Medical Research Council/National Preventive Research Initiative. CA is additionally supported by the National Institute for Health Research Manchester Biomedical Research Centre and the National Institute of Health Research Greater Manchester Patient Safety Translational Research Centre. All authors report receiving grants from the National Prevention Research Initiative during the study. Competing interests: None declared.	None
Dai et al. 2019[22]	Role of funding source: Research reported in this publication was supported by the National Cancer Institute and the FDA Center for Tobacco Products (CTP) under Award Number R03CA228909 (Dai) and Award Number U54CA180905 (Leventhal). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration. Conflict of interests: No conflict declared.	None
Kinnunen et al. 2019[23]	Role of funding source: Nothing declared. Conflict of interest: Not reported.	Unclear
McMillen et al. 2019[24]	Declaration of conflicting interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Funding: The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This article was made possible by the Flight Attendant Medical Research Institute under award No. 052302_CoE to the American Academy of Pediatrics. The information, views, and opinions contained herein are those of the authors and do not necessarily reflect the views and opinions of the funding organizations.	None

Reference	Funding/ conflict of interest statement	Assessment
Osibogun et al. 2020[25]	Funding; OO is supported by the NIDA T32DA043449 grant. ZB is sup- ported by the FIU-Research Center in Minority Institution (grant U54MD012393-01). WM is supported by NIH (grants R01- DA035160, R01-TW010654, R01-DA042477) and the NIDA T32DA043449 grant. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH. Conflict of interest: Not reported. No other financial disclosures were reported by the authors of this paper.	Unclear
Penzes et al. 2018[26]	Role of funding sources: This work was supported by the Fogarty International Center and National Cancer Institute of the National Institutes of Health under Grant Number 1R01TW009280. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Fogarty International Center and National Cancer Institute of the National Institutes of Health had no involvement in study design, collection, analysis, or interpretation of data, writing the manuscript, and the decision to submit the manuscript for publication. Conflict of interest: None.	None
Studies in previous meta-analyses		
Barrington-Trimis et al. 2018[27]	Financial disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose Funding: Supported by grant P50CA180905 (Drs Barrington-Trimis, Leventhal, Cruz, and McConnell and Ms Liu) from the National Cancer Institute at the National Institutes of Health and the Food and Drug Administration Center for Tobacco Products and grants R01DA033296 (Dr Leventhal), P50DA036151 (Drs Kong and Krishnan-Sarin and Ms Mayer), and K01DA042950 (Dr Barrington-Trimis) from the National Institute on Drug Abuse at the National Institutes of Health. The funders had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the article. Funded by the National Institutes of Health (NIH). Potential conflict of interest: The authors have indicated they have no potential conflicts of interest to disclose.	None
Best et al. 2017[28]	Funding: This project was funded by the UK National Institute for Health Research (NIHR) PHR project 10/3000/07. The study sponsor had no influence on study design and the collection, analysis, and interpretation of data and the writing of the article and the decision to submit it for publication. Competing interests: None declared.	None

Reference	Funding/ conflict of interest statement	Assessment
East et al. 2017[29]	Conflicts of interest: Katherine East, Sara Hitchman, and Ann McNeill are members of the UK Centre for Tobacco and Alcohol Studies. Ioannis Bakolis is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and by the NIHR Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. Sarah Williams is an employee at Public Health England and was previously an employee at Action on Smoking and Health at the time this study was conducted. Hazel Cheeseman and Deborah Arnott are employees of Action on Smoking and Health, which receives funding from the British Heart Foundation, Cancer Research UK (CRUK), and the Department of Health. This study was funded by CRUK grant code A21559. CRUK was not involved in the study design, data collection, analysis or interpretation of the data, the write up of the manuscript, or decision to submit the article for publication. The views expressed are those of the author(s) and not necessarily those of Public Health England, CRUK, Action on Smoking and Health, the NHS, the NIHR or the Department of Health. Funding sources: This work was funded by Cancer Research UK grant code A21559. Thanks are also given to the UK Public Health Research Consortium (grant number PHPEHF50/13) for funding the development of some of the covariates included in this study.	None
Leventhal et al. 2015[30]	Conflict of interest disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported. Funding/support: This research was supported by grants R01-DA033296 and P50-CA180905 from the National Institutes of Health. Role of funder/sponsor: The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.	None
Loukas et al. 2018[31]	Role of funding source: Research reported in this publication was supported by grant number [1 P50 CA180906] from the National Cancer Institute and the Food and Drug Administration (FDA) Center for Tobacco Products. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the FDA. Conflict of interest: All authors declare that they have no conflicts of interest.	None
Lozano et al. 2017[32]	Conflict of interest: No conflict declared. Source of funding: This research was supported by a grant from the Fogarty International Center and the National Cancer Institute of the United States' National Institute of Health (R01 TW009274). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.	None

Reference	Funding/ conflict of interest statement	Assessment
Meich et al. 2017[33]	Funding: This study was supported by the National Institute on Drug Abuse, part of the National Institutes of Health, by grants numbers R01DA001411 and R01DA016575. Competing interests: None declared.	None
Primack et al. 2015[34]	Conflict of interest disclosures: None reported. Funding/Support: This study was supported by grant R01-CA077026 for the survey from the National Cancer Institute (Dr Sargent), grants R01-CA140150 and R21-CA185767 from the National Cancer Institute (Dr Primack), and grant KL2-TR001088 from the National Center for Advancing Translational Sciences (Dr Soneji). Role of the funder/sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.	None
Primack et al. 2018[35]	Funding source: National Cancer Institute (R01-CA140150). Dr. Primack is supported by a two grants from the National Cancer Institute (R01-CA140150 and R21-CA185767). Dr. Sargent is supported by the National Cancer Institute (R01-CA077026). Dr. Soneji is supported by the National Cancer Institute (R21-CA197912). The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. Conflict of interest: The authors have no conflicts of interest to report.	None
Spindle et al. 2017[36]	Conflict of interest: The authors have no conflicts of interest to declare. Funding: Spit for Science: The VCU Student Survey has been supported by Virginia Commonwealth University, P20AA107828, R37AA011408, K02AA018755, and P50 AA022537 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and UL1RR031990 from the National Center for Research Resources (NCRR) and National Institutes of Health Roadmap for Medical Research. Research reported in this publication was also supported by the National Institute on Drug Abuse (NIDA) of the National Institutes of Health under Award Numbers P50DA036105 and F31DA040319 and the Center for Tobacco Products of the U.S. Food and Drug Administration (FDA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration. NIAAA, NCRR, NIDA, NIH, and FDA had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.	None

Reference	Funding/ conflict of interest statement	Assessment
Treur et al. 2018[37]	Funding: This work was supported by the European Research Council (ERC; 284167), Netherlands Organization for Health Research and Development (ZonMw; 200100003) and the National Institute for Public Health and the Environment (RIVM). Conflict of interest: Not reported.	Unclear
Unger et al. 2016[38]	Role of funding source: This research was supported by the National Institutes of Health (grant 5R01DA016310). Conflict of interest: The authors report no conflicts of interest.	None
Wills et al. 2017[39]	Funding: This research was supported by grants R01 CA153154 and P30 071789-16S2 from the National Cancer Institute. Competing interests: None declared.	None

Uptake Review – Quality Assessment

Background

The *Uptake Review* assessed the relationship of e-cigarette use to smoking uptake. In the *Uptake Review*, a quality assessment was performed on non-randomised studies using the Newcastle Ottawa Scale (NOS).[40] The NOS totals (out of 10 stars) ranged from 5 to 8, with ascertainment of exposure, assessment of outcome and adequacy of follow-up of cohorts as the main areas impacting the NOS scores.

