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The Impact of Non-Menthol Flavors in E-Cigarettes on Perceptions and Use: An Updated Systematic Review

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The Impact of Non-Menthol Flavors in E-Cigarettes on Perceptions and Use: An Updated Systematic Review

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Objective: Given the exponential increase in both the use of e-cigarettes among younger age groups and in the growth in research on e-cigarette flavors, we conducted a systematic review examining the impact of non-menthol flavored e-cigarettes on e-cigarette perceptions and use among youth and adults.

Methods: Observational and experimental studies that assessed the effect of non-menthol flavors in e-cigarettes on perceptions and use behaviors were included. PubMed, Embase, PyscINFO, and CINAHL were systematically searched for studies published and indexed between through March 2018, resulting in 2,822 unique articles.

Results: The review included 51 final articles for synthesis, including 17 published up to 2016, and an additional 34 published between 2016-2018. Results indicate non-tobacco flavors in e-cigarettes decrease harm perceptions (5 studies) and increase willingness to try and initiation of e-cigarettes among youth and young adults (6 studies). Among adults, e-cigarette flavors increase product appeal (7 studies) and are a primary reason many adults use the product (5 studies). The role of flavored e-cigarettes on smoking cessation remains unclear (6 studies).

Conclusions: This review provides summary data on the role of non-menthol flavors in e-cigarette perceptions and use across the age spectrum. Consistent evidence shows that these flavors attract both youth and adults to use e-cigarettes. Given the clear findings that such flavors increase product appeal, willingness to try, and initiation among youth, banning non-menthol flavors in e-cigarettes may reduce youth e-cigarette use. Longitudinal research is needed to examine any role flavors may play in quit behaviors among adults.

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Strengths and Limitations of the Study

- This large comprehensive review that included 51 final articles for synthesis, including 17 published up to 2016, and an additional 34 published between 2016-2018.
- The majority of studies were cross-sectional and were from convenience samples, limiting the ability to make causal inferences as well as the generalizability of findings from these articles.
- We used a quality assessment tool (QATSDD) to rate the quality of articles included in the review.
- A review of the literature on flavors perceptions and use among youth and adults may provide evidence for policymakers who are considering legislation related to flavored e-cigarette products.

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INTRODUCTION

Despite a ban on non-menthol flavors in cigarettes, current regulations in the United States allow for the sale of non-menthol flavors in other tobacco products, including e-cigarettes.[1] However, The FDA continues to seek out and prioritize research that explores the issue of non-menthol flavors in tobacco products other than cigarettes, and as such has issued an advance notice of proposed rulemaking seeking comments on the role that flavors play in tobacco product use.[2] Similarly, in fall of 2018 the FDA proposed a policy framework that would only allow non-menthol flavored e-cigarettes to be sold in age-restricted locations or online under heightened age verification standards.[3]

Some studies have shown that flavors are particularly appealing to youth and are cited as a primary reason for use among this age group.[4] The use of e-cigarettes among youth may be a gateway to future cigarette use,[5,6] and nicotine (which is found in most e-cigarettes) is especially harmful to developing adolescent brains.[7–9] This makes the recent precipitous increase in e-cigarette use among youth particularly alarming.[7] Policymakers, including the FDA, are increasingly concerned about the rise in popularity of pod-type e-cigarette devices (e.g. Juul), which now own a large market share and deliver more nicotine than older generations of e-cigarettes.[10,11]

E-cigarettes are also regarded by many experts in tobacco control as a potential means of harm reduction among adult smokers if they use e-cigarettes to transition away from combustible tobacco products.[12] A few studies have suggested a positive association between e-cigarettes and quitting behaviors, including a recent randomized controlled trial.[13–16] Unraveling the relationship between potential harms or benefits of e-cigarette use among adult smokers is important in the development of regulations for e-cigarettes, and in particular, regulations regarding product flavors.

It is well known that recent years have seen a precipitous increase in the use of e-cigarettes in the US and other countries among both youth and adults.[17] This increase in use has coincided with an exponential rise in e-cigarette flavors, with over 7,000 flavors existing. Many of these flavors utilize names that may appeal to younger populations such as cotton candy, gummy bear, cookies ‘n cream, and other sweet-flavored brands.[18] The intense public health interest in e-cigarettes’ impact on the tobacco control landscape and population health has resulted in a sharp increase in research conducted on flavors and e-cigarettes. Given this changing landscape, we conducted a systematic review of non-menthol flavored e-cigarettes that extends previous research.[4] Specifically, this new review examines the role of non-menthol flavored e-cigarettes among youth and adults, including appeal, harm perceptions, intentions, use, and cessation in the US and globally.

METHODS

We used methods similar to previously published research,[4] and implemented two alterations: 1) updated the range of eligible publication dates (with the original including articles ever published until April 4, 2016, and the current review including articles published and indexed on or after April 4, 2016), and 2) focused this review specifically on e-cigarettes rather than all tobacco products, based on the precipitous increase in literature on e-cigarettes, as well as the increase in use of these products among youth and adults. This research was done without public involvement.

Eligibility criteria

We included observational and experimental studies that assessed the impact of non-menthol flavors in e-cigarettes on perceptions and use behaviors such as initiation, preference, and cessation. We did not exclude studies based on participant characteristics. Studies included populations of any age, race, sex, ethnicity, or country.

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We excluded the following types of articles: those that were not English-language; were not peer-reviewed (e.g., dissertations, technical reports); did not contain original data about flavored tobacco products (e.g., editorials, commentaries, literature reviews); did not address the impact of flavors on e-cigarette perceptions and use behaviors (e.g., biological/medical/chemical toxicology/animal studies, sales trends, effects of flavor bans); were related to smoking marijuana; or limited findings to menthol flavored e-cigarettes only. In order to maintain a semblance of consistency across studies examined, we chose to exclude articles that used qualitative study designs.

Type of outcome measures and intervention

Outcome measures include perceptions about appeal, reasons for use, and risk perceptions; susceptibility and intentions to try; and use behaviors, including initiation, preference, current use, quit intentions, and cessation.

Data sources and study selection

Literature search. One author (HMB) conducted searches of PubMed, Embase, PsycINFO and CINAHL for studies published and indexed in a database between April 4, 2016 and March 21, 2018. To maintain consistency with the previous systematic review, we maintained the same search string[1] rather than modifying the search to include only e-cigarettes. We used Boolean language to connect variants of words related to tobacco products, use, and flavor for PubMed, which was translated to match the search string requirements for other databases. A total of 3,191 articles resulted from searching the four databases during the initial search (March 21, 2018). After authors removed duplicates, 2,822 articles remained for title and abstract review, including 14 articles identified through manual search of references.

Study selection. Two authors (CM and HMB) reviewed the titles and abstracts of all 2,822 articles. A third author (SDK) resolved any discrepancies. Following this step, two authors (CM and HMB) reviewed the full text of all 114 articles eligible for full-text screening. A third author (SDK) resolved any discrepancies. Eighty articles were excluded for the following reasons: they did not have data on the specified outcomes (n=27), used qualitative methodologies (n=27), focused on a tobacco product other than e-cigarettes (n=12), were only focused on menthol flavor (n=2), was a duplicate (n=1), or were not peer-reviewed, did not include original data, did not include full-text, or included only a conference abstract (n=11). Articles that addressed e-cigarettes from the original systematic review (n=17) were then added to the 34 articles identified from this current review, combining for a total of 51 articles included in the final analysis. The study selection processes, which approximate but do not exactly follow the PRISMA methodology, are illustrated in Figure 1.[19]

Data extraction and synthesis

For the articles identified in the most current review, three authors (CM, HMB, SDK) independently extracted data using a data extraction sheet, which assessed study aim, type of flavored tobacco product, characteristics of study populations and study design, and main results and findings related to the impact of flavors in tobacco products. We used a validated quality assessment tool (QATSDD) to examine the

[1] Final PubMed search string: (((((smoke OR smoker OR smokers OR smokes OR smokings OR smoking OR cigarette OR cigarettes OR cigar OR cigars OR cigarillos OR cigarillo OR hookahs OR hookah OR waterpipe OR waterpipes OR narghile OR narghiles OR argila OR argiles OR tobacco OR tobaccos OR cigar* OR smoke* OR tobacco* OR ends OR "electronic nicotine delivery system*" OR vape OR vapor OR vapour OR vapours OR vapors OR vapor OR vapors OR vaping OR snus OR pipe OR pipes OR "e-cigarette" OR "e-cigarettes" OR bidi OR bidis OR kretek OR kreteks OR chewing tobacco OR snuff OR shisha OR "water pipe" OR "water pipes" OR goza OR narkeela OR "hubble bubble" OR hukkah OR hukkas OR hukka OR argileh) AND (flavor OR flavor* OR flavour OR flavour* OR flavors OR flavours OR flavoring OR flavouring OR flavorings OR flavourings OR flavoured OR flavoured OR flavoring OR flavorings OR flavouring OR flavourings OR flavouring OR flavoring OR flavourants OR flavorants)) OR (kretek OR kreteks OR bidi OR bidis))) 2016/04/04:2018/03/21 [edat])

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quality of quantitative studies with a diverse range of research designs.[20] Studies were scored on a 4-point scale from 0 (did not address criteria at all) to 3 (completely addressed criteria), with specified guidance to inform scorers based on the level of detail provided by study authors.[20] Specific scores were not used for inclusion/exclusion or used in any analysis. Rather, the tool was used to provide a valuable overall assessment of the general quality of included studies from which our conclusions are based. To ensure agreement in data extraction and quality assessment, three authors (CM, HMB, SDK) reviewed and extracted the same three articles, then compared results of review and extraction, resolving discrepancies through an iterative approach of discussion. Once mutual standards were decided upon based on this process, each of the three authors then split up the remainder of articles to extract and assess on their own. We created evidence tables using pertinent information extracted from each study, and we grouped the results by outcome measures. A similar procedure was conducted in the previous review, and all data were combined for final data analysis. A meta-analysis was not conducted due to the heterogeneity in outcomes across studies.

RESULTS

The review included 51 final articles for synthesis, including 17 published up to 2016 and 34 published between 2016-2018. Most studies included adults only (n=30), though 13 included youth and 8 included both youth and adults (Table 1).

Table 1. Characteristics of included studies (N=51)

Sample characteristics		**N (%)**	**US Studies (N=37), N (%)**	**International Studies (N=14), N (%)**
Population	Youth only	13 (25)	9 (24)	4 (29)
	Adults only	30 (59)	22 (59)	8 (57)
	Both youth and adults	8 (16)	6 (16)	2 (14)
Design	Cross-sectional	47 (92)	33 (89)	14 (100)
	Longitudinal	4 (8)	4 (11)	0 (0)
Sampling (not mutually exclusive)	Convenience	35 (69)	23 (62)	12 (86)
	Probability	19 (37)	17 (46)	2 (14)
Outcome measure (not mutually exclusive)	Taste, appeal, perceived risk	14 (27)	10 (27)	4 (29)
	Reasons for use	13 (25)	11 (30)	2 (14)
	Susceptibility, intention to try/initiation	17 (33)	11 (30)	6 (43)
	Preference	9 (18)	7 (19)	2 (14)
	Current use behaviors	12 (24)	10 (27)	2 (14)
	Quit intention/quitting behavior	10 (20)	7 (19)	3 (21)

Results of this review are broken out into three age categories: youth, adults, and youth and adults combined. Studies defined these age groups differently, and we therefore used the age groups as defined by the study authors. Most youth were defined as anyone below age 18 (though some went up to age 19[21]), and most adults were defined as 18+. Additionally, though young adults are an important population and were included as a separate age group in some studies in the review, the variability in

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definitions of this age group made it difficult to separate for purposes of the results, (some defining as ages 19-34, some as ages 18-29, etc.) and we therefore included all young adults in the adult category. Specific age groups used by authors can be found in Table 2.

Table 2. Sample characteristics and objectives of included articles (* indicates study was included in original 2016 review)

Study ID (Country)	Sample size and study population	Study aim	Main findings on flavors' impact
Amato, 2015[34] (US)*	n=9,301 Adults (18+) Tobacco users and non-users	Investigate patterns of e-cigarettes' use in order to establish a standard definition of e-cigarette current use prevalence for the purpose of population surveillance.	Current e-cigarette users cited flavors as a reason for use more often than past users.
Audrain-McGovern, 2016[22] (US)	n=32 Young adults (18-30) Current cigarette smokers and had ever used an e-cigarette	Determine whether flavoring enhances the subjective rewarding value, relative reinforcing value, and absolute reinforcing value of an e-cigarette with nicotine compared to an unflavored e-cigarette with nicotine.	E-cigarette flavoring enhanced the rewarding and reinforcing value of e-cigarettes with nicotine compared to unflavored e-cigarettes with nicotine.
Barnes, 2017[25] (US)	n=36 Adults (18+) Current cigarette smokers naïve to e-cigarettes	Examine e-cigarettes' abuse liability compared to conventional tobacco cigarettes that varied in e-cigarette flavor and modified-risk message.	Cherry flavor increased abuse liability relative to unflavored e-cigarettes (i.e., increased the degree to which e-cigarettes led to physical/psychological dependence).
Berg, 2016[38] (US)*	n=1,567 Young adults (18-34) E-cigarette users, non-users; cigarette	Compare (1) e-cigarette never, current, and former users; (2) never, current, and former traditional cigarette smokers in relation to e-cigarette use characteristics, flavors	Flavors were frequently indicated as reason for use across smoking and non-smoking e-cigarette users

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	users, non-users	preferred and reasons for use; and (3) reasons for discontinued use among former e-cigarette users across never, current, and former smokers.	
Bold, 2016[45] (US)	n=340 Youth (middle school and high school students) Ever e-cigarette users	Investigate whether certain reasons for trying e-cigarettes would predict continued use over time.	Good flavors were highly endorsed by youth as a reason for trying e-cigarettes; in univariate models, endorsing good flavors as a reason for trying e-cigarettes predicted continued e-cigarette use and e-cigarette frequency, but was no longer a significant predictor after adjusting for other covariates including cigarette smoking status.
Brozek, 2017[48] (Poland)	n=46 Adults (18-35) E-cigarette users	Assess prevalence of e-cigarette and tobacco cigarette use; to compare the patterns of smoking; and to assess the attitudes and motivations for e-cigarette use.	More than one-fourth of e-cigarette users started using e-cigarettes because of the unique flavors.
Buckell, 2018[58] (US)	n=2,031 Adults (18-64) Current cigarette smokers or recent quitters	Estimate preferences for flavors in cigarettes and e-cigarettes while controlling for other attributes of both products, and study how these preferences vary with individual characteristics.	Among e-cigarette flavors, adult smokers preferred tobacco flavor over fruit/sweet and menthol flavors; younger adult smokers, those with a higher education, and those with a recent quit attempt prefer all flavors of e-cigarettes compared to tobacco cigarettes.
Camenga, 2017[67] (US)	n=189 Youth (14-18) and young adults (18-24)	Examine the prevalence and predictors of current and former smokers' use of e-cigarettes for smoking cessation.	Preference for using a combination of two or more e-cigarette flavors mixed together was associated with increased odds of using e-cigarettes for smoking

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	Lifetime cigarette smokers and ever e-cigarette users		cessation, relative to e-cigarette users without a preferred flavor.
Chen, 2017[46] (US)	n=18,392 Youth (11-18) Non-smokers	Explore association between e-cigarette use and smoking susceptibility among non-smoking youth.	Flavored e-cigarette use was associated with increased smoking susceptibility among non-smoking youth, particularly among females and those not susceptible to tobacco marketing.
Chen, 2018[27] (US)	n=4,645 Young adults (18-34) Current cigarette smokers at Wave 1	Examine differences in smoking reduction and cessation among young adult smokers who did not use e-cigarettes, who used e-cigarettes with tobacco and menthol/mint flavors, and who used e-cigarettes with one or multiple non-tobacco and non-menthol flavors.	Compared to non-e-cigarette users, users of non-tobacco/menthol e-cigarette flavors were more likely to have reduced or quit smoking cigarettes in the past year; current e-cigarette users highly endorsed using e-cigarettes because of appealing flavors, with those endorsing this reason for use more than twice as likely to have reduced or quit smoking in the past year than e-cigarette users who did not endorse this reason for use.
Clarke, 2017[17] (UK)	n=256 Youth (16-19) Tobacco users and non-users	Investigate factors that lead to willingness to try e-cigarettes among UK youth.	Youth reported a preference for non-tobacco flavored e-cigarettes, regardless of smoking status; youth with a more positive prototype of smokers were more willing to try flavored e-cigarettes, while youth with a more negative prototype of e-cigarette users were less willing to try flavored e-cigarettes.
Coleman, 2017[35] (US)	n=3,373 Adults (18+)	Examine patterns of current e-cigarette use among daily and non-daily adult users.	Appealing flavors were highly cited as a reason for e-cigarette use, particularly among never smokers; more

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	Current e-cigarette users		frequent e-cigarette users (daily vs. moderate or infrequent) were more likely to initiate with a non-tobacco flavored e-cigarette.
Cooper, 2016[20] (US)	n=3,704 Youth (grades 6, 8, and 10) Tobacco users and non-users	Evaluate harm perceptions and perceived addictiveness of e-cigarettes among youth.	Youth who were ever or current e-cigarette users had higher odds of reporting flavored e-cigarettes as less harmful than non-e-cigarette users.
Czoli, 2015[31] (Canada)*	n=915 Youth and young adults (16-24) and adults (25+) Users and non-users (youth and young adults) and users (adults)	Determine the effect of distinct attributes of e-cigarettes (flavors, nicotine content, health warnings, price) and attribute levels on consumer choice.	Flavors in e-cigarettes significantly predicted lower perceptions of product harm and ability to help someone quit smoking.
Dai, 2016[21] (US)	n=21,491 Youth (middle and high school students) Tobacco users and non-users	Examine the 1) association between flavored e-cigarette use and intention to initiate cigarette smoking among never-smoking youth, 2) association between flavored e-cigarette use and intention to quit tobacco use in the next 12 months among current youth smokers, and 3) association between flavored e-cigarette use and youth	Compared with not using e-cigarettes, flavored e-cigarette use was associated lower perceived harm of tobacco, higher intention to initiate cigarette use among never smoking youth, and lower quit intentions among current smoking youth.

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		perception of the danger of tobacco.	
Elkalmi, 2016[28] (Malaysia)	n=277 Primarily adults (18+) but 7.2% of sample was 17 or younger Tobacco users and non-users	Determine the prevalence of current e-cigarette use and identify sociodemographic factors, motivators, attitudes, and perceptions that are associated with current e-cigarette use.	The majority of respondents who had tried e-cigarettes reported that the variety of flavors contributed to more enjoyment of the product compared to conventional cigarettes.
Etter, 2010[29] (France, Belgium, and other countries)*	n=81 Adults (18+) Current e-cigarette users	Assess usage patterns of e-cigarettes, reasons for use and users' opinions of these products.	Adult e-cigarette users reported flavors as being the most positive feature of the product.
Etter, 2016[64] (France, US, Switzerland, UK, and other countries)	n=1,685 Adults (18+) Current e-cigarette users	Describe personal characteristics of vapers, their utilization patterns, any modifications of the devices, and compare users of pre-filled cartridges, refillable tanks, and modified models for their patterns of use, reasons for use, satisfaction, and perceived effects on smoking.	Tobacco flavor was reported to be the most preferred e-cigarette flavor among current users, particularly among those who had recently started vaping; most respondents reported that flavors helped them to either quit smoking or reduce their smoking consumption.
Farsalinos, 2013[63] (Online survey in 10 languages)*	n=4,618 Adults (18+) E-cigarette users	Examine the patterns and perceptions of flavoring use in e-cigarettes among dedicated users.	E-cigarette users who were former smokers were more likely to prefer fruit and sweet flavors compared to current smokers. E-cigarette users reported that the variability of e-cigarette flavors is an important factor in reducing or quitting cigarette smoking and a

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			greater number of flavors used was associated with smoking abstinence.
Farsalinos, 2014[50] (Online survey in 10 languages)*	n=19,441 Adults (18+) E-cigarette users	Assess the characteristics and experiences of a large, worldwide sample of e-cigarette users and examine the differences between those who partially and completely substituted smoking with e-cigarette use.	The variability of flavors was cited as one of the reasons for initiating e-cigarette use, though it was not a primary reason.
Ford, 2016[19] (UK)*	n=1,205 Youth (11-16) Tobacco users and non-users	Examine adolescents' awareness of e-cigarette marketing and investigate the impact of e-cigarette flavor descriptors on perceptions of product harm and user image.	Fruit and sweet flavors were perceived as more likely to be tried by young never smokers than adult smokers trying to quit. The perceived harmfulness of e-cigarettes was moderated by product flavors.
Goldenson 2016[23] (US)	n=20 Young adults (19-34) Current e-cigarette users	Assess whether sweet flavorings and nicotine affect e-cigarette appeal; sweet flavorings increase perceived sweetness; nicotine increases throat hit; and perceived sweetness and throat hit are associated with appeal.	Sweet-flavored e-cigarette solutions increased appeal (including liking, willingness to use again, and amount willing to pay) and perceived sweetness ratings.
Gubner 2017[37] (US)	n=168 Adults (18+) Weekly or daily e-cigarette users	Examine e-cigarette use by individuals in treatment for substance abuse.	A large proportion of daily and weekly e-cigarette users reported using e-cigarettes because they have good flavors; daily e-cigarette users were more likely to use more types of flavors compared to weekly users.
Harrell, 2017a[42] (US)	n=3,907 youth n=5,482 young adults	Investigate whether the use of flavored e-cigarettes varies	Initiation with and current use of flavored e-cigarettes was higher among youth and young adults compared to

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	n=6,051 adults Youth (12-17), young adults (18-29), and adults (30+) Tobacco users and non-users	between youth, young adults, and adults.	older adults, and citing flavor availability as a reason for use was higher among youth current users relative to young adults and older adults.
Harrell, 2017b[61] (US)	n=143 youth and n=1,325 young adults Youth (12-17) and young adults (18-29) Current tobacco product users	Determine the potential for reductions in the prevalence of young people's e-cigarette and tobacco use if characterizing flavors were not present.	The large majority of youth and young adult current tobacco users reported use of flavored e-cigarettes, and about three-fourths of flavored e-cigarette users reported they would no longer use the product if it was not flavored.
Kim, 2016[24] (US)	n=31 Adults (18+) Current e-cigarette users	Examine the extent to which the perception of sweet and other flavors is associated with liking and disliking of flavored e-cigarettes.	Flavors influenced hedonic ratings of e-cigarettes, such that, in general, sweetness and coolness were positively associated with liking while bitterness and harshness were negatively associated with liking of e-cigarettes.
Kinouani, 2017[49] (France)	n=1,086 University students (18+; more than 90% 18-24) Ever e-cigarette users	Describe the relationship between e-cigarette use and tobacco smoking and describe reasons for experimenting with e-cigarettes.	The third most cited reason for trying e-cigarettes was because of attractive flavors, behind reasons of curiosity and offered to try by someone.
Kong, 2014[54] (US)*	n=1,157	Assess reasons for e-cigarette experimentation and	Availability of flavors was a primary reason for experimentation with e-

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	Youth and young adults E-cigarette users	discontinuation and examine whether these reasons differed by school level (MS, HS, college) and cigarette smoking status.	cigarettes, and appealing flavors were particularly important to high school students.
Krishnan-Sarin, 2014[56] (US)*	n=4,780 Youth (middle school and high school students) Tobacco users and non-users	Examine e-cigarette awareness, use patterns, susceptibility to future use, preferences, product components used, and sources of marketing and access among youth.	Use and preference for sweet e-cigarette flavors was high among adolescents regardless of cigarette smoking status.
Lee, 2017a[52] (US)	n=1,185 Young adults (18-25) Tobacco users and non-users	Investigate the characteristics of potential and current e-cigarette users based on four different levels of use acceptability and determinants that promote e-cigarette acceptability.	A higher preference for the availability of flavors in e-cigarettes was associated with experimentation and current use of e-cigarettes among college students.
Lee, 2017b[32] (South Korea)	n=6,656 Youth (13-18) Ever e-cigarette users	Determine the relation between frequency of e-cigarette use and the frequency and intensity of conventional cigarette smoking; and identify the association between reasons for e-cigarette use and frequency of use.	Nearly 1 in 10 youth cited good flavors as the main reason for using e-cigarettes, though this reason ranked behind five others, including curiosity and potentially being less harmful.
Litt, 2016[62] (US)	n=88 Adults (18-55) Cigarette smokers	Examine the influence of flavoring on the smoking and vaping behavior of cigarette smokers asked to adopt e-cigarettes for 6 weeks.	Cigarette smoking frequency was most reduced in participants assigned to menthol-flavored e-cigarettes, while it was least reduced in those assigned to cherry and chocolate flavors; participants

