

Youth use of e-liquid flavours—a systematic review exploring patterns of use of e-liquid flavours and associations with continued vaping, tobacco smoking uptake or cessation

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Abstract

Background and Aims: There is concern that young people may be attracted to e-liquid flavours, prompting long-term vaping in naive users and potentially subsequent tobacco smoking. We aimed to review the use of e-liquid flavours by young people and describe associations with uptake or cessation of both regular vaping and tobacco smoking, adverse effects and subjective experiences.

Design: Systematic review, including interventional, observational and qualitative studies reporting on the use of e-cigarette flavours by young people (aged < 18 years).

Setting: Studies published in English language from any country or cultural setting.

Participants: Young people and their carers (aged < 18 years).

Measurements: A meta-analysis was not possible due to substantial heterogeneity, inconsistency in reporting of flavour categorizations and non-interventional study designs; thus, we narratively report findings.

Findings: In total, 58 studies were included. The quality of the evidence was extremely low. Most ($n = 39$) studies were cross-sectional survey designs. In total, 11 longitudinal cohort studies assessed trajectories; eight qualitative studies reported on user experiences. Studies reported views and experiences of a total of 512 874 young people. Both cross-sectional and longitudinal studies suggested that flavours are important for initiation and continuation of vaping. Qualitative evidence shows interest and enjoyment in flavours. There was judged to be insufficient evidence that use of e-liquid flavours specifically is associated with uptake of smoking. No studies found clear associations between flavours and cessation in this population. We found no included reports of adverse effects of flavours.

Conclusions: Flavours may be an important motivator for e-cigarette uptake, but the role of flavours in tobacco smoking uptake or cessation is unclear. The quality of the evidence on use of e-cigarette flavours by young people is low overall.

KEYWORDS

E-cigarettes, flavours, harm reduction, smoking cessation, smoking uptake or continuation, systematic review, young people

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INTRODUCTION

Use of e-cigarettes, defined as: ‘An electronic hand-held vaping device that produces for inhalation by a person an aerosol formed by heating a liquid, called an e-liquid’ [1], has increased internationally in recent years among young people [2]. There are widespread cultural differences in e-cigarette uptake and use by young people (aged < 18 years). In the United States the use of e-cigarettes by high-school students increased sharply between 2017 and 2019, with past 30-day e-cigarette use increasing from 11.7% in 2017 to 27.5% in 2019, although frequent use and signs of e-cigarette dependence remain low [3]. Regular use remains stable at a much lower rate in Great Britain: 1.2% of 11–18-year-olds reported using an e-cigarette more than once a week (a more stringent measure of frequency than past 30 day use) in 2021 [4], with similar low prevalence for regular use reported across the European Union [5]. Recent toxicological evidence on e-cigarettes reported that ‘while not without risk they are significantly less harmful than smoking’, but highlights a significant evidence gap with regard to the specific role of flavours in reducing the public health burden of smoking [6]. The use of flavoured e-cigarette liquids is of particular concern to policymakers. Flavours that are attractive in name, description, advertising and actual sensory experience may appeal particularly to young people who may be susceptible to persuasive descriptions and flavouring names [7], and may also prefer sweet flavours due to more sensitive taste buds [8]. Flavours have been central to the interpretation of youth use of e-cigarettes in the United States, often cited as a key motivational factor for use [9]. It is apparent that there is a dominant policy concern focused on the consumption behaviour of young people, rather than the possible benefits to smokers. Monitoring e-cigarette trends in youth, including use of flavours, is essential for assessing wider public health impact. Policy response needs to be finely balanced; a ‘precautionary approach’ [10] may risk excluding the needs of adult smokers who may benefit from switching to e-cigarettes, and flavours may help to achieve this goal.

There is concern in the literature and among policymakers that flavoured e-liquids may promote the use of e-cigarettes among young nicotine naïve users, and that this may then act as a gateway to smoking [11]. A counter position suggests that attractively flavoured e-cigarettes may displace smoking, being an alternative that may inhibit smoking uptake. Observable population-level data supports, although does not confirm, this latter position, as increased levels of youth use of e-cigarettes in both the United States [12] and the United Kingdom [13] coincide with reductions in tobacco smoking prevalence. Flavours that are enjoyed by the user may also promote continued vaping, which may be considered either negative, through continued use of and dependence upon nicotine (if nicotine-containing flavoured liquids are indeed used), or positive, in prompting smoking cessation and perhaps supporting sustained abstinence from tobacco smoking.

The process of policy change is complex, influenced by public opinion, political drivers and scientific evidence. Systematic,

high-quality evidence should form the cornerstone of policy decisions but this is often not the observed reality, as policy decisions may need to be swiftly determined in the absence of sufficient evidence or based on an assessment of the probable best possible outcome in weighing up costs and benefits of proposed policy change. Currently, in the United Kingdom e-liquid flavours are regulated as a consumer product [14]. UK regulation takes a ‘proportionate’ approach, such that there is a vast array of available flavours readily available for purchase, but advertising of products is controlled under the Tobacco and Related Products Regulations (TRPR) [14] and advertising standards to restrict ‘cross-border’ advertising, with the aim of limiting exposure of advertising to young people in particular. Regulation in the United States has been less stringent, allowing widespread advertising of products and flavours. Federal regulation is limited but States and municipalities have very diverse regulation, with some jurisdictions limiting or completely banning the sale of flavoured e-liquids [15]. The US Food and Drug Administration (FDA) announced that it will enforce sales restrictions on e-cigarette cartridges with flavours other than tobacco and menthol unless the product has obtained FDA pre-market authorization. In the United Kingdom, the TRPR post-implementation review re-assesses regulations on sales and marketing of e-liquid flavours. It is vital that policy review is underpinned by the best available evidence.