Aims and Methods

This section presents the results of an updated risk of bias assessment of the articles included in the *Uptake Review*.

The Risk Of Bias In Non-randomized Studies of Interventions[41] (ROBINS-I) was used to assess the risk of bias in the primary research studies included in the systematic review. Two authors (AY and SB) independently assessed each article as per the ROBINS-I guidelines[42] and discussed any conflicts to reach a consensus. If no consensus was found, a third author (KB) was consulted. No data requests were made of the authors of any papers to seek additional information.

Findings

See the *Uptake Review* for details of identified studies. Of the 12 newly identified studies in the *Uptake Review*, three were considered to be at a serious risk of bias and nine at a moderate risk of bias using the ROBINS-I tool (Table 9). No study was deemed a low risk. All studies, with the exception of Brose et al., 2019[19], had a low risk of bias for classification of the intervention, deviation from intended intervention and measurement of outcomes. Confounding and participant selection were the main domains that introduced bias. In all studies, no information regarding the selection of the reported risk was found (study protocols and details suggesting *a priori* analyses were absent).

Summary

- Of the 12 newly identified studies included in the *Uptake Review*, three were considered to be at a serious risk of bias and nine at a moderate risk of bias, using the ROBINS-I tool.

Table 9:ROBINS-I risk assessment for the primary research studies included in the smoking uptake systematic review

Reference	Bias domain							Final Judgement
	Confounding	Participant selection	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported risk	
Aleyan et al. 2019[16]	Moderate	Moderate	Low	Low	Low	Low	No information	Moderate
Barrington-Trimis et al. 2019[17]	Moderate	Moderate	Low	Low	Low	Low	No information	Moderate
Berry et al. 2019[7]	Moderate	Low	Low	Low	Low	Low	No information	Moderate
Bold et al. 2018[18]	Serious	Moderate	Low	Low	Low	Low	No information	Serious
Brose et al. 2019[19]	Serious	Moderate	Serious	Low	No information	Low	No information	Serious
Chien et al. 2019[20]	Moderate	Moderate	Low	Low	Low	Low	No information	Moderate
Conner et al. 2019[21]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
Dai et al. 2019[22]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
Kinnunen et al. 2019[23]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
McMillen et al. 2019[24]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
Osibogun et al. 2020[25]	Moderate	Moderate	Low	Low	No information	Low	No information	Moderate
Penzes et al. 2018[26]	Serious	Moderate	Low	Low	No information	Low	No information	Serious

Uptake Review – Discussion update

Background

The *Uptake Review* assessed the relationship of e-cigarette use to smoking uptake. The main findings from the *Uptake Review* included that:

- There is substantial and consistent evidence from observational studies that never smokers who have used e-cigarettes are more likely than those who have not used e-cigarettes to try smoking conventional cigarettes and to transition to becoming regular tobacco smokers.
- The current evidence indicates that, on average, never smokers who have used e-cigarettes have around three times the odds of becoming a smoker of combustible cigarettes compared to never smokers who have not used e-cigarettes. Studies consistently observe increased risks of smoking uptake with e-cigarette use, the magnitude of which varies substantially between studies.
- There is uncertainty regarding the constituents of the e-liquids in the studies reviewed. Where evidence on nicotine content was available, it indicated that a substantial majority of e-cigarettes in those studies delivered nicotine.

Aims and Methods

The aim of this section is to consider the evidence from the *Uptake Review* in relation to the following points:

- Demographic characteristics of participants in studies included in the *Uptake Review*;
- Likelihood that e-cigarettes will increase the number of young people using nicotine and smoking combustible cigarettes; and
- High concentration nicotine salt products.

No data requests were made of the authors of any papers to seek additional information.

Demographic data from the primary research articles – including articles that had been included in previous systematic reviews and newly identified studies – were extracted into Microsoft Excel by one report author (MM) using the data extraction template of the *Uptake Review*. The data extraction was checked by a second author (AY or SB). Discrepancies were resolved through consensus or by a third review author (KB).

Information extracted in the process described above was used to document the age distribution of the study populations and to allow specific consideration of studies of young people. Where only school grade was reported, age was estimated based on the usual age group of students of that grade in the relevant country.

Studies included in the *Uptake Review* were searched for consideration of high nicotine salt devices or JUUL. To supplement the discussion based on articles included in the *Uptake Review*, a brief informal, non-systematic literature search was conducted to identify relevant additional discussion points in articles and grey literature.

Resultant findings from the above three processes are then considered and discussed.

Discussion

Distribution of demographic factors

Primary research papers

Out of the 12 studies, three[19, 22, 24] were of an adult population aged 18 years and over (Table 10). All other studies were with school-aged children ranging from 12–17 years. Four studies[16, 17, 20, 23] did not specify age but listed the school grade. Sex was reported in all studies, except for Penzes et al.,[26] with females accounting for 44.8%–56.3%. Ten studies[7, 16-22, 24, 25] reported data on ethnicity. The most common ethnic subgroup was white/Caucasian, present in nine studies and omitted only from Chien et al.,[20] a Taiwanese based study. Of these studies, all but Connor et al.[21] reported a white majority, with 94.1% (British and other white combined) reported in Brose et al.[19]

Education level, either participant education for the adult samples or parent's education in the youth samples, was reported in five studies.[7, 20, 22, 24, 25] Dai and Leventhal,[22] McMillen et al.[24] and Osibogun et al.[25] reported college or above in 60–70% of the sample while Berry et al.[7] and Chien et al.[20] reported a lower proportion with college education or greater (35%).

Affluence was reported in five studies.[16, 18, 19, 21, 22] Bold et al.[18] found a mean family affluence score of 5.92 in participants (standard deviation (SD) 1.38; score of 8 indicates most affluent) and Connor et al.,[21] using the same measure, reported a mean score of 2.72 (SD 0.49). Brose et al.[19] measured annual income with 41.3% of respondents reporting a high annual income greater than £30,000. Dai and Leventhal[22] measured household income relative to the federal poverty line with 54.2% more than 200% above the poverty line. Aleyan et al.[16] measured the amount of money available to the child to be spent or saved with the majority (44.1%) receiving between $1-20 and 7.1% receiving greater than $100.

One study[7] (Berry et al.) measured urbanisation status with 80.4% of participants living in urban areas and 19.6% in rural areas. Chien et al.[20] was the only study to measure parent's employment status and family living arrangements.

One study examined the association of e-cigarettes on combustible cigarette initiation and another on relapse. Barrington-Trimis et al.[17] found the adjusted odds of dual use at follow-up was considerably higher in non-Hispanic whites (aOR 7.44; 95% CI 3.63–15.3) compared to Hispanic whites (aOR 3.64; 95% CI 1.62–8.18), however, confidence intervals overlapped. Among ex-smoking e-cigarette users, Brose et al.[19] found that there was no statistically significant difference in the likelihood of relapse for sex, age and income.