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			assigned to tobacco-flavored e-cigarettes had the highest rates of vaping, while those assigned to chocolate had the lowest rates of vaping.
Maglalang, 2016[39] (US)	n=56 Asian American and Pacific Islander young adults (18-25) Current e-cigarette users	Characterize e-cigarette use and risk perceptions among Asian American and Pacific Islander young adults in California.	Fruit and candy/sweet flavors were most preferred by current e-cigarette uses, though citing flavors as a reason for using e-cigarettes was reported by a low percentage of respondents, behind a variety of other reasons.
Morean, 2018[60] (US)	n=396 adolescents and n=590 adults Adolescents (high school students) and adults (18+) Past-month e-cigarette users	Examine differences in adolescents' and adults' preferences for e-liquid flavors and whether their preferences or the total number of flavors preferred were associated with number of days of e-cigarette use in the past month.	Compared to adults, adolescents were more likely to prefer e-liquid flavors such as fruit, candy/dessert, and vanilla, while adults were more likely to prefer tobacco, menthol/mint, coffee, and spice flavors. Among adolescents (though not adults), preferences for particular e-liquid flavors (i.e., fruit, dessert, or alcohol flavored) and the total number of flavors preferred were associated with more frequent e-cigarette use.
Nonnemaker, 2016[26] (US)*	n=765 Adults (18+) Current or former smokers	Examines how e-cigarette attributes influence willingness to pay for e-cigarettes.	Losing flavors significantly reduced the price participants are willing to pay for e-cigarettes, though this relationship was not found for dual users of cigarettes and e-cigarettes.
Patel, 2016[40] (US)	n=2,448 Adults (18+)	Assess reasons for e-cigarette use among current e-cigarette users.	Reasons for e-cigarette use among current adult users varied by sociodemographic and user characteristics; notably, flavorings were more

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	Current e-cigarette users		likely to be cited as a reason for use among younger age groups (ages 18-24, 25-34, and 35-54).
Pepper, 2013[44] (US)*	n=228 Youth (11-19), males Tobacco users and non-users	Sought to understand awareness of and willingness to try e-cigarettes among adolescent males.	Flavored e-cigarettes did not increase male adolescents' willingness to try e-cigarettes compared to plain varieties.
Pepper, 2014[51] (US)*	n=3,878 Adults (18+) Tobacco users and non-users	Explore reasons for starting and then stopping e-cigarettes use and examine differences in discontinuation by reason for trying among population-based sample of US adults.	Few adult e-cigarette users reported starting e-cigarette use because of the available flavors.
Pepper, 2016[18] (US)	n=1,125 Youth (13-17) Tobacco users and non-users	Examine the impact of flavor on interest in trying e-cigarettes and harm beliefs.	Adolescents were more interested in trying menthol, candy, or fruit-flavored e-cigarettes than tobacco or alcohol flavors; belief that these particular flavors were less harmful than tobacco or alcohol flavors party mediated this relationship.
Pesko, 2016[59] (US)	n=1,020 Adults (18+) Current cigarette smokers	Determine the preferences and relative importance placed on e-cigarette warning labels, flavor regulation, and prices.	Restriction of flavor availability in e-cigarettes to tobacco and menthol was associated with a significant reduction in e-cigarette selection, particularly among young adults compared to older adults.
Russell, 2018[53] (US)	n=20,836 Adults (18+) Frequent e-cigarette users	Examine flavor preferences of frequent e-cigarette users.	Adults are increasingly initiating e-cigarette use with non-tobacco flavors, particularly fruit and dessert flavors; never smoker e-cigarette users were more likely to initiate with and

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			currently use fruit/fruit beverage-flavored e-cigarettes compared to switchers, dual users, and former smoker e-cigarette users.
Rutten, 2015[41] (US)	n=582 Adults (18+) Current dual users of cigarettes and e-cigarettes	Assess attitudes, beliefs, and behaviors relating to e-cigarette use among current cigarette smokers.	Dual users of cigarettes and e-cigarettes ranked appealing flavors relatively low on the list of reasons for using e-cigarettes; no differences in smoking quit intentions or reduction in the use of cigarettes was observed for those reporting using e-cigarettes because of flavors compared to those not reporting using e-cigarettes because of the flavors.
Shang, 2017[55] (US)	n=515 Youth (14-17) Tobacco users and non-users	Understand how different attributes (flavors, health warnings, device types) influence youth's decisions to choose e-cigarettes.	Among youth ever and never e-cigarette users, fruit/sweet/beverage flavors increased the probability that a youth chose an e-cigarette product.
Shiffman, 2015[30] (US)*	n=216 (youth) n=432 (adults) Youth (13-17) Adults (19-80) Non-users (youth) and users (adult)	Compare e-cigarettes interest between nonsmoking teens and adult smoker, across flavors and assess differences in flavor preferences among adult smokers based on e-cigarettes use history.	The interest of nonsmoking teens in trying flavored e-cigarettes was very low, and interest was not influenced by flavor descriptors. Though adult smokers' interest was also modest, their interest was significantly higher than that of nonsmoking teens for each flavor.
Shiplo, 2015[43] (Canada)*	n=1,095 Youth and young adults (16-24)	Examines e-cigarette ever and current use, types of products used, and reasons for use.	Use of flavored e-cigarettes varies by smoking status, with smokers being more likely to try flavors than non-smokers. A common reason

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	Adults (25+) Non-smokers and smokers (youth and young adults) and smokers (adults)		for e-cigarette use is for the taste.
Spears, 2018[36] (US)	n=550 Adults (18+) Current e-cigarette users	Examine reasons for e-cigarette use and related risk perceptions among individuals with and without mental health conditions.	Compared to former smokers without mental health conditions, former smokers with mental health conditions placed higher importance on appealing flavors as a reason for e-cigarette.
Tackett, 2015[66] (US)*	n=215 Adults (18+) E-cigarette users	Estimate e-cigarettes preference, e-cigarettes use behaviors, perceived harm and health beliefs of various smoking cessation medications, nicotine replacement therapies and nicotine/tobacco products, and smoking history and current biochemically verified smoking status.	Most e-cigarette users reported a preference for vaping non-traditional flavors. Those who reported vaping non-tobacco and non-menthol flavors were more likely to have quit smoking compared to those who vaped traditional (tobacco/menthol) flavors.
Tsai, 2018[33] (US)	n=4,049 Youth (grades 6-12) Ever e-cigarette users	Assess self-reported reasons for e-cigarette use among middle school and high school student e-cigarette users.	One of the primary reasons for e-cigarette use by middle school and high school students was the availability of flavors, particularly among high school students.
Vasiljevic, 2015[47] (UK)*	n=471 Youth (11-16) Non-e-cigarette users	Assess the impact on appeal of tobacco smoking after exposure to advertisements for e-cigarettes with and without candy-like flavors.	Flavored, compared to non-flavored, e-cigarette advertisements elicited greater interest in buying and trying e-cigarettes.

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Weaver, 2018[65] (US)	n=858 Adults (18+) Current cigarette smokers	Assess the effect of "real world" e-cigarette use on population quit rates of adult smokers, accounting for frequency of use, device type, e-liquid flavor, and reasons for use.	Compared to non-e-cigarette users, users of menthol/wintergreen/mint or other non-tobacco/menthol flavor e-cigarettes (e.g., fruit, dessert, spice) were more likely to report a quit attempt, but users of other non-tobacco/menthol e-cigarette flavors had significantly lower odds of quitting smoking than non-users of e-cigarettes in the past year.
Yingst, 2015[57] (US and other countries)*	n=421 (87% in US; 13% outside US) Adults (18+) E-cigarette users	Examine the frequency with which e-cigarette users transition between device types and identify device characteristics and user preferences that may influence such transitions.	Most e-cigarette users began use with a device shaped like a cigarette (first generation devices) and transitioned to a larger advanced generation device with a more powerful battery and a wider choice of liquid flavors. Advanced generation device e-cigarette users report the variety of flavors as being important characteristic of e-cigarettes.

Seventy-two percent (n=37) of included studies were conducted in the US. While four studies used longitudinal designs, most (n=47; 92%) were cross-sectional. Study populations, aims, and relevant outcomes are provided in Table 2, with more detailed descriptions of analytical methods and results included in Supplementary Table 1.

Taste, appeal, and risk perceptions

Youth

Four studies surveyed probability samples of youth and assessed harm perceptions of e-cigarettes, all observing similar results. Three studies of youth in the US (two national samples and one state-wide sample) and one national sample of youth in the UK found that perceptions of e-cigarette harm differed depending on the product flavoring. Specifically, fruit and candy-flavored e-cigarettes were perceived as less harmful than tobacco-flavored e-cigarettes,[22,23] and ever or current e-cigarette users were less likely than non-users to perceive flavored e-cigarettes or tobacco as harmful.[24,25]

Adults

Eight studies were conducted among adults, including three laboratory experiments and one discrete choice experiment that examined the effect of e-cigarette flavors on factors such as ratings of taste and appeal.[26–29] Four studies included relatively small convenience samples of adults, each finding similar results: flavors in e-cigarettes enhanced the rewarding and reinforcing value of e-cigarettes compared to unflavored e-cigarettes[26], and the appealing sensory characteristics of flavors (i.e., sweetness and

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coolness) were positively associated with liking of the product,[27,28] the willingness to use again, and an increase in amount willing to pay for the product.[27,29] Similarly, in a cross-sectional survey of 765 current or former adult smokers, removal of flavors significantly reduced the price respondents were willing to pay for e-cigarettes, though this association was not observed among dual users of cigarettes and e-cigarettes.[30] One study in the US and two international studies likewise found that among ever or current e-cigarette users, the taste and variety of flavors were positive features of e-cigarettes and contributed to increased enjoyment of the product.[31–33]

Youth and Adults

Two studies examined appeal and harm perceptions in convenience samples of youth and adults. A sample of 216 youth and 432 adults in the US found that adult smokers rated interest toward e-cigarettes significantly higher than non-smoking teens for each e-cigarette flavor examined (note: study was funded by an e-cigarette company).[34] One discrete choice experiment in Canada (n=915) found that e-cigarette flavor significantly predicted lower perceptions of product harm; specifically, in the overall sample, menthol and coffee flavors were perceived as less harmful; among younger non-smokers, coffee-flavored was perceived as less harmful, while younger smokers perceived cherry flavor as less harmful and older smokers perceived tobacco-flavored as less harmful.[35]

Reasons for use

Youth

Two national probability samples of youth examining reasons for e-cigarette use found varied results. Less than 10% of South Korean youth who ever used e-cigarettes reported using the product because of good flavors,[36] compared to roughly a third of US students reporting ever using e-cigarettes because of the availability of flavors, with high school students more likely than middle school students to report flavors as a reason for use.[37]

Adults

Nine studies in the US examined reasons for using e-cigarettes among adults, also finding varied results. Three probability samples (two national and one state-wide) found that a majority of current e-cigarette users cited appealing flavors as a reason for using e-cigarettes,[31,38] particularly among never cigarette smokers compared to current and former smokers.[39] Another national probability sample in the US (n=550) found that former smokers with mental health conditions placed a higher importance on appealing flavors as a reason for use compared to former smokers without mental health conditions.[40] Further, about 40% of daily and weekly e-cigarette users (n=168) at substance use treatment centers reported good flavors as a reason for using e-cigarettes.[41] Among a convenience sample of 1,567 young adults, roughly a third of those who were non-e-cigarette users reported appealing flavors as a reason for possible e-cigarette use in the future, while a majority of current e-cigarette users reported appealing flavors and the ability to experiment with a variety of flavors as reasons for use.[42] Three other studies in the US (two national probability samples and one small convenience sample) observed relatively low proportions of current adult e-cigarette users reporting using e-cigarettes because of product flavorings, behind a variety of other reasons for use,[43–45] though flavors were more likely to be cited as a reason for use among younger age groups, particularly young adults ages 18-24, and among users of tank devices compared to disposables.[44]

Youth and Adults

Two studies in the US and Canada among youth and adults found that citing flavor availability or taste as a reason for e-cigarette use was higher among younger e-cigarette users compared to older users.[46,47]

Susceptibility, intention to try, and initiation

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Youth

Seven studies in the US and the UK examined susceptibility, intention to try, or initiation of e-cigarettes among youth. One study of a national probability sample of 228 adolescent males in the US found no differences in willingness to try flavored e-cigarettes compared to plain e-cigarettes.[48] However, the other six studies reported positive associations between flavors and e-cigarette use intentions. In a convenience sample of 340 youth in the US who were ever e-cigarette users, more than 40% endorsed good flavors as a reason for first trying e-cigarettes, the second highest endorsed reason.[49] Similarly, in a convenience sample of 256 UK youth, cigarette smokers and non-smokers were more willing to try flavored e-cigarettes than tobacco-flavored e-cigarettes (90% vs. 73% and 34% vs. 12%, respectively); further, having a positive prototype of smokers was associated with increased willingness to try flavored e-cigarettes.[21] Three different studies using national probability samples of US youth found similar relationships between flavors and e-cigarette use susceptibility and intentions to use. Adolescents were more likely to try menthol-, candy-, or fruit-flavored e-cigarettes compared to tobacco-flavored e-cigarettes;[22] and flavored e-cigarette use among non-smoking youth was associated with increased intention to initiate cigarette use[25] and smoking susceptibility, particularly among females and those not susceptible to tobacco marketing.[50] Finally, a convenience sample of 471 non-e-cigarette using youth in the UK found that exposure to flavored e-cigarette ads, compared to non-flavored e-cigarette ads, increased interest in buying and trying e-cigarettes.[51]

Adults

Six studies conducted in the US and internationally examined intention to try or initiation of e-cigarettes among adults. Two studies using convenience samples of young adults in Poland (n=46) and France (n=1,086) both found roughly 25-30% of e-cigarette users tried or started using e-cigarettes because of the variability of flavors, though other reasons for initiation were rated more highly than flavors.[52,53] Similarly, among an online convenience sample of international e-cigarette users (n=19,441) (note: study was funded by an e-cigarette advocacy group) and among a combined probability and non-probability sample of US adults (n=3,878), the availability of appealing flavors was not frequently cited as a reason for e-cigarette initiation.[54,55] However, two convenience samples of US adults found that the availability of flavors in e-cigarettes was associated with increased intention to use the product among young adult college students,[56] and never smoker e-cigarette users were more likely to have initiated e-cigarette use with a fruit-flavored product compared to switchers (from regular cigarette smoking to regular e-cigarette use), dual users, and former smoker e-cigarette users.[57]

Youth and Adults

Four studies examined interest in trying and initiation of e-cigarettes among youth and adults. One study of 648 youth and adults in the US observed that adult smokers' interest in trying e-cigarettes was significantly higher than non-smoking teens' interest for all fifteen e-cigarette flavors investigated (note: study was funded by an e-cigarette company).[34] However, the three other studies conducted found similar results in that youth and younger adults in Canada expressed more interest in trying non-tobacco-flavored e-cigarettes than older adults;[35] high school students in the US were more likely to experiment with e-cigarettes because of flavors compared to college students, with 40% of the overall sample (n=1,157) reporting the availability of flavors as a reason for experimentation with e-cigarettes;[58] and youth and young adults reported higher initiation with flavored e-cigarette use compared to tobacco-flavored e-cigarettes.[46]

Preference

Youth

In three studies of youth, one discrete choice experiment of 515 e-cigarette ever and never users in the US found that fruit, sweet, and beverage flavors increased the probability (relative to tobacco flavor) of choosing an e-cigarette product.[59] A national probability sample of 1,205 UK youth examined how youth perceive others to use e-cigarettes; youth perceived adult smokers who were trying to quit smoking as less

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likely to prefer cherry, candy floss, or coffee flavored e-cigarettes, whereas youth perceived adolescents their age to be more likely to try flavored e-cigarettes compared to tobacco-flavored.[23] Further, a convenience sample of 4,780 middle school and high school students in the US found that most ever e-cigarette users—regardless of cigarette smoking status—had tried and preferred sweet flavors compared to menthol and tobacco flavors.[60]

Adults

Four studies examined preference among adults in relation to e-cigarette flavors. One international study of 421 e-cigarette users found that those using an advanced generation e-cigarette device were more likely to rate a variety of flavor choices as important, relative to users of first-generation devices.[61] A laboratory experiment of a small convenience sample of adults in the US observed that ever e-cigarette users took twice as many puffs from flavored e-cigarettes compared to unflavored e-cigarettes.[26] Further, a discrete choice experiment of 2,031 adults in the US found that adult smokers preferred tobacco-flavored e-cigarettes to fruit/sweet and menthol flavors,[62] while another discrete choice experiment of 1,020 adults observed that increased flavor availability increased e-cigarette selection for younger cigarette smokers, but not for older smokers.[63] Additionally, regardless of interest in quitting cigarettes, greater flavor availability increased e-cigarette selection.[63]

Youth and Adults

Two convenience samples of US youth and adults found that, compared to adult e-cigarette users, adolescent users were more likely to prefer e-cigarette flavors such as fruit and alcohol, while adults were more likely to prefer tobacco, menthol/mint, coffee, and spice flavors; further, adult users preferred a greater number of e-cigarette flavors than adolescents.[64] Among 1,468 youth and young adults currently using tobacco, most reported use of flavored e-cigarettes, and roughly three-quarters of those reported they would not use e-cigarettes if they were not available in a flavored form, such as candy, fruit, or mint/menthol.[65]

Current use behaviors

Youth

Two studies among US youth examined e-cigarette use behaviors. In a longitudinal study of 340 ever e-cigarette users, youth who initiated e-cigarette use because of good flavors were more frequent users of e-cigarettes, though this association was no longer significant after adjustment for other covariates.[49] Additionally, in a national probability sample of 18,395 never smoking youth, those who used e-cigarettes three or more days in the past 30 days were more likely to be flavored e-cigarette users than those who had used e-cigarettes only one or two days in the past 30 days.[50]

Adults

Eight studies among adults examined current e-cigarette use behaviors in relation to flavors. A two-phase longitudinal laboratory study of 88 current cigarette smokers in the US assigned e-cigarettes to participants as substitution for cigarettes; the highest vaping rates were observed for those assigned to tobacco flavored e-cigarettes, and the lowest rates were observed for those assigned to chocolate-flavored.[66] A convenience sample of 168 e-cigarette users found that daily e-cigarette users reported using more types of flavors and were more likely to have used tobacco flavor or fruit/berry flavor compared to weekly users,[41] while a national probability sample of 4,645 young adults in the US found that users of non-tobacco/menthol flavors were more likely to vape daily compared to tobacco/menthol flavored e-cigarette users.[31] Another national probability sample of 3,373 current e-cigarette users in the US found that daily e-cigarette users were more likely to have initiated with a non-tobacco flavored e-cigarette, compared to moderate or infrequent e-cigarette users.[39] A convenience sample of 1,185 college students in the US found that a higher preference for the availability of flavors in e-cigarettes was associated with a higher likelihood of currently using e-cigarettes.[56] One international survey of 4,618 e-cigarette users showed that users who were former smokers were more likely to prefer fruit and sweet flavors compared

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to current smokers (note: study was promoted by an e-cigarette advocacy group).[67] Another survey of 1,685 e-cigarette users found that tobacco flavor was used by nearly half of the respondents who had started vaping the past three months, compared to only a quarter of those who had been vaping for at least four months.[68] Lastly, a convenience sample of 20,836 frequent e-cigarette users in the US found that the highest rate of current tobacco-flavored e-cigarette use was reported by those who initiated e-cigarettes five or more years ago, while the lowest rate of tobacco-flavored e-cigarette use was reported by those who initiated within the past year; those who initiated in the past year had the highest rate of fruit, dessert, and candy/sweet flavored e-cigarette use, and never smoker e-cigarette users were more likely to use fruit-flavored products and less likely to use tobacco-flavored products compared to ever cigarette smokers.[57]

Youth and Adults

Two studies of youth and adults in the US reported similar findings related to a preference for flavors among younger e-cigarette users. Nearly all youth and young adult current users (a probability and convenience sample in Texas and nationwide) reported a usual e-cigarette that was flavored with something other than tobacco (97-98%), compared to roughly 70% of older adults.[46] Similarly, a survey of 986 adolescents and adults in the US found that adolescents who preferred to use fruit, dessert, or alcohol-flavored e-cigarettes reported using e-cigarettes more frequently, and preferring to use a greater number of flavors was associated with using the product more frequently in the past month, though these relationships were not seen among adult e-cigarette users.[64]

Quit intentions and quitting behavior

Youth

In regards to smoking cessation, one national probability sample of 21,491 youth in the US found that among current smokers, students who reported using flavored e-cigarettes were less likely to quit tobacco use compared with those who reported not using e-cigarettes or with those who had used non-flavored e-cigarettes.[25]

Adults

Seven studies examined the relation between flavors in e-cigarettes and quit intentions and quitting behavior among adults, finding varied results. One longitudinal study of 4,645 young adult cigarette smokers in the US found that e-cigarette users who used at least one non-tobacco/menthol flavor were more likely to have reduced or quit smoking cigarettes in the past year compared to non-e-cigarette users, and e-cigarette users who reported using e-cigarettes because of appealing flavors were more than twice as likely to have reduced or quit smoking compared to those who did not endorse using e-cigarettes for that reason.[31] Another longitudinal study of 858 cigarette smokers in the US similarly found that users of menthol/wintergreen/mint or other non-tobacco flavor e-cigarettes (e.g., fruit, dessert, spice) were more likely than non-e-cigarette users to report a quit attempt in the past 12 months; however, users of non-tobacco/menthol flavors were less likely to have quit smoking compared to non-e-cigarette users.[69] In a two-phase longitudinal laboratory study among 88 cigarette smokers, cigarette smoking frequency was most reduced in participants assigned to menthol-flavored e-cigarettes, while it was least reduced in those assigned to cherry or chocolate flavored e-cigarettes.[66] Two international surveys of current e-cigarette users both found that e-cigarette flavors were an important factor in helping to reduce or quit cigarette smoking,[67,68] and the number of e-cigarette flavors used was associated with smoking abstinence (note: study was promoted by an e-cigarette advocacy group).[67] Further, a convenience sample of 215 e-cigarette users in the US found that e-cigarette users reporting use of non-tobacco/menthol flavors were more likely to have quit smoking compared to those vaping tobacco/menthol flavors,[70] while a national probability sample of 582 dual users in the US found no differences in smoking quit intentions or smoking reduction for those reporting using e-cigarette because of the flavors compared to e-cigarette users not endorsing use of e-cigarettes for that reason.[45]

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Youth and Adults

Two studies among youth and adults examined quit intentions and behaviors. A discrete choice experiment of 915 Canadian tobacco users and non-users observed that menthol and coffee flavored e-cigarettes were perceived as having a greater quit efficacy.[35] In a convenience sample of 189 youth and young adult ever e-cigarette users in the US, preference for using a combination of at least two e-cigarette flavors mixed together was associated with increased likelihood of using e-cigarettes to quit smoking, relative to not having a preferred e-cigarette flavor.[71]

Quality assessment

We used a validated quality assessment tool (QATSDD) to examine the quality of studies with a diverse range of research designs.[20] In this quality assessment tool, there are 14 criteria and each criterion is rated on a 4-point scale (0-3), with a maximum score of 42. Because the studies examined in this review use a variety of methodological approaches, the QATSDD tool was chosen as it was developed specifically for this purpose and has been shown to provide valid, reliable assessments of study quality.[20] Studies were scored on the criteria listed below, and all scores and criteria can be found in Supplementary Table 2. Quality assessment scores relative to the maximum score possible ranged from 38% to 88% with a mean score of 66%. Nearly all studies sufficiently detailed their aims and objectives, the research setting, recruitment and data collection, the fit between their research question and method of data collection and analysis, justification for their analytical method, and the study strengths and limitations (see QATSDD scores in Supplementary Table 2). However, few studies reported an explicit theoretical framework, user involvement in study design (e.g., cognitive interviewing of survey measures), evidence of sample size consideration, or statistical assessment of reliability and validity of measurement tools. A low score on these criteria do not necessarily mean that the study authors did not consider it (e.g., power calculations that were not reported); rather, the criteria was not sufficiently described in the manuscript. Of note, three studies were funded or promoted by the e-cigarette industry or e-cigarette user advocacy groups.[34,54,67]

DISCUSSION

Given the sharp increase in both the use of e-cigarettes (particularly among youth) and in the amount of research related to e-cigarettes and flavors published in the past two years, this systematic review provides a necessary update of a previous review on e-cigarettes and non-menthol flavors among youth and adults.[4] This synthesis of evidence regarding the role of non-menthol flavors in e-cigarettes on product perceptions and use is particularly relevant to the FDA's recently proposed policy framework that seeks to place additional regulations on the sale of non-menthol flavored e-cigarettes.[3] Seventeen studies examining flavors in e-cigarettes were published up to 2016; since 2016, 34 new studies were published, *doubling* the research in just two years.