This review aimed to systematically review the available evidence on youth use of e-liquid flavours, to inform policy decision-making and to provide evidence to inform the TRPR post-implementation review.

Review questions

1. What is the incidence and prevalence of use of e-cigarette flavours among young people (smokers and non-smokers)? What are their patterns of use?
2. Is use of electronic cigarette flavours associated with uptake of vaping among young people (smokers and non-smokers)?
3. Is use of electronic cigarette flavours associated with smoking uptake among young people?
4. Is use of electronic cigarette flavours associated with smoking cessation among young people?
5. How are any adverse effects of use of e-cigarette flavours by young people reported and experienced?
6. What are the perspectives of young people and their carers on electronic cigarette flavours and what are the implications for policy? What are their experiences of e-cigarette flavours?

METHODS

This review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [16] and the protocol pre-registered on the open science framework (doi: <https://osf.io/hcbyu/>).

Eligibility criteria

Included studies were limited to those reporting on:

- Population: young people and their carers (including participants aged < 18 years).
- Interventions: flavoured e-liquid in electronic cigarettes.
- Study design: interventional, observational and qualitative studies.

For assessing review questions 1–5 we included the following study designs: randomized controlled trials (RCTs), cluster-RCTs (cRCTs), quasi-RCTs, controlled before-and-after studies, interrupted time-series, cohort studies, cross-sectional studies, case-control studies and uncontrolled before-and-after studies (as long as baseline measurement is reported). A broad range of study designs were considered for inclusion, as e-cigarette flavour use among young people is an emerging field of research.

For assessing review questions 5 and 6 we included both quantitative (i.e. longitudinal, cross-sectional or cohort surveys) and qualitative (any recognized method of data collection, including but not limited to individual interviews, focus groups, participant observations, documentary analysis and analysis from any discipline or theoretical tradition, including but not limited to phenomenological analysis, grounded theory, thematic analysis) study designs.

Comparators/control

We included studies that made the following comparisons:

- flavoured electronic cigarette versus another flavour of e-cigarette;
- flavoured electronic cigarette versus unflavoured electronic cigarettes;
- behaviours [uptake (defined as experimentation and regular use), prevalence, incidence, patterns of use] and outcomes (smoking cessation, adverse events) for smokers compared with non-smokers; and
- studies with no comparison group.

Outcomes

Outcomes of interest included effectiveness (smoking cessation) for interventional studies, descriptive reporting of observational data (uptake, prevalence and incidence, patterns of use) and qualitative findings, including reported adverse effects.

Settings

Studies published in English language from any country or cultural setting were included.

Time-frame

We searched from 2004, when the modern e-cigarette became available, to 22 September 2020.

Search strategy

Electronic databases searched were as follows:

- MEDLINE (via Ovid SP)
- EMBASE (via Ovid SP)
- PsycINFO (via EBSCOhost)
- CINAHL (via EBSCOhost)
- Applied Social Sciences Index and Abstracts (ASSIA)
- Cochrane database
- ProQuest Dissertation and Theses Database
- Open Grey

Medline search strategy is included as Supporting information, Appendix S1.

We undertook backwards and forwards citation tracking using a citation database to screen the reference lists of all included studies and of systematic reviews identified by our electronic searches. Searches of trial registries and published protocols were included to report on ongoing studies. A Google search supplemented with expert input was used to search for further relevant studies, grey and unpublished literature sources.

Study selection and data extraction

Data were collated using Covidence review software. Three independent reviewers (C.N., S.G., S.C.) screened title and abstracts for eligibility. Reviewers double-screened blind all included abstracts for full text inclusion; full texts were double-screened for inclusion. Disagreements were resolved through discussion. A piloted data extraction form was agreed as initial data extraction was discussed following extraction across two studies. Data extracted included: study design; participant demographic characteristics and any data on associations between particular demographic characteristics and flavour use; smoking status; for smokers, number of cigarettes smoked per day or in pack years; type of e-cigarette used; flavours used; control group (if present); study outcomes (smoking cessation); and duration of follow-up. All data extraction was checked by a second reviewer and discussed to reach consensus.

Outcomes synthesis

Broad outcomes were extracted including effectiveness estimates where available. Most outcomes were descriptive (e.g. patterns

of use, reports of frequency in flavour use) and qualitative (e.g. experience of use).

Risk of bias assessment

Risk of bias in individual studies was assessed independently by two assessors using the critical appraisal skills programme (CASP) tool for cohort studies, as best-fitting across different included study designs. Due to the heterogeneity of the included studies, we supplemented this with a brief narrative assessment of key strengths/limitations.

Data synthesis

A meta-analysis was not possible due to heterogeneity of categorizations and outcome reporting of e-liquid flavours and the non-interventional nature of the included studies; thus we narratively synthesize and report findings, following Cochrane guidance [17].

For qualitative studies, a thematic analysis of reported qualitative data was undertaken [18]. 'First-level' codes were extracted to summarize the meaning of the text or capture authors' original language. Synthesis involved organization of first-level codes into second-level descriptive themes, summarizing first-level codes while remaining close to the included studies. There were insufficient qualitative data to undertake a third-level analysis, which might involve 'going beyond' or 'interpreting' the first- and second-level codes to capture the line of argument and generate new findings from pooled data.