Papers from systematic reviews

Thirteen studies were extracted from systematic reviews (Table 1111), with nine being conducted in the United States,[27, 30, 31, 33-36, 38, 39] two in the United Kingdom,[28, 29] one in Mexico[32] and one in The Netherlands.[37] Eight studies[27-30, 32, 33, 37, 39] used youth populations (11–18 years) and five[31, 34-36, 38] used adult populations (greater than 18 years). Age was reported in all but two studies,[27, 33] in which instance school grade was reported (ranging from ninth to twelfth grade). In studies reporting the mean age of participants, the range was 13.8 years in Treur et al.[37] to 22.7 years in Unger et al.[38] The mean age across studies providing an average was 17.5 years.[28, 30, 31, 34, 36-39] In studies which categorised age, the lowest limit was 11 years[29, 32, 37] and the upper limit was 30 years.[35]

Sex was reported in all but one study, Best et al.[28] The proportion of females ranged from 48.2%[37] to 67.7%.[31]

Ethnicity was reported in eleven of the publications.[27, 30-39] Non-Hispanic white was the most prevalent ethnic subgroup (ranging from 31.8% to 76.5%) in five[31, 33-36] studies and Hispanic/Latino white (ranging from 37.9% to 100.0%) in four[27, 30, 32, 38], two[32, 38] of which included Hispanic ethnicity only. Filipino-Americans (27.0%) accounted for the largest proportion of participants in Wills et al.[39] In Treur et al.,[37] Dutch individuals accounted for the largest proportion of participants in both cohorts (78.1% and 81.4% respectively).

Several studies also reported on educational attainment, both of the participants' parents[30, 32, 34, 39], and the participants[35, 37] themselves. In Leventhal et al.,[30] the most common highest parental education level achieved was 'College graduate' (33.7%), whilst '≤8th grade' was the least common (3.3%). Lozano et al.[32] found 'Secondary education' (38.0%) to be the most prevalent parental education level, with 'Primary education' being the least prevalent (16.0%). ENDS use at baseline was associated with more advanced maternal education compared to no ENDS use at baseline (mean scores 7.5 and 6.9 respectively) in Primack et al.[34] In a weighted sample of predominately white, non-Hispanic participants, a 'High school or less' education was the most common educational level (45.8%) among ENDS users, whilst 'Bachelors or higher' was the least common (19.3%), in Primack et al.[35] Educational level differed across each cohort in Treur et al.,[37] with the most common educational level in Cohort 1 (mean age 13.8 years, 48.2% female) being 'Low' level (students with learning difficulties and lowest levels of pre-vocational secondary education; 33.4%), in contrast to Cohort 2 (mean age 17.3 years, 61.3% female) where the most common educational level was 'High' (pre-university or university education; 36.7%).

Best et al.,[28] conducted in Scotland, presented the distribution of study participants according to the socioeconomic status and urban-rural profile of their school's location. The greatest proportion was from accessible small town/medium-low deprivation areas. In the Primack et al.[35] weighted sample, ENDS users were most commonly in the 'High' (>$75,000) yearly household income category (47.6%) and least common in the 'Low' (<$30,000) yearly household income category (16.3%). Wills et al.[39] presented data on family structure demographics with 'Two biological parents' being the most common category (60.0%) and 'Extended family structure' (two parents plus two or more relatives in the household) being the least common (11.0%).

Table 10: Demographic data - primary research articles

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Aleyan et al. 2019 Canada	Age not reported Grade 9th: 56.1% 10th: 43.9%	Female: 52.2% Male: 47.8%	White: 76.1% Black: 3.1% Latin-American: 1.9% Asian: 5.4% Aboriginal: 2.2% Other: 11.3%	Weekly spending money $0: 26.0% $1-20: 44.1% $20-100: 22.8% Over $100: 7.1%	No analysis
Barrington-Trimis et al. 2019 US	Age not reported Grade 9th: 58.7% 10th: 6.2% 11th: 19.6% 12th: 15.4%	Female: 46.5% Male: 53.5%	Non-Hispanic white (NHW): 37.4% Hispanic white (HW): 37.9% Other: 24.7%		Current (past 30 day) smoking at follow-up, baseline never smokers aOR (95% CI)^ Non-Hispanic White Nonusers: Reference Dual use: 7.44 (3.63–15.3) Hispanic White Nonusers: Reference Dual use: 3.64 (1.62–8.18) ^Adjusted for sex; random effect for school or community
Berry et al. 2019 US	12 years: 27.3% 13 years: 26.5% 14 years: 25.0% 15 years: 21.3% Mean (SD): 13.4 (1.2) years	Female: 49.5% Male: 50.5%	Non-Hispanic, white: 54.1% Non-Hispanic, black: 13.9% Hispanic: 22.8% Non-Hispanic, other: 9.2%	Parental Education Lower than a college degree: 64.1% College or higher: 35.9% Residence Urban: 80.4% Rural: 19.6%	No analysis
Bold et al. 2018 US	Age 13–17 years Mean (SD): 15.04 (0.90) years	Female: 53% Male: 47%	White: 87.6% Asian: 5.7% Hispanic and/or Latino: 5.1% Black or African American: 2.6% American Indian or Alaskan Native: 1.0% Native Hawaiian or Pacific Islander: 0.7% Middle Eastern: 0.9% Other: 0.4%	Socioeconomic status Mean (SD): 5.92 (1.38) (Family Affluence Scale: scored out of 8, higher score equals greater affluence)	No analysis

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Brose et al. 2019 UK	Age-Mean (SD) Ex-smokers: 48.1 (15.3) Vaping ex-smokers: 49.2 (14.1)	Female: 45.2% Male: 54.8%	White English/Welsh/Scottish /Northern Irish/British: 90.9% Any other white: 3.2% Mixed/multiple ethnic groups: 1.1% Asian/Asian British: 2.9% Black/African/Caribbean/Black British: 1.3% Other ethnic group: 0% Prefer not to say: 0.5%	Annual Income Low (< £15,000): 16.7% Moderate (£15,001-£30,000): 28.7% High(> £30,000): 41.3% Not disclosed: 13.3%	Relapse to smoking during follow-up, baseline ex-smokers to vaping ex-smokers at follow-up (n = 159) OR (95% CI); p value **Sex** Female: Reference Male: 0.99 (0.52-1.87); p=0.96 **Age** Per year increase: 0.98 (0.96-1.00); p=0.068 **Income** High: Reference Other: 0.70 (0.36-1.34); p=0.28
Chien et al. 2019 Taiwan	Age not reported Grade 7th (Junior High): 42.3% 10th (Senior High): 57.7%	Female: 56.3 Male: 43.7%	Mother's ethnicity* Native: 87.9% Indigenous: 3.0% Foreigner: 7.7%	Father's education* Below junior high: 17.6% Senior/vocational high: 37.4% Above college: 35.5% Parent's employment status* Full-time job: 93.5% Part-time job: 1.9% Unemployed: 3.6% Family living arrangement Parents/extended family: 78.9% Single parents: 16.4% Grandparents: 2.1% Other relatives: 2.5%	No analysis
Conner et al. 2019 UK	Age 13-14 years	Female: 52.3% Male: 47.7%	White: 17.2% Non-white: 82.8%	Family affluence Low: 2.72 (0.49) (Family Affluence Scale) Children per school eligible for free school meals (no. of schools): Low: 48.9% High: 44.4%	No analysis

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Dai & Leventhal 2019 US	18-24: 10.0% 25-34: 18.6% 35-44: 16.3% 45-54: 16.5% 55-64: 18.4% 65+: 20.2%	Female: 54.8% Male: 45.2%	Non-Hispanic White: 74.9% Non-Hispanic Black: 7.6% Hispanic: 10.5% Other: 7.0%	Education Less than high school: 8.1% High school graduate: 23.3% Some College: 38.5% Bachelor's degree or above: 29.8% Household income Below poverty line: 16.4% 100%-200% poverty line: 21.0% >200% poverty line: 54.2% Unknown: 8.5%	No analysis
Kinnunen et al. 2019 Finland	Age not reported Grade 9 (age 15-16 years)	Female: 51.8% Male: 48.2%	Not reported	Not reported	No analysis
McMillen et al. 2019 US	18-34: 46.1% ≥35: 53.6% (Unweighted)	Female: 44.8% Male: 55.0% (Unweighted)	Non-Hispanic white: 69.9% Non-Hispanic black: 17.0% Other: 10.3% (Unweighted)	Education <High school: 10.6% High school/GED: 26.1% Some college: 34.5% ≥ College degree: 28.0% (Unweighted)	No analysis
Osibogun et al. 2020 US	12-14 years: 76.4% 15-17 years: 23.6%	Female: 48.0% Male: 52.0%	White: 47.1% African American: 14.0% Hispanic: 29.6% Other: 9.3%	Parent's education level* High school or less: 38.1% Some college: 31.1% Bachelor's degree or higher: 30.3%	No analysis
Penzes et al. 2018 Romania	Mean (SD): 14.88 (0.48) years Grade 9	Not reported	Not reported	Not reported	No analysis

*Numbers may not sum to the total because of missing data

Table 11: Demographic data - articles from systematic reviews

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Barrington-Trimis et al. 2018 US	Age not reported <u>Grade</u> 9th: 58.7% 10th: 6.2% 11th: 19.6% 12th: 15.4%	Female: 53.5% Male: 46.5%	Non-Hispanic white: 37.4% Hispanic white: 37.9% Other: 24.7%	Not reported	No analysis
Best et al. 2017 UK	Mean (SD): 14.4 (1.58) years	Not reported	Not reported	<u>Number of pupils from each school by SES/urban profile</u> School 1 - Accessible small town/medium–low deprivation: 858 School 2 - Urban/medium–low deprivation: 738 School 3 - Other urban/high deprivation: 672 School 4 - Urban/high deprivation: 733 Total: 3001	No analysis
East et al. 2017 UK	11-13 years: 38.02% 14-15 years: 29.34% 16-18 years: 32.64%	Female: 53.8% Male: 46.2%	Not reported	Not reported	No analysis
Leventhal et al. 2015 US	Mean (95% CI): 14.06 (14.04-14.07) years	Female: 53.2% Male: 46.8%	American Indian/Alaska Native: 0.8% Asian: 19.0% Black: 4.8% Hispanic: 44.2% Native Hawaiian/Pacific Islander: 3.6% White: 16.2% Other: 5.7% Multi-ethnic or multi-racial: 5.7%	<u>Highest parental education level</u> ≤8th grade: 3.3% Some high school: 7.8% High school graduate: 15.2% Some college: 19.5% College graduate: 33.7% Graduate degree: 20.6%	No analysis
Loukas et al. 2018 US	Mean (SD): 19.71 (1.61) years	Female 67.7% Male: 32.3%	Non-Hispanic white: 31.8% Hispanic/Latino: 27.4% Asian: 23.4% African-American/Black: 9.8% Other or reported two or more race/ethnicities: 7.5%	Not reported	No analysis

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Lozano et al. 2018 Mexico	11-12 years: 33.0% 13+ years: 67.0%	Female: 52.0% Male: 48.0%	Hispanic/Latino-Mexican: 100.0%	Parental education Primary: 16.0% Secondary: 38.0% High school: 19.0% University: 19.0% Unknown: 8.0%	No analysis
Miech et al. 2017 US	Age not reported Grade 12th grade	Female: 56.3% Male: 43.7%	White: 60.1% Non-white: 39.9%	Not reported	No analysis
Primack et al. 2015 US	Age - mean (SD) ENDS use at baseline, n=16: 19.5 (2.0) years No ENDS use at baseline, n=678: 20.0 (2.4) years	Female: 53.9% Male: 46.1%	Non-Hispanic white: 76.5% Non-Hispanic black: 6.8% Hispanic: 7.6% Other: 9.1%	Maternal Education* - Mean (SD) ENDS use at baseline, n = 16: 7.5 (1.8) No ENDS use at baseline, n = 678: 6.9 (2.5) (*Higher scores equates to higher education)	No analysis
Primack et al. 2018 US	Unweighted data 18-20 years: 21.8% 21-23 years: 32.7% 24-26 years: 24.2% 27-30 years: 21.4% Weighted data 18-20 years: 31.6% 21-23 years: 23.9% 24-26 years: 18.7% 27-30 years: 25.7%	Unweighted Female: 61.6% Male: 38.4% Weighted Female: 50.3% Male: 49.7%	Unweighted White, non-Hispanic: 64.8% Black, non-Hispanic: 10.9% Hispanic: 14.2% Other: 10.1% Weighted White, non-Hispanic: 55.2% Black, non-Hispanic: 14.6% Hispanic: 19.7% Other: 10.4%	Yearly Household Income Unweighted Low (<$30,000): 25.0% Medium ($30,000-$74,999): 38.1% High (>$75,000): 36.8% Weighted Low (<$30,000): 16.3% Medium ($30,000-$74,999): 36.0% High (>$75,000): 47.6% Education Unweighted High school or less: 28.0% Some college: 39.6% Bachelors or higher: 32.5% Weighted High school or less: 45.8% Some college: 34.9% Bachelors or higher: 19.3%	No analysis

Study (Author, date, country)	Age at baseline	Sex	Ethnicity	Other	Effect measure
Spindle et al. 2017 US	Mean (SD): 18.5 (0.43) years	Female: 62.0% Male: 48.0%	White: 47.0% Black: 19.0% Asian: 17.0% Hispanic/Latino: 6.0% Mixed race/ethnicity: 7.0% American Indian/Alaskan Native, Native Hawaiian/Other Pacific Islander, unknown race or ethnicity, or chose not to answer: 4.0%	Not reported	No analysis
Treur et al. 2018 Netherlands	Cohort 1 Age - Mean (SD): 13.8 (1.1) years 11-13 years: 39.7% 14-15 years: 54.3% 16-17 years: 6.0% Cohort 2 Age - Mean (SD): 17.3 (1.8) years 14-15 years: 17.4% 16-17 years: 39.9% 18-21 years: 42.7%	Cohort 1 Female: 48.2% Male: 51.8% Cohort 2 Female: 61.3% Male: 38.7%	Cohort 1 - Ethnicity Netherlands: 78.1% Surinam/Aruba/Netherlands Antilles: 1.8% Morocco: 2.9% Turkey: 2.0% Other: 10.1% Missing data: 5.1% Cohort 2 - Ethnicity Netherlands: 81.4% Surinam/Aruba/Netherlands Antilles: 1.9% Morocco: 2.0% Turkey: 2.1% Other: 4.1% Missing data: 8.5%	Cohort 1 - Educational level Low: 33.4% Average: 31.3% Middle: 17.2% High: 16.2% Missing data: 1.9% Cohort 2 - Educational level Low/Average: 34.2% Middle: 27.3% High: 36.7% Missing data: 1.8%	No analysis
Unger et al. 2016 US	Mean (SD): 22.7 (0.39) years	Female: 59.0% Male: 41.0%	Hispanic: 100.0%	Not reported	No analysis
Wills et al. 2017 US	Mean (SD): 14.7 (0.7) years Grade 9th: 49.0% 10th: 42.0% 11th: 9.0%	Female: 53.0% Male: 47.0%	Asian-American: 24.0% Caucasian: 19.0% Filipino-American: 27.0% Native Hawaiian or other Pacific Islander: 20.0% Other: 10.0%	Father's education (1-6 scale) Mean (SD): 4.2 (1.2) Family structure Single parent: 17.0% Step-parent family: 12.0% Two biological parents: 60.0% Extended family structure: 11.0%	No analysis

Uptake of nicotine and combustible cigarette smoking among young people

The two uptake outcomes reviewed in the *Uptake Review* were:

Outcome 1. Cigarette smoking initiation among never smokers at baseline, in relation to e-cigarette use; and

Outcome 2. Current (past 30-day) cigarette smoking among non-smokers (never smokers or no past 30-day-use) at baseline, in relation to e-cigarette use.

Additional analyses were reported in the *Uptake Review*, that assessed the odds of taking up regular combustible cigarette smoking, as associated with e-cigarette use:

Outcome 3. Current (past 30-day) regular cigarette smoking among non-smokers (never smokers or no past 30-day-use) at baseline, in relation to e-cigarette use.

The risk of uptake of other nicotine products was not assessed in any of the included studies as an outcome. However, as e-cigarettes commonly deliver nicotine, use of e-cigarettes will generally result in increased use of nicotine by young people.

The populations of the included papers in the *Uptake Review* could be divided into school-aged young people (ages ≤18 years), and young people (ages ≤30 years) (Table 12), which incorporated 17 and 22 papers respectively out of the original included 25. Two studies[19, 22] were excluded from the following discussion altogether as the only outcome investigated was smoking relapse, and the study populations included ages over 30 years. One paper remained that had been included in the meta-analyses for Outcomes 1 and 2 with a population of 18 years and over and no upper age limit, making it out-of-scope for both young people populations. This allowed for consideration of how the exclusion of this study's data might impact on the calculated pooled adjusted odds ratios (aOR) and gave an indication of the likely risk applicable to the young populations of interest.

Outcome 1: Cigarette smoking initiation among never smokers at baseline, in relation to e-cigarette use

Overall, 17 studies investigated cigarette smoking initiation among never smokers at baseline, in relation to e-cigarette use, including both newly identified studies and studies drawn from previous meta-analyses. Eleven studies[7, 20, 21, 26-30, 32, 33, 39] assessed populations of school-aged young people (ages ≤18 years). These 11 studies and an additional five studies[31, 34-37] assessed populations of young people aged up to 30 years (ages ≤30 years). One study[24] included all ages over 18 years, and was thus out of scope (Figure 6).

Among studies of school-aged young people (ages ≤18 years), all of the studies found that those who used e-cigarettes were significantly more likely than non-users to initiate smoking of combustible cigarettes, with odds ratios varying substantially from 1.60 to 10.57, and two studies with a comparatively high degree of intra-study variance[29, 33] and associated lower weight of contribution to the overall aOR for all included studies

(Figure 6). The studies with the least amount of intra-study variance tended to have a lower aOR (1.60 to 4.09);[7, 20, 21, 32, 39] likewise, the two studies with the highest degree of within-study variance had the highest aOR.[29, 33]

Among studies of young people to the age of 30 years (ages ≤30 years), the odds ratios ranged from 1.36 to 11.90, and five studies had a high degree of intra-study variance (Figure 6)[34, 35, 37]

The single study with a sample population including people aged older than 30 years (aged 18 years and older, no upper age limit), McMillen et al.,[24] had a comparatively higher aOR (aOR 6.60 (95% CI 3.70 – 11.79)) and moderate intra-study variance. While the removal of this study from analysis may result in a slight decrease in the overall aOR reported in the review, the effect is liable to be minor, indicating an overall aOR for studies assessing populations aged up to 30 years would remain relatively unchanged from the overall aOR reported in the review (pooled aOR 3.19 (95% CI 2.44 – 4.16)) (Figure 7: Adjusted odds and meta-analysis of current smoking at follow-up among baseline non-smokers in relation to current versus not current e-cigarette use at baseline, with age group and rating of comparative odds ratio, variance and weight

). In support of this inference, the 'studies in previous meta-analyses', as shown in Figure 7: Adjusted odds and meta-analysis of current smoking at follow-up among baseline non-smokers in relation to current versus not current e-cigarette use at baseline, with age group and rating of comparative odds ratio, variance and weight

, assessed populations aged ≤30 years and had similar pooled aOR (pooled aOR 3.17 (95% CI 2.44 – 4.61)) to the overall aOR.

Interestingly, the meta-analysis of 'newly identified studies' as shown in Figure 7: Adjusted odds and meta-analysis of current smoking at follow-up among baseline non-smokers in relation to current versus not current e-cigarette use at baseline, with age group and rating of comparative odds ratio, variance and weight

, included four studies on people aged ≤18, and the out-of-scope McMillen et al. 2019 study[24] (Figure 7: Adjusted odds and meta-analysis of current smoking at follow-up among baseline non-smokers in relation to current versus not current e-cigarette use at baseline, with age group and rating of comparative odds ratio, variance and weight

). The pooled aOR for these five studies does not differ materially from the overall aOR found in the review, and restriction of data to the four studies on school-aged young people (ages ≤18 years) only would yield a result consistent with the overall aOR figure.

In summary, based on the current evidence, young people, whether school-aged or aged up to 30 years, who used e-cigarettes had a risk of initiating smoking of combustible cigarettes that was approximately three-fold that of those who do not use e-cigarettes.

Outcome 2: Current (past 30-day) cigarette smoking among non-smokers (never smokers or no past 30-day-use) at baseline, in relation to e-cigarette use

Eight studies investigated current (past 30-day) cigarette smoking among non-smokers (never smokers or no past 30-day-use) at baseline, in relation to e-cigarette use, including both newly identified studies and studies drawn from previous meta-analyses. Six studies[16-18, 21, 23, 25] assessed populations of school-aged young people (ages ≤18 years). These six studies and an additional one study[37] assessed populations of young people aged up to 30 years (ages ≤30 years). One study[24] included all ages over 18 years, and was thus out of scope (Figure 7).

Among studies of school-aged young people (ages ≤18 years), all of the studies found the risk of transitioning from being a non-smoker to current smoker was higher in people who had used e-cigarettes than those that had not used e-cigarettes. Odds ratios varied substantially from 1.18 to 7.44, and two studies[23, 25] showed a comparatively high degree of intra-study variance and associated lower weight of contribution to the pooled aOR for all included studies (Figure 7). The studies with the least amount of intra-study variance were those with the lowest aOR (1.18 and 2.17).[16, 21]

With the additional one study by Unger et al.[38] that included young people to the age of 30 years (ages ≤30 years), the variation in aOR remained the same, with a comparative aOR of 3.32 (95% CI 1.55 – 7.11) and moderate intra-study variance for the additional study (Figure 7). This suggests that the overall findings from studies of school-aged young people and young people aged up to 30 years are likely to be similar.

There was a single study with a sample population including people aged older than 30 years,[24] which found that non-smokers who used e-cigarettes had an aOR of 8.00 (95% CI 2.81 – 22.78) of going on to be a current smoker (Figure 7). This study had a relatively high variance. Focusing results on the remaining seven studies would be likely to give a similar finding to the reported pooled aOR of 3.14 (95% CI 1.93 – 5.11).

In summary, based on the current evidence, young people, whether school-aged or aged up to 30 years, who use e-cigarettes had an approximate three-fold risk of transitioning from being a non-smoker to a current smoker compared to those who do not use e-cigarettes.

Outcome 3: Current (past 30-day) regular cigarette smoking among non-smokers (never smokers or no past 30-day-use) at baseline, in relation to e-cigarette use

Four studies were identified that assessed current regular use of combustible cigarettes (Table 13). Of these, three[21, 23, 25] were conducted among school-aged populations (≤18 years), and one was out-of-scope, having assessed a sample population including people aged older than 30 years.[24] The three in-scope studies used definitions of regular use (smoking at least 20 out of 30 days)[21, 25] or daily use[23] of combustible cigarettes as assessed outcomes.

Conner et al.[21] investigated the association of e-cigarette use at baseline and combustible tobacco smoking in

adolescents (13 to 14 years old) between Waves 3 and 5 (2014 to 2016) of a cluster RCT in 20 schools in England. Participants were found to have significantly higher odds of taking up regular current combustible cigarette smoking by follow-up, based on ever-use of e-cigarettes at baseline (aOR 1.27; 95% CI 1.17 – 1.39).

Kinnunen et al.[23] used MEtLoFIN, a school-based longitudinal cohort dataset in 3,474 Finnish adolescents between 2014 and 2016. Kinnunen et al., separated the use of e-cigarettes using nicotine contents and found among baseline never smokers, ever-use of nicotine-containing e-cigarettes predicted uptake of daily smoking (aOR 2.92; 95% CI 1.09 – 7.85) but non-nicotine containing e-cigarettes did not (aOR 0.94; 95% CI 0.22 – 4.08).

Osibogun et al.[25] used data on youth (12-17 years old) non-smokers from Waves 1 to 3 of the Population Assessment of Tobacco and Health (PATH) study, a US nationally representative longitudinal study. At one-year follow-up, current e-cigarettes users at baseline had significantly higher odds of having become regular current combustible cigarette users (aOR 5.0; 95% CI 1.9 – 12.8), an affect which had attenuated at two-year follow-up (aOR 3.4; 95% CI 1.0 – 11.5).

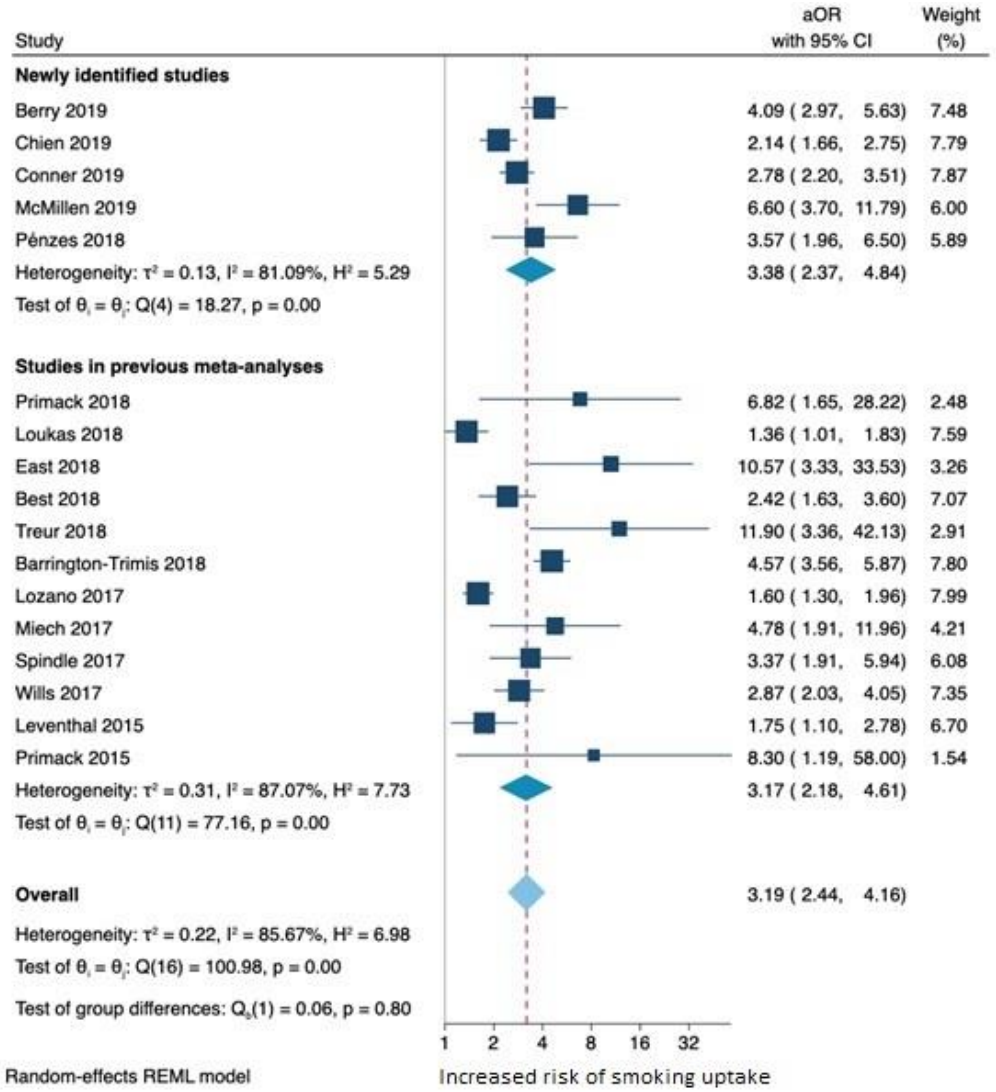
The available evidence from three studies indicates that, among young people, there is an elevated risk for those who had used e-cigarettes of transitioning from being a non-smoker to a current regular smoker compared to those that had not used e-cigarettes. Nicotine content of e-cigarettes may influence the degree of risk. At this time, however, there is insufficient available evidence to draw firm conclusions.

Table 12: Studies included in the *Uptake Review* by young person age group, ordered by age group of sample

Reference	Age (yrs)	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	>30
Lozano et al. 2017[32]	12 - 13		■	■																		
Conner et al. 2019[21]	13 - 14			■	■																	
Berry et al. 2019[7]	12 - 15		■	■	■	■																
Penzes et al. 2018[26]	14 - 15				■	■																
Leventhal et al. 2015[30]	14 - 15				■	■																
Chien et al. 2019[20]	13, 16			■			■															
Wills et al. 2017[39]	14 - 16				■	■	■															
Aleyan et al. 2019[16]	14 - 16				■	■	■															
Kinnunen et al. 2019[23]	15 - 16					■	■															
Osibogun et al. 2020[25]	12 - 17		■	■	■	■	■	■														
Bold et al. 2018[18]	13 - 17			■	■	■	■	■														
Best et al. 2017[28]	11 - 18	■	■	■	■	■	■	■	■													
East 2017[29]	11 - 18	■	■	■	■	■	■	■	■													
Barrington-Trimis et al. 2019[17]	14 - 18				■	■	■	■	■													
Barrington-Trimis et al. 2018[27]	14 - 18				■	■	■	■	■													
Miech et al. 2017[33]	17 - 18							■	■													
Spindle et al. 2017[36]	18 - 19								■	■												
Treur et al. 2018[37]	14 - 21				■	■	■	■	■	■	■	■										
Unger et al. 2016[38]	22 - 23												■	■								
Loukas et al. 2018[31]	18 - 25								■	■	■	■	■	■	■	■						
Primack et al. 2015[34]	16 - 26						■	■	■	■	■	■	■	■	■	■	■					
Primack et al. 2018[35]	18 - 30								■	■	■	■	■	■	■	■	■	■	■	■	■	
McMillen et al. 2019[24]	18+								■	■	■	■	■	■	■	■	■	■	■	■	■	■

Green outline denotes studies included in discussion for school-aged young people (ages ≤18 years)
Yellow outline denotes studies included in discussion for young people aged ≤30 years

Figure 6: Adjusted odds ratios and meta-analysis of smoking initiation at follow-up among baseline never smokers in relation to current versus never e-cigarette use at baseline, with age group and rating of comparative odds ratio, variance and weight



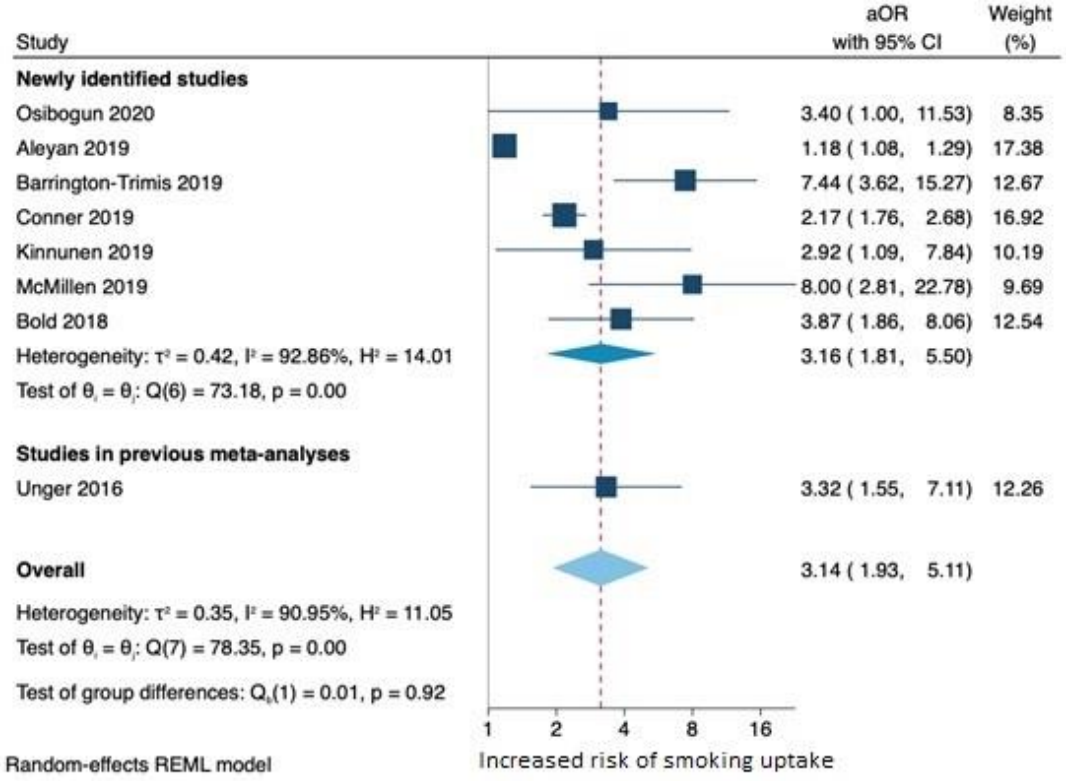
Comparative rating	
Variance	Weight
L	H
L	H
L	H
M	M
M	M

H	L
L	H
H	L
M	M
H	L
M	H
L	H
H	L
M	M
L	H
M	M
H	L

L = Low; M = Medium; H = High.

Aged <=18 years (and <=30 years)
Aged <=30 years
Out-of-scope (aged 18+ years)

Figure 7: Adjusted odds and meta-analysis of current smoking at follow-up among baseline non-smokers in relation to current versus not current e-cigarette use at baseline, with age group and rating of comparative odds ratio, variance and weight



Comparative rating	
Variance	Weight
H	L
L	H
M	M
L	H
H	L
H	L
M	M

M	M

L = Low; M = Medium; H = High.

Aged <=18 years (and <=30 years)
Aged <=30 years
Out-of-scope (aged 18+ years)

Table 13: Odds ratios and adjusted odds ratios of the association between e-cigarette use and current[a] (past 30-day) combustible tobacco smoking initiation among non-smokers (never or no past 30-day use) at baseline.

Study	Ages	Country	Baseline cigarette use	E-cigarette use at baseline	Cigarette use at follow-up	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Conner et al., 2019[21]	≤18 years	UK (England)	Never smokers	Ever	Current	3.38 (2.72–4.21)	2.17 (1.76–2.69)
				Ever	Regular[a]	3.60 (2.35–5.51)	1.27 (1.17–1.39)
Kinnunen et al., 2019[23]	≤18 years	Finland	Never smokers	Ever	Daily use	Nicotine containing 11.52 (4.91–27.01) Firth: 11.70 (4.91–26.56) Non-nicotine containing 1.88 (0.25–14.45) Firth: 2.71 (0.29–11.14)	Nicotine-containing 8.50 (2.14–29.19) With school clustering: 2.92 (1.09–7.85) Non-nicotine containing 2.50 (0.25–12.05) With school clustering: 0.94 (0.22–4.08)
Osibogun et al., 2020[25]	≤18 years	US	Non-smokers (never or no current use)	Current	Regular use[a]	Year 1: 16.4 (7.8–34.5) Year 2: 11.1 (3.5–35.2)	Year 1: 5.0 (1.9 – 12.8) Year 2: 3.4 (1.0 – 11.5)
McMillen et al., 2019[24]	18+ years	US	Never smoker	Ever (not current)	Established[b]	5.9 (1.7–20.7)	2.5 (0.6–10.9)
				Current	Established[b]	25.5 (10.6–61.4)	8.0 (2.8–22.7)

[a] Regular defined as ≥20 days/30 days; [b] Established defined as ≥100 combustible cigarettes in the past 12 months and currently smokes every day or some days

Aged ≤18 years (and ≤30 years)

Out-of-scope (aged 18+ years)

High concentration nicotine salt products

Nicotine salts are an alternative to free-base e-liquid in e-cigarette devices. Unlike free-base e-liquids, they do not contain glycerol or propylene glycol, instead consisting of a nicotine base and a weak organic acid that forms a nicotine salt upon activation of the device, which is then released as an aerosol for inhalation.[43]

Nicotine salts are used in 'pod vaporizers' or 'vape pods', the leading product in the US market being JUUL developed by JUUL Labs.[44, 45] There is evidence of considerable concern among researchers, health bodies and policy makers about pod devices, centred around JUUL, with JUUL Labs facing investigation in the US for their role in what has been called the 'youth nicotine addiction epidemic'[46] in the US. The main points of concern are summarised below.

The substance is based on the nicotine salts found in leaf-based tobacco rather than free-base nicotine.[44] Nicotine salt products deliver comparatively high levels of nicotine,[44, 47, 48] with the standard US JUUL or Puffbar having a nicotine concentration of 5% or 59mg/mL and a single cartridge containing as much nicotine as 1-2 packets of cigarettes.[49] The nicotine is delivered more rapidly than when using standard e-liquids,[49] with a peak at about five minutes, creating an experience similar to combustible cigarette smoking.[44]

The design of nicotine pods is generally small, light, easy to conceal and easy to use inconspicuously[50] - with the design resembling a USB stick – these design features are appealing to young people.[44, 49] They are discrete enough to evade detection in class at school or from parents.[44, 45] The flavoured nicotine cartridges, with flavours such as Fruit Medley and Crème Brulee,[44] were also considered to appeal to youth.[49] Numerous easily concealable devices have come on to the market following widespread use of JUUL.[45]

This youth appeal has been compounded by marketing tactics which have been shown to deliberately target children and youth.[47] The JUUL device was prolifically advertised through social media campaigns including on Instagram and Twitter, employing memes, hashtags, tag lines, and promotional friend-tagging, and recruiting 'thousands of online 'influencers'' to market JUUL.[46] JUUL reportedly marketed directly to teenagers and children as young as 8 years old by gaining access to schools, summer camps, and public out-of-school programs.[47] A significant number of retailers in the US were warned by the FDA for reported illegal sales of JUUL products to youth.[47]

Further compounding of these issues is a lack of knowledge and awareness among young users of nicotine pods. Many young users are unaware or unsure that they are e-cigarettes.[48] Several studies have shown that most students do not know the nicotine content of nicotine pods or that they have a high content.[47, 48] In the US hearing into JUUL, The Respiratory Health Association reported that around 60% of young people using JUUL were not aware that the product contained nicotine.[49]

In the Australian context, while limited evidence indicates that Australian youth have been subjected to e-cigarette marketing, particularly via social media, the extent to which this relates to nicotine salt products is not known.[46, 51]

As noted in the *Uptake Review*, there is uncertainty regarding the constituents of the e-liquids in the studies reviewed. Where evidence on nicotine content was available, it indicated that a substantial majority of e-cigarettes in those studies delivered nicotine. Detail on the specific devices used by participants was generally not reported. Three papers[19, 21, 22] contained some device information and none of these indicated use of nicotine salt vaping devices. A further three papers[31, 32, 36] noted the likely impact of device type and other characteristics on uptake of combustible cigarette smoking as an important area for future research.

One paper referenced nicotine salt products,[16] specifically the JUUL device, in the discussion section. This was in the context of the product's entry into the market as a driver of the need for revised policies to discourage e-cigarette use among young people, referencing the deleterious effect of nicotine on the developing adolescent brain.

After completion of study searches and following submission of the first verison of this report, in early July 2021 Health Canada reduced the cap on nicotine concentrations permitted in e-cigarettes to 20mg/mL. They noted in their justification that "Health Canada has identified the availability of high-nicotine-concentration vaping products in the Canadian market since 2018 as one of the key factors that have contributed to the rapid rise in youth vaping."[52] In particular, they noted a doubling in the prevalence of current/recent e-cigarette use (defined as use within the past 30 days) among school students from 2016-2017 to 2018-2019. They also state: "In 2018, a new generation of vaping products were introduced to the Canadian market, characterized by high concentrations of nicotine in salt form (called "nicotine salts") that made nicotine less aversive when inhaled. As a result, vaping products above 20 mg/mL nicotine (a majority of which contained nicotine salts) quickly took a dominant market position, capturing 62% of the domestic market by value of nicotine-containing vaping substances in 2019.[52]footnote 13 footnote 14[53, 54]

In summary, despite concerns about nicotine salt products, no research specifically examining their relationship to combustible cigarette uptake was able to be located during the specified search period. Thus, whether the higher nicotine content or the more rapid release of nicotine associated with nicotine salt products impacts the uptake of combustible cigarette smoking is not known. From a safety perspective, at this stage, the findings regarding e-cigarettes and smoking uptake should be considered to apply to the range of devices in use by participants in the studies that have been summarised. Nicotine e-cigarettes which have not been the subject of studies regarding their impact on smoking should be assumed to increase the uptake of combustible smoking, unless specific evidence to the contrary is available. Moreover, the emerging evidence that high-concentration nicotine salt products are likely to increase the prevalence of youth e-cigarette use means they may be particularly hazardous with respect to increasing combustible tobacco smoking, as they are associated with increasing prevalence of exposure.

Summary

Distribution of demographic factors

- Demographic factors reported in the studies in the *Uptake Review* included age, sex, ethnicity, education, affluence, urbanisation, SES, and family structure.
- Participants with a range of demographic characteristics were included although most studies were of people aged between 11 and 18 years.
- Analysis according to demographic subgroups was scant. There was no specific evidence available of any variation in the relationship of e-cigarette use to smoking uptake according to demographic factors. Where assessed, no statistically significant difference in the likelihood of smoking relapse was identified for sex, age, income or non-Hispanic white compared to Hispanic white ethnic/cultural groups.

Uptake of nicotine and combustible cigarette smoking among young people

- Based on the current evidence, young people, whether school-aged or aged up to 30 years, who used e-cigarettes had a risk of initiating smoking of combustible cigarettes that was approximately three-fold that of those who did not use e-cigarettes. There was substantial variation in the results between studies.
- Based on the current evidence, young people, whether school-aged or aged up to 30 years, who use e-cigarettes had an approximate three-fold risk of transitioning from being a non-smoker to a current smoker compared to those who did not use e-cigarettes. There was substantial variation in the results between studies.
- Based on evidence from three studies, the risk of transitioning from being a non-smoker to a current regular smoker is elevated for young people aged ≤18 years who had used e-cigarettes compared to those who had not, and this risk may be impacted by nicotine content, however evidence is limited.
- E-cigarettes commonly deliver nicotine, so use of e-cigarettes will generally result in increased use of nicotine by young people.

High concentration nicotine salt products

- Information on the nicotine content and delivery devices used by participants in the studies including in the uptake review was extremely limited.
- No research specifically examining the relationship of nicotine salt products to combustible cigarette uptake was located.
- From a safety perspective, at this stage, the findings regarding e-cigarettes and smoking uptake should be considered to apply to the range of devices in use by participants in the studies that have been summarised. Furthermore, nicotine e-cigarettes which have not been the subject of studies regarding their impact on smoking should be assumed to increase the uptake of combustible smoking, unless specific evidence to the contrary is available.

- Since high concentration nicotine salt products have been identified as key drivers of increased youth e-cigarette use, they may be particularly hazardous for increasing youth smoking uptake, through higher prevalence of e-cigarette use.

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