Findings highlight the following: youth prefer non-tobacco flavored e-cigarettes;[59,60,64,65] flavors—particularly sweet flavors such as fruit and candy—decrease perceived product harm among youth and young adults;[22–25,35] and the availability of appealing flavors is associated with an increased willingness to try e-cigarettes, initiation of e-cigarettes, and susceptibility to cigarette smoking among youth and young adults.[21,22,25,49–51] Findings among adults are more varied, but demonstrate that non-menthol flavors in e-cigarettes increase appeal, enjoyment, and the price users are willing to pay for the product[26–28,30–33] and are a primary reason many adults use e-cigarettes.[31,38–42] Evidence on whether non-menthol flavored e-cigarettes promote or disrupt cessation among adult smokers remains unclear.[31,66–70] It is clear that the non-menthol flavors available in e-cigarettes attract youth to use these products, which should provide impetus for policymakers to address the issue. Results from the current review make it clear that banning flavors in e-cigarettes would discourage youth use of these products; however, doing so may also discourage adult smokers from using e-cigarettes for smoking cessation.[72]

Policy action at the federal level regarding flavored tobacco products has recently been undertaken, with the FDA seeking to limit the sale of non-menthol flavored e-cigarettes to age-restricted locations and

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heightening age verification practices for products sold online.[3] FDA's recent proposed action appears to be affecting manufacturers; the tobacco company Altria recently announced they would halt the sale of multiple e-cigarette products they produce, including flavored products,[73] and Juul Labs also announced a suspension of its non-menthol flavored e-cigarettes in retail stores.[74] In the meantime, states and localities have the authority to restrict the sale of flavored tobacco products, including flavored e-cigarettes. A comprehensive review of flavored e-cigarette regulations from 2017 showed that at the time, over 100 localities had implemented restrictions on the sale of flavored e-cigarettes.[75] Movement has continued to be made on this topic since that review; for instance, San Francisco passed a measure to ban the sale of all flavored tobacco products,[76] including e-cigarettes, in 2018. Jurisdictions globally have taken steps to more broadly regulate flavors in all tobacco products, recognizing their impact on youth.[17,77] This is in accordance with the 2010 WHO Framework Convention on Tobacco Control guidelines that recommends restricting or banning flavors in all tobacco products.[78]

Other policy options could impact youth e-cigarette use, including raising the minimum age of e-cigarettes. While this policy intervention has been shown to reduce initiation of tobacco product use particularly among youth aged 15 to 17,[79] this policy is only available to state and local entities, as the FDA does not have the authority to raise the minimum legal age of purchase past 18.[80] Taxation of e-cigarettes is another policy option that states have the authority to consider and implement, as youth and young adults are particularly susceptible to the effects of increased product price.[7] Currently only eight states and Washington, DC have implemented taxes on e-cigarettes.[81] The FDA recently proposed heightened age-restriction requirements for online sales, which is of particular importance as research shows that youth are easily able to access e-cigarettes via the internet.[82,83] Internationally, the European Union has enacted other e-cigarette regulations, including restricting the strength of nicotine fluids and e-cigarette advertising, limiting tank sizes, and requiring child-resistant packaging.[84] The United Kingdom has promoted e-cigarettes as a smoking cessation tool and allows for the licensing of e-cigarettes to be used as medicinal cessation aids.[84]

Based on the results of this review, it is important to consider deficits in the literature that would assist policymakers in developing the most impactful regulations. For one, it is important to note that the literature does not have a consistent and standardized way to categorize flavors. Yingst and colleagues (2017) have attempted to identify such a classification system, which, if used by researchers, would allow results to be more easily compared across studies. This would also assist policymakers in regulated flavors more easily, as it is possible that some categories of flavors may be more appealing to youth than others. Similarly, because much of the research uses varying categories to examine age, it makes it difficult to disaggregate the effects flavors have on different age groups. Doing so would especially be helpful to policymakers who are trying to create regulations that would have the most impact on youth initiation while maintaining the potential for adult harm reduction, though more research is needed to explore the latter. Furthermore, use of the QATSDD tool shines a light on deficits in the existing literature. Few studies provided evidence of sample size consideration or commented on the reliability or validity of their measurement tools. Reviewing these types of parameters before publishing may ensure that researchers are providing the most rigorous explanation of their research as possible. Finally, since so few longitudinal studies are present, it may be beneficial for researchers to use such data sets as PATH to show longitudinal trends in the outcomes presented in this review, in an effort to strengthen the existing body of literature with longitudinal data.

Limitations

Our review is limited in several ways. First, relevant articles may have been missed due to the exclusion of grey literature, doctoral dissertations, and non-English language articles; articles published within the search period (before March 2018) may also have been missed if they were not indexed in one of the searched databases by the time of the search. Similarly, we excluded qualitative articles in order to maintain consistency in data reviewed, though we recognize that qualitative data could potentially provide

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important contextual information on this topic. Second, a minimum threshold for study quality was not set, though only three studies received a score lower than 50% on the quality assessment (with scores of 48%, 45%, and 38%), and the mean score of all studies was 66%. Further, three studies were funded or supported by the e-cigarette industry or user advocacy groups.[34,54,67] Findings from these studies, and studies scoring lower in study quality, should be interpreted with caution. Third, more than 90% of studies were cross-sectional in nature, preventing us from making causal inferences between flavors and the perceptions and use of flavored e-cigarettes. Future research using longitudinal designs could further elucidate the role of flavors, particularly their effect on behavioral outcomes such as initiation among youth and cessation among adult smokers. Lastly, nearly half of all studies were conducted with convenience samples in the US, limiting the generalizability of findings, though nearly 40% of all studies did use probability-based sampling.

Conclusions

This systematic review provides a necessary update and extension of all evidence published to date on the role of flavors in e-cigarette perceptions and use behaviors. The increasing evidence among youth is clear: flavors in e-cigarettes (particularly sweet flavors) increase product appeal, decrease product harm perceptions, and increase willingness to use and initiation of e-cigarettes. Similarly, findings among adults demonstrate that flavors increase product appeal and enjoyment, and the availability of flavors are a primary reason for use for many adults. As the role of e-cigarettes in smoking cessation—and particularly how flavors impact this relationship—remains unclear, longitudinal studies of adult smokers are needed to assess the effect that e-cigarettes may have promoting or disrupting efforts to reduce or quit cigarette use. Regardless, findings are clear that banning flavors in e-cigarettes would discourage youth use of these products.

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REFERENCES

1. U.S. Food and Drug Administration. Menthol and Other Flavors in Tobacco Products. https://www.fda.gov/tobaccoproducts/labeling/productsingredientscomponents/ucm2019416.htm. Published 2018. Accessed July 24, 2018.
2. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to reduce tobacco use, especially among youth, by exploring options to address the role of flavors – including menthol – in tobacco products. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM601690.htm?utm_source=Eloqua&utm_medium=email&utm_term=StratComms&utm_content=pressrelease&utm_campaign=CTP News%26Connect%26SOS%3A ANPRM Flavors—32018. Published 2018. Accessed October 9, 2018.
3. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on proposed new steps to protect youth by preventing access to flavored tobacco products and banning menthol in cigarettes. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-proposed-new-steps-protect-youth-preventing-access. Published 2018. Accessed May 3, 2019.
4. Huang L-L, Baker HM, Meernik C, Ranney LM, Richardson A, Goldstein AO. Impact of non-menthol flavours in tobacco products on perceptions and use among youth, young adults and adults: A systematic review. *Tob Control*. 2017;26(6). doi:10.1136/tobaccocontrol-2016-053196
5. Bold KW, Kong G, Camenga DR, et al. Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth. *Pediatrics*. 2018;141(1).
6. Chaffee BW, Watkins SL, Glantz SA. Electronic Cigarette Use and Progression From Experimentation to Established Smoking. *Pediatrics*. 2018;141(4). doi:10.1542/peds.2017-3594
7. U.S. Department of Health and Human Services. *E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta, GA; 2016. https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf. Accessed July 27, 2018.
8. Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. *J Physiol*. 2015;593(16):3397-3412. doi:10.1113/JP270492
9. England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the Developing Human: A Neglected Element in the Electronic Cigarette Debate. *Am J Prev Med*. 2015;49(2):286-293. doi:10.1016/j.amepre.2015.01.015
10. Goniewicz ML, Boykan R, Messina CR, Eliscu A, Tolentino J. High exposure to nicotine among adolescents who use Juul and other vape pod systems ('pods'). *Tob Control*. 2018;0:1-2. doi:10.1136/tobaccocontrol-2018-054565
11. Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tob Control*. 2018:1-6. doi:10.1136/tobaccocontrol-2018-054382
12. Warner KE, Mendez D. E-cigarettes: Comparing the Possible Risks of Increasing Smoking Initiation with the Potential Benefits of Increasing Smoking Cessation. *Nicotine Tob Res*. 2018:1-7. doi:10.1093/ntr/nty062
13. Hajek P, Phillips-Waller A, Przulj D, et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N Engl J Med*. 2019;380(7):629-637. doi:10.1056/NEJMoa1808779
14. Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *BMJ*. 2016;354:i4645. doi:10.1136/bmj.i4645
15. Bullen C, Knight-West O. E-cigarettes for the management of nicotine addiction. *Subst Abuse Rehabil*. 2016;7:111-118. doi:10.2147/SAR.S94264
16. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction (Review). *Cochrane Libr*. 2014;12(CD010216).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

doi:10.1002/14651858.CD010216.pub2.www.cochranelibrary.com
17. Kennedy RD, Awopegba A, De León E, Cohen JE. Global approaches to regulating electronic cigarettes. *Tob Control*. 2017;26:440-445. doi:10.1136/tobaccocontrol-2016-053179
18. Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. *Tob Control*. 2014;23(January):iii3-iii9. doi:10.1136/tobaccocontrol-2014-051670
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:doi:10.1371/journal.pmed.1000097
20. Sirriyeh R, Lawton R, Gardner P, Armitage G. Reviewing studies with diverse designs: The development and evaluation of a new tool. *J Eval Clin Pract*. 2012;18(4):746-752. doi:10.1111/j.1365-2753.2011.01662.x
21. Clarke TN, Lusher JM. Willingness to Try Electronic Cigarettes Among UK Adolescents. *J Child Adolesc Subst Abuse*. 2017;26(3):175-182. doi:10.1080/1067828x.2016.1242098
22. Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tob Control An Int J*. 2016;25:ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174
23. Ford A, MacKintosh AM, Bauld L, Moodie C, Hastings G. Adolescents' responses to the promotion and flavouring of e-cigarettes. *Int J Public Health*. 2016;61(2):215-224. doi:10.1007/s00038-015-0769-5
24. Cooper M, Harrell MB, Perez A, Delk J, Perry CL. Flavorings and Perceived Harm and Addictiveness of E-cigarettes among Youth. *Tob Regul Sci*. 2016;2(3 PG-278-289):278-289. doi:10.18001/trs.2.3.7
25. Dai H, Hao J. Flavored electronic cigarette use and smoking among youth. *Pediatrics*. 2016;138(6):e2016513. doi:10.1542/peds.2016-2513
26. Audrain-McGovern J, Strasser AA, Wileyto EP. The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers. *Drug Alcohol Depend*. 2016;166(PG-263-267):263-267. doi:10.1016/j.drugalcdep.2016.06.030
27. Goldenson NI, Kirkpatrick MG, Barrington-Trimis JL, et al. Effects of sweet flavorings and nicotine on the appeal and sensory properties of e-cigarettes among young adult vapers: Application of a novel methodology. *Drug Alcohol Depend*. 2016;168:176-180. doi:10.1016/j.drugalcdep.2016.09.014
28. Kim H, Lim J, Buehler SS, et al. Role of sweet and other flavours in liking and disliking of electronic cigarettes. *Tob Control*. 2016;25:ii55-ii61. doi:10.1136/tobaccocontrol-2016-053221
29. Barnes AJ, Bono RS, Lester RC, Eissenberg TE, Cobb CO. Effect of Flavors and Modified Risk Messages on E-cigarette Abuse Liability. *Tob Regul Sci*. 2017;3(4):374-387. doi:10.18001/trs.3.4.1
30. Nonnemaker J, Kim AE, Lee YO, MacMonegle A. Quantifying how smokers value attributes of electronic cigarettes. *Tob Control An Int J*. 2016;25:e37-e43. doi:10.1136/tobaccocontrol-2015-052511
31. Chen JC. Flavored E-cigarette Use and Cigarette Smoking Reduction and Cessation—A Large National Study among Young Adult Smokers. *Subst Use Misuse*. 2018;53(12):2017-2031. doi:10.1080/10826084.2018.1455704
32. Elkalmi RM, Bhagavathul AS, Ya'u A, et al. Familiarity, perception, and reasons for electronic-cigarette experimentation among the general public in Malaysia: Preliminary insight. *J Pharm Bioallied Sci*. 2016;8(3):240-247. doi:10.4103/0975-7406.180768
33. Etter J-F. Electronic cigarettes: a survey of users. *BMC Public Health*. 2010;10(231). doi:10.1186/1471-2458-10-231
34. Shiffman S, Sembower MA, Pillitteri JL, Gerlach KK, Gitchell JG. The impact of flavor descriptors on nonsmoking teens' and adult smokers' interest in electronic cigarettes. *Nicotine Tob Res*. 2015;17(10):1255-1262. doi:10.1093/ntr/ntu333
35. Czoli CD, Goniewicz M, Islam T, Kotnowski K, Hammond D. Consumer preferences for

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

electronic cigarettes: Results from a discrete choice experiment. *Tob Control*. 2016;25(E1):e30-e36. doi:10.1136/tobaccocontrol-2015-052422
36. Lee JA, Lee S, Cho HJ. The Relation between Frequency of E-Cigarette Use and Frequency and Intensity of Cigarette Smoking among South Korean Adolescents. *Int J Env Res Public Heal*. 2017;14(3 PG-). doi:10.3390/ijerph14030305
37. Tsai J, Walton K, Coleman BN, et al. Reasons for Electronic Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(6 PG-196-200):196-200. doi:10.15585/mmwr.mm6706a5
38. Amato MS, Boyle RG, Levy D. How to define e-cigarette prevalence? Finding clues in the use frequency distribution. *Tob Control*. 2016;25(E1):e24-e29. doi:10.1136/tobaccocontrol-2015-052236
39. Coleman BN, Rostron B, Johnson SE, et al. Electronic cigarette use among US adults in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2014. *Tob Control*. 2017;26(e2):e117-e126. doi:10.1136/tobaccocontrol-2016-053462
40. Spears CA, Jones DM, Weaver SR, Pechacek TF, Eriksen MP. Motives and perceptions regarding electronic nicotine delivery systems (ENDS) use among adults with mental health conditions. *Addict Behav*. 2018;80:102-109. doi:10.1016/j.addbeh.2018.01.014
41. Gubner NR, Pagano A, Tajima B, Guydish J. A comparison of daily versus weekly electronic cigarette users in treatment for substance abuse. *Nicotine Tob Res*. 2018;20(5):636-642. doi:10.1093/ntr/ntx116
42. Berg CJ. Preferred Flavors and Reasons for E-cigarette Use and Discontinued Use Among Never, Current, and Former Smokers. *Int J Public Health*. 2016;61(2):225-236. doi:10.1007/s00038-015-0764-x
43. Maglalang DD, Brown-Johnson C, Prochaska JJ. Associations with E-cigarette use among Asian American and Pacific Islander young adults in California. *Prev Med Rep*. 2016;4:29-32. doi:10.1016/j.pmedr.2016.05.011
44. Patel D, Davis KC, Cox S, et al. Reasons for current E-cigarette use among U.S. adults. *Prev Med (Baltim)*. 2016;93:14-20. doi:10.1016/j.ypmed.2016.09.011
45. Rutten LJ, Blake KD, Agunwamba AA, et al. Use of E-Cigarettes Among Current Smokers: Associations Among Reasons for Use, Quit Intentions, and Current Tobacco Use. *Nicotine Tob Res*. 2015;17(10):1228-1234. doi:10.1093/ntr/ntv003
46. Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. *Prev Med Reports*. 2017;5:33-40. doi:10.1016/j.pmedr.2016.11.001
47. Shiplo S, Czoli CD, Hammond D. E-cigarette use in Canada: Prevalence and patterns of use in a regulated market. *BMJ Open*. 2015;5(8):1-7. doi:10.1136/bmjopen-2015-007971
48. Pepper JK, Reither PL, McRee A-L, Cameron LD, Gilkey MB, Brewer NT. Adolescent Males' Awareness of and Willingness to Try Electronic Cigarettes. *J Adolesc Heal*. 2013;52(2):144-150. doi:10.1016/j.jadohealth.2012.09.014
49. Bold KW, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Trying E-cigarettes and Risk of Continued Use. *Pediatrics*. 2016;138(3):e20160895-e20160895. doi:10.1542/peds.2016-0895
50. Chen JC, Das B, Mead EL, Borzekowski DLG. Flavored E-cigarette Use and Cigarette Smoking Susceptibility among Youth. *Tob Regul Sci*. 2017;3(1):68-80. doi:10.18001/TRS.3.1.7
51. Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: An experimental study. *Tob Control*. 2016;25(e2):e107-e112. doi:10.1136/tobaccocontrol-2015-052593
52. Brozek G, Jankowski M, Zejda J, Jarosinska A, Idzik A, Banka P. E-smoking among students of medicine - frequency, pattern and motivations. *Adv Respir Med*. 2017;85:8-14. doi:10.5603/arm.2017.0003
53. Kinouani S, Pereira E, Tzourio C. Electronic cigarette use in students and its relation with Tobacco-Smoking: A Cross-Sectional analysis of the I-Share study. *Int J Environ Res Public*

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Health. 2017;14:1345. doi:10.3390/ijerph14111345
54. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: A worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*. 2014;11(4):4356-4373. doi:10.3390/ijerph110404356
55. Pepper JK, Ribisl KM, Emery SL, Brewer NT. Reasons for starting and stopping electronic cigarette use. *Int J Environ Res Public Health*. 2014;11(10):10345-10361. doi:10.3390/ijerph111010345
56. Lee H-Y, Lin H-C, Seo D-C, Lohrmann DK. Determinants associated with E-cigarette adoption and use intention among college students. *Addict Behav*. 2017;65:102-110. doi:10.1016/j.addbeh.2016.10.023
57. Russell C, McKeganey N, Dickson T, Nides M. Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. *Harm Reduct J*. 2018;15(1 PG-33):33. doi:10.1186/s12954-018-0238-6
58. Kong G, Morean ME, Cavallo DA, et al. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res*. 2015;17(7):847-854. doi:10.1093/ntr/ntu257
59. Shang C, Huang J, Chaloupka FJ, Emery SL. The impact of flavour, device type and warning messages on youth preferences for electronic nicotine delivery systems: evidence from an online discrete choice experiment. *Tob Control*. 2017;0:1-8. doi:10.1136/tobaccocontrol-2017-053754
60. Krishnan-Sarin S, Morean ME, Camenga DR, Cavallo DA, Kong G. E-cigarette use among high school and middle school adolescents in Connecticut. *Nicotine Tob Res*. 2015;17(7):810-818. doi:10.1093/ntr/ntu243
61. Yingst JM, Veldheer S, Hrabovsky S, Nichols TT, Wilson SJ, Foulds J. Factors associated with electronic cigarette users' device preferences and transition from first generation to advanced generation devices. *Nicotine Tob Res*. 2015;17(10):1242-1246. doi:10.1093/ntr/ntv052
62. Buckell J, Marti J, Sindelar JL. Should flavours be banned in cigarettes and e-cigarettes? Evidence on adult smokers and recent quitters from a discrete choice experiment. *Tob Control*. 2018. doi:10.1136/tobaccocontrol-2017-054165
63. Pesko MF, Kenkel DS, Wang H, Hughes JM. The effect of potential electronic nicotine delivery system regulations on nicotine product selection. *Addiction*. 2016;111(4):734-744. doi:10.1111/add.13257
64. Morean ME, Butler ER, Bold KW, et al. Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. *PLoS One*. 2018;13(1). doi:10.1371/journal.pone.0189015
65. Harrell MB, Loukas A, Jackson CD, Marti CN, Perry CL. Flavored Tobacco Product Use among Youth and Young Adults: What if Flavors Didn't Exist? *Tob Regul Sci*. 2017;3(2):168-173. doi:10.18001/TRS.3.2.4
66. Litt MD, Duffy V, Oncken C. Cigarette smoking and electronic cigarette vaping patterns as a function of e-cigarette flavourings. *Tob Control An Int J*. 2016;25(Suppl 2 PG-67-72):67-72. doi:10.1136/tobaccocontrol-2016-053223
67. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: An internet survey. *Int J Environ Res Public Health*. 2013;10(12):7272-7282. doi:10.3390/ijerph10127272
68. Etter JF. Characteristics of users and usage of different types of electronic cigarettes: findings from an online survey. *Addiction*. 2016;111(4):724-733. doi:10.1111/add.13240
69. Weaver SR, Huang J, Pechacek TF, Heath JW, Ashley DL, Eriksen MP. Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015-2016. *PLoS One*. 2018;13(7):e0198047. doi:10.1371/journal.pone.0198047
70. Tackett AP, Lechner W V., Meier E, et al. Biochemically verified smoking cessation and vaping beliefs among vape store customers. *Addiction*. 2015;110(5):868-874. doi:10.1111/add.12878
71. Camenga DR, Kong G, Cavallo DA, Krishnan-Sarin S. Current and Former Smokers' Use of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Electronic Cigarettes for Quitting Smoking: An Exploratory Study of Adolescents and Young Adults. *Nicotine Tob Res*. 2017;19(12):1531-1535. doi:10.1093/ntr/ntw248

72. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620185.htm. Published 2018. Accessed October 26, 2018.
73. Bomey N. Marlboro maker Altria stops sales of flavored vaping liquid. *USA Today*. https://www.usatoday.com/story/money/2018/10/25/altria-group-flavored-vaping-liquid/1759794002/. Published October 25, 2018. Accessed October 25, 2018.
74. Kaplan S, Hoffman J. Juul Suspends Selling Most E-Cigarette Flavors in Stores. *The New York Times*. https://www.nytimes.com/2018/11/13/health/juul-ecigarettes-vaping-teenagers.html. Published November 13, 2018.
75. Chen JC, Green KM, Chen J, Hoke KS, Borzekowski DLG. Restricting the Sale of Flavored E-cigarettes in the US: An Examination of Local Regulations. *Tob Regul Sci*. 2018;4(4):32-40. doi:10.18001/trs.4.4.4
76. Hoffman J. San Francisco Voters Uphold Ban on Flavored Vaping Products. NY Times. https://www.nytimes.com/2018/06/06/health/vaping-ban-san-francisco.html. Published 2018. Accessed October 9, 2018.
77. Campaign for Tobacco-Free Kids. Brazil's Highest Court Upholds Ban on Flavored Tobacco Products. https://www.tobaccofreekids.org/press-releases/2018_02_01_brazil-court-upholds-flavor-ban. Published 2018. Accessed July 24, 2018.
78. World Health Organization. *Partial Guidelines for Implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control*.; 2012. http://www.who.int/fctc/guidelines/Guideliness_Articles_9_10_rev_240613.pdf.
79. The Institute of Medicine. *Public Health Implications of Raising the Minimum Age of Legal Access to Tobacco Products*. Washington, DC; 2015. www.iom.edu/TobaccoMinimumAge. Accessed July 26, 2018.
80. U.S. Food and Drug Administration. *Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products; Final Rule*. Silver Spring, MD; 2016. https://www.gpo.gov/fdsys/pkg/FR-2016-05-10/pdf/2016-10685.pdf. Accessed August 29, 2018.
81. Marynak K, Kenemer B, King BA, Tynan MA, MacNeil A, Reimels E. State Laws Regarding Indoor Public Use, Retail Sales, and Prices of Electronic Cigarettes-U.S. States, Guam, Puerto Rico, and U.S. Virgin Islands, September 30, 2017. *Morb Mortal Wkly Rep*. 2017;66(49):1341-.
82. Nikitin D, Timberlake DS, Williams RS. Is the e-liquid industry regulating itself? A look at e-liquid internet vendors in the United States. *Nicotine Tob Res*. 2016;18(10):1967-1972. doi:10.1093/ntr/ntw091
83. Williams RS, Derrick J, Ribisl KM. Electronic cigarette sales to minors via the internet. *JAMA Pediatr*. 2015;169(3):e1563. doi:10.1001/jamapediatrics.2015.63
84. Truth Initiative. *E-Cigarettes*. Washington, DC; 2018. https://truthinitiative.org/sites/default/files/Truth_E-Cigarette_FactSheet_FINAL.pdf. Accessed October 22, 2018.

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Author's Contributions:

Ms. Meernik, Ms. Baker, and Dr. Kowitt conducted data review and analysis, drafted the initial manuscript, and revised and reviewed the full manuscript.

Dr. Ranney and Dr. Goldstein conceptualized the study and provided critical feedback to the intellectual content during drafting and revisions of the manuscript, as well as to the interpretation of data analyses.

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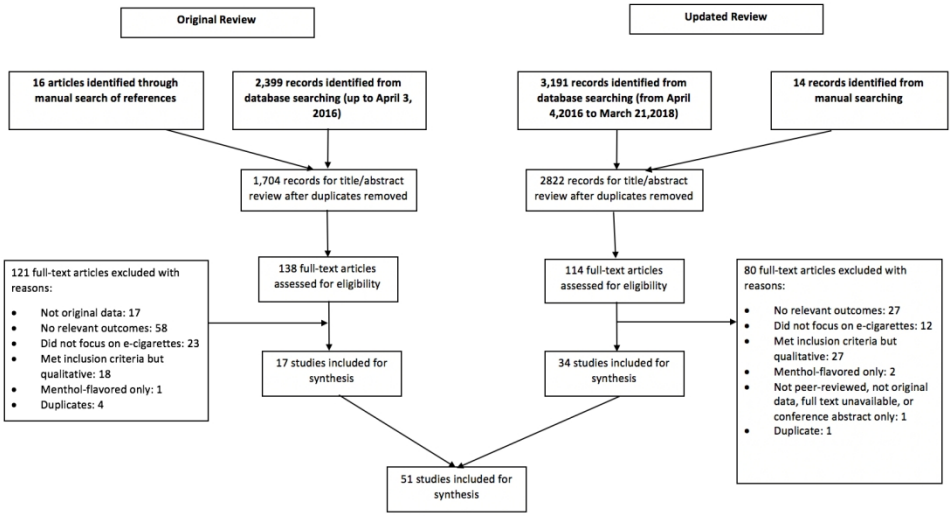

Figure 1. PRISMA Flow Diagram

Supplementary Table 1. Main results of all studies (* indicates study was included in original 2016 review)

Study	Study design	Measures / Analysis	Results
Amato, 2015[38]*	Cross-sectional survey Probability sample	Descriptive statistics were used to examine reasons for e-cigarette use.	A greater proportion of current e-cigarette users cited "come in flavors other than menthol" as a reason for their e-cigarette use than past users (55.5% vs. 25.0%).
Audrain-McGovern, 2016[26]	Cross-sectional laboratory experiment Convenience sample	Regression models used to evaluate the effect of flavor on subjective rewarding value, relative reinforcing value, and absolute reinforcing value.	The average subjective rewarding value across the three e-cigarettes included: unflavored (M = 3.11, SD = 1.55), dessert flavored (M = 3.69, SD = 1.78), and fruit flavored (M = 4.22, SD = 1.55). Both the fruit flavored (β = 1.11, CI: 0.58-1.64, p<.0001) and the dessert flavored e-cigarettes (β = 0.57, CI: 0.47-1.11, p=.03) were rated significantly more rewarding than the unflavored e-cigarette. Subjective reward was higher for the flavored e-cigarette compared to unflavored (β = 0.83, CI: 0.35–1.32, p=.001). This group difference meant that participants rated the unflavored e-cigarettes as “a little” and the flavored e-cigarette as “moderately” satisfying and good tasting. Participants took twice as many flavored puffs than unflavored e-cigarette puffs (IRR = 2.03, CI: 1.18-3.47, p=.01).
Barnes, 2017[29]	Cross-sectional laboratory experiment Convenience sample	Linear mixed effects models used to assess abuse liability for tobacco products.	The crossover point (i.e., the largest dollar amount at which participants still choose the tobacco product over the money) for cherry flavored e-cigarettes was significantly higher than for e-cigarettes without a flavor ($0.71 vs $0.51, p<.05).
Berg, 2016[42]*	Cross-sectional survey	ANOVAs were used to compare continuous variables across	32% of nonusers included ‘‘they come in appealing flavors’’ as a reason for possible future e-cigarette use.

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	Convenience sample	groups, and Chi-square tests were used to compare categorical variables.	39% of current smokers, who were non-e-cigarette users, chose “they come in appealing flavors” as a reason for possible e-cigarette use; this is compared to <31% of nonsmokers and former smokers, p<0.001. 60.2% of current e-cigarette users chose “they come in appealing flavors” as a reason for e-cigarette use; 59.5% of those same users chose “I like experimenting with various flavors” as a reason for e-cigarette use. 69.7% of never cigarette smokers who use e-cigarettes chose “they come in appealing flavors” as a reason for e-cigarette use; 61.4% of former cigarette smokers who use e-cigarettes chose “I like experimenting with various flavors” as a reason for e-cigarette use. 20.3% of former e-cigarette users reported no recent use of e-cigarettes because they ‘‘don’t like the flavor(s)’’.
Bold, 2016[49]	Longitudinal survey Convenience sample	Logistic regression models used to examine reasons for trying e-cigarettes at wave 1 as predictors of continuing e-cigarette use at wave 2; linear regression models used to examine reasons for trying e-cigarettes at wave 1 as predictors of e-cigarette frequency at wave 2 among those who continued e-cigarette use.	"Good flavors" was endorsed by 41.8% of students as a reason for first trying e-cigarettes among ever e-cigarette users, the second most highly endorsed reason for trying behind curiosity (reasons not exclusive). In univariate models, good flavors as a reason for first trying e-cigarettes predicted continued e-cigarette use, though it was no longer significant after adjusting for cigarette smoking status. In univariate models, good flavors a reason for first trying e-cigarettes predicted more frequent use, though it was no longer significant after adjusting for other covariates.

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Brozek, 2017[52]	Cross-sectional survey Convenience sample	Descriptive statistics used to describe attitudes and motivations for e-cigarette use.	28.3% of e-cigarette users decided to start using e-cigarettes because of the unique flavors, the fourth most cited reason behind other reasons such as desire to quit traditional cigarettes (58.7%) and less harmful effect on health (43.5%).
Buckell, 2018[62]	Cross-sectional discrete choice experiment Convenience sample	Exploded multinomial logit models used to analyze respondents' preferences.	Adult smokers prefer the following e-cigarette flavors, from most to least: tobacco, fruit/sweet, and menthol. Adult smokers with at least one quit attempt in the past year preferred all flavored (including tobacco) e-cigarettes, relative to tobacco cigarettes.
Camenga, 2017[71]	Cross-sectional survey Convenience sample	Multivariable logistic regression used to evaluate association between using e-cigarettes to quit smoking and age, gender, race, e-cigarette frequency, cigarette smoking status, preferred e-cigarette flavor, and risk perceptions.	Having a preference for "a combination of 2 or more flavors mixed together" predicted increased likelihood of using e-cigarettes to quit smoking, relative to not having a preferred flavor (aOR = 1.92, 95% CI: 1.31-2.81; p=.0008).
Chen, 2017[50]	Cross-sectional survey Probability sample	Logistic regression used to estimate association between cigarette susceptibility and e-cigarette use status, demographic characteristics, and risk factors for cigarette smoking. Multivariate logistic regression used to explore moderating variables	Among those who used e-cigarettes, youth who used the product 3 days or more were more likely to be flavored e-cigarette users than those who used e-cigarettes 1 or 2 days in the past 30 days (p<.05). The unadjusted odds ratio of being susceptible to cigarette smoking was the largest for flavored e-cigarette use (OR = 6.6, CI: 3.8-9.1, p <.0001), followed by nicotine dependence and cigarette experimentation. In the adjusted regression analysis, flavored e-cigarette users had higher

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		influencing direction and strength of association between e-cigarette use and smoking susceptibility.	odds of being susceptible to cigarette smoking than plain e-cigarette users (AOR = 1.7, CI: 1.3-2.4, p<.001) and non-users (AOR = 3.8, CI: 2.8-5.3, p<.0001), the largest effect across all demographic characteristics and smoking risk factors. In stratified analyses, the association between smoking susceptibility and flavored e-cigarette use was significantly higher for females (AOR = 6.5, CI: 4.2-9.9, p<.01) than males (AOR = 2.5, CI: 1.5-4.1, p<.01). The association between smoking susceptibility and flavored e-cigarette use was significantly higher for those who were not receptive to tobacco marketing (AOR = 5.0, CI: 3.5-7.0, p<.01) than those who were receptive (AOR = 2.5, CI: 1.2-3.1, p<.05).
Chen, 2018[31]	Longitudinal survey Probability sample	Univariate and multivariate regressions used to examine associations between past-year smoking reduction and cessation and current e-cigarette flavor use at wave 2.	Users of one non-tobacco/menthol flavor (37.1%) were more likely than non-e-cigarette users (24.7%) to adopt smoking cessation methods (p<.001). In adjusted analysis, wave 2 e-cigarette users who used one (AOR = 2.5, p<.001) or multiple (AOR = 3.0, p<.001) non-tobacco/menthol flavors were more likely to have reduced or quit smoking cigarettes in the past year than non-e-cigarette users. The third most endorsed reason for using e-cigarettes among current users (subsample of 844 respondents) were that e-cigarettes “come in flavors I like” (80.2%), behind “might be less harmful to people around me than cigarettes” (85.4%) and “can be used where smoking cigarettes is not allowed” (82.2%).

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			Compared to users of tobacco/menthol flavors, users of non-tobacco/menthol flavors were more likely to enjoy e-cigarette flavors (p<.001) and to vape daily (p<.001). E-cigarette users who said that e-cigarettes "come in flavors I like" (OR = 2.1, p=.007) were more than twice as likely to have reduced or quit smoking in the past year compared to those who did not endorse e-cigarette use for this reason.
Clarke, 2017[21]	Cross-sectional survey Convenience sample	Sequential hierarchical multiple regression used to identify predictors of adolescents' willingness to try flavored and tobacco-flavored e-cigarettes.	The majority of cigarette smokers (90.6%) were more willing to try flavored e-cigarettes than tobacco-flavored products (73.4%), with around one-third (33.9%) of non-smoking participants willing to try flavored e-cigarettes, as opposed to tobacco-flavored (12.0%). The more positively adolescents perceived a smoker, the more willing they were to try a flavored e-cigarette (p<.05), while the more negatively they perceived an e-cigarette user, the less willing they were to try a flavored e-cigarette (p<.05).
Coleman, 2017[39]	Cross-sectional survey Probability sample	Poisson regression used to examine association between everyday versus someday e-cigarette use and demographic, tobacco use, and product characteristics.	Never smokers were more likely to endorse appealing flavors as a reason for e-cigarette use (75.3%) compared with current (63.7%, p<.0001) and former (60.1%, p<.0001) smokers. Daily e-cigarette users were more likely to report that their first e-cigarette was non-tobacco flavored (65.2%) than moderate (60.7%) or infrequent (54.8%) e-cigarette users (p<.0001).
Cooper, 2016[24]	Cross-sectional survey Probability sample	Logistic regression models used to investigate relationship between perceptions of	27.0% of youth reported that flavored e-cigarettes were "less harmful" than non-flavored e-cigarettes. Youth who currently used e-cigarettes had higher odds (OR = 2.84, 95% CI:

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		harm and addictiveness and e-cigarette use.	1.91–4.21) of reporting flavored e-cigarettes as "less harmful" than non-flavored e-cigarettes compared to non-current users, after adjusting for covariates. Youth who had ever used e-cigarettes had higher odds (OR = 2.88, 95% CI: 2.42–3.42) of reporting that flavored e-cigarettes were "less harmful" than non-flavored products compared to never users, after adjusting for covariates.
Czoli, 2015[35]*	Cross-sectional discrete choice experiment Convenience sample	Multinomial logit regression was used to analyze the effect of attributes on consumer choice for each outcome in a discrete choice experiment.	Participants were significantly more interested in trying e-cigarettes with cherry ($p<0.0001$, $r=0.2$) and menthol ($p=0.01$, $r=0.1$) flavors. Younger smokers expressed interest in trying e-cigarettes with a preference for products with cherry flavor ($p<.001$, $r=0.2$) while younger nonsmokers indicated interest in trying cherry ($p<.0001$, $r=0.3$), menthol ($p<.0001$, $r=0.2$) and coffee flavor ($p<.001$, $r=0.2$); Older smokers indicated greater interest in trying tobacco-flavored e-cigarettes ($p<0.0001$, $r=0.6$). E-cigarettes with the following characteristics were perceived as less harmful and greater quit efficacy: menthol ($p<0.0001$, $r=0.6$; $p<0.0001$, $r=0.2$) and coffee flavors ($p<0.0001$, $r=0.3$; $p<0.001$, $r=0.2$). Younger non-smokers were more likely to perceive coffee-flavored ($p=0.02$, $r=0.1$) e-cigarettes as less harmful while younger smokers held these beliefs about products with cherry flavor ($p=0.03$, $r=0.1$); Older smokers perceived products with tobacco flavor ($p<0.001$, $r=0.2$) as less harmful.

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			Compared to other attributes, flavor accounted for 24% of the relative importance on intention to try, 36% for perceptions of reduced product harm, and 25% on perceptions of enhanced product quit efficacy.
Dai, 2016[25]	Cross-sectional survey Probability sample	Logistic regression model used to examine associations between flavored e-cigarette use and tobacco use and perception of tobacco's danger.	Among all respondents, students who reported using flavored e-cigarettes were least likely to perceive tobacco's danger compared with those who reported not using e-cigarettes (74.8% vs 91.3%; aOR = 0.5; p<.0001) or with those who reported using non-flavored e-cigarettes (74.8% vs 77.1%). Among never smokers, the use of flavored e-cigarettes was associated with a higher prevalence of intention to initiate cigarette use compared with those who had not used e-cigarettes in the past 30 days (58.3% vs 20.1%; aOR = 5.7; p<.0001) or with those who had used non-flavored e-cigarettes (58.3% vs 47.4%; aOR = 1.7; p=.02). Among current smokers, students who reported using flavored e-cigarettes were less likely to quit tobacco use compared with those who reported not using e-cigarettes (24.1% vs 32.7%; aOR = 0.6; p=.006) or with those who had used non-flavored cigarettes (24.1% vs 33.5%).
Elkalmi, 2016[32]	Cross-sectional survey Convenience sample	Descriptive statistics used to report frequencies.	66.7% of respondents who had tried e-cigarettes in the past reported that variety of flavors contribute to better enjoyment of e-cigarettes compared to traditional cigarettes.
Etter, 2010[33]*	Cross-sectional survey Convenience sample	Open-ended questions about the most positive and negative points about e-cigarettes were analyzed.	The most frequently cited positive feature of e-cigarettes was that respondents liked the taste and variety of flavors (18% of total open-ended comments).

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Etter, 2016[68]	Cross-sectional survey Convenience sample	T-tests used to compare means, Mann-Whitney U-tests and Wilcoxon's signed-ranks test to compare medians between or within groups, and chi-square tests to compare proportions.	Tobacco flavor e-cigarettes were used by 44% of users who had recently started vaping (i.e. those who had used e-cigarettes for 0–3 months) versus 25% of long-term users (who had used e-cigarettes for ≥ 4 months, $\chi 2 = 79.0$, $p<.001$). Most participants (80%) said that the e-cigarette flavors helped them either to quit smoking or reduce their cigarette consumption, while 18% said that the flavors had no impact on their smoking and 2% said that the flavors made them want to smoke.
Farsalinos, 2013[67]*	Cross-sectional survey Convenience sample	X^2 tests compared categorical variables (e.g., type of e-cigarette flavors regularly used) between current and former smokers. A stepwise binary logistic regression analysis was used with smoking status (former vs current smoker) as the independent variable and age, gender, education level, smoking duration, number of flavorings used regularly, and e-cigarette consumption as covariates.	More current smokers were using tobacco flavors compared to former smokers ($X^2=14.6$, $p<.001$), while more former smokers were using fruit ($X^2=14.0$, $p<.001$) and sweet flavors ($X^2=21.8$, $p<.001$). The average score for importance of flavors variability in reducing or quitting smoking was 4 ("very important") on a 5-point scale. 39.7% of participants reported that restricting variability of flavors would make reducing or completely substituting smoking less likely. Binary logistic regression analysis showed that number of flavors regularly used ($\beta=0.089$, $p=0.038$) was associated with complete smoking abstinence among dedicated long-term users.
Farsalinos, 2014[54]*	Cross-sectional survey Convenience sample	Descriptive statistics examined reasons for initiating e-cigarette use.	Initiating e-cigarette use to enjoy the variability of flavors in e-cigarettes was ranked as 3 on a 5-point scale from 1 (not important) to 5 (most important).

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Ford, 2016[23]*	Cross-sectional survey Probability sample	Paired t-tests were run on weighted data to produce mean scores; the Friedman test was used on ordinal data, then post hoc tests were conducted using the Wilcoxon signed rank test	Perceptions of harm from the different flavors ranged from a mean of 3.00 (SD = 1.35) for candy floss flavor to 3.06 (SD = 1.29) for cherry, 3.47 (SD = 1.22) for coffee and 3.99 (SD = 1.14) for tobacco flavor. Perceptions of harm differed depending on the flavor, χ^2 (4) = 851.59, p<0.001. Post hoc analysis showed that, when compared against perceptions of harm of e-cigarettes in general, tobacco flavor e-cigarettes were perceived as being more harmful (p<0.001) while cherry and candy floss flavors were each perceived as less harmful (p<0.001). Coffee flavor e-cigarettes were perceived as having the same level of harm as e-cigarettes in general. Perceptions of likelihood of an adult smoker using each differed depending on the flavor, χ^2 (3) = 153.9, p <0.001 as did perceptions of likelihood of a never smoker of their age, χ^2 (3) = 879.01, p<0.001. Post hoc analysis showed that, when compared with tobacco flavor e-cigarettes, adult smokers who were trying to give up smoking were perceived by youth to be less likely to use cherry, candy floss or coffee flavors (p<0.001). Conversely, a never smoker of their age was perceived to be more likely to try cherry (p<0.001), candy floss (p<0.001) or coffee flavor (p<0.01) than a tobacco flavor e-cigarette. An adult smoker was perceived by youth to be more likely than a never smoker of their age to use tobacco (p<0.001) and coffee (p<0.001) flavors whereas a never smoker of their age was perceived to be more likely than an

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			adult smoker to try candy floss (p<0.001) and cherry (p<0.01) flavors.
Goldenson, 2016[27]	Cross-sectional laboratory experiment Convenience sample	Multilevel linear models used to examine associations between each sensory rating (sweetness or throat hit) and appeal outcomes.	A significant main effect of e-liquid flavor was found for each appeal outcome (i.e., liking, willingness to use again, and amount willing to pay) and sweetness (ps<.0001). Sweet-flavored e-liquids resulted in higher appeal ratings than non-sweet and flavorless solutions (ps<.0001). Ratings of sweetness were positively associated with each appeal outcome (ps<.0001). For instance, each one-point increase in sweetness rating (0-100) was associated with a 0.51 increase in liking, a 0.51 increase in willingness to use again, and a $0.04 increase in amount willing to pay for a day's worth of the solution.
Gubner, 2017[41]	Cross-sectional survey Convenience sample	Bivariate analyses and logistic regression used to examine factors associated with daily vs. weekly e-cigarette use.	Daily and weekly e-cigarette users both reported similar reasons for use of e-cigarettes, including because they have good flavors (41.1% overall). Daily e-cigarette users reported using more types of e-juice flavors (2.2 ± 1.3 vs. 1.8 ± 1.4), t(168) = 2.15, p=.03), and were more likely to have used tobacco flavor, fruit/berry flavor, or select "other" flavor compared to weekly users.
Harrell, 2017a[46]	Cross-sectional survey Probability and convenience sample	Proportions and 95% confidence intervals used to examine percentage of flavored e-cigarette use at initiation and current use; Chi-square tests used to examine differences in flavored e-cigarette use by combustible	The proportion of current e-cigarette users who initiated with an e-cigarette flavored with something other than tobacco was considerably higher in Texas youth (98.6%) and young adults in Texas (95.2%) and nationwide (71.2%) compared to older adults nationwide (44.1%). At initiation, the use of tobacco-flavored e-cigarettes was more common among current dual users (e-cigarette and combustible tobacco product users)

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		tobacco product use and demographic characteristics.	than exclusive e-cigarette users (i.e., former combustible tobacco product users), for both age groups (p<.05). Among adults nationwide, 43.5% of current combustible users said their first e-cigarette was flavored to taste like tobacco, compared to 27.8% of former combustible product users. The proportion of current users whose "usual" e-cigarette was flavored with something other than tobacco was higher for Texas youth (97.9%) and young adults (96.7%) in Texas and nationwide (82.2%) compared to older adults nationwide (69.3%). Among current e-cigarette users, more Texas youth (72.9%) than young adult college students in Texas (57.4%) and young adults (64.8%) and adults (54.0%) nationwide cited using e-cigarettes because they "come in flavors I like."
Harrell, 2017b[65]	Cross-sectional survey Probability sample (youth) and convenience sample (young adults)	Chi-square tests used to test for differences between subgroups (sex and school/age level).	Roughly 3 out of every 4 youth (78%) and young adult (74%) flavored e-cigarette users said that they would not use an e-cigarette if it was not available in a flavored form (e.g., candy, fruit, mint/menthol). Significantly more young adult females than males reported that they would not use e-cigarettes if it were not flavored (77% vs 69%, p=.03).
Kim, 2016[28]	Cross-sectional laboratory experiment Convenience sample	One-way analysis of variance (ANOVA) used to examine differences between e-cigarette flavors in hedonic ratings and sensory attribute ratings; regression models used to examine	In terms of mean hedonic (liking/disliking) ratings of the 6 e-cigarette flavors, Pina Colada was liked significantly more than Classic Tobacco (p<.05). One-way ANOVAs found a significant main effect of e-cigarette flavors on sweetness (F = 14.56, p<.0001), coolness (F = 11.96, p<.00001), and bitterness (F = 3.56, p<.01), but not on

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		relative effects of flavor attributes on hedonic ratings.	harshness and own flavor. The four non-tobacco flavored e-cigarette samples were rated significantly sweeter than Classic Tobacco. Pina Colada was perceived as sweetest and liked the most; Classic Tobacco was perceived as least sweet and liked the least. Hedonic ratings were significantly positively correlated for sweetness for Pina Colada ($r = 0.36$, $p<.05$) and Peach Schnapps ($r= 0.56$, $p<.05$). Hedonic ratings were significantly positively correlated with coolness for Classic Tobacco, Magnificent Menthol, and Vivid Vanilla ($r = 0.41–0.52$, $p<.05$). Harshness ratings were significantly negatively correlated with hedonic ratings for Cherry Crush, Pina Colada, and Peach Schnapps ($r = 0.37–0.40$, $p<.05$). When regressing sensory attributes on hedonic ratings, sweetness and coolness had a positive contribution to liking and disliking of the six e-cigarette flavors, while bitterness and harshness had a negative contribution.
Kinouani, 2017[53]	Cross-sectional survey Convenience sample	Descriptive statistics used to describe reasons for trying e-cigarettes among current and former e-cigarette users, stratified by smoking status.	24.6 % of respondents reporting trying e-cigarettes because of the flavor, behind reasons of curiosity (77.4%) and because someone offered one to try (63.5%); there was no significant difference between men and women using for this reason (20.7% and 26.0%, respectively; $p=.07$). 28.6% of former smokers, 25.1% of current smokers, and 17.8% of never smokers tried e-cigarettes because of flavors.

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Kong, 2014[58]*	Cross-sectional survey Convenience sample	X^2 tests evaluated school level differences (middle school, high school, college) on all variables. Multinomial logistic regression analyses evaluated the extent to which reasons for e-cigarette experimentation differed based on cigarette smoking status.	43.8% of respondents reported the availability of flavors as a reason for experimentation with e-cigarettes. School level differences were observed ($X^2(2,N=1,157)=18.63$, $p\leq.001$), with high school students more likely to experiment with e-cigarettes because of appealing flavors compared to college students (47.0% vs 32.8%, $X^2(1,N=1,116)=13.61$, $p\leq.001$).
Krishnan-Sarin, 2014[60]*	Cross-sectional survey Convenience sample	Descriptive statistics explored flavors of e-cigarettes that had been tried and preferred.	Most lifetime e-cigarette users in middle school and high school, across cigarette smoking status, reported that they had tried and preferred sweet flavors compared to menthol and tobacco flavors.
Lee, 2017[56]	Cross-sectional survey Convenience sample	Multinomial logistic regression models and Heckman two-step selection procedures used to examine determinants that promote e-cigarette use acceptability.	A higher preference for the availability of flavors in e-cigarettes increased intention to use e-cigarettes (OR = 1.49) and likelihood of currently using e-cigarettes (OR = 1.82).
Lee, 2017b[36]	Cross-sectional survey Probability sample	Chi-square tests used to assess association between reason for using e-cigarettes and frequency of use.	9.3% of respondents reported using e-cigarettes "since they have good flavor," behind reasons of curiosity (22.9%), being potentially less harmful (18.9%), for smoking cessation (13.1%), for indoor use (10.7%), or being better tasting (9.6%).
Litt, 2016[66]	Two-phase longitudinal laboratory study	Multilevel modelling with maximum likelihood estimation used to evaluate effects of	The largest drop in cigarette smoking occurred among those assigned menthol e-cigarettes (smoking 4.0 per day by week 7), and the smallest drop in smoking occurred among those assigned cherry and chocolate flavors

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	Convenience sample	assigned e-cigarette flavor on use of usual cigarettes and e-cigarettes over 6-week study period.	(smoking 9.8 per day by week 7) (contrast: menthol vs all others: F(1, 3143) = 2.48; p<.05). E-cigarette vaping rates differed significantly by flavor assigned, with the highest vaping rates (about 12.3 vaping episodes per day) for tobacco e-cigarettes and the lowest rates for those assigned to chocolate (8.6 episodes per day) (contrast: tobacco vs chocolate: F(1, 3143) = 3.86; p<.001).
Maglalang, 2016[43]	Cross-sectional survey Convenience sample	Frequencies reported for preferred e-cigarette flavors and reasons for e-cigarette use.	Among current e-cigarette users who responded to the question (n=39), 8% cited "enjoying the flavor" as a reason for using e-cigarettes. This ranked the lowest behind use as a cessation aid or healthier alternative to conventional cigarettes; use for recreational/social reasons; use for stress relief/coping; and use for nicotine's highs.
Morean, 2018[64]	Cross-sectional survey Convenience sample	Chi-squares and independent samples t-tests used to examine differences in sex, age, smoking status, e-cigarette nicotine content, e-liquid flavor preferences, the total number of e-liquid flavors preferred, and e-cigarette use frequency; univariate general linear modeling used to examine associations between flavor preferences and total number of flavors preferred with e-cigarette use frequency	The most commonly preferred flavors among adults were fruit (40.0%), tobacco (32.0%) and menthol/mint (27.6%). Compared to adolescents, a larger percentage of adult e-cigarette users preferred tobacco, menthol/mint, coffee (16.6%), and spice (12.2%) flavor e-liquids. Adults preferred a greater total number of e-liquid flavors than did adolescents (M = 15.56, SD = 12.48 among adults compared to M = 9.98, SD = 10.52 among adolescents). The most commonly preferred flavors among adolescents were fruit (52.3%), candy/dessert (16.2%), and vanilla (11.4%). Compared to adults, more adolescents preferred fruit, alcohol (9.8%), and "other" flavored (2.0%) e-liquids or reported not knowing what their preferred flavor was (15.4%).

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		among adolescents and adults separately.	Adolescents who preferred to use fruit (ηp2 = 0.02, p = .003), dessert (ηp2 = 0.02, p=.007), and/or alcohol flavored e-liquids (ηp2 = 0.02, p=.002) reported using e-cigarettes more frequently. Among adolescents, the total number of e-cigarette flavors preferred was associated with e-cigarette frequency; preferring to use a greater number of e-cigarette flavors was associated with using e-cigarette on more days in the past month (ηp2 = 0.04, p<.001).
Nonnemaker, 2016[30]*	Cross-sectional survey Convenience sample	Calculated coefficients and corresponding 95% CIs for a series of multivariate linear regression models; regressed indicators for each characteristic on respondents' reported willingness to pay for an e-cigarette with a specific set of attributes	Among the full sample, removing the attribute "coming in flavors" significantly reduced the price respondents were willing to pay for an e-cigarette (p<0.05). Among cigarette-only users, losing the attribute "coming in flavors" significantly reduced the price respondents were willing to pay for an e-cigarette (p<.01); this relationship was not significant for dual users.
Patel, 2016[44]	Cross-sectional survey Probability sample	Wald tests and multivariate Poisson regressions used to assess differences in reasons for e-cigarette use across respondent characteristics.	Flavoring was the 5th most reported reason for using e-cigarettes (34.4%), behind cessation/health, consideration of others, convenience, and curiosity. Current e-cigarette users aged 18 to 24 years (adjusted prevalence ratio [aPR] = 2.02, 95% CI: 1.60–2.55), 25 to 34 years (aPR = 1.61, 95% CI: 1.30–2.01), and 35 to 54 years (aPR = 1.29, 95% CI: 1.08–1.54) were more likely to cite flavoring as a reason for use than those aged 55 years or older. The prevalence of citing flavoring as a reason for use was greater among current e-cigarette users living in the

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			South than those in the Northeast (aPR = 1.36, 95% CI: 1.01–1.83). Compared with current e-cigarette users who used disposables the most, tank users had a greater odds of citing flavoring as reason for use (aPR = 2.55, 95% CI: 1.97–3.32).
Pepper, 2013[48]*	Cross-sectional survey Probability sample	Logistic regression examined willingness to try any kind of e-cigarette (plain, flavored, or both).	The same proportion of respondents were willing to try plain e-cigarettes or to try flavored e-cigarettes (p=.15).
Pepper, 2014[55]*	Cross-sectional survey Probability and convenience sample	Descriptive statistics assessed reasons for first trying e-cigarettes.	Less than 10% of respondents reported starting e-cigarette use because "e-cigarettes come in flavors they like."
Pepper, 2016[22]	Cross-sectional survey Probability sample	Logistic regression models used to examine the effects of flavor condition on interest in trying e-cigarettes; linear regression models used to assess association between flavor and perceived harm.	Adolescents perceived fruit-flavored e-cigarettes to be less harmful than tobacco-flavored ones (mean 2.71 vs. 2.87, $\beta = -0.08$, $p<.05$). Adolescents reported that, if offered by a friend, they were more likely to try menthol-flavored (8.3%, OR = 4.00, 95% CI 1.46-10.97), candy-flavored (9.3%, OR = 4.53, 95% CI: 1.67-12.31) or fruit-flavored e-cigarettes (12.8%, OR = 6.49, 95% CI: 2.48-17.01) compared with tobacco-flavored e-cigarettes (2.2%). Perceptions of e-cigarette harm partly mediated the relationship between flavor and interest in trying e-cigarettes. Adolescents believed that menthol-flavored, candy-flavored or fruit-flavored e-cigarettes were less harmful than tobacco-flavored or alcohol flavored ones ($\beta = -0.15$, $p<.01$). Greater perceived harmfulness was

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			associated with less interest in trying e-cigarettes (OR = 0.31, 95% CI: 0.22-0.43).
Pesko, 2016[63]	Cross-sectional discrete choice experiment Convenience sample	Linear probability model estimated probability of choosing the e-cigarette option as a function of indicator variables for each attribute level.	Increased flavor availability increased e-cigarette selection for younger adults, from 17.5% to 21.9% (p<.001) but was not associated with a significant increase for older adults. Increased flavor availability increased e-cigarette selection for individuals that have not used vaping devices in the past month (p<.001) but was not associated with a significant increase in e-cigarette selection for individuals that have. Regardless of interest in quitting cigarettes, greater flavor availability increased e-cigarette selection. In linear probability models, greater flavor availability was associated with a 2.1 percentage point increase in e-cigarette selection (p<.001). In the interaction model, young adults were 3.7 percentage points more likely to choose e-cigarettes when multiple flavors were available compared to older adults (p<.001).
Russell, 2018[57]	Cross-sectional survey Convenience sample	Chi-square tests used to compare prevalence of first e-cigarette flavor purchased for each time period of first e-cigarette purchase; logistic regression analysis used to examine association between current use of tobacco-flavored e-liquids and fruit/fruit beverage flavored	Switchers (from regular cigarette smoking to regular e-cigarette use) (OR = 4.03, 95% CI: 3.26-4.97), dual users (OR = 4.14, 95% CI: 3.26-5.26), and former smokers (OR = 2.33, 95% CI: 1.85-2.93) were more likely than never smoker e-cigarette users to have initiated e-cigarette use with a tobacco-flavored product. Switchers (OR = 0.43, 95% CI: 0.38-0.49), dual users (OR = 0.41, 95% CI: 0.34-0.48), and former smoker (OR = 0.58, 95% CI: 0.50-0.67) e-cigarette users were all significantly less likely than never smoker e-cigarette users to

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		e-liquids and Tobacco Use Pathway Group and time of first e-cigarette purchase.	have initiated e-cigarette use with fruit-flavored products. The highest rate of current use of tobacco-flavored e-liquid was reported by those who initiated e-cigarette use ≥ 5 years ago; the lowest rate of current use of tobacco flavor was reported by those who initiated e-cigarette use in the past 12 months. The highest rate of current use of fruit/fruit beverage e-liquid flavors was among those who initiated e-cigarette use in the past 12 months, while the lowest rate was among those who initiated e-cigarette use ≥5 years ago; a similar effect of time since first e-cigarette purchase was found for current use of dessert/pastry flavors and for candy/chocolate/sweets flavors. As was observed for tobacco-flavored first e-cigarette purchases, switchers (OR = 2.18, 95% CI: 1.69-2.81), dual users (OR = 2.63, 95% CI: 1.97-3.51), and former smoker (OR = 1.54, 95% CI: 1.16-2.03) e-cigarette users all had significantly higher odds of current use of tobacco-flavored e-liquid compared to never smoker e-cigarette users. Switchers (OR = 0.64, 95% CI: 0.54-0.75), dual users (OR = 0.70, 95% CI: 0.57-0.86), and former smoker (OR = 0.70, 95% CI: 0.59-0.85) e-cigarette users were significantly less likely than never smoker e-cigarette users to be current users of fruit-flavored products.
Rutten, 2015[45]	Cross-sectional survey Probability sample	Logistic regression models used to assess association between reasons for use of e-cigarettes smoking	14.7% of smokers who also used e-cigarettes reported using e-cigarettes because of appealing flavors, behind eight other reasons including to quit smoking (58.4%), reduce smoking (57.9%), and to reduce the health risks of smoking (51.9%).

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		reduction behaviors.	Smoking reduction behaviors (i.e., decreased use of cigarettes or considered quitting) did not vary among those reporting using e-cigarettes because of appealing flavors vs. those that did not report using e-cigarettes because of appealing flavors.
Shang, 2017[59]	Cross-sectional discrete choice experiment Probability sample	Conditional logit regressions used to analyze the effects of flavors, warnings, and device types on the choice of using e-cigarettes.	For both e-cigarette ever and never users, fruit/sweets/beverage flavors marginally significantly increased ($p<.01$) the probability of choosing an e-cigarette product compared to tobacco flavor.
Shiffman, 2015[34]*	Cross-sectional survey Convenience sample	Comparisons of teen and adult respondents' ratings of their interest by flavor and comparisons of ratings by flavor within the adult sample by e-cigarette use status (recent user, past user, never user).	Adult smokers' e-cigarette ratings (overall mean=1.73±1.0 on a 0-10 scale) were significantly higher ($p<.0001$) than non-smoking teens' (overall mean=0.41±0.14) for each e-cigarette flavor. For each of the 15 flavors, adult smokers' interest in trying e-cigarettes was significantly higher than non-smoking teens' interest (all p values<.05, most p values<.0001).
Shiplo, 2015[47]*	Cross-sectional survey Convenience sample	Logistic regression models examined factors associated with use of flavors	Among current e-cigarette users, a common reason for use was taste (32.3% of younger non-smokers, 18.4% of younger smokers, 6.5% of older smokers).
Spears, 2018[40]	Cross-sectional survey Probability sample	Rao-Scott chi-square tests, independent samples t-tests of mean differences, and ordinal logistic regression used to examine associations between mental health condition	Compared to former smokers without mental health conditions, former smokers with mental health conditions gave higher importance ratings for appealing flavors as a reason for use ($t[79] = 3.83$, $p=.0001$).

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		and variables of interest.	
Tackett, 2015[70]*	Cross-sectional survey Convenience sample	Descriptive statistics examined preferred e-liquid flavors. Logistic regression, controlling for age and sex, was performed to assess associations between flavor (traditional tobacco/menthol vs non-traditional e.g., fruity, coffee, candy) on participants' biochemically verified smoking status.	E-cigarette users who reported using non-tobacco and non-menthol flavors were more likely to have quit smoking compared to those who vaped traditional (tobacco/menthol) flavors (OR=2.626, 95% CI=1.133-6.085, p=.024).
Tsai, 2018[37]	Cross-sectional survey Probability sample	Chi-square tests used to assess differences in reasons for e-cigarette use across groups.	Among students who reported ever using e-cigarettes, the second most commonly selected reason for use was availability of flavors such as mint, candy, fruit, or chocolate (31.0%), behind use by friend or family member (39.0%). High school students were more likely than middle school students to report the availability of flavors as a reason for e-cigarette use (32.3% vs. 26.8%, respectively; p<.05).
Vasiljevic, 2015[51]*	Cross-sectional survey Convenience sample	Mann-Whitney tests and logistic regression were used to assess exposure to advertisements and increase in ratings of appeal, interest in buying and trying e-cigarettes.	Exposure to the flavored e-cigarette ads increased interest in buying and trying e-cigarettes (Mann-Whitney test, U=9140.000, Z=−3.949, p<0.001), whereby those who saw the flavored e-cigarette ads expressed greater interest in buying and trying e-cigarettes (mean rank=176.44) than those who saw the non-flavored e-cigarette ads (mean rank=136.26).

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		Logistic regression was also used to examine exposure to advertisements and effects on susceptibility to smoking.	
Weaver, 2018[69]	Longitudinal survey Probability sample	Weighted logistic regression or weighted general linear models used to assess associations between e-cigarette use and outcomes, such as making a smoking quit attempt and 30-day smoking abstinence; both a complete-case analysis and a multiple-imputation approach used to account for missing data.	Among baseline daily smokers, both menthol/wintergreen/mint users and other flavor e-cigarette users were more likely to report a quit attempt (AORs = 6.0 and 2.4, respectively) than non-users of e-cigarettes, and menthol/wintergreen/mint users were more likely to report a quit attempt than tobacco/unflavored e-cigarette users in the past year ($p<.05$). Users of other e-cigarette flavors (e.g., fruit, dessert, spice; 8.8%; AOR = 0.22, 95% CI: 0.08–0.59) had significantly lower adjusted odds of quitting than non-users of e-cigarettes in the past year, which remained significant in multiple imputation analysis.
Yingst, 2015[61]*	Cross-sectional survey Convenience sample	T-tests and X^2 tests were used to identify differences between current first generation device (FGD) and advanced generation device (AGD) users. Descriptive statistics examined how respondents transitioned between devices.	Participants using an AGD were more likely to rate variety of flavor choices as important (FGD 54.6% vs AGD 94.9%, $p<.0001$).

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Supplementary Table 2. Risk of bias assessed by Quality Assessment Tool (QATSDD) (* indicates study was included in original 2016 review)

Note. [a] Percentage = the total score of a study / the full score 42 (14 items x 3 per item)

Study ID (Author, Year)	Amato, 2015[38]*	Audrain-McGovern 2016[26]	Barnes 2017[29]	Berg, 2016[42]*	Bold 2016[49]	Brozek, 2017[52]	Buckell, 2018[62]	Camenga 2017[71]	Chen 2017[50]	Chen 2018[31]	Clarke, 2017[21]	Coleman 2017[39]	Cooper 2016[24]	Czoli, 2016[35]*
Total score	35	22	27	29	26	24	31	26	25	29	31	28	37	31
%[a]	83%	52%	64%	69%	62%	57%	74%	62%	60%	69%	74%	67%	88%	74%
Explicit theoretical framework	0	1	0	0	0	0	0	0	0	0	3	0	2	3
Statement of aims/objectives in main body of report	3	2	3	3	3	3	3	3	3	3	3	3	3	3
Clear description of research setting	3	1	1	3	2	3	3	2	2	3	3	3	3	3
Evidence of sample size considered in terms of analysis	3	0	1	3	1	1	1	1	1	1	0	0	1	0
Representative sample of target group of a reasonable size	3	1	1	2	2	2	3	1	3	3	1	3	2	2
Description of procedure for data collection	3	3	3	3	3	1	3	3	1	3	2	3	3	3
Rationale for choice of data collection tool(s)	3	3	2	2	1	0	2	1	3	2	3	1	3	2
Detailed recruitment data	3	1	3	3	2	0	1	3	1	2	1	3	3	1
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	1	1	1	0	0	2	3	0	0	0	1	0	2	0
Fit between stated research question and method of data collection (Quantitative)	3	3	3	2	3	3	3	3	3	3	3	3	3	2
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Good justification for analytical method selected	1	3	3	2	3	3	3	3	2	3	3	3	3	3
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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Evidence of user involvement in design	3	0	0	0	0	1	0	0	0	0	2	0	3	3
Strengths and limitations critically discussed	3	0	3	3	3	2	3	3	3	3	3	3	3	3

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Study ID (Author, Year)	Dai 2016[25]	Elkami 2016[32]	Etter, 2010[33]*	Etter 2016[68]	Farsalinos, 2013[67]*	Farsalinos, 2014[54]*	Ford, 2016[23]*	Goldenson 2016[27]	Gubner 2018[41]	Harrell 2017[46]	Harrell 2017[65]	Kim 2016[28]	Kinouani 2017[53]	Kong, 2014[58]*	Krishnan-Sarin, 2014[60]*
Total score	31	33	20	27	16	19	32	22	28	31	27	28	27	31	26
% [a]	74%	79%	48%	64%	38%	45%	76%	52%	67%	74%	64%	67%	64%	74%	62%
Explicit theoretical framework	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Statement of aims/objectives in main body of report	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Clear description of research setting	3	3	3	3	3	3	3	2	3	3	3	3	3	3	3
Evidence of sample size considered in terms of analysis	0	2	1	3	0	0	3	1	0	1	0	1	0	1	1
Representative sample of target group of a reasonable size	3	1	2	1	1	2	3	1	2	2	2	1	1	3	3
Description of procedure for data collection	3	3	2	2	1	2	3	3	3	3	2	3	3	3	3
Rationale for choice of data collection tool(s)	2	3	1	2	1	1	2	2	2	3	2	3	2	3	0
Detailed recruitment data	3	3	1	1	1	1	1	1	3	3	2	1	3	3	3
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	1	2	0	0	0	0	0	0	0	1	1	1	0	0	0
Fit between stated research question and method of data collection (Quantitative)	3	3	2	3	1	2	3	3	3	3	3	3	3	2	2
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	2	3	2	2	3	3	3	3	3	3	3	3	3
Good justification for analytical method selected	3	2	1	3	1	1	3	3	3	3	3	3	3	3	3
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Evidence of user involvement in design	0	3	0	0	0	0	2	0	1	0	0	0	0	2	0
Strengths and limitations critically discussed	3	2	2	3	2	2	3	0	2	3	3	3	3	2	2

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Study ID (Author, Year)	Lee 2017[56]	Lee 2017[36]	Litt 2016[66]	Maglalang 2016[43]	Morean 2018[64]	Nonnemaker, 2016[30]*	Patel 2017[44]	Pepper, 2013[48]*	Pepper, 2014[55]*	Pepper 2016[22]	Russell 2018[57]	Rutten 2015[45]	Shang 2017[59]
Total score	32	28	27	27	26	24	34	35	34	28	24	32	27
% [a]	76%	67%	64%	64%	62%	57%	81%	83%	81%	67%	57%	76%	64%
Explicit theoretical framework	3	0	0	0	0	0	3	3	2	0	0	0	0
Statement of aims/objectives in main body of report	3	3	3	3	3	3	3	3	3	3	3	3	3
Clear description of research setting	3	3	3	3	3	3	3	3	3	2	3	1	
Evidence of sample size considered in terms of analysis	0	0	0	1	0	0	1	1	1	0	1	1	3
Representative sample of target group of a reasonable size	2	3	1	1	1	2	3	2	3	3	1	3	3
Description of procedure for data collection	3	3	3	3	3	3	3	3	2	3	3	3	2
Rationale for choice of data collection tool(s)	3	3	2	1	1	0	3	2	3	1	0	2	3
Detailed recruitment data	3	3	3	3	3	1	3	3	3	3	3	3	1
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	0	0	0	0	0	0	0	3	0	0	0	0	0
Fit between stated research question and method of data collection (Quantitative)	3	3	3	3	3	3	3	3	3	3	3	3	3
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	3	3	3	3	3	3	3	3	3	3	3
Good justification for analytical method selected	3	2	3	3	3	3	3	3	3	3	2	3	3
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-	-	-	-	-	-
Evidence of user involvement in design	0	0	0	0	0	0	0	0	2	0	0	2	0
Strengths and limitations critically discussed	3	2	3	3	3	3	3	3	3	3	3	3	2

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Study ID (Author, Year)	Shiffman, 2015[34]*	Shiplo, 2015[47]*	Spears 2018[40]	Tackett, 2015[70]*	Tsai 2018[37]	Vasiljevic, 2016[51]*	Weaver 2018[69]	Yingst, 2015[61]*
Total score	26	27	29	26	22	33	30	21
% [a]	62%	64%	69%	62%	52%	79%	71%	50%
Explicit theoretical framework	0	0	0	0	0	2	0	0
Statement of aims/objectives in main body of report	3	3	3	3	2	3	3	3
Clear description of research setting	3	3	3	3	3	3	3	2
Evidence of sample size considered in terms of analysis	2	3	0	3	1	3	1	0
Representative sample of target group of a reasonable size	1	2	3	1	3	2	3	2
Description of procedure for data collection	3	3	2	2	2	2	3	2
Rationale for choice of data collection tool(s)	2	0	2	2	0	3	2	1
Detailed recruitment data	3	3	3	2	0	1	3	3
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	1	0	1	0	0	3	0	0
Fit between stated research question and method of data collection (Quantitative)	1	2	3	3	3	2	3	3
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	3	3	3	3	3	2
Good justification for analytical method selected	1	2	3	2	2	1	3	1
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-
Evidence of user involvement in design	0	0	0	0	0	2	0	0
Strengths and limitations critically discussed	3	3	3	2	3	3	3	2

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

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The Impact of Non-Menthol Flavors in Tobacco Products in the United States: An Updated Systematic Review of Studies Published 2016-2018

Research Aims and Questions: To review the literature regarding the impact of non-menthol flavors in tobacco products on perceptions and use behaviors such as experimentation, initiation, preference, switch, progression to regular use, relapse and cessation.

Search Terms

Flavored tobacco products*:* All non-menthol flavored tobacco products

Population: General populations [Analyses will be separated by age: adults and youth; will tag non-US articles as "International"—may or may not be included in review update]

Language: English

Time period: Articles published between April 2016 and March 2018

General search terms*:* (1) Tobacco; (2) Flavor

PubMed search strategy with subject headings:

(electronic cigarettes[mesh] OR tobacco products[mesh] OR smoking[mesh]) AND flavoring agents[mesh]

General search strategy for all databases:

((smoke OR smoker OR smokers OR smokes OR smokings OR smoking OR cigarette OR cigarettes OR cigar OR cigars OR cigarillos OR cigarillo OR hookahs OR hookah OR waterpipe OR waterpipes OR narghile OR narghiles OR argila OR argiles OR tobacco OR tobaccos OR cigar* OR smoke* OR tobacco* OR ends OR "electronic nicotine delivery system*" OR vape OR vapor OR vapour OR vapours OR vapors OR vapor OR vapors OR vaping OR snus OR pipe OR pipes OR "e-cigarette" OR "e-cigarettes" OR bidi OR bidis OR kretek OR kreteks OR chewing tobacco OR snuff OR shisha OR "water pipe" OR "water pipes" OR goza OR narkeela OR "hubble bubble" OR hukkah OR hukkas OR hukka OR argileh)

AND

(flavor OR flavor* OR flavour OR flavour* OR flavors OR flavours OR flavoring OR flavouring OR flavorings OR flavourings OR flavoured OR flavoured OR flavoring OR flavorings OR flavouring OR flavourings OR flavouring OR flavoring OR flavourants OR flavorants))

OR

(kretek OR kreteks OR bidi OR bidis)

Search limiters, when available: English only, human subjects, peer reviewed articles, articles in press, conference papers, reviews; excluded dissertations

Research database to search: PubMed, Embase, CINAHL, and PsycInfo

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Domains	Search Terms
Flavored Tobacco	Flavored tobacco or tobaccos (excluding menthol) Smoking (not marijuana smoking) or smoke or smoker or smokers Flavored cigarette or cigarettes Cigar, Cigarillo or cigars or cigarillos Hookah, waterpipe or waterpipes or narghile or arghila ENDS, "electronic cigarette" or "electronic cigarettes" or e-cigarette or e-cigarettes or vape or vaper or vaping or vapour Smokeless tobacco, dissolvable tobacco, snus, bidis, kretek
Flavor	Flavored, flavor/flavour, flavoring/flavoring/flavouring, flavour/flavours, flavorint/flavourint, flavorant/flavourant
Outcome/Key Measures for Data Abstraction/Coding	**Abstracted Terms**
Populations	General US and non-US populations, separated by age: adults and youth; may exclude non-US articles at a later time
Age	Youth, children, minors, adolescent or adolescents "Young adults," "college students", "emerging adults"
Perceptions about flavors	Attitudes, reasons for use, attractiveness, health risks,
Experimentation	Try
Initiation	Uptake
Preference	Preferred, switch/change between flavored brands or between non-flavored and flavored brands
Progression to regular use	
Relapse	(use of tobacco products by former tobacco users)
Cessation	Quitting

Supplemental search:

Hand searches of the references from retrieved articles and solicitation from experts in the field

Study inclusion criteria:

Observational studies (cohort studies and cross-sectional studies) and experimental studies that assess the impact of non-menthol flavors in tobacco product consumption on perceptions and use behaviors such as initiation, experimentation, preference, switching, progression to regular use, and cessation

Study exclusion criteria:

Articles that do not contain original data about non-menthol flavored tobacco products, such as editorials, commentaries, literature reviews and information about regulations and/or policies

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Articles that are not peer-reviewed, such as technical reports, industry reports, dissertations/theses, conference papers

Articles that do not include appropriate dependent variables of interest

Articles that do not primarily address the impact of non-menthol flavors in tobacco products on perceptions and use behaviors of flavored tobacco products, such as biological/medical studies/chemical toxicology (non-human, animal studies), drug/substance/food studies

Articles that include smoking marijuana or menthol flavored tobacco product only

Articles that are non-English

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BMJ Open

The Impact of Non-Menthol Flavors in E-Cigarettes on Perceptions and Use: An Updated Systematic Review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031598.R1
Article Type:	Original research
Date Submitted by the Author:	02-Aug-2019
Complete List of Authors:	Meernik, Clare ; University of North Carolina at Chapel Hill, Epidemiology Baker, Hannah; University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center Kowitt, Sarah; University of North Carolina at Chapel Hill, Family Medicine Ranney, Leah; University of North Carolina at Chapel Hill, Family Medicine Goldstein, A; University of North Carolina at Chapel Hill, Family Medicine
Primary Subject Heading:	Public health
Secondary Subject Heading:	Smoking and tobacco
Keywords:	PUBLIC HEALTH, tobacco control, electronic cigarettes

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Manuscripts

The Impact of Non-Menthol Flavors in E-Cigarettes on Perceptions and Use: An Updated Systematic Review

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Objectives: Given the exponential increase in the use of e-cigarettes among younger age groups and in the growth in research on e-cigarette flavors, we conducted a systematic review examining the impact of non-menthol flavored e-cigarettes on e-cigarette perceptions and use among youth and adults.

Design: PubMed, Embase, PyscINFO, and CINAHL were systematically searched for studies published and indexed through March 2018.

Eligibility criteria: Quantitative observational and experimental studies that assessed the effect of non-menthol flavors in e-cigarettes on perceptions and use behaviors were included. Specific outcome measures assessed are: appeal, reasons for use, risk perceptions, susceptibility, intention to try, initiation, preference, current use, quit intentions, and cessation.

Data Extraction and Synthesis: Three authors independently extracted data related to the impact of flavors in tobacco products. Data from a previous review were then combined with those from the updated review for final analysis. Results were then grouped and analyzed by outcome measure.

Results: The review included 51 articles for synthesis, including 17 published up to 2016, and an additional 34 published between 2016-2018. Results indicate non-tobacco flavors in e-cigarettes decrease harm perceptions (5 studies) and increase willingness to try and initiation of e-cigarettes (6 studies). Among adults, e-cigarette flavors increase product appeal (7 studies) and are a primary reason many adults use the product (5 studies). The role of flavored e-cigarettes on smoking cessation remains unclear (6 studies).

Conclusions: This review provides summary data on the role of non-menthol flavors in e-cigarette perceptions and use. Consistent evidence shows that flavors attract both youth and adults to use e-cigarettes. Given the clear findings that such flavors increase product appeal, willingness to try, and initiation among youth, banning non-menthol flavors in e-cigarettes may reduce youth e-cigarette use. Longitudinal research is needed to examine any role flavors may play in quit behaviors among adults.

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Strengths and Limitations of the Study

- This large comprehensive review that included 51 final articles for synthesis, including 17 published up to 2016, and an additional 34 published between 2016-2018.
- The majority of studies were cross-sectional and were from convenience samples, limiting the ability to make causal inferences as well as the generalizability of findings from these articles.
- We used a quality assessment tool (QATSDD) to rate the quality of articles included in the review.
- Qualitative data, while excluded, could have provided additional contextual information to the conclusions.

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INTRODUCTION

Despite a ban on non-menthol flavors in cigarettes, current regulations in the United States allow for the sale of non-menthol flavors in other tobacco products, including e-cigarettes.[1] However, The FDA continues to seek out and prioritize research that explores the issue of non-menthol flavors in tobacco products other than cigarettes, and as such has issued an advance notice of proposed rulemaking seeking comments on the role that flavors play in tobacco product use.[2] Similarly, in fall of 2018 the FDA proposed a policy framework that would only allow non-menthol flavored e-cigarettes to be sold in age-restricted locations or online under heightened age verification standards.[3]

Some studies have shown that flavors are particularly appealing to youth and are cited as a primary reason for use among this age group.[4] The use of e-cigarettes among youth may be a gateway to future cigarette use,[5,6] and nicotine (which is found in most e-cigarettes) is especially harmful to developing adolescent brains.[7–9] This makes the recent precipitous increase in e-cigarette use among youth particularly alarming.[7] Policymakers, including the FDA, are increasingly concerned about the rise in popularity of pod-type e-cigarette devices (e.g. Juul), which now own a large market share and deliver more nicotine than older generations of e-cigarettes.[10,11]

E-cigarettes are also regarded by many experts in tobacco control as a potential means of harm reduction among adult smokers if they use e-cigarettes to transition away from combustible tobacco products.[12] A few studies have suggested a positive association between e-cigarettes and quitting behaviors, including a recent randomized controlled trial.[13–16] Unraveling the relationship between potential harms or benefits of e-cigarette use among adult smokers is important in the development of regulations for e-cigarettes, and in particular, regulations regarding product flavors.

It is well known that recent years have seen a precipitous increase in the use of e-cigarettes in the US and other countries among both youth and adults.[17] Recent data suggest that 20.8% of US youth[18] and 4.5% of US adults are current e-cigarette users.[19] These numbers vary globally, with 5.9% of adults and 8.2% of adolescents in Poland but only 0.3% of adults in Indonesia reporting current use.[20] However, upward trajectories of use have been noted globally,[20] and this increase in use has coincided with an exponential rise in e-cigarette flavors, with over 7,000 flavors existing.[21] Many of these flavors utilize names that may appeal to younger populations such as cotton candy, gummy bear, cookies ‘n cream, and other sweet-flavored brands.[21] The intense public health interest in e-cigarettes’ impact on the tobacco control landscape and population health has resulted in a sharp increase in research conducted on flavors and e-cigarettes. Given this changing landscape, we conducted a systematic review of non-menthol flavored e-cigarettes that extends previous research[4] by providing evidence specific to e-cigarettes about the role of non-menthol flavors in appeal, harm perceptions, intentions, use, and cessation among youth and adults in the US and globally.

METHODS

We used methods similar to previously published research,[4] and implemented two alterations: 1) updated the range of eligible publication dates (with the original including articles ever published until April 4, 2016, and the current review including articles published and indexed on or after April 4, 2016), and 2) focused this review specifically on e-cigarettes rather than all tobacco products, based on the precipitous increase in literature on e-cigarettes, as well as the increase in use of these products among youth and adults. All data relevant to the study are included in the article or uploaded as supplementary information.

Eligibility criteria

We included observational and experimental studies that assessed the impact of non-menthol flavors in e-cigarettes on perceptions and use behaviors such as initiation, preference, and cessation. We did not

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exclude studies based on participant characteristics. Studies included populations of any age, race, sex, ethnicity, or country.

We excluded the following types of articles: those that were not English-language; were not peer-reviewed (e.g., dissertations, technical reports); did not contain original data about flavored e-cigarettes (e.g., editorials, commentaries, literature reviews); did not address the impact of flavors on e-cigarette perceptions and use behaviors (e.g., biological/medical/chemical toxicology/animal studies, sales trends, effects of flavor bans); were related to smoking marijuana; or limited findings to menthol flavored e-cigarettes only. In order to maintain a semblance of consistency across studies examined, we chose to exclude articles that used qualitative study designs. Additionally, because menthol and tobacco are often treated differently as it relates to policy implementation (e.g., in 2009, FDA banned characterizing flavors except for tobacco and menthol in cigarettes) and is also often viewed separately from other flavors in the literature, this review excludes articles that examine just menthol as a flavor.[22]

Type of outcome measures and intervention

Outcome measures include perceptions about appeal, reasons for use, and risk perceptions; susceptibility and intentions to try; and use behaviors, including initiation, preference, current use, quit intentions, and cessation.

Data sources and study selection

Literature search. One author (HMB) conducted searches of PubMed, Embase, PsycINFO and CINAHL for studies published and indexed in a database between April 4, 2016 and March 21, 2018. To maintain consistency with the previous systematic review, we maintained the same search string rather than modifying the search to include only e-cigarettes. We used Boolean language to connect variants of words related to tobacco products, use, and flavor for PubMed, which was translated to match the search string requirements for other databases. A total of 3,191 articles resulted from searching the four databases during the initial search (March 21, 2018). After authors removed duplicates, 2,822 articles remained for title and abstract review, including 14 articles identified through manual search of references.

Study selection. Two authors (CM and HMB) reviewed the titles and abstracts of all 2,822 articles. A third author (SDK) resolved any discrepancies. Following this step, two authors (CM and HMB) reviewed the full text of all 114 articles eligible for full-text screening. A third author (SDK) resolved any discrepancies. 80 articles were excluded for the following reasons: they did not have data on the specified outcomes (n=27), used qualitative methodologies (n=27), focused on a tobacco product other than e-cigarettes (n=12), were only focused on menthol flavor (n=2), was a duplicate (n=1), or were not peer-reviewed, did not include original data, did not include full-text, or included only a conference abstract (n=11). Articles that addressed e-cigarettes from the original systematic review (n=17) were then added to the 34 articles identified from this current review, combining for a total of 51 articles included in the final analysis. The study selection processes, which approximate but do not exactly follow the PRISMA methodology, are illustrated in Figure 1.[23]

Data extraction and synthesis

For the articles identified in the most current review, three authors (CM, HMB, SDK) independently extracted data using a data extraction sheet, which assessed study aim, type of flavored tobacco product, characteristics of study populations and study design, and main results and findings related to the impact of flavors in tobacco products. We used a validated quality assessment tool (QATSDD) to examine the quality of quantitative studies with a diverse range of research designs.[24] Studies were scored on a 4-point scale from 0 (did not address criteria at all) to 3 (completely addressed criteria), with specified guidance to inform scorers based on the level of detail provided by study authors.[24] Specific scores were not used for inclusion/exclusion or used in any analysis. Rather, the tool was used to provide a valuable overall assessment of the general quality of included studies from which our conclusions are

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based. To ensure agreement in data extraction and quality assessment, three authors (CM, HMB, SDK) reviewed and extracted the same three articles, then compared results of review and extraction, resolving discrepancies through an iterative approach of discussion. Once mutual standards were decided upon based on this process, each of the three authors then split up the remainder of articles to extract and assess on their own. We created evidence tables using pertinent information extracted from each study, and we grouped the results by outcome measures. A similar procedure was conducted in the previous review, and all data were combined for final data analysis. A meta-analysis was not conducted due to the heterogeneity in outcomes across studies.

Patient and public involvement

This research did not include input from patients or the public.

RESULTS

The review included 51 final articles for synthesis, including 17 published up to 2016 and 34 published between 2016-2018. Most studies included adults only (n=30), though 13 included youth and eight included both youth and adults (Table 1).

Table 1. Characteristics of included studies (N=51)

Sample characteristics		N (%)	US Studies (N=37), N (%)	International Studies (N=14), N (%)
Population	Youth only	13 (25)	9 (24)	4 (29)
	Adults only	30 (59)	22 (59)	8 (57)
	Both youth and adults	8 (16)	6 (16)	2 (14)
Design	Cross-sectional	47 (92)	33 (89)	14 (100)
	Longitudinal	4 (8)	4 (11)	0 (0)
Sampling (not mutually exclusive)	Convenience	35 (69)	23 (62)	12 (86)
	Probability	19 (37)	17 (46)	2 (14)
Outcome measure (not mutually exclusive)	Taste, appeal, perceived risk	14 (27)	10 (27)	4 (29)
	Reasons for use	13 (25)	11 (30)	2 (14)
	Susceptibility, intention to try/initiation	17 (33)	11 (30)	6 (43)
	Preference	9 (18)	7 (19)	2 (14)
	Current use behaviors	12 (24)	10 (27)	2 (14)
	Quit intention/quitting behavior	10 (20)	7 (19)	3 (21)

Results of this review are broken out into three age categories: youth, adults, and youth and adults combined. Studies defined these age groups differently, and we therefore used the age groups as defined by the study authors. Most youth were defined as anyone below age 18 (though some went up to age 19[25]), and most adults were defined as 18+. Additionally, though young adults are an important population and were included as a separate age group in some studies in the review, the variability in definitions of this age group made it difficult to separate for purposes of the results, (some defining as ages 19-34, some as ages 18-29, etc.) and we therefore included all young adults in the adult category. Specific age groups used by authors can be found in Table 2.

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Table 2. Sample characteristics and objectives of included articles (* indicates study was included in original 2016 review)

Study ID (Country)	Sample size and study population	Study aim	Main findings on flavors' impact
Amato, 2015[26] (US)*	n=9,301 Adults (18+) Tobacco users and non-users	Investigate patterns of e-cigarettes' use in order to establish a standard definition of e-cigarette current use prevalence for the purpose of population surveillance.	Current e-cigarette users cited flavors as a reason for use more often than past users.
Audrain-McGovern, 2016[27] (US)	n=32 Young adults (18-30) Current cigarette smokers and had ever used an e-cigarette	Determine whether flavoring enhances the subjective rewarding value, relative reinforcing value, and absolute reinforcing value of an e-cigarette with nicotine compared to an unflavored e-cigarette with nicotine.	E-cigarette flavoring enhanced the rewarding and reinforcing value of e-cigarettes with nicotine compared to unflavored e-cigarettes with nicotine.
Barnes, 2017[28] (US)	n=36 Adults (18+) Current cigarette smokers naïve to e-cigarettes	Examine e-cigarettes' abuse liability compared to conventional tobacco cigarettes that varied in e-cigarette flavor and modified-risk message.	Cherry flavor increased abuse liability relative to unflavored e-cigarettes (i.e., increased the degree to which e-cigarettes led to physical/psychological dependence).
Berg, 2016[29] (US)*	n=1,567 Young adults (18-34) E-cigarette users, non-users; cigarette users, non-users	Compare (1) e-cigarette never, current, and former users; (2) never, current, and former traditional cigarette smokers in relation to e-cigarette use characteristics, flavors preferred and reasons for use; and (3)	Flavors were frequently indicated as reason for use across smoking and non-smoking e-cigarette users

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		reasons for discontinued use among former e-cigarette users across never, current, and former smokers.	
Bold, 2016[30] (US)	n=340 Youth (middle school and high school students) Ever e-cigarette users	Investigate whether certain reasons for trying e-cigarettes would predict continued use over time.	Good flavors were highly endorsed by youth as a reason for trying e-cigarettes; in univariate models, endorsing good flavors as a reason for trying e-cigarettes predicted continued e-cigarette use and e-cigarette frequency, but was no longer a significant predictor after adjusting for other covariates including cigarette smoking status.
Brozek, 2017[31] (Poland)	n=46 Adults (18-35) E-cigarette users	Assess prevalence of e-cigarette and tobacco cigarette use; to compare the patterns of smoking; and to assess the attitudes and motivations for e-cigarette use.	More than one-fourth of e-cigarette users started using e-cigarettes because of the unique flavors.
Buckell, 2018[32] (US)	n=2,031 Adults (18-64) Current cigarette smokers or recent quitters	Estimate preferences for flavors in cigarettes and e-cigarettes while controlling for other attributes of both products, and study how these preferences vary with individual characteristics.	Among e-cigarette flavors, adult smokers preferred tobacco flavor over fruit/sweet and menthol flavors; younger adult smokers, those with a higher education, and those with a recent quit attempt prefer all flavors of e-cigarettes compared to tobacco cigarettes.
Camenga, 2017[33] (US)	n=189 Youth (14-18) and young adults (18-24)	Examine the prevalence and predictors of current and former smokers' use of e-cigarettes for smoking cessation.	Preference for using a combination of two or more e-cigarette flavors mixed together was associated with increased odds of using e-cigarettes for smoking cessation, relative to e-

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	Lifetime cigarette smokers and ever e-cigarette users		cigarette users without a preferred flavor.
Chen, 2017[34] (US)	n=18,392 Youth (11-18) Non-smokers	Explore association between e-cigarette use and smoking susceptibility among non-smoking youth.	Flavored e-cigarette use was associated with increased smoking susceptibility among non-smoking youth, particularly among females and those not susceptible to tobacco marketing.
Chen, 2018[35] (US)	n=4,645 Young adults (18-34) Current cigarette smokers at Wave 1	Examine differences in smoking reduction and cessation among young adult smokers who did not use e-cigarettes, who used e-cigarettes with tobacco and menthol/mint flavors, and who used e-cigarettes with one or multiple non-tobacco and non-menthol flavors.	Compared to non-e-cigarette users, users of non-tobacco/menthol e-cigarette flavors were more likely to have reduced or quit smoking cigarettes in the past year; current e-cigarette users highly endorsed using e-cigarettes because of appealing flavors, with those endorsing this reason for use more than twice as likely to have reduced or quit smoking in the past year than e-cigarette users who did not endorse this reason for use.
Clarke, 2017[25] (UK)	n=256 Youth (16-19) Tobacco users and non-users	Investigate factors that lead to willingness to try e-cigarettes among UK youth.	Youth reported a preference for non-tobacco flavored e-cigarettes, regardless of smoking status; youth with a more positive prototype of smokers were more willing to try flavored e-cigarettes, while youth with a more negative prototype of e-cigarette users were less willing to try flavored e-cigarettes.
Coleman, 2017[36] (US)	n=3,373 Adults (18+)	Examine patterns of current e-cigarette use among daily and non-daily adult users.	Appealing flavors were highly cited as a reason for e-cigarette use, particularly among never smokers; more frequent e-cigarette users

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	Current e-cigarette users		(daily vs. moderate or infrequent) were more likely to initiate with a non-tobacco flavored e-cigarette.
Cooper, 2016[37] (US)	n=3,704 Youth (grades 6, 8, and 10) Tobacco users and non-users	Evaluate harm perceptions and perceived addictiveness of e-cigarettes among youth.	Youth who were ever or current e-cigarette users had higher odds of reporting flavored e-cigarettes as less harmful than non-e-cigarette users.
Czoli, 2015[38] (Canada)*	n=915 Youth and young adults (16-24) and adults (25+) Users and non-users (youth and young adults) and users (adults)	Determine the effect of distinct attributes of e-cigarettes (flavors, nicotine content, health warnings, price) and attribute levels on consumer choice.	Flavors in e-cigarettes significantly predicted lower perceptions of product harm and ability to help someone quit smoking.
Dai, 2016[39] (US)	n=21,491 Youth (middle and high school students) Tobacco users and non-users	Examine the 1) association between flavored e-cigarette use and intention to initiate cigarette smoking among never-smoking youth, 2) association between flavored e-cigarette use and intention to quit tobacco use in the next 12 months among current youth smokers, and 3) association between flavored e-cigarette use and youth perception of the danger of tobacco.	Compared with not using e-cigarettes, flavored e-cigarette use was associated lower perceived harm of tobacco, higher intention to initiate cigarette use among never smoking youth, and lower quit intentions among current smoking youth.

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Elkalmi, 2016[40] (Malaysia)	n=277 Primarily adults (18+) but 7.2% of sample was 17 or younger Tobacco users and non-users	Determine the prevalence of current e-cigarette use and identify sociodemographic factors, motivators, attitudes, and perceptions that are associated with current e-cigarette use.	The majority of respondents who had tried e-cigarettes reported that the variety of flavors contributed to more enjoyment of the product compared to conventional cigarettes.
Etter, 2010[41] (France, Belgium, and other countries)*	n=81 Adults (18+) Current e-cigarette users	Assess usage patterns of e-cigarettes, reasons for use and users' opinions of these products.	Adult e-cigarette users reported flavors as being the most positive feature of the product.
Etter, 2016[42] (France, US, Switzerland, UK, and other countries)	n=1,685 Adults (18+) Current e-cigarette users	Describe personal characteristics of vapers, their utilization patterns, any modifications of the devices, and compare users of pre-filled cartridges, refillable tanks, and modified models for their patterns of use, reasons for use, satisfaction, and perceived effects on smoking.	Tobacco flavor was reported to be the most preferred e-cigarette flavor among current users, particularly among those who had recently started vaping; most respondents reported that flavors helped them to either quit smoking or reduce their smoking consumption.
Farsalinos, 2013[43] (Online survey in 10 languages)*	n=4,618 Adults (18+) E-cigarette users	Examine the patterns and perceptions of flavoring use in e-cigarettes among dedicated users.	E-cigarette users who were former smokers were more likely to prefer fruit and sweet flavors compared to current smokers. E-cigarette users reported that the variability of e-cigarette flavors is an important factor in reducing or quitting cigarette smoking and a greater number of flavors

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			used was associated with smoking abstinence.
Farsalinos, 2014[44] (Online survey in 10 languages)*	n=19,441 Adults (18+) E-cigarette users	Assess the characteristics and experiences of a large, worldwide sample of e-cigarette users and examine the differences between those who partially and completely substituted smoking with e-cigarette use.	The variability of flavors was cited as one of the reasons for initiating e-cigarette use, though it was not a primary reason.
Ford, 2016[45] (UK)*	n=1,205 Youth (11-16) Tobacco users and non-users	Examine adolescents' awareness of e-cigarette marketing and investigate the impact of e-cigarette flavor descriptors on perceptions of product harm and user image.	Fruit and sweet flavors were perceived as more likely to be tried by young never smokers than adult smokers trying to quit. The perceived harmfulness of e-cigarettes was moderated by product flavors.
Goldenson 2016[46] (US)	n=20 Young adults (19-34) Current e-cigarette users	Assess whether sweet flavorings and nicotine affect e-cigarette appeal; sweet flavorings increase perceived sweetness; nicotine increases throat hit; and perceived sweetness and throat hit are associated with appeal.	Sweet-flavored e-cigarette solutions increased appeal (including liking, willingness to use again, and amount willing to pay) and perceived sweetness ratings.
Gubner 2017[47] (US)	n=168 Adults (18+) Weekly or daily e-cigarette users	Examine e-cigarette use by individuals in treatment for substance abuse.	A large proportion of daily and weekly e-cigarette users reported using e-cigarettes because they have good flavors; daily e-cigarette users were more likely to use more types of flavors compared to weekly users.
Harrell, 2017a[48] (US)	n=3,907 youth n=5,482 young adults	Investigate whether the use of flavored e-cigarettes varies between youth, young adults, and adults.	Initiation with and current use of flavored e-cigarettes was higher among youth and young adults compared to older adults, and citing flavor

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	n=6,051 adults Youth (12-17), young adults (18-29), and adults (30+) Tobacco users and non-users		availability as a reason for use was higher among youth current users relative to young adults and older adults.
Harrell, 2017b[49] (US)	n=143 youth and n=1,325 young adults Youth (12-17) and young adults (18-29) Current tobacco product users	Determine the potential for reductions in the prevalence of young people's e-cigarette and tobacco use if characterizing flavors were not present.	The large majority of youth and young adult current tobacco users reported use of flavored e-cigarettes, and about three-fourths of flavored e-cigarette users reported they would no longer use the product if it was not flavored.
Kim, 2016[50] (US)	n=31 Adults (18+) Current e-cigarette users	Examine the extent to which the perception of sweet and other flavors is associated with liking and disliking of flavored e-cigarettes.	Flavors influenced hedonic ratings of e-cigarettes, such that, in general, sweetness and coolness were positively associated with liking while bitterness and harshness were negatively associated with liking of e-cigarettes.
Kinouani, 2017[51] (France)	n=1,086 University students (18+; more than 90% 18-24) Ever e-cigarette users	Describe the relationship between e-cigarette use and tobacco smoking and describe reasons for experimenting with e-cigarettes.	The third most cited reason for trying e-cigarettes was because of attractive flavors, behind reasons of curiosity and offered to try by someone.
Kong, 2014[52] (US)*	n=1,157	Assess reasons for e-cigarette experimentation and	Availability of flavors was a primary reason for experimentation with e-

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	Youth and young adults E-cigarette users	discontinuation and examine whether these reasons differed by school level (MS, HS, college) and cigarette smoking status.	cigarettes, and appealing flavors were particularly important to high school students.
Krishnan-Sarin, 2014[53] (US)*	n=4,780 Youth (middle school and high school students) Tobacco users and non-users	Examine e-cigarette awareness, use patterns, susceptibility to future use, preferences, product components used, and sources of marketing and access among youth.	Use and preference for sweet e-cigarette flavors was high among adolescents regardless of cigarette smoking status.
Lee, 2017a[54] (US)	n=1,185 Young adults (18-25) Tobacco users and non-users	Investigate the characteristics of potential and current e-cigarette users based on four different levels of use acceptability and determinants that promote e-cigarette acceptability.	A higher preference for the availability of flavors in e-cigarettes was associated with experimentation and current use of e-cigarettes among college students.
Lee, 2017b[55] (South Korea)	n=6,656 Youth (13-18) Ever e-cigarette users	Determine the relation between frequency of e-cigarette use and the frequency and intensity of conventional cigarette smoking; and identify the association between reasons for e-cigarette use and frequency of use.	Nearly 1 in 10 youth cited good flavors as the main reason for using e-cigarettes, though this reason ranked behind five others, including curiosity and potentially being less harmful.
Litt, 2016[56] (US)	n=88 Adults (18-55) Cigarette smokers	Examine the influence of flavoring on the smoking and vaping behavior of cigarette smokers asked to adopt e-cigarettes for 6 weeks.	Cigarette smoking frequency was most reduced in participants assigned to menthol-flavored e-cigarettes, while it was least reduced in those assigned to cherry and chocolate flavors; participants

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			assigned to tobacco-flavored e-cigarettes had the highest rates of vaping, while those assigned to chocolate had the lowest rates of vaping.
Maglalang, 2016[57] (US)	n=56 Asian American and Pacific Islander young adults (18-25) Current e-cigarette users	Characterize e-cigarette use and risk perceptions among Asian American and Pacific Islander young adults in California.	Fruit and candy/sweet flavors were most preferred by current e-cigarette uses, though citing flavors as a reason for using e-cigarettes was reported by a low percentage of respondents, behind a variety of other reasons.
Morean, 2018[58] (US)	n=396 adolescents and n=590 adults Adolescents (high school students) and adults (18+) Past-month e-cigarette users	Examine differences in adolescents' and adults' preferences for e-liquid flavors and whether their preferences or the total number of flavors preferred were associated with number of days of e-cigarette use in the past month.	Compared to adults, adolescents were more likely to prefer e-liquid flavors such as fruit, candy/dessert, and vanilla, while adults were more likely to prefer tobacco, menthol/mint, coffee, and spice flavors. Among adolescents (though not adults), preferences for particular e-liquid flavors (i.e., fruit, dessert, or alcohol flavored) and the total number of flavors preferred were associated with more frequent e-cigarette use.
Nonnemaker, 2016[59] (US)*	n=765 Adults (18+) Current or former smokers	Examines how e-cigarette attributes influence willingness to pay for e-cigarettes.	Losing flavors significantly reduced the price participants are willing to pay for e-cigarettes, though this relationship was not found for dual users of cigarettes and e-cigarettes.
Patel, 2016[60] (US)	n=2,448 Adults (18+)	Assess reasons for e-cigarette use among current e-cigarette users.	Reasons for e-cigarette use among current adult users varied by sociodemographic and user characteristics; notably, flavorings were more

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	Current e-cigarette users		likely to be cited as a reason for use among younger age groups (ages 18-24, 25-34, and 35-54).
Pepper, 2013[61] (US)*	n=228 Youth (11-19), males Tobacco users and non-users	Sought to understand awareness of and willingness to try e-cigarettes among adolescent males.	Flavored e-cigarettes did not increase male adolescents' willingness to try e-cigarettes compared to plain varieties.
Pepper, 2014[62] (US)*	n=3,878 Adults (18+) Tobacco users and non-users	Explore reasons for starting and then stopping e-cigarettes use and examine differences in discontinuation by reason for trying among population-based sample of US adults.	Few adult e-cigarette users reported starting e-cigarette use because of the available flavors.
Pepper, 2016[63] (US)	n=1,125 Youth (13-17) Tobacco users and non-users	Examine the impact of flavor on interest in trying e-cigarettes and harm beliefs.	Adolescents were more interested in trying menthol, candy, or fruit-flavored e-cigarettes than tobacco or alcohol flavors; belief that these particular flavors were less harmful than tobacco or alcohol flavors party mediated this relationship.
Pesko, 2016[64] (US)	n=1,020 Adults (18+) Current cigarette smokers	Determine the preferences and relative importance placed on e-cigarette warning labels, flavor regulation, and prices.	Restriction of flavor availability in e-cigarettes to tobacco and menthol was associated with a significant reduction in e-cigarette selection, particularly among young adults compared to older adults.
Russell, 2018[65] (US)	n=20,836 Adults (18+) Frequent e-cigarette users	Examine flavor preferences of frequent e-cigarette users.	Adults are increasingly initiating e-cigarette use with non-tobacco flavors, particularly fruit and dessert flavors; never smoker e-cigarette users were more likely to initiate with and

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			currently use fruit/fruit beverage-flavored e-cigarettes compared to switchers, dual users, and former smoker e-cigarette users.
Rutten, 2015[66] (US)	n=582 Adults (18+) Current dual users of cigarettes and e-cigarettes	Assess attitudes, beliefs, and behaviors relating to e-cigarette use among current cigarette smokers.	Dual users of cigarettes and e-cigarettes ranked appealing flavors relatively low on the list of reasons for using e-cigarettes; no differences in smoking quit intentions or reduction in the use of cigarettes was observed for those reporting using e-cigarettes because of flavors compared to those not reporting using e-cigarettes because of the flavors.
Shang, 2017[67] (US)	n=515 Youth (14-17) Tobacco users and non-users	Understand how different attributes (flavors, health warnings, device types) influence youth's decisions to choose e-cigarettes.	Among youth ever and never e-cigarette users, fruit/sweet/beverage flavors increased the probability that a youth chose an e-cigarette product.
Shiffman, 2015[68] (US)*	n=216 (youth) n=432 (adults) Youth (13-17) Adults (19-80) Non-users (youth) and users (adult)	Compare e-cigarettes interest between nonsmoking teens and adult smoker, across flavors and assess differences in flavor preferences among adult smokers based on e-cigarettes use history.	The interest of nonsmoking teens in trying flavored e-cigarettes was very low, and interest was not influenced by flavor descriptors. Though adult smokers' interest was also modest, their interest was significantly higher than that of nonsmoking teens for each flavor.
Shiplo, 2015[69] (Canada)*	n=1,095 Youth and young adults (16-24)	Examines e-cigarette ever and current use, types of products used, and reasons for use.	Use of flavored e-cigarettes varies by smoking status, with smokers being more likely to try flavors than non-smokers. A common reason

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	Adults (25+) Non-smokers and smokers (youth and young adults) and smokers (adults)		for e-cigarette use is for the taste.
Spears, 2018[70] (US)	n=550 Adults (18+) Current e-cigarette users	Examine reasons for e-cigarette use and related risk perceptions among individuals with and without mental health conditions.	Compared to former smokers without mental health conditions, former smokers with mental health conditions placed higher importance on appealing flavors as a reason for e-cigarette.
Tackett, 2015[71] (US)*	n=215 Adults (18+) E-cigarette users	Estimate e-cigarettes preference, e-cigarettes use behaviors, perceived harm and health beliefs of various smoking cessation medications, nicotine replacement therapies and nicotine/tobacco products, and smoking history and current biochemically verified smoking status.	Most e-cigarette users reported a preference for vaping non-traditional flavors. Those who reported vaping non-tobacco and non-menthol flavors were more likely to have quit smoking compared to those who vaped traditional (tobacco/menthol) flavors.
Tsai, 2018[72] (US)	n=4,049 Youth (grades 6-12) Ever e-cigarette users	Assess self-reported reasons for e-cigarette use among middle school and high school student e-cigarette users.	One of the primary reasons for e-cigarette use by middle school and high school students was the availability of flavors, particularly among high school students.
Vasiljevic, 2015[73] (UK)*	n=471 Youth (11-16) Non-e-cigarette users	Assess the impact on appeal of tobacco smoking after exposure to advertisements for e-cigarettes with and without candy-like flavors.	Flavored, compared to non-flavored, e-cigarette advertisements elicited greater interest in buying and trying e-cigarettes.

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Weaver, 2018[74] (US)	n=858 Adults (18+) Current cigarette smokers	Assess the effect of "real world" e-cigarette use on population quit rates of adult smokers, accounting for frequency of use, device type, e-liquid flavor, and reasons for use.	Compared to non-e-cigarette users, users of menthol/wintergreen/mint or other non-tobacco/menthol flavor e-cigarettes (e.g., fruit, dessert, spice) were more likely to report a quit attempt, but users of other non-tobacco/menthol e-cigarette flavors had significantly lower odds of quitting smoking than non-users of e-cigarettes in the past year.
Yingst, 2015[75] (US and other countries)*	n=421 (87% in US; 13% outside US) Adults (18+) E-cigarette users	Examine the frequency with which e-cigarette users transition between device types and identify device characteristics and user preferences that may influence such transitions.	Most e-cigarette users began use with a device shaped like a cigarette (first generation devices) and transitioned to a larger advanced generation device with a more powerful battery and a wider choice of liquid flavors. Advanced generation device e-cigarette users report the variety of flavors as being important characteristic of e-cigarettes.

72% (n=37) of included studies were conducted in the US. While four studies used longitudinal designs, most (n=47; 92%) were cross-sectional. Study populations, aims, and relevant outcomes are provided in Table 2, with more detailed descriptions of analytical methods and results included in Supplementary Table 1.

Taste, appeal, and risk perceptions

Youth

Four studies surveyed probability samples of youth and assessed harm perceptions of e-cigarettes, all observing similar results. Three studies of youth in the US (two national samples and one state-wide sample) and one national sample of youth in the UK found that perceptions of e-cigarette harm differed depending on the product flavoring. Specifically, fruit and candy-flavored e-cigarettes were perceived as less harmful than tobacco-flavored e-cigarettes,[45,63] and ever or current e-cigarette users were less likely than non-users to perceive flavored e-cigarettes or tobacco as harmful.[37,39]

Adults

Eight studies were conducted among adults, including three laboratory experiments and one discrete choice experiment that examined the effect of e-cigarette flavors on factors such as ratings of taste and appeal.[27,28,46,50] Four studies included relatively small convenience samples of adults, each finding similar results: flavors in e-cigarettes enhanced the rewarding and reinforcing value of e-cigarettes compared to unflavored e-cigarettes,[27] and the appealing sensory characteristics of flavors (i.e.,

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sweetness and coolness) were positively associated with liking of the product,[46,50] the willingness to use again, and an increase in amount willing to pay for the product.[28,46] Similarly, in a cross-sectional survey of 765 current or former adult smokers, removal of flavors significantly reduced the price respondents were willing to pay for e-cigarettes, though this association was not observed among dual users of cigarettes and e-cigarettes.[59] One study in the US and two international studies likewise found that among ever or current e-cigarette users, the taste and variety of flavors were positive features of e-cigarettes and contributed to increased enjoyment of the product.[35,40,41]

Youth and Adults

Two studies examined appeal and harm perceptions in convenience samples of youth and adults. A sample of 216 youth and 432 adults in the US found that adult smokers rated interest toward e-cigarettes significantly higher than non-smoking teens for each e-cigarette flavor examined (note: study was funded by an e-cigarette company).[68] One discrete choice experiment in Canada (n=915) found that e-cigarette flavor significantly predicted lower perceptions of product harm; specifically, in the overall sample, menthol and coffee flavors were perceived as less harmful; among younger non-smokers, coffee-flavored was perceived as less harmful, while younger smokers perceived cherry flavor as less harmful and older smokers perceived tobacco-flavored as less harmful.[38]

Reasons for use

Youth

Two national probability samples of youth examining reasons for e-cigarette use found varied results. Less than 10% of South Korean youth who ever used e-cigarettes reported using the product because of good flavors,[55] compared to roughly a third of US students reporting ever using e-cigarettes because of the availability of flavors, with high school students more likely than middle school students to report flavors as a reason for use.[72]

Adults

Nine studies in the US examined reasons for using e-cigarettes among adults, also finding varied results. Three probability samples (two national and one state-wide) found that a majority of current e-cigarette users cited appealing flavors as a reason for using e-cigarettes,[26,35] particularly among never cigarette smokers compared to current and former smokers.[36] Another national probability sample in the US (n=550) found that former smokers with mental health conditions placed a higher importance on appealing flavors as a reason for use compared to former smokers without mental health conditions.[70] Further, about 40% of daily and weekly e-cigarette users (n=168) at substance use treatment centers reported good flavors as a reason for using e-cigarettes.[47] Among a convenience sample of 1,567 young adults, roughly a third of those who were non-e-cigarette users reported appealing flavors as a reason for possible e-cigarette use in the future, while a majority of current e-cigarette users reported appealing flavors and the ability to experiment with a variety of flavors as reasons for use.[29] Three other studies in the US (two national probability samples and one small convenience sample) observed relatively low proportions of current adult e-cigarette users reporting using e-cigarettes because of product flavorings, behind a variety of other reasons for use,[57,60,66] though flavors were more likely to be cited as a reason for use among younger age groups, particularly young adults ages 18-24, and among users of tank devices compared to disposables.[60]

Youth and Adults

Two studies in the US and Canada among youth and adults found that citing flavor availability or taste as a reason for e-cigarette use was higher among younger e-cigarette users compared to older users.[48,69]

Susceptibility, intention to try, and initiation

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Youth

Seven studies in the US and the UK examined susceptibility, intention to try, or initiation of e-cigarettes among youth. One study of a national probability sample of 228 adolescent males in the US found no differences in willingness to try flavored e-cigarettes compared to plain e-cigarettes.[61] However, the other six studies reported positive associations between flavors and e-cigarette use intentions. In a convenience sample of 340 youth in the US who were ever e-cigarette users, more than 40% endorsed good flavors as a reason for first trying e-cigarettes, the second highest endorsed reason.[30] Similarly, in a convenience sample of 256 UK youth, cigarette smokers and non-smokers were more willing to try flavored e-cigarettes than tobacco-flavored e-cigarettes (90% vs. 73% and 34% vs. 12%, respectively); further, having a positive prototype of smokers was associated with increased willingness to try flavored e-cigarettes.[25] Three different studies using national probability samples of US youth found similar relationships between flavors and e-cigarette use susceptibility and intentions to use. Adolescents were more likely to try menthol-, candy-, or fruit-flavored e-cigarettes compared to tobacco-flavored e-cigarettes;[63] and flavored e-cigarette use among non-smoking youth was associated with increased intention to initiate cigarette use[39] and smoking susceptibility, particularly among females and those not susceptible to tobacco marketing.[34] Finally, a convenience sample of 471 non-e-cigarette using youth in the UK found that exposure to flavored e-cigarette ads, compared to non-flavored e-cigarette ads, increased interest in buying and trying e-cigarettes.[73]

Adults

Six studies conducted in the US and internationally examined intention to try or initiation of e-cigarettes among adults. Two studies using convenience samples of young adults in Poland (n=46) and France (n=1,086) both found roughly 25-30% of e-cigarette users tried or started using e-cigarettes because of the variability of flavors, though other reasons for initiation were rated more highly than flavors.[31,51] Similarly, among an online convenience sample of international e-cigarette users (n=19,441) (note: study was funded by an e-cigarette advocacy group) and among a combined probability and non-probability sample of US adults (n=3,878), the availability of appealing flavors was not frequently cited as a reason for e-cigarette initiation.[44,62] However, two convenience samples of US adults found that the availability of flavors in e-cigarettes was associated with increased intention to use the product among young adult college students,[54] and never smoker e-cigarette users were more likely to have initiated e-cigarette use with a fruit-flavored product compared to switchers (from regular cigarette smoking to regular e-cigarette use), dual users, and former smoker e-cigarette users.[65]

Youth and Adults

Four studies examined interest in trying and initiation of e-cigarettes among youth and adults. One study of 648 youth and adults in the US observed that adult smokers' interest in trying e-cigarettes was significantly higher than non-smoking teens' interest for all 15 e-cigarette flavors investigated (note: study was funded by an e-cigarette company).[68] However, the three other studies conducted found similar results in that youth and younger adults in Canada expressed more interest in trying non-tobacco-flavored e-cigarettes than older adults;[38] high school students in the US were more likely to experiment with e-cigarettes because of flavors compared to college students, with 40% of the overall sample (n=1,157) reporting the availability of flavors as a reason for experimentation with e-cigarettes;[52] and youth and young adults reported higher initiation with flavored e-cigarette use compared to tobacco-flavored e-cigarettes.[48]

Preference

Youth

In three studies of youth, one discrete choice experiment of 515 e-cigarette ever and never users in the US found that fruit, sweet, and beverage flavors increased the probability (relative to tobacco flavor) of choosing an e-cigarette product.[67] A national probability sample of 1,205 UK youth examined how youth perceive others to use e-cigarettes; youth perceived adult smokers who were trying to quit smoking

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as less likely to prefer cherry, candy floss, or coffee flavored e-cigarettes, whereas youth perceived adolescents their age to be more likely to try flavored e-cigarettes compared to tobacco-flavored.[45] Further, a convenience sample of 4,780 middle school and high school students in the US found that most ever e-cigarette users—regardless of cigarette smoking status—had tried and preferred sweet flavors compared to menthol and tobacco flavors.[53]

Adults

Four studies examined preference among adults in relation to e-cigarette flavors. One international study of 421 e-cigarette users found that those using an advanced generation e-cigarette device were more likely to rate a variety of flavor choices as important, relative to users of first-generation devices.[75] A laboratory experiment of a small convenience sample of adults in the US observed that ever e-cigarette users took twice as many puffs from flavored e-cigarettes compared to unflavored e-cigarettes.[27] Further, a discrete choice experiment of 2,031 adults in the US found that adult smokers preferred tobacco-flavored e-cigarettes to fruit/sweet and menthol flavors,[32] while another discrete choice experiment of 1,020 adults observed that increased flavor availability increased e-cigarette selection for younger cigarette smokers, but not for older smokers.[64] Additionally, regardless of interest in quitting cigarettes, greater flavor availability increased e-cigarette selection.[64]

Youth and Adults

Two convenience samples of US youth and adults found that, compared to adult e-cigarette users, adolescent users were more likely to prefer e-cigarette flavors such as fruit and alcohol, while adults were more likely to prefer tobacco, menthol/mint, coffee, and spice flavors; further, adult users preferred a greater number of e-cigarette flavors than adolescents.[58] Among 1,468 youth and young adults currently using tobacco, most reported use of flavored e-cigarettes, and roughly three-quarters of those reported they would not use e-cigarettes if they were not available in a flavored form, such as candy, fruit, or mint/menthol.[49]

Current use behaviors

Youth

Two studies among US youth examined e-cigarette use behaviors. In a longitudinal study of 340 ever e-cigarette users, youth who initiated e-cigarette use because of good flavors were more frequent users of e-cigarettes, though this association was no longer significant after adjustment for other covariates.[30] Additionally, in a national probability sample of 18,395 never smoking youth, those who used e-cigarettes three or more days in the past 30 days were more likely to be flavored e-cigarette users than those who had used e-cigarettes only one or two days in the past 30 days.[34]

Adults

Eight studies among adults examined current e-cigarette use behaviors in relation to flavors. A two-phase longitudinal laboratory study of 88 current cigarette smokers in the US assigned e-cigarettes to participants as substitution for cigarettes; the highest vaping rates were observed for those assigned to tobacco flavored e-cigarettes, and the lowest rates were observed for those assigned to chocolate-flavored.[56] A convenience sample of 168 e-cigarette users found that daily e-cigarette users reported using more types of flavors and were more likely to have used tobacco flavor or fruit/berry flavor compared to weekly users,[47] while a national probability sample of 4,645 young adults in the US found that users of non-tobacco/menthol flavors were more likely to vape daily compared to tobacco/menthol flavored e-cigarette users,[35] Another national probability sample of 3,373 current e-cigarette users in the US found that daily e-cigarette users were more likely to have initiated with a non-tobacco flavored e-cigarette, compared to moderate or infrequent e-cigarette users.[36] A convenience sample of 1,185 college students in the US found that a higher preference for the availability of flavors in e-cigarettes was associated with a higher likelihood of currently using e-cigarettes.[54] One international survey of 4,618 e-cigarette users showed that users who were former smokers were more likely to prefer fruit and sweet

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flavors compared to current smokers (note: study was promoted by an e-cigarette advocacy group).[43] Another survey of 1,685 e-cigarette users found that tobacco flavor was used by nearly half of the respondents who had started vaping the past three months, compared to only a quarter of those who had been vaping for at least four months.[42] Lastly, a convenience sample of 20,836 frequent e-cigarette users in the US found that the highest rate of current tobacco-flavored e-cigarette use was reported by those who initiated e-cigarettes five or more years ago, while the lowest rate of tobacco-flavored e-cigarette use was reported by those who initiated within the past year; those who initiated in the past year had the highest rate of fruit, dessert, and candy/sweet flavored e-cigarette use, and never smoker e-cigarette users were more likely to use fruit-flavored products and less likely to use tobacco-flavored products compared to ever cigarette smokers.[65]

Youth and Adults

Two studies of youth and adults in the US reported similar findings related to a preference for flavors among younger e-cigarette users. Nearly all youth and young adult current users (a probability and convenience sample in Texas and nationwide) reported a usual e-cigarette that was flavored with something other than tobacco (97-98%), compared to roughly 70% of older adults.[48] Similarly, a survey of 986 adolescents and adults in the US found that adolescents who preferred to use fruit, dessert, or alcohol-flavored e-cigarettes reported using e-cigarettes more frequently, and preferring to use a greater number of flavors was associated with using the product more frequently in the past month, though these relationships were not seen among adult e-cigarette users.[58]

Quit intentions and quitting behavior

Youth

In regards to smoking cessation, one national probability sample of 21,491 youth in the US found that among current smokers, students who reported using flavored e-cigarettes were less likely to quit tobacco use compared with those who reported not using e-cigarettes or with those who had used non-flavored e-cigarettes.[39]

Adults

Seven studies examined the relation between flavors in e-cigarettes and quit intentions and quitting behavior among adults, finding varied results. One longitudinal study of 4,645 young adult cigarette smokers in the US found that e-cigarette users who used at least one non-tobacco/menthol flavor were more likely to have reduced or quit smoking cigarettes in the past year compared to non-e-cigarette users, and e-cigarette users who reported using e-cigarettes because of appealing flavors were more than twice as likely to have reduced or quit smoking compared to those who did not endorse using e-cigarettes for that reason.[35] Another longitudinal study of 858 cigarette smokers in the US similarly found that users of non-tobacco flavor e-cigarettes (e.g., fruit, dessert, spice) were more likely than non-e-cigarette users to report a quit attempt in the past 12 months; however, users of non-tobacco/menthol flavors were less likely to have quit smoking compared to non-e-cigarette users.[74] In a two-phase longitudinal laboratory study among 88 cigarette smokers, cigarette smoking frequency was most reduced in participants assigned to menthol-flavored e-cigarettes, while it was least reduced in those assigned to cherry or chocolate flavored e-cigarettes.[56] Two international surveys of current e-cigarette users both found that e-cigarette flavors were an important factor in helping to reduce or quit cigarette smoking,[42,43] and the number of e-cigarette flavors used was associated with smoking abstinence (note: study was promoted by an e-cigarette advocacy group).[43] Further, a convenience sample of 215 e-cigarette users in the US found that e-cigarette users reporting use of non-tobacco/menthol flavors were more likely to have quit smoking compared to those vaping tobacco/menthol flavors,[71] while a national probability sample of 582 dual users in the US found no differences in smoking quit intentions or smoking reduction for those reporting using e-cigarette because of the flavors compared to e-cigarette users not endorsing use of e-cigarettes for that reason.[66]

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Youth and Adults

Two studies among youth and adults examined quit intentions and behaviors. A discrete choice experiment of 915 Canadian tobacco users and non-users observed that menthol and coffee flavored e-cigarettes were perceived as having a greater quit efficacy.[38] In a convenience sample of 189 youth and young adult ever e-cigarette users in the US, preference for using a combination of at least two e-cigarette flavors mixed together was associated with increased likelihood of using e-cigarettes to quit smoking, relative to not having a preferred e-cigarette flavor.[33]

Quality assessment

We used a validated quality assessment tool (QATSDD) to examine the quality of studies with a diverse range of research designs.[24] In this quality assessment tool, there are 14 criteria and each criterion is rated on a 4-point scale (0-3), with a maximum score of 42. Because the studies examined in this review use a variety of methodological approaches, the QATSDD tool was chosen as it was developed specifically for this purpose and has been shown to provide valid, reliable assessments of study quality.[24] Studies were scored on the criteria listed below, and all scores and criteria can be found in Supplementary Table 2. Quality assessment scores relative to the maximum score possible ranged from 38% to 88% with a mean score of 66%. Nearly all studies sufficiently detailed their aims and objectives, the research setting, recruitment and data collection, the fit between their research question and method of data collection and analysis, justification for their analytical method, and the study strengths and limitations (see QATSDD scores in Supplementary Table 2). However, few studies reported an explicit theoretical framework, user involvement in study design (e.g., cognitive interviewing of survey measures), evidence of sample size consideration, or statistical assessment of reliability and validity of measurement tools. A low score on these criteria do not necessarily mean that the study authors did not consider it (e.g., power calculations that were not reported); rather, the criteria was not sufficiently described in the manuscript. Of note, three studies were funded or promoted by the e-cigarette industry or e-cigarette user advocacy groups.[43,44,68]

DISCUSSION

Given the sharp increase in both the use of e-cigarettes (particularly among youth) and the amount of new research related to e-cigarettes and flavors published from 2016-2018 alone, this systematic review provides a necessary update of a previous review that included research on e-cigarettes and non-menthol flavors among youth and adults.[4] This synthesis of evidence regarding the role of non-menthol flavors in e-cigarettes on product perceptions and use is particularly relevant to the FDA's recently proposed policy framework that seeks to place additional regulations on the sale of non-menthol flavored e-cigarettes to youth.[3] 17 studies examining flavors in e-cigarettes were published up to 2016; from 2016-2018, 34 new studies were published, *doubling* the research in just two years.

This new review significantly expands earlier findings about e-cigarettes and flavor among youth and adults. The previous review showed initial evidence that flavors in e-cigarettes were primary reasons for willingness to try or use the products. This expanded systematic review includes emerging longitudinal data and adds evidence on the role of flavors in e-cigarettes among youth and adults. Among youth, flavors increase not only preferences for e-cigarettes, but they also increase e-cigarette product appeal, willingness to use, susceptibility to use, and initiation, as well as decrease e-cigarette product harm perceptions. Among adults, the expanded research now shows that e-cigarette flavors increase product appeal and enjoyment, and the availability of flavors are a primary reason for use for many adults. Further, our quality review process provides important insight for researchers in this field to improve the rigor of e-cigarette research and includes essential information on study sample size and the reliability or validity of measures.

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Findings highlight the following: youth prefer non-tobacco flavored e-cigarettes;[49,53,58,67] flavors—particularly sweet flavors such as fruit and candy—decreased perceived product harm;[37–39,45,63] and the availability of appealing flavors is associated with an increased willingness to try e-cigarettes, initiation of e-cigarettes, and susceptibility to cigarette smoking.[25,30,34,39,63,73] Findings specific to adults are more varied, but demonstrate that non-menthol flavors in e-cigarettes increase appeal, enjoyment, and the price users are willing to pay for the product[27,35,40,41,46,50,59] and are a primary reason many adults use e-cigarettes.[26,29,35,36,47,70] Evidence on whether non-menthol flavored e-cigarettes promote or disrupt cessation among adult smokers remains unclear.[35,42,43,56,71,74]

Given that non-menthol flavors available in e-cigarettes attract youth to use these products, the impetus for policymakers to address the issue is strong. Results from the current review make it clear that banning flavors in e-cigarettes would discourage youth use of these products; however, doing so may also discourage adult smokers from using e-cigarettes for smoking cessation.[76] It is also important to consider the context in which each of these studies was conducted; because this review included results from both US and global studies, policies may differ and individual cultural contexts around e-cigarette use may have affected the outcomes.

Policy action at the federal level regarding flavored tobacco products has recently been undertaken, with the FDA seeking to limit the sale of non-menthol flavored e-cigarettes to age-restricted locations and heightening age verification practices for products sold online.[3] Also of note in that same announcement is FDA's consideration of banning menthol in cigarettes, which would significantly impact the tobacco control landscape.[3] FDA's recent proposed action appears to be affecting manufacturers; the tobacco company Altria recently announced they would halt the sale of multiple e-cigarette products they produce, including flavored products,[77] and Juul Labs also announced a suspension of its non-menthol flavored e-cigarettes in retail stores.[78] In the meantime, states and localities have the authority to restrict the sale of flavored tobacco products, including flavored e-cigarettes. A comprehensive review of flavored e-cigarette regulations from 2017 showed that at the time, over 100 localities had implemented restrictions on the sale of flavored e-cigarettes.[79] Movement has continued to be made on this topic since that review; for instance, San Francisco passed a measure to ban the sale of all flavored tobacco products,[80] including e-cigarettes, in 2018. Jurisdictions globally have taken steps to more broadly regulate flavors in all tobacco products, recognizing their impact on youth.[17,81] This is in accordance with the 2010 WHO Framework Convention on Tobacco Control guidelines that recommends restricting or banning flavors in all tobacco products.[82]

Based on the results of this review, it is important to consider deficits in the literature that would assist policymakers in developing the most impactful regulations. For one, it is important to note that the literature does not have a consistent and standardized way to categorize flavors. Yingst and colleagues (2017) have attempted to identify such a classification system, which, if used by researchers, would allow results to be more easily compared across studies.[83] This would also assist policymakers in regulating flavors more easily, as it is possible that some categories of flavors may be more appealing to youth than others. Similarly, because much of the research uses varying categories to examine age, it makes it difficult to disaggregate the effects flavors have on different age groups. Doing so would especially be helpful to policymakers who are trying to create regulations that would have the most impact on youth initiation while maintaining the potential for adult harm reduction, though more research is needed to explore the latter. Furthermore, use of the QATSDD tool reveals deficits in the existing literature. Few studies provided evidence of sample size consideration or commented on the reliability or validity of their measurement tools. Reviewing these types of parameters before publishing may ensure that researchers are providing the most rigorous explanation of their research as possible. Finally, since so few longitudinal studies are present, it may be beneficial for researchers to use such data sets as PATH to show longitudinal trends in the outcomes presented in this review, in an effort to strengthen the existing body of literature with longitudinal data.

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Limitations

Our review is limited in several ways. First, relevant articles may have been missed due to the exclusion of grey literature, doctoral dissertations, and non-English language articles; articles published within the search period (before March 2018) may also have been missed if they were not indexed in one of the searched databases by the time of the search. Similarly, we excluded qualitative articles in order to maintain consistency in data reviewed, though we recognize that qualitative data could potentially provide important contextual information on this topic. Second, a minimum threshold for study quality was not set, though only three studies received a score lower than 50% on the quality assessment (with scores of 48%, 45%, and 38%), and the mean score of all studies was 66%. Further, three studies were funded or supported by the e-cigarette industry or user advocacy groups.[43,44,68] Findings from these studies, and studies scoring lower in study quality, should be interpreted with caution. Third, more than 90% of studies were cross-sectional in nature, preventing us from making causal inferences between flavors and the perceptions and use of flavored e-cigarettes. Future research using longitudinal designs could further elucidate the role of flavors, particularly their effect on behavioral outcomes such as initiation among youth and cessation among adult smokers. Fourth, nearly half of all studies were conducted with convenience samples in the US, limiting the generalizability of findings, though nearly 40% of all studies did use probability-based sampling. Lastly, as research on e-cigarette flavors continues to evolve and additional research is regularly published, periodic updates of this review will be needed.

Conclusions

This systematic review provides a necessary update and extension of all evidence published to date on the role of flavors in e-cigarette perceptions and use behaviors. The increasing evidence among youth is clear: flavors in e-cigarettes (particularly sweet flavors) increase product appeal, decrease product harm perceptions, and increase willingness to use and initiation of e-cigarettes. Similarly, findings among adults demonstrate that flavors increase product appeal and enjoyment, and the availability of flavors are a primary reason for use for many adults. As the role of e-cigarettes in smoking cessation—and particularly how flavors impact this relationship—remains unclear, longitudinal studies of adult smokers are needed to assess the effect that e-cigarettes may have promoting or disrupting efforts to reduce or quit cigarette use. Regardless, findings are clear that banning flavors in e-cigarettes would discourage youth use of these products.

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REFERENCES

1. U.S. Food and Drug Administration. Menthol and Other Flavors in Tobacco Products. https://www.fda.gov/tobaccoproducts/labeling/productsingredientscomponents/ucm2019416.htm. Published 2018. Accessed July 24, 2018.
2. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to reduce tobacco use, especially among youth, by exploring options to address the role of flavors – including menthol – in tobacco products. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM601690.htm?utm_source=Eloqua&utm_medium=email&utm_term=StratComms&utm_content=pressrelease&utm_campaign=CTP News%26Connect%26SOS%3A ANPRM Flavors—32018. Published 2018. Accessed October 9, 2018.
3. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on proposed new steps to protect youth by preventing access to flavored tobacco products and banning menthol in cigarettes. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-proposed-new-steps-protect-youth-preventing-access. Published 2018. Accessed May 3, 2019.
4. Huang L-L, Baker HM, Meernik C, Ranney LM, Richardson A, Goldstein AO. Impact of non-menthol flavours in tobacco products on perceptions and use among youth, young adults and adults: A systematic review. *Tob Control*. 2017;26(6). doi:10.1136/tobaccocontrol-2016-053196
5. Bold KW, Kong G, Camenga DR, et al. Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth. *Pediatrics*. 2018;141(1).
6. Chaffee BW, Watkins SL, Glantz SA. Electronic Cigarette Use and Progression From Experimentation to Established Smoking. *Pediatrics*. 2018;141(4). doi:10.1542/peds.2017-3594
7. U.S. Department of Health and Human Services. *E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta, GA; 2016. https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf. Accessed July 27, 2018.
8. Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. *J Physiol*. 2015;593(16):3397-3412. doi:10.1113/JP270492
9. England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the Developing Human: A Neglected Element in the Electronic Cigarette Debate. *Am J Prev Med*. 2015;49(2):286-293. doi:10.1016/j.amepre.2015.01.015
10. Goniewicz ML, Boykan R, Messina CR, Eliscu A, Tolentino J. High exposure to nicotine among adolescents who use Juul and other vape pod systems ('pods'). *Tob Control*. 2018;0:1-2. doi:10.1136/tobaccocontrol-2018-054565
11. Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tob Control*. 2018:1-6. doi:10.1136/tobaccocontrol-2018-054382
12. Warner KE, Mendez D. E-cigarettes: Comparing the Possible Risks of Increasing Smoking Initiation with the Potential Benefits of Increasing Smoking Cessation. *Nicotine Tob Res*. 2018:1-7. doi:10.1093/ntr/nty062
13. Hajek P, Phillips-Waller A, Przulj D, et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N Engl J Med*. 2019;380(7):629-637. doi:10.1056/NEJMoa1808779
14. Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *BMJ*. 2016;354:i4645. doi:10.1136/bmj.i4645
15. Bullen C, Knight-West O. E-cigarettes for the management of nicotine addiction. *Subst Abuse Rehabil*. 2016;7:111-118. doi:10.2147/SAR.S94264
16. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction (Review). *Cochrane Libr*. 2014;12(CD010216).

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doi:10.1002/14651858.CD010216.pub2.www.cochranelibrary.com
17. Kennedy RD, Awopegba A, De León E, Cohen JE. Global approaches to regulating electronic cigarettes. *Tob Control*. 2017;26:440-445. doi:10.1136/tobaccocontrol-2016-053179
18. Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students — United States, 2011–2018. *Morb Mortal Wkly Rep*. 2018;67(45):1276-1277. doi:10.15585/mmwr.mm6745a5
19. Mirbolouk M, Charkhchi P, Kianoush S, et al. Prevalence and Distribution of E-Cigarette Use Among U.S. Adults: Behavioral Risk Factor Surveillance System, 2016. *Ann Intern Med*. 2018;169(7):429. doi:10.7326/M17-3440
20. Breland A, Soule E, Lopez A, Ramôa C, El-Hellani A, Eissenberg T. Electronic cigarettes: what are they and what do they do? *Ann N Y Acad Sci*. 2017;1394(1):5-30. doi:10.1111/nyas.12977
21. Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. *Tob Control*. 2014;23(January):iii3-iii9. doi:10.1136/tobaccocontrol-2014-051670
22. U.S. Food and Drug Administration. Family Smoking Prevention and Tobacco Control Act - An Overview. https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/family-smoking-prevention-and-tobacco-control-act-overview. Published 2018. Accessed July 24, 2019.
23. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:doi:10.1371/journal.pmed.1000097
24. Sirriyeh R, Lawton R, Gardner P, Armitage G. Reviewing studies with diverse designs: The development and evaluation of a new tool. *J Eval Clin Pract*. 2012;18(4):746-752. doi:10.1111/j.1365-2753.2011.01662.x
25. Clarke TN, Lusher JM. Willingness to Try Electronic Cigarettes Among UK Adolescents. *J Child Adolesc Subst Abuse*. 2017;26(3):175-182. doi:10.1080/1067828x.2016.1242098
26. Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tob Control An Int J*. 2016;25:ii62-ii66. doi:10.1136/tobaccocontrol-2016-053174
27. Ford A, MacKintosh AM, Bauld L, Moodie C, Hastings G. Adolescents' responses to the promotion and flavouring of e-cigarettes. *Int J Public Health*. 2016;61(2):215-224. doi:10.1007/s00038-015-0769-5
28. Cooper M, Harrell MB, Perez A, Delk J, Perry CL. Flavorings and Perceived Harm and Addictiveness of E-cigarettes among Youth. *Tob Regul Sci*. 2016;2(3 PG-278-289):278-289. doi:10.18001/trs.2.3.7
29. Dai H, Hao J. Flavored electronic cigarette use and smoking among youth. *Pediatrics*. 2016;138(6):e2016513. doi:10.1542/peds.2016-2513
30. Audrain-McGovern J, Strasser AA, Wileyto EP. The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers. *Drug Alcohol Depend*. 2016;166(PG-263-267):263-267. doi:10.1016/j.drugalcdep.2016.06.030
31. Goldenson NI, Kirkpatrick MG, Barrington-Trimis JL, et al. Effects of sweet flavorings and nicotine on the appeal and sensory properties of e-cigarettes among young adult vapers: Application of a novel methodology. *Drug Alcohol Depend*. 2016;168:176-180. doi:10.1016/j.drugalcdep.2016.09.014
32. Kim H, Lim J, Buehler SS, et al. Role of sweet and other flavours in liking and disliking of electronic cigarettes. *Tob Control*. 2016;25:ii55-ii61. doi:10.1136/tobaccocontrol-2016-053221
33. Barnes AJ, Bono RS, Lester RC, Eissenberg TE, Cobb CO. Effect of Flavors and Modified Risk Messages on E-cigarette Abuse Liability. *Tob Regul Sci*. 2017;3(4):374-387. doi:10.18001/trs.3.4.1
34. Nonnemaker J, Kim AE, Lee YO, MacMonegle A. Quantifying how smokers value attributes of electronic cigarettes. *Tob Control An Int J*. 2016;25:e37-e43. doi:10.1136/tobaccocontrol-2015-052511

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

35. Chen JC. Flavored E-cigarette Use and Cigarette Smoking Reduction and Cessation—A Large National Study among Young Adult Smokers. *Subst Use Misuse*. 2018;53(12):2017-2031. doi:10.1080/10826084.2018.1455704
36. Elkalmi RM, Bhagavathul AS, Ya'u A, et al. Familiarity, perception, and reasons for electronic-cigarette experimentation among the general public in Malaysia: Preliminary insight. *J Pharm Bioallied Sci*. 2016;8(3):240-247. doi:10.4103/0975-7406.180768
37. Etter J-F. Electronic cigarettes: a survey of users. *BMC Public Health*. 2010;10(231). doi:10.1186/1471-2458-10-231
38. Shiffman S, Sembower MA, Pillitteri JL, Gerlach KK, Gitchell JG. The impact of flavor descriptors on nonsmoking teens' and adult smokers' interest in electronic cigarettes. *Nicotine Tob Res*. 2015;17(10):1255-1262. doi:10.1093/ntr/ntu333
39. Czoli CD, Goniewicz M, Islam T, Kotnowski K, Hammond D. Consumer preferences for electronic cigarettes: Results from a discrete choice experiment. *Tob Control*. 2016;25(E1):e30-e36. doi:10.1136/tobaccocontrol-2015-052422
40. Lee JA, Lee S, Cho HJ. The Relation between Frequency of E-Cigarette Use and Frequency and Intensity of Cigarette Smoking among South Korean Adolescents. *Int J Env Res Public Heal*. 2017;14(3 PG-). doi:10.3390/ijerph14030305
41. Tsai J, Walton K, Coleman BN, et al. Reasons for Electronic Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(6 PG-196-200):196-200. doi:10.15585/mmwr.mm6706a5
42. Amato MS, Boyle RG, Levy D. How to define e-cigarette prevalence? Finding clues in the use frequency distribution. *Tob Control*. 2016;25(E1):e24-e29. doi:10.1136/tobaccocontrol-2015-052236
43. Coleman BN, Rostron B, Johnson SE, et al. Electronic cigarette use among US adults in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2014. *Tob Control*. 2017;26(e2):e117-e126. doi:10.1136/tobaccocontrol-2016-053462
44. Spears CA, Jones DM, Weaver SR, Pechacek TF, Eriksen MP. Motives and perceptions regarding electronic nicotine delivery systems (ENDS) use among adults with mental health conditions. *Addict Behav*. 2018;80:102-109. doi:10.1016/j.addbeh.2018.01.014
45. Gubner NR, Pagano A, Tajima B, Guydish J. A comparison of daily versus weekly electronic cigarette users in treatment for substance abuse. *Nicotine Tob Res*. 2018;20(5):636-642. doi:10.1093/ntr/ntx116
46. Berg CJ. Preferred Flavors and Reasons for E-cigarette Use and Discontinued Use Among Never, Current, and Former Smokers. *Int J Public Health*. 2016;61(2):225-236. doi:10.1007/s00038-015-0764-x
47. Maglalang DD, Brown-Johnson C, Prochaska JJ. Associations with E-cigarette use among Asian American and Pacific Islander young adults in California. *Prev Med Rep*. 2016;4:29-32. doi:10.1016/j.pmedr.2016.05.011
48. Patel D, Davis KC, Cox S, et al. Reasons for current E-cigarette use among U.S. adults. *Prev Med (Baltim)*. 2016;93:14-20. doi:10.1016/j.ypmed.2016.09.011
49. Rutten LJ, Blake KD, Agunwamba AA, et al. Use of E-Cigarettes Among Current Smokers: Associations Among Reasons for Use, Quit Intentions, and Current Tobacco Use. *Nicotine Tob Res*. 2015;17(10):1228-1234. doi:10.1093/ntr/ntv003
50. Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. *Prev Med Reports*. 2017;5:33-40. doi:10.1016/j.pmedr.2016.11.001
51. Shiplo S, Czoli CD, Hammond D. E-cigarette use in Canada: Prevalence and patterns of use in a regulated market. *BMJ Open*. 2015;5(8):1-7. doi:10.1136/bmjopen-2015-007971
52. Pepper JK, Reither PL, McRee A-L, Cameron LD, Gilkey MB, Brewer NT. Adolescent Males' Awareness of and Willingness to Try Electronic Cigarettes. *J Adolesc Heal*. 2013;52(2):144-150. doi:10.1016/j.jadohealth.2012.09.014
53. Bold KW, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Trying E-cigarettes

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and Risk of Continued Use. *Pediatrics*. 2016;138(3):e20160895-e20160895. doi:10.1542/peds.2016-0895

54. Chen JC, Das B, Mead EL, Borzekowski DLG. Flavored E-cigarette Use and Cigarette Smoking Susceptibility among Youth. *Tob Regul Sci*. 2017;3(1):68-80. doi:10.18001/TRS.3.1.7
55. Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: An experimental study. *Tob Control*. 2016;25(e2):e107-e112. doi:10.1136/tobaccocontrol-2015-052593
56. Brozek G, Jankowski M, Zejda J, Jarosinska A, Idzik A, Banka P. E-smoking among students of medicine - frequency, pattern and motivations. *Adv Respir Med*. 2017;85:8-14. doi:10.5603/arm.2017.0003
57. Kinouani S, Pereira E, Tzourio C. Electronic cigarette use in students and its relation with Tobacco-Smoking: A Cross-Sectional analysis of the I-Share study. *Int J Environ Res Public Health*. 2017;14:1345. doi:10.3390/ijerph14111345
58. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: A worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*. 2014;11(4):4356-4373. doi:10.3390/ijerph110404356
59. Pepper JK, Ribisl KM, Emery SL, Brewer NT. Reasons for starting and stopping electronic cigarette use. *Int J Environ Res Public Health*. 2014;11(10):10345-10361. doi:10.3390/ijerph111010345
60. Lee H-Y, Lin H-C, Seo D-C, Lohrmann DK. Determinants associated with E-cigarette adoption and use intention among college students. *Addict Behav*. 2017;65:102-110. doi:10.1016/j.addbeh.2016.10.023
61. Russell C, McKeganey N, Dickson T, Nides M. Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. *Harm Reduct J*. 2018;15(1 PG-33):33. doi:10.1186/s12954-018-0238-6
62. Kong G, Morean ME, Cavallo DA, et al. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res*. 2015;17(7):847-854. doi:10.1093/ntr/ntu257
63. Shang C, Huang J, Chaloupka FJ, Emery SL. The impact of flavour, device type and warning messages on youth preferences for electronic nicotine delivery systems: evidence from an online discrete choice experiment. *Tob Control*. 2017;0:1-8. doi:10.1136/tobaccocontrol-2017-053754
64. Krishnan-Sarin S, Morean ME, Camenga DR, Cavallo DA, Kong G. E-cigarette use among high school and middle school adolescents in Connecticut. *Nicotine Tob Res*. 2015;17(7):810-818. doi:10.1093/ntr/ntu243
65. Yingst JM, Veldheer S, Hrabovsky S, Nichols TT, Wilson SJ, Foulds J. Factors associated with electronic cigarette users' device preferences and transition from first generation to advanced generation devices. *Nicotine Tob Res*. 2015;17(10):1242-1246. doi:10.1093/ntr/ntv052
66. Buckell J, Marti J, Sindelar JL. Should flavours be banned in cigarettes and e-cigarettes? Evidