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[Intervention Protocol]

Electronic cigarettes and subsequent cigarette smoking in young people

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the evidence on the relationship between the use and availability of e-cigarettes and subsequent cigarette smoking in young people (aged 29 years or less), and whether the relationship differs by socioeconomic status, gender, or other demographic characteristics.

BACKGROUND

Throughout this review, we discuss (1) conventional cigarettes; and (2) electronic cigarettes, defined as handheld electronic vaping devices that produce aerosol for inhalation formed by heating an e-liquid. In this review, all mention of smoking, smoking cessation, cigarette use, smoke intake, etc. concerns combustible tobacco cigarettes. When the text concerns electronic cigarettes we use the abbreviation 'ECs'. EC users are sometimes described as vapers, and EC use as vaping. This review does not address the use of vaping devices to inhale substances other than nicotine, such as cannabis. In this review, we define young people as people aged 29 years or younger.

Description of the condition

Combustible tobacco use kills more than 8 million people each year (WHO 2021). Cigarette smoking is the most common form of tobacco use worldwide. Despite declines in adolescent cigarette use over time in many countries, the most recent global prevalence estimates of cigarette smoking in adolescents remains substantial: 11.3% in boys and 6.1% in girls (Ma 2021).

Over two-thirds of people who try one cigarette transition to daily smoking (Birge 2018). Globally, the average age of initiation is 19; around 89% of new smokers smoke tobacco regularly by the age of 25 (Reitsma 2021). Quitting smoking is extremely challenging for many people who smoke regularly. There are no interventions for smoking cessation with high-certainty evidence of effectiveness in adolescents (Fanshawe 2017). In adults, most attempts to quit smoking using first-line treatments will fail (Cahill 2013; Hartmann-Boyce 2021; Hartmann-Boyce 2021a). Tobacco smoking is a key driver of health inequalities, with people from less advantaged groups more likely to smoke and more likely to die from smoking-related diseases (WHO 2014). Preventing uptake of smoking remains, as ever, a key public health priority.

Description of the exposure

Electronic cigarettes are electronic vaping devices that are handheld and produce an aerosol formed by heating an e-liquid, designed for inhalation by the user (Addiction Ontology 2021). The e-liquid, usually comprising propylene glycol and glycerol, with or without nicotine and flavours, is stored in disposable or refillable cartridges, or a reservoir or 'pod'. The commonly-used term for this aerosol is vapour. ECs are marketed as consumer products. There are many different brands and models of EC available. Variation exists both in the EC type and e-liquid used.

Regulatory approaches being used for ECs currently vary widely, from no regulation to partial and complete bans (McNeill 2021). Where ECs are permitted, sales are often restricted in younger age groups. Within the USA, for example, the Food and Drug Administration (FDA) has classified them as tobacco products and there are a range of laws that include prohibition of EC use indoors, the requirement of retailers to have a licence to sell, and prohibition of sales to minors. Laws prohibiting sales to minors apply nationwide, but other laws vary by state, with the age of sale ranging between 18 and 21 years (Du 2020). The European Union includes ECs in their Tobacco Products Directive, and they cannot be sold to people under the age of 18. If therapeutic claims are made, or if they contain over 20 milligrams per millilitre (mg/mL) of nicotine, they require medicines or research authorisation in the European Union (European Parliament 2014).

Expert consensus broadly holds that ECs are considerably less harmful than smoking (RCP 2016; NASEM 2018). However, the large number of devices and e-liquids available, and the frequent addition of new products to the market, render categorical statements about the toxicity of ECs impossible. Among the nicotine ECs that have been tested, levels of toxins have been found to be substantially lower than in cigarettes (Hartmann-Boyce 2021a; McNeill 2021). In 2019 and 2020, there were particular concerns regarding reports in the USA of cases of severe lung injury associated with EC use (known as e-cigarette or vaping-associated lung injury, or EVALI) (CDC 2020; Hall 2021). It was eventually found that these injuries were primarily related to use of tetrahydrocannabinol (THC)-containing ECs, and in particular THC products adulterated with vitamin E acetate (Blount 2020; Hartnett 2020).

As with adults, regular use of ECs in Canada, England and the USA is greatest among young people who also smoke and lowest among people who have never smoked. Regular EC use among young people was rare in these countries prior to 2017, but increased in Canada and the USA between 2017 and 2019, with no significant change in England (Hammond 2020).

How electronic cigarette use and availability might influence smoking uptake

There are multiple routes through which ECs might influence cigarette smoking in young people. ECs may act as a 'gateway' into smoking, whereby a young person first uses a nicotine EC and then goes on to use combustible tobacco. The biologically plausible pathway is that exposure of the adolescent brain to nicotine creates neuroadaptations that drive addiction, and that cigarettes are more effective and rewarding vehicles of administration of nicotine than ECs (Yuan 2015). There are also concerns that ECs, particularly those which resemble cigarettes, may renormalise smoking, and that involvement in ECs gives the tobacco industry routes into tobacco control, from which they had previously been excluded. On the other hand, there are also conceivable ways in which ECs may reduce youth smoking uptake and prevalence. It could be that young people who would have smoked, use ECs instead, and never progress to smoking. Alternatively, regular smokers might use ECs to transition out of smoking. Parental and peer smoking are also known to be key drivers of youth smoking (Bauman 1990), and it could be that parents or peers (or both) using ECs in the place of cigarette smoking also has a protective effect against youth smoking, though to the best of our knowledge this has yet to be formally tested.

Longitudinal studies have shown a consistent association between initial EC use and later smoking uptake in young people (Wills 2017), but whether the relationship is causal remains contested (Khouja 2020). Studies find that both initial EC use predicts later smoking uptake and that smoking uptake predicts EC use, which could suggest that these are manifestations of a tendency to experiment with substance use and with nicotine-containing products in particular. On the other hand, this could represent biological priming. A key issue is whether ECs help or hinder declines in youth smoking prevalence, and whether any effects of vaping on risk of smoking differ across key population subgroups or between regulatory environments.

Why it is important to do this review

Previous systematic reviews and meta-analyses in this area have lacked definitive conclusions, and there is heterogeneity in estimates within and across reviews (Soneji 2017; Khouja 2020; Chan 2021). Given the controversy and complexity of the topic, an unbiased, robust, and thorough review of the available evidence is urgently needed to inform policy and interventions, as well as to guide future research.

OBJECTIVES

To assess the evidence on the relationship between the use and availability of e-cigarettes and subsequent cigarette smoking in young people (aged 29 years or less), and whether the relationship differs by socioeconomic status, gender, or other demographic characteristics.

METHODS

Criteria for considering studies for this review

Types of studies

We will include population- and individual-level data. Population-level data will include aggregate data on smoking rates. Studies must have repeated measures (e.g. repeat cross-sectional studies with measures at different time points from different individuals) and evaluate cigarette use in young people in relation to EC use or availability (or both) in the same population/participants. This design is likely to provide good evidence on population impact.

Individual-level data, which follow tobacco use trajectories in individuals, will come from cohort studies (e.g. longitudinal surveys of people not smoking at baseline, which compare the incidence of smoking by baseline EC use). To be included, studies must prospectively collect data on EC and smoking behaviours from the same individuals at a minimum of two time points (with no minimum length of time between exposure and outcome), and consider at least one covariate related to propensity to smoke (for example, parental smoking, measure of susceptibility to smoking, or socioeconomic status) in their analysis. Randomised controlled trials will not be included as they are not feasible for this topic due to ethical issues associated with randomising young people to an EC intervention for the purpose of assessing uptake of smoking. Studies will be included regardless of comparator.

Types of participants

We expect, based on scoping searches and knowledge of the literature, that most studies investigating this issue will be conducted in people aged 18 years or younger. However, the USA definition of 'young people' in this context includes people aged 18 to 24 (US Department of Health and Human Services 2016). As some studies will use a broader definition, we will use a cut-off of 29 years. We will include population-wide surveys including adults both under and over 29 only if they stratify results by age group, which will allow us to extract information from the younger age groups reported.

Types of interventions

This review evaluates an exposure rather than an intervention. The exposure of interest is any type of EC use (at the individual level, ranging from one-time experimentation to regular use, but excluding cannabis) or EC availability (e.g. policies affecting EC availability or aggregate data on e-cigarette usage, including sales data).

Types of outcome measures

Primary outcomes

The primary outcome will be the association between EC use/availability and change in population rate of tobacco use in young people, assessed through the proportion reporting current cigarette use (using definitions provided by study authors) or, where this information is not available, proxy measures such as cigarette sales data. We view this association encompassing both benefits and harms (where harm is considered as uptake of cigarette smoking).

These outcome data will primarily come from the population-level studies only, or from individual-level studies if samples are weighted to be representative. If a study only reports on combustible tobacco use but does not provide a breakdown by type (e.g. cigarettes, cigars), we will include these data as a proxy measure for cigarette smoking, given that the vast majority of studies published in this area concern cigarette smoking.

Secondary outcomes

The secondary outcomes will be the association between EC use/availability and incidence of cigarette smoking (defined as the rate at which young people begin smoking in a specified time frame), progression (to include progression from never-smoking to ever smoking, occasional use or regular use), and cessation of cigarette smoking, in young people (as defined by study authors).

Search methods for identification of studies

Electronic searches

We will search MEDLINE, Embase, PsycINFO, and the Cochrane Tobacco Addiction Group's Specialised Register. The Register is populated by searches of the Cochrane Central Register of Controlled trials (CENTRAL), MEDLINE, Embase, PsycINFO, and two online trial registries: ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). See the Tobacco Addiction Group's website for full details of how the Register is compiled. Our search strategy is listed in Appendix 1.

Searching other resources

We will issue a call to other researchers in the field and our networks on social media and via email to help identify studies, including in-press or unpublished studies. We will also screen reference lists of included studies and other reviews in this area.

Data collection and analysis

Selection of studies

Screening will be conducted independently by two review authors in Covidence (Covidence), with discrepancies resolved via discussion or through referral to a third author. It will occur in two stages; firstly with screening of titles and abstracts, with those records that appear potentially eligible going on to full-text screening.

Data extraction and management

Data extraction will be conducted using a prespecified and piloted data extraction form. We will extract data for the following fields.

- Country.
- Setting.
- Study design.
- Study dates.
- Participants (number, mean age, ethnicity, gender, measures of socioeconomic status, cigarette and EC use at baseline).
- Study methods (including confounders and how these were controlled for).
- Exposure(s) (including EC use (e.g. ever use, past 30-day use) and availability (e.g. restrictions such as bans on use, bans on flavours, price changes)).
- Outcomes (population rate of tobacco use in young people, uptake, progression or cessation of cigarette smoking, e.g. ever use, use during past six months, past 30-day use, daily use).
- Analysis methods.
- Study funding.

The extraction of outcome data will be conducted independently by two reviewers, with discrepancies resolved via discussion or through referral to a third reviewer. Extraction of study characteristics will be carried out by one review author and checked by another.

Assessment of risk of bias in included studies

Cochrane is currently piloting a new risk of bias tool for evaluating studies of exposures (ROBINS-E). We anticipate that this will be developed in time for us to use it to judge risk of bias for this review; if it is not available, we will draw on Cochrane guidance for best available tools in its absence. Risk of bias judgements will be conducted independently and in duplicate by two reviewers, with discrepancies resolved by discussion or referral to a third review author. Studies at high risk of bias for any domain will be judged to be at high risk of bias overall; studies with low risk of bias across all domains will be judged to be at low risk of bias overall; all other studies will be judged as being at unclear risk of bias.

We will also add a domain to assess risk of bias in relation to the length of time between the exposure and outcome. Studies with a time frame of less than three months between exposure and outcome will be judged as being at high risk of bias and will be compared in sensitivity analyses with studies that have a time frame of three months or more.

Measures of treatment effect

See Data synthesis.

Unit of analysis issues

We anticipate that studies may vary in the unit of analysis reported, depending on the study design used. For example, cohort studies may follow up individual participants over time, while other studies may report summary figures at the population level. Summary effects at the population level will not be statistically combined with those from individual-level cohort studies. We will consider the possible effects of these differences in units of analysis and study design types when summarising our findings.

Where multiple analyses relate to the same underlying dataset, we will consider this as one study, listing all references. In our main syntheses, we will use the results from the study that is judged to have the lowest risk of bias; where there is no difference in risk of bias between studies, we will use the results from analyses containing the most data (i.e. data that cover the longest time period), preferring published to unpublished data. We will also narratively synthesise the results by dataset.

Dealing with missing data

Where needed, we will contact study authors or sponsors in order to verify key study characteristics and obtain missing numerical outcome data. Where this is not possible, and the missing data are thought to introduce the possibility of bias (as determined by our risk of bias assessment), we will explore the impact of including such studies in the overall assessment of results using sensitivity analyses, and will also conduct sensitivity analyses to test if conclusions are sensitive to the assumptions made regarding missing data.

Assessment of heterogeneity

We will examine study characteristics to assess the presence of clinical and methodological heterogeneity. We anticipate that methodological heterogeneity will preclude traditional meta-analysis; however, if data can be combined meaningfully, we will assess statistical heterogeneity using the I^2statistic. We will consider an I^2 value greater than 50% as evidence of substantial heterogeneity.

Assessment of reporting biases

Selective outcome reporting will be considered for each included study. Where we are aware of unpublished data that meet our inclusion criteria but are not sufficient to be included in our analyses, we will consider this as another potential source of reporting bias. This will be taken into account in our GRADE assessment when considering publication bias (see below).

Data synthesis

We anticipate that heterogeneity in study designs, outcome measures, and exposure measures may preclude meta-analyses. However, if studies have the same study designs and use similar outcome measures and exposure measures, we will consider combining them in meta-analysis using standard Cochrane methods. For all other analyses, we will follow Cochrane guidance on synthesis without meta-analysis (Higgins 2021) and will use novel evidence synthesis techniques which go beyond traditional methods. We will create a series of causal chains (depicted through logic models), summarising the sequence of activities and changes that link exposures and outcomes (Kneale 2018). These models will be developed a priori in an iterative process, through conversations with the project team, members of the public, and key stakeholders, as well as by drawing on models presented in the included studies. After the models are developed, we will interrogate the data to see if the included studies support the models. We will use two methods to do so: temporal qualitative comparative analysis (tQCA) and framework synthesis (Booth 2015; Caren 2005).

Qualitative comparative analysis is a method originating in the social sciences that aims to identify variables (e.g. vaping regulations, socioeconomic status characteristics) present when an

outcome occurs (e.g. youth smoking prevalence, progression to smoking). Standard QCA lacks a temporal element, whereas tQCA allows for sequencing of events (Caren 2005). As long as sufficient data are available (recommended set size approximately 18 studies), we will conduct two separate tQCAs, one on population-level studies (e.g. those that look at the association between aggregated estimates), and one on individual-level studies (e.g. cohort studies). In tQCAs, the recommended condition set is 3 to 4. The outcome will be progression to/prevalence of regular smoking. Condition choice will be shaped by conversations with the project team, members of the public, and key stakeholders, as well as by the data available (e.g. if a condition is not reported, we cannot study it), but we anticipate it will include conditions related to EC use/availability, and related to population characteristics (e.g. socioeconomic status).

Framework synthesis, following inductive and deductive approaches, will also be used to categorise studies into cases that fit the models and those that do not, again with a focus on the role of socioeconomic status. Increasingly, this technique is being applied to quantitative data as a way to evaluate complex interventions (Kneale 2018).

Subgroup analysis and investigation of heterogeneity

Both the tQCA and framework synthesis will take into account possible drivers of heterogeneity, as described above. We will use PROGRESS-Plus indicators where reported in studies (e.g. socioeconomic status, gender, and other demographic factors) to assess whether the effects of vaping on risk of smoking differ across subgroups. These have been selected because they are thought to be the most relevant factors when considering inequalities in health (O'Neill 2014).

We will also tabulate studies based on the covariates included in the analyses, in order to identify any associations between covariates included in analyses and the outcomes of those analyses. Within this we will also group studies by definitions of EC and conventional cigarette use (e.g. ever use, past 30-day use, daily use, etc).

If we conduct meta-analysis, we will be guided by the degree of statistical heterogeneity, assessed by calculating the I^2 statistic (Higgins 2021), and consider a value greater than 50% as evidence of substantial heterogeneity. We will consider whether it is appropriate to present pooled results where I^2 values exceed 75%.

Sensitivity analysis

Where multiple different measures of effect are provided within a study (e.g. different definitions of 'regular' use) we will test the sensitivity of our findings to choice of effect. All measures of effect will be presented. We intend to explore the degree to which findings are sensitive to definition used in terms of both EC and conventional cigarette use.

We will conduct sensitivity analyses in which we will remove studies judged to be at high risk of bias from our tQCAs. We will also assess the impact of excluding unpublished studies on our findings.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table for all primary and secondary outcomes. Certainty will be assessed using GRADE guidance and software (GRADEpro GDT) for observational data, assessed using the following five domains: risk of bias or limitations in the detailed design and implementation; unexplained heterogeneity or inconsistency of results; indirectness of evidence; imprecision of results; and probability of publication bias (Higgins 2021).

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REFERENCES

Additional references

Addiction Ontology 2021

E-cigarette v1. Qeios. [URL: https://doi.org/10.32388/0WX80U]

Bauman 1990

Bauman KE, Foshee VA, Linzer MA, Koch GG.Effect of parental smoking classification on the association between parental and adolescent smoking. *Addictive Behaviors* 1990;**15**(5):413-22.

Birge 2018

Birge M, Duffy S, Miler JA, Hajek P.What proportion of people who try one cigarette become daily smokers? A meta-analysis of representative surveys. *Nicotine & Tobacco Research* 2018;**20**(12):1427-33.

Blount 2020

Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-BlasiniL, GardnerM, et al.Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI. *New England Journal of Medicine* 2020;**382**(8):697-705.

Booth 2015

Booth A, Carroll C.How to build up the actionable knowledge base: the role of 'best fit' framework synthesis for studies of improvement in healthcare. *BMJ Quality & Safety* 2015;**24**(11):700-8.

Cahill 2013

Cahill K, Stevens S, Perera R, Lancaster T.Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews* 2013, Issue 5. Art. No: CD009329. [DOI: 10.1002/14651858.CD009329.pub2]

Caren 2005

Caren N, Panofsky A.TQCA: a technique for adding temporality to qualitative comparative analysis. *Sociological Methods & Research* 2005;**34**(2):147-72.

CDC 2020

Centres for Disease Control and Prevention.Outbreak of lung injury associated with the use of e-cigarette, or vaping, products. www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information (accessed 12 August 2020).

Chan 2021

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

Covidence [Computer program]

Veritas Health Innovation Covidence.Version accessed 29 November 2021. Melbourne, Australia: Veritas Health Innovation. Available at covidence.org.

Du 2020

Du Y, Liu B, Xu G, Rong S, Sun Y, Wu Y, et al.Association of electronic cigarette regulations with electronic cigarette use among adults in the United States. *JAMA Network Open* 2020;**3**(1):e1920255.

European Parliament 2014

European Parliament and Council of the European Union.Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC. (accessed 25 November 2014).

Fanshawe 2017

Fanshawe TR, Halliwell W, Lindson N, Aveyard P, Livingstone-Banks J, Hartmann-Boyce J.Tobacco cessation interventions for young people. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No: CD003289. [DOI: 10.1002/14651858.CD003289.pub6]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT.Version accessed 30 July 2020. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Hall 2021

Hall W, Gartner C, Bonevski B.Lessons from the public health responses to the US outbreak of vaping-related lung injury. Addiction 2021;**116**(5):985-93.

Hammond 2020

Hammond D, Rynard VL, Reid JL.Changes in prevalence of vaping among youths in the United States, Canada, and England from 2017 to 2019. *JAMA Pediatrics* 2020;**174**(8):797-800.

Hartmann-Boyce 2021

Hartmann-Boyce J, Livingstone-Banks J, Ordóñez-Mena JM, Fanshawe TR, Lindson N, Freeman SC, et al.Behavioural interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No: CD013229. [DOI: 10.1002/14651858.CD013229.pub2]

Hartmann-Boyce 2021a

Hartmann-Boyce J, McRobbie H, Butler AR, Lindson N, Bullen C, Begh R, et al.Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2021, Issue 4. Art. No: CD010216. [DOI: 10.1002/14651858.CD010216.pub4]

Hartnett 2020

Hartnett KP, Kite-Powell A, Patel MT, Haag BL, Sheppard MJ, Dias TP, et al.Syndromic surveillance for e-cigarette, or vaping, product use-associated lung injury. *New England Journal of Medicine* 2020;**382**(8):766-72.

Higgins 2021

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors).Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

HSE.ie 2021

HSEie.Smoking facts and figures: reasons to quit smoking. www2.hse.ie/wellbeing/quit-smoking/reasons-to-quit-smoking/smoking-facts-and-figures.html (accessed 20 July 2021).

Khouja 2020

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

Kneale 2018

Kneale D, Thomas J, Bangpan M, Waddington H, Gough D.Conceptualising causal pathways in systematic reviews of international development interventions through adopting a causal chain analysis approach. *Journal of Development Effectiveness* 2018;**10**(4):422-37.

Ma 2021

Ma C, Xi B, Li Z, Wu H, Zhao M, Liang Y, Bovet P.Prevalence and trends in tobacco use among adolescents aged 13-15 years in 143 countries, 1999-2018: findings from the Global Youth Tobacco Surveys. *The Lancet Child & Adolescent Health* 2021;**5**(4):245-55.

McNeill 2021

McNeill A, Brose LS, Calder R, Bauld L, Robson D.Vaping in England: an evidence update including vaping for smoking cessation, February 2021: a report commissioned by Public Health England London, UK: Public Health England. assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/962221/Vaping_in_England_evidence_update_February_2021.pdf 2021.

NASEM 2018

National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice.Public Health Consequences of E-Cigarettes. Washington (DC): National Academies Press (US), 2018.

O'Neill 2014

O'Neill J, Tabish H, Welch V, Petticrew M, Pottie K, Clarke M, et al.Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. *Journal of Clinical Epidemiology* 2014;**67**(1):56-64.

RCP 2016

Tobacco Advisory Group of the Royal College of Physicians.Nicotine Without Smoke—Tobacco Harm Reduction. London: Royal College of Physicians, 2016.

Reitsma 2021

Reitsma M B, Flor L S, Mullany E C, Gupta V, Hay S I, Gakidou E.Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and initiation among young people in 204 countries and territories, 1990-2019. *The Lancet Public Health* 2021;**6**(7):e472-e481.

Soneji 2017

Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, et al.Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. *JAMA Pediatrics* 2017;**171**(8):788-97.

US Department of Health and Human Services 2016

US Department of Health and Human Services.E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General—Executive Summary.. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016. e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_non-508.pdf.

WHO 2014

World Health Organization.Tobacco and inequities. *www.euro.who.int/__data/assets/pdf_file/0005/247640/tobacco-090514.pdf* (accessed 20 July 2021).

WHO 2021

World Health Organization.Tobacco. www.who.int/news-room/fact-sheets/detail/tobacco (accessed 21 July 2021).

Wills 2017

Wills TA, Knight R, Sargent JD, Gibbons FX, Pagano I, Williams RJ.Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii. *Tobacco Control* 2017;**26**(1):34-9.

Yuan 2015

Yuan M, Cross SJ, Loughlin SE, Leslie FM.Nicotine and the adolescent brain. *Journal of Physiology* 2015;**593**(16):3397-412.

APPENDICES

Appendix 1. Search strategy

OVID Databases (MEDLINE, Embase, PsycINFO)

1. randomized controlled trial.pt. OR controlled clinical trial.pt. OR clinical trials as topic.sh. OR trial.ti.

2. (teen* or young* or youth* or child* or paed* or college* or school* or university* or pupil* or student* or minor* or adolescent* or uptake or gateway or commenc* or prevalence).mp.

3. e-cig*.mp. OR ecig*.mp. OR electr* cigar*.mp. OR electronic nicotine.mp. OR (vape or vapes or vaporizer or vapourizer or vaporiser or vapouriser or vaper or vapers or vaping).ti,ab. OR Exp Electronic Nicotine Delivery Systems/

4. (smok* or cigar* or tobacco or combust*).mp.

5. 2 and 3 and 4

6. 5 not 1

7. exp animals/ not human/

8. 6 not 7

Cochrane Tobacco Addiction Group Specialised Register

1. (trial): TI

2. (teen* or young* or youth* or child* or paed* or college* or school* or university* or pupil* or student* or minor* or adolescent* or uptake or gateway or commenc* or prevalence): TI,AB,MH,EMT,KY,XKY

3. (e-cig* OR ecig* OR electr* cigar* OR electronic nicotine): TI,AB,MH,EMT,KY,XKY

4. (vape or vapes or vaporizer or vapourizer or vaporiser or vapouriser or vaper or vapers or vaping): TI,AB,MH,EMT,KY,XKY

5. MESH DESCRIPTOR Electronic Nicotine Delivery Systems EXPLODE ALL

6. (smok* or cigar* or tobacco or combust*): TI,AB,MH,EMT,KY,XKY

7. 3 or 4 or 5

8. 2 and 6 and 7

9. 8 not 1

CONTRIBUTIONS OF AUTHORS

JHB led the grant application for this work and drafted the initial protocol. RB led on subsequent drafts of the protocol. All authors were involved in designing the protocol and all authors reviewed and commented on the protocol prior to submission.

DECLARATIONS OF INTEREST

PA has no conflict of interest to declare.

RB's work on this review has been supported by Cancer Research UK (CRUK) Project Award funding. This is not deemed a conflict of interest. She has received funds to her institution from the National Institute for Health Research (NIHR) to examine the effectiveness of a general practitioner (GP)- and nurse-led intervention on e-cigarettes for smoking reduction and cessation in smokers with chronic diseases. She has written on e-cigarettes (unpaid).

TF has no conflict of interest to declare.

JHB has written articles on e-cigarettes (unpaid) and is a voluntary member of Health Canada's Advisory Board on e-cigarettes. She has participated in two Best Brains Exchanges on e-cigarettes, arranged by Health Canada and the Canadian Institute for Health Research (money paid to herself). She is principal investigator on the CRUK-funded grant to undertake this review.

DK has no conflict of interest to declare.

NL has written articles on e-cigarettes (unpaid).

JLB has no conflict of interest to declare.

AM has no conflict of interest to declare other than authorship of a study which may be eligible for inclusion in this review (CRUK grant code A21559)

NR has written a review of e-cigarettes for an online medical textbook (UpToDate) and received renumeration for this. She is co-author of a National Academies of Science, Engineering and Medicine report, entitled 'Public health consequences of e-cigarettes', published in 2018.

LS declares an unrestricted research grant to investigate the impact of combining e-cigarettes with varenicline for smoking cessation, paid from Pfizer to his institution; funding from the US-India Strategic Partnership Forum, paid to himself for attendance at a meeting on novel nicotine products (2019); and funding from Guidepoint to himself to provide advice on the future of the e-cigarette market to a law firm. He has also written on e-cigarettes (unpaid).

JT has received funds to his institution from the National Institute for Health Research (NIHR) for a grant to develop automated tools to identify and classify inequalities in public health research.

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