Confidence in cumulative evidence

The strength of the overall body of quantitative evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [19] process for the questions on associations between flavours and e-cigarette uptake, smoking uptake and smoking cessation.

RESULTS

Number of studies

The inclusion of studies is shown in Figure 1. Electronic, citation and hand-searching identified 1860 records, with 1289 references remaining after the removal of duplicates. Based upon title and abstract screening, 116 relevant articles were retrieved for full-text assessment. Three articles were identified for which we were unable to access full texts. Fifty-eight primary research studies were finally included (associated with 60 articles, Table 1). We identified no relevant ongoing trials.

Study characteristics

Further study characteristics are shown in Table 1. Thirty-nine of the 58 included studies were cross-sectional survey designs, 11 were longitudinal cohort studies and eight were qualitative studies or of mixed-methods design. There were no identified randomized controlled trials, uncontrolled trials or experimental studies that met review inclusion criteria.

Studies were primarily undertaken in the United States ($n = 48$). The remaining studies were conducted in the United Kingdom ($n = 8$, with one specifically mentioned as located in England, one in Scotland and one in Ireland), two studies in Korea, one in Taiwan and one in Mexico. Most studies recruited young people from a school setting ($n = 39$), with the rest recruiting via community routes ($n = 19$).

Quality appraisal of studies

Most studies were assessed as of high quality methodologically (i.e. methods were suitable to meet the aims of the study) (Supporting information, Appendix S2), but it was not possible to apply many standard quality assessment criteria used in the CASP tool for cohort studies. A lack of clear definitions of key independent and dependent factors—age, young people, tobacco products, e-cigarettes and flavours—was observed among the included papers. Due to this and heterogeneous study designs a GRADE assessment assessed the overall quality of the evidence as low (Supporting information, Appendix S3).

Participant characteristics

Supporting information, Table S1 details study participants. Studies reported on the views and experiences of a total of 512 874 young people (although the total number may have been somewhat lower due to repeat waves of longitudinal surveys reported across unique studies, possibly including the same participants in more than one study). The mean age of participants, where reported in age rather than age band or school year-group category ($n = 19$ studies), was 15. Twenty-eight studies did not adequately report ethnicity or ethnic mix of the study participants.

Studies varied considerably in reporting of 'baseline' characteristics. Eleven studies did not report baseline e-cigarette use (either 'ever' use, 'trying' or 'regular use'). Two studies specifically sampled young people who had never used e-cigarettes in order to ask about 'perceived use' of variables, including flavours [20,21]. Twenty studies reported between 3 and 77% of respondents to have used an e-cigarette more than once during the last 30 days (defined as 'regular use'). The wide range reported is probably an artefact of sampling strategy used (ranging from community-based or young school-aged pupils to purposively sampling those who had used an e-cigarette). A total of 28 studies reported e-cigarette use at least once, but not in the past 30 days ('ever use'). The range for reported ever use was

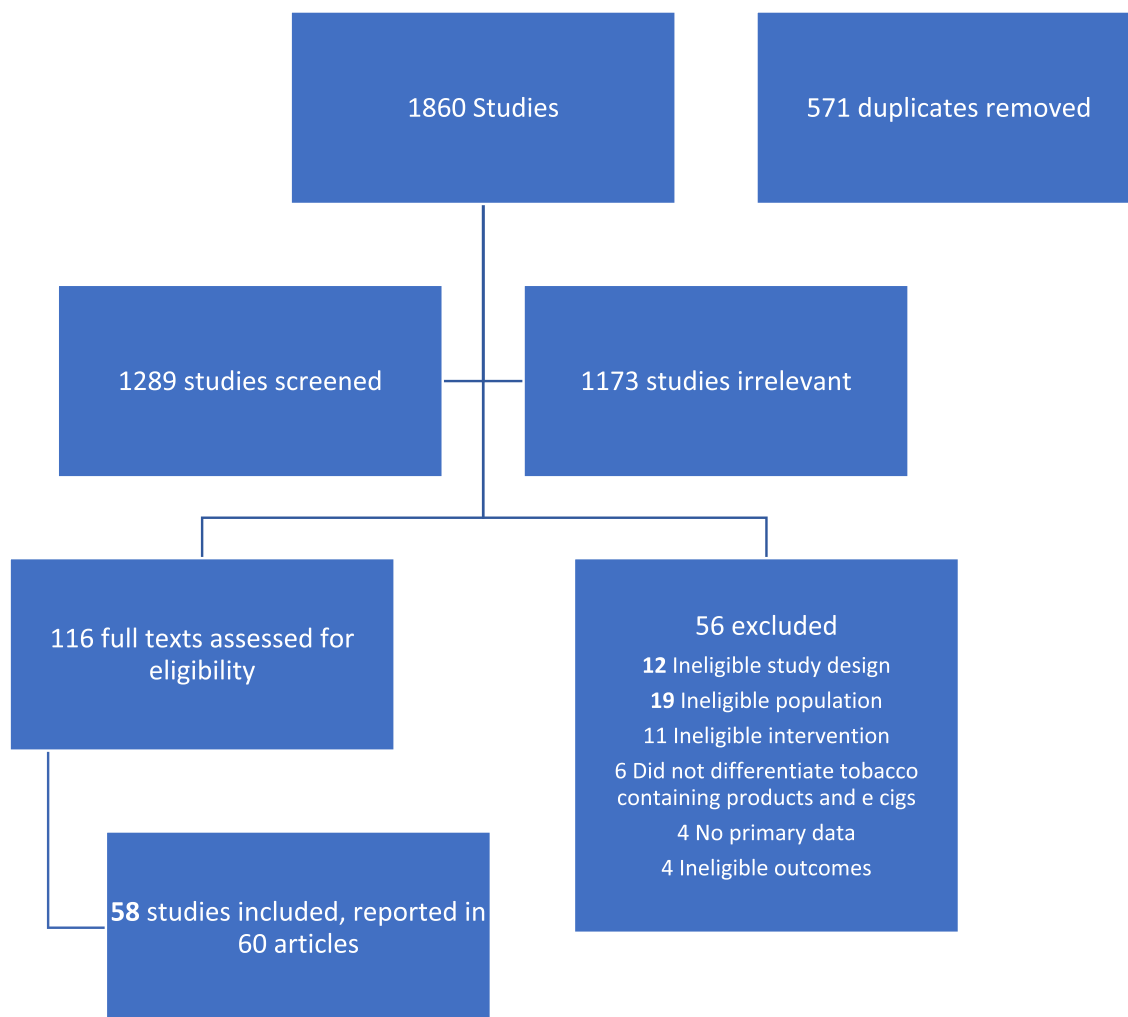


FIGURE 1 Review flow diagram

between 5 and 81%. Again, the wide range is a probable artefact of sampling strategy among studies. For past tobacco use, 24 studies reported baseline ‘ever’ use (combining together reports of ever or past 30-day tobacco use). In these studies, the reported range was from 5 to 82%. Here again, the range was wide but notably similar to the range of ever reported e-cigarette use. Only three studies reported family e-cigarette use. This was not accurately captured in terms of frequency of use, but in the three studies that included reporting on this variable, approximately one-third of participants reported family members or parents who vaped e-cigarettes.

Incidence and prevalence of use of e-cigarette flavours among young people

Most cross-sectional surveys ($n = 39$) recruiting samples of young people who had vaped and who had ever or never smoked reported the popularity of use of e-cigarette flavours, and overwhelmingly demonstrated that flavours were more often tried and regularly used than non-flavoured e-liquids. Supporting information, Table S2 shows

included cross-sectional studies. The largest included study (Cullen [22]), with a sample size aggregated from repeat years of the National Youth Tobacco Survey (NYTS) of 98 454 young people, reported that: ‘The percentage of current tobacco users who reported flavoured product use in the past 30 days was 65.2% for e-cigarettes’. Due to regulations in the United States defining e-cigarettes as tobacco products, in this study an exclusive e-cigarette user was defined as a ‘current tobacco user’. This categorization of e-cigarette users as tobacco users is problematic, as it precludes comparison and synthesis with other studies where e-cigarette-only users are not defined as tobacco users, as they are not using a product which contains tobacco. Studies where it was difficult to disaggregate e-cigarette-only users from tobacco users are highlighted in Supporting information, Table S2. Nonetheless, data from studies where clear distinctions were made is supportive of this general trend in favour of flavoured e-liquid use by young people. For example, Rostron *et al.* [23], in an analysis of the Population Assessment of Tobacco and Health (PATH) study data published in 2020 ($n = 2221$), reported that: ‘Of those who had ever used e-cigarettes 93.2% (91.9, 94.3) reported that the first product they ever used was flavoured’. It would be meaningless to give an

TABLE 1 Included study characteristics

Study number and reference	Author/s	Year	Title	Country	Setting	Design
1 [37]	Alexander	2018	Youth who use e-cigarettes regularly: a qualitative study of behavior, attitudes and familial norms	USA	Community	Qualitative
2 [49]	Ambrose	2015	Flavored tobacco product use among US youth aged 12–17 years, 2013–14	USA	Community	Cross-sectional
3 [29]	Audrain-McGovern	2019	Initial e-cigarette flavoring and nicotine exposure and e-cigarette uptake among adolescents	USA	School	Longitudinal cohort
4 [30]	Boccio	2020	Nicotine and marijuana attitudes among flavor-only vaping youth: new evidence from Monitoring the Future	USA	School	Longitudinal cohort
5 [31]	Bold	2016	Reasons for trying e-cigarettes and risk of continued use	USA	School	Longitudinal cohort
6 [36]	Brown	2020	A qualitative study of e-cigarette emergence and the potential for re-normalization of smoking in UK youth	UK	School	Qualitative
7 [50]	Camenga	2018	Adolescents' perceptions of flavored tobacco products, including e-cigarettes: a qualitative study to inform FDA tobacco education efforts through video games	USA	Community	Qualitative
8 [51]	Camenga	2017	Current and former smokers' use of electronic cigarettes for quitting smoking: an exploratory study of adolescents and young adults	USA	School	Cross-sectional
9 [52]	Chen	2017	Flavored e-cigarette use and cigarette smoking susceptibility among youth	USA	School	Cross-sectional
10 [20]	Chen-Sankey	2019	Perceived ease of flavored e-cigarette use and e-cigarette use progression among youth never tobacco users	USA	Community	Longitudinal cohort
11 [53]	Chung	2018	Use of e-cigarettes rising among junior and senior high school students in Taiwan	Taiwan	School	Cross-sectional
12 [21]	Clarke	2015	Adolescent's views of the electronic cigarette: a new gateway to addiction?	UK	School	Cross-sectional
13 [54]	Cooper	2016	Flavorings and perceived harm and addictiveness of e-cigarettes among youth	USA	School	Cross-sectional
14 [55]	Corey	2015	Frequency of tobacco use among middle and high school students—United States, 2014	USA	School	Cross-sectional
15 [56]	Cullen	2019	E-cigarette use among youth in the United States, 2019	USA	School	Cross-sectional
16 [22]	Cullen	2019	Flavored tobacco product use among middle and high school students—United States, 2014–18	USA	School	Longitudinal cohort
17 [57]	Czaplicki	2019	Support for e-cigarette and tobacco control policies among parents of adolescents	USA	Community	Cross-sectional

(Continues)

TABLE 1 (Continued)

Study number and reference	Author/s	Year	Title	Country	Setting	Design
18 [58]	Dai	2018	Single, dual and poly use of flavored tobacco products among youths	USA	School	Cross-sectional
19 [59]	Dai	2019	Changes in flavored tobacco product use among current youth tobacco users in the United States, 2014–17	USA	School	Cross-sectional
20 [60]	Dai	2020	Use of e-cigarettes for nicotine, marijuana and just flavoring among US youth	USA	School	Cross-sectional
21 [61]	DeAndrade	2016	Teenage perceptions of electronic cigarettes in Scottish tobacco-education school interventions: co-production and innovative engagement through a pop-up radio project	Scotland	School	Qualitative
22 [34]	Evans-Polce	2018	Reasons for vaping among US 12th graders	USA	School	Longitudinal cohort
23 [21]	Friedman	2020	Associations of flavored e-cigarette uptake with subsequent smoking initiation and cessation	UK	Community	Longitudinal cohort
24 [62]	Ford	2016	Adolescents' responses to the promotion and flavouring of e-cigarettes	UK	Community	Cross-sectional
25 [63]	Han	2019	What influences adolescents to continuously use e-cigarettes?	Korea	School	Cross-sectional
26 [64]	Harrell	2017	Flavored e-cigarette use: characterizing youth, young adult and adult users	USA	School	Cross-sectional
27 [65]	Harrell	2017	Flavored tobacco product use among youth and young adults: what if flavors didn't exist?	USA	School	Cross-sectional
28 [66]	Hilton	2016	E-cigarettes, a safer alternative for teenagers? A UK focus group study of teenagers' views	UK	Community	Qualitative
29 [40]	Jackson	2019	Use of alcohol-named e-liquids and alcohol use behaviors among high school youth	USA	School	Cross-sectional
30 [67]	Jackson	2020	Association between preference for using alcohol beverage-named e-liquids and alcohol use among high school youth	USA	School	Cross-sectional
31 [68]	Jackson	2019	It's all the rage! Exploring the nuances in the link between vaping and adolescent delinquency	USA	School	Cross-sectional
32 [69]	Jinyoung	2017	Using focus group interviews to analyze the behavior of users of new types of tobacco products	Korea	Community	Qualitative
33 [70]	Kong	2015	Reasons for e-cigarette initiation and discontinuation among adolescents and young adults	USA	School	Qualitative
34 [27]	Kong	2015	Informing the regulation of e-cigarettes to restrict youth access	USA	School	Cross-sectional

(Continues)

TABLE 1 (Continued)

Study number and reference	Author/s	Year	Title	Country	Setting	Design
35 [71]	Kong	2020	Dripping and vape tricks: alternative e-cigarette use behaviors among adolescents	USA	School	Cross-sectional
36 [72]	Kong	2019	Appeal of JUUL among adolescents	USA	School	Cross-sectional
37 [24]	Krishnan-Sarin	2015	E-cigarette use among high school and middle school adolescents in Connecticut	USA	School	Cross-sectional
38 [73]	Krishnan-Sarin	2015	E-cigarettes and 'dripping' among high-school youth	USA	School	Cross-sectional
39 [74]	Leventhal	2019	Flavored e-cigarette use and progression of vaping in adolescents	USA	School	Longitudinal cohort
40 [75]	Leventhal	2019	Flavors of e-cigarettes used by youths in the United States	USA	School	Cross-sectional
41 [76]	McElvaney	2020	Attitudes of Irish second-level students towards vaping	Ireland	school	Cross-sectional
42 [77]	McMillen	2019	Adolescent use of different e-cigarette products	USA	school	Longitudinal cohort
43 [78]	Measham	2016	'Skittles & Red Bull is my favourite flavour': e-cigarettes, smoking, vaping and the changing landscape of nicotine consumption amongst British teenagers—implications for the normalization debate	England	Community	Mixed methods
44 [79]	Merianos	2019	Characteristics of daily e-cigarette use and acquisition means among a national sample of adolescents	USA	School	Cross-sectional
45 [28]	Miech	2017	What are kids vaping? Results from a national survey of US adolescents	USA	School	Cross-sectional
46 [80]	Morean	2018	Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults	USA	School	Cross-sectional
47 [81]	Rose	2019	Flavour types used by youth and adult tobacco users in wave 2 of the Population Assessment of Tobacco and Health (PATH) study 2014–15	USA	Community	Cross-sectional
48 [82]	Ross	2019	Vaping flavors associated with vaping dependence symptoms among adolescents: a pilot study using vape factor fast find (VF3)	USA	Community	Cross-sectional
49 [23]	Rostron	2020	Prevalence and reasons for use of flavored cigars and ENDS among US youth and adults: estimates from wave 4 of the PATH study, 2016–17	USA	Community	Cross-sectional
50 [26]	Schneller	2018	Use of flavored electronic cigarette refill liquids among adults and youth in the US—results from wave 2 of the Population Assessment of Tobacco and Health study (2014–15)	USA	Community	Cross-sectional
51 [83]	Schneller	2019	Use of flavored e-cigarettes and the type of e-cigarette devices used among adults and youth in the US—results	USA	Community	Cross-sectional

(Continues)

TABLE 1 (Continued)

Study number and reference	Author/s	Year	Title	Country	Setting	Design
52 [84]	Tsai	2018	from wave 3 of the Population Assessment of Tobacco and Health Study (2015–16) Reasons for electronic cigarette use among middle and high school students—National Youth Tobacco Survey, United States, 2016	USA	School	Cross-sectional
53 [85]	Villanti	2017	Flavored tobacco product use in youth and adults: findings from the first wave of the PATH study (2013–14)	USA	Community	Longitudinal cohort
54 [33]	Villanti	2019	Association of flavored tobacco use with tobacco initiation and subsequent use among US youth and adults, 2013–15	USA	Community	Longitudinal cohort
55 [86]	Vogel	2019	Adolescents' e-cigarette use: increases in frequency, dependence and nicotine exposure over 12 months	USA	Community	Longitudinal cohort
56 [87]	Wang	2019	Tobacco product use and associated factors among middle and high school students—United States, 2019	USA	School	Cross-sectional
57 [88]	Zavala-Arciniega	2019	E-cigarette use frequency and motivations among current users in middle school	Mexico	School	Cross-sectional
58 [89]	Pepper	2016	Adolescents' interest in trying flavoured e-cigarettes	USA	Community	Cross-sectional

aggregate number or percentage of young people across surveys reporting flavoured e-liquid use, due to differences in the way in which the question is asked (e.g. awareness, ever use, current use) and sampling approaches (from community- and school-based young people who may have never tried an e-cigarette nor smoked tobacco to sampling strategies specifically targeting young e-cigarette or tobacco users).

It was difficult to meaningfully extract specific information on which flavours might be preferred by young people. Many surveys grouped flavours into categories (fruit, sweet, tobacco, menthol, for example), although some collected data on specific flavour names and others simply referred to 'flavoured' or 'unflavoured' e-liquids. Reports of unflavoured e-liquid use were rare—perhaps reflecting the less visible nature of unflavoured e-liquid on the consumer market.

There was an apparent trend across studies for a stated preference for fruit and sweet flavours over menthol and tobacco flavours. Krishnan-Sarin *et al.* [24], for example, in a sample of 3614 high school and 1166 middle school-aged students, reported that: 'most lifetime e-cigarette users reported that: 'they had tried and preferred sweet flavours... Menthol and tobacco flavours appeared to be used mostly by e-cigarette users who were also cigarette smokers, although at considerably lower rates than sweet flavours. Of $n = 96,356$, 8% preferred a sweet flavour'. Some studies noted a preference among young people for unusual flavour names, or flavour names that mimic alcoholic drinks [25]. It is not possible to conclude whether this preference is drawn from the attraction to the name, the product description or the actual flavour itself. Jackson *et al.* [25] notes an association between young people's alcohol use and a preference for e-liquid flavours with names mimicking alcoholic drinks, suggesting a continuum of interest in consumption behaviours, but with no evidence of a causal association in either direction. However, this was not a consistent finding across studies, as Schneller *et al.* [26], reporting on PATH survey data, found that: 'Fruit was the most popular individual flavour category chosen (55.0%; 95CI: 46.6%, 63.0%), followed by candy/other sweets (21.0%, 95CI: 14.5%, 29.3%) and alcoholic drinks was the least popular individually reported flavour category (1.1%, 95CI: 0.3%, 4.1%)'. Other studies (e.g. Kong *et al.* [27]) have noted observationally the tendency for young people to report using a range of flavours, suggesting an interest in experimentation with flavours and perhaps a dominant preference for switching or changing between flavours. Many studies were limited, in that they did not collect data on nicotine use alongside flavoured e-liquid use, but one study reporting on a school-based US sample reported a clear preference for using 'just flavouring' without nicotine [28].

Associations with uptake of vaping

There were six longitudinal studies following the same cohort over time able to robustly assess a possible causal association between first use of a flavoured e-liquid and subsequent uptake of regular e-cigarette use ($n = 6$ with any data on uptake of vaping [20,29–33];

see Supporting information, Table S3, outcomes RQ2). Overall, these six studies suggested a positive association between the first use of a flavoured e-liquid product and continued vaping. Only three of these six studies simultaneously reported on any tobacco use behaviour (ranging from 3 to 25% of participants who had ever tried tobacco).

Audrain-McGovern *et al.* [29], in a longitudinal cohort study with 24-month follow-up, reported that use of e-liquid flavours at self-reported first use was significantly associated with continued e-cigarette use: considering change from baseline, flavouring in the initial e-cigarette used had a significant and positive effect on the continuous e-cigarette trend factor. This indicated that: ‘initial use of a flavoured versus un-flavoured e-cigarette was associated with a more rapid rate of escalation in the number of days e-cigarettes were used ($\beta = 0.35$, $z = 2.58$, $P = 0.01$), across the following 18 months’. Similarly, Bold *et al.* [31] reported that flavoured e-cigarette use at baseline predicted continued vaping 6 months later, and Leventhal *et al.* [32] demonstrated that: ‘Use of e-cigarettes in non-traditional flavors (versus only tobacco, mint or menthol, or flavourless) was positively associated with vaping continuation [64.3% vs 42.9%; adjusted odds ratio = 3.76 (95% confidence interval 1.20 to 10.31)]’.

Boccio *et al.* [30], in a secondary analysis of data from the Monitoring the Future study, took an unusual stance focused upon self-reported behaviours and associations with views of vaping nicotine or cannabis. They found that: ‘youth who reported flavour-only vaping during the 30 days prior to the survey were nearly 250% more likely to fail to disapprove of nicotine vaping’, suggesting that flavoured e-liquid users were also permissive towards nicotine vaping. Other included studies did not clearly differentiate between flavoured tobacco and flavoured e-liquids and thus we were unable to extract objective data.

Associations with smoking uptake

One included longitudinal study was able to robustly address the specific question: ‘Is use of electronic cigarette flavours associated with smoking uptake among young people?’ [21]. Other included studies reported observationally that young people reported initiating either vaping or smoking first, before also reporting use of the other product, with no clear direction of association and often with poor reporting of flavoured use or not. In the one longitudinal study, Friedman [21], reporting 48-month follow-up data, found no association with flavoured e-liquid use and subsequent tobacco smoking initiation: ‘For both youths and emerging adults, the association of flavored e-cigarette use and smoking initiation was not significantly different from that for unflavored e-cigarette use (AOR for youth, 0.66; 95%CI, 0.16-2.76; $P = 0.56$; AOR for emerging adults, 3.15; 95%CI, 0.14-71.78; $P = 0.46$)’.

Of note were examples where studies drew conclusions not justified by the data, for example reporting that: ‘These data support tobacco industry research on the role of flavors to promote uptake in nonusers’ [33].

Associations with smoking cessation

One longitudinal study specifically addressed the question exploring the association of use of e-liquid flavours with smoking cessation. Evans-Polce *et al.* [34] split their sample into three groups: (1) vaping to experiment (29.4%), (2) vaping to replace-cigarettes (7.3%) and (3) vaping for taste + entertainment (63.4%). They reported that ‘the-cigarette replacement subgroup did not have a high probability of vaping because of taste. This suggests that flavors may not be an important cessation tool for this subgroup interested in smoking cessation’. However, among observational, cross-sectional and qualitative studies data converge to suggest that use of flavoured e-liquids may be an important sensory aspect of e-cigarette use users enjoy; thus, it suggests that those seeking to quit smoking using an e-cigarette might prefer flavoured e-liquids [35]. However, the one included longitudinal study in this review of young people did not corroborate this logic.

Adverse effects

No included studies focused upon or reported adverse effects specifically related to flavoured e-liquid use.

Perspectives and experiences

A total of eight qualitative studies, that were mainly of focus-group design, were included that reported on subjective perspectives, experiences and views of flavoured e-liquid use among young people (Supporting information, Table S4). A consistent overarching theme throughout the views gathered within these qualitative studies was expressed enjoyment of flavours. Brown *et al.* [36], in a focus group study of UK schoolchildren, clearly exemplified this theme: ‘I just liked the different flavours. Cos my friend had jam donut, another friend had gummy bear flavour and Heisenberg which is a minty flavour which is quite nice (B1, 1, M)’.

There was a consistent theme of enjoyment with experimentation with different flavours, preferring to switch between flavours and try new flavours rather than sticking to one preferred flavour, suggesting the importance of variety and choice: ‘Yeah, it’s a cool thing. It’s like you can have like one flavor in and then the next tank is a totally different flavor’ (Alexander *et al.* [37]).

There were different aspects to flavours that were attractive to young people that the qualitative data highlighted—enjoying the names, the descriptions, the labels and designs, as well as the actual taste: ‘I think what makes it more appealing, there are some designs on them. So people are just like, “Oh that’s a cool design”. And different flavours and they are comparing with their friends. “Oh look at yours, yours is red and mine’s like camouflage”’ (A2, 4, M) (Brown [36]).

In summary, synthesis of the qualitative findings triangulated findings of the cross-sectional and longitudinal studies by suggesting clear

enjoyment and preference for flavoured e-liquid use by young people, but also demonstrating nuances to the sensory enjoyment that went beyond simply taste but encompassed the aesthetic qualities (e.g. packaging designs and descriptions of flavours) of flavoured e-liquids.

CONCLUSIONS

Overall, the included studies meeting eligibility criteria appear to demonstrate, across study designs, countries and community versus school-based samples, that young people generally prefer initiating and continuing e-cigarette use using flavoured e-liquids. Fruit and sweet flavour categories are reported as the most popular choices among young people. This is in line with other review findings [38], and also reported consistently in the wider literature for adult e-cigarette users [26,39], so is not a finding unique to young people. There is some evidence that young people may also be attracted to flavours with names mimicking alcoholic drinks [40]. The qualitative evidence demonstrated that flavour descriptions, labelling designs and experimentation with different flavours are also important aspects of enjoyment of flavours, suggesting a sensory attraction and enjoyment beyond simply taste.

The enjoyment and dominant use of flavoured e-liquids in comparison to non-flavoured liquids may promote ongoing or regular vaping among young people. Indeed, the albeit limited, longitudinal evidence available suggested an association between first use of a flavoured e-liquid and continued vaping. A 'common liability' explanation may offer an explanation for this association, as young people attracted to using e-liquid flavours may also be more likely to be attracted to vaping. The interpretation of this evidence summary in terms of implications for public health may depend upon the stance. One position might be that the use of flavoured e-liquids used in e-cigarettes could be diverting young people away from tobacco smoking. Indeed, this position is supported by population-level data demonstrating that as young peoples' use of e-cigarettes has increased, rates of tobacco use have not increased [13]. Alternative positions of concern may be for the uptake of e-cigarette use itself, independent of tobacco smoking, or a concern that young people using e-liquid flavours may progress towards uptake of tobacco smoking: the so-called 'gateway effect'. This review found no strong evidence of an association between flavoured e-liquid use specifically and subsequent uptake of tobacco smoking, although this is clearly an important policy question, where more evidence including a wider range of study designs, e.g. longitudinal cohort and propensity matching studies, is required. Studies included could support a wider 'common liability' explanation, that young people experimenting with e-cigarettes may also be likely to experiment with tobacco smoking, but there was no clear conclusion to be drawn regarding whether flavoured e-liquid use might have a specific effect. Further, because e-cigarettes devices are themselves a widely heterogeneous product group with varying pharmacokinetics, which also influences their appeal and use, in future studies there is an urgent need for more

accurate descriptions and measurement of precise product use characteristics [41]. There is also a pressing need for continual monitoring of precise e-liquid product use, as products are continually evolving. Importantly, it is vital that the use of e-cigarettes by young people is carefully monitored to understand 'real world' patterns of use behaviour.

An important goal for public health is to protect youth from the harms of primary and secondary exposure to tobacco smoke, including diverting young people from harmful tobacco smoking. E-liquid flavours, in their attractiveness to young people as demonstrated by this review, may play an important role as both a diversion from smoking and an aid for smoking cessation—but, as above, other studies which are designed specifically to test this over a longer term are needed. Only one included study focused specifically on the association of flavours with smoking cessation—reporting no association. Longitudinal and experimental studies should focus specifically on the role of flavours in smoking cessation for young people. This might also contribute to our understanding of relapse prevention as, for maximum health benefit, young people need to be supported to switch to attractive alternatives that not only promote cessation, but also full and sustained abstinence from tobacco smoking.

One important point is that the pattern noted across the cross-sectional, longitudinal and qualitative studies included in this review was the observed preference for trying different flavours, experimentation and switching, suggesting that variety is an important aspect of the user experience. Of note, this variety is more often offered by independent, non-industry-funded manufacturers. Tobacco industry products and e-liquids tend to focus upon a more limited range of flavours [42]. If variety is important to young people, it is therefore possible that young people may be choosing independent manufactured products rather than tobacco industry-funded products, which may reduce the risk of exposure to tobacco industry tactics. Furthermore, there are indirect ways in which flavours may influence the health and welfare of vulnerable youth, including via their effect on the smoking behaviours of adults around them (e.g. by reducing role modelling of smoking by adults if flavours play a role in adults switching to vaping).

There are some potential implications for the use of e-liquid flavours among young people for addressing smoking-related inequalities. Smoking among young people follows a social gradient, with the most disadvantaged having higher smoking rates [43]. These groups have much to gain from switching to reduced-harm products as quit rates are also substantially lower. Arguably, this might be easier to achieve if alternatives deliver enough nicotine to reduce cravings and are attractive and pleasurable to use.

The generalizability of this review is limited by the characteristics of the included studies and a GRADE rating of low overall evidence quality. It was not possible to contact study authors for further information due to resource limitations, but we acknowledge that this would have strengthened the review. Most studies were conducted in the United States, so were specific to that policy context. Studies were mainly cross-sectional, able to report upon

self-reported data regarding flavoured e-liquid use but not able to provide any data on trajectories of use towards continued e-cigarette use, smoking uptake or cessation. Cross-sectional studies were sometimes limited by inconsistencies with definitions. The age of participants was not always clear. Due to regulation, many US studies were limited by describing tobacco use together with flavoured e-liquid use, making it difficult to extract focused data. Definitions of 'use', from awareness and experimentation to past 30-day or daily use, were often not clarified. Others have also noted substantial heterogeneity in reporting of outcome measures across observational studies and a risk of reporting bias [44]. Furthermore, 'flavours' were poorly described, often simply as a binary distinction between 'flavoured' and 'unflavoured' products. Often 'unflavoured' may correspond to 'tobacco' flavour, but this was not clear in many studies. In most studies, flavours were amalgamated into broad categories of 'sweet' or 'fruit' flavours. This is far removed from the 'real world' consumer market, where there is a proliferation of flavour names, types and varieties and, indeed, individuals may mix flavours [45]. There is an urgent need for a clear method and consensus to classify flavours [46,47]. Many studies also did not collect data on nicotine use alongside flavours, a limitation that has previously been noted [48]. These are critical limitations when aggregating and synthesizing data which meant that our synthesis was limited to narrative description, rather than being able to integrate study findings.

Taken together, studies synthesized in this review suggest that young people are interested in e-liquid flavours and are experimenting with them. There is no evidence that flavoured e-liquid use specifically is associated with tobacco smoking uptake. An alternative interpretation of is the common liability explanation, such that young people who are interested in experimenting with consumption behaviours may try a number of different products, possibly including tobacco, or indeed alcohol and other substances. In the United Kingdom, low rates of regular e-cigarette use suggest that most experimentation will be just that, and will not progress to regular use. Synthesis of the existing research does not yet provide a clear understanding of the risks and benefits to young smokers and non-smokers on the role of e liquid flavours specifically as either a route away from or towards tobacco smoking.

DECLARATION OF INTERESTS

None.

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AUTHOR CONTRIBUTIONS

Caitlin Notley: Conceptualization; data curation; formal analysis; funding acquisition; methodology; project administration; software; supervision; validation; visualization. **Sarah Gentry:** Data curation;

formal analysis; investigation; methodology; software; validation.

Sharon Cox: Formal analysis; software; validation. **Martin Dockrell:** Conceptualization. **Michelle Havill:** Conceptualization; project administration. **Angela Attwood:** Conceptualization. **Matthew Smith:** Methodology; project administration; software. **Marcus Munafò:** Conceptualization; funding acquisition.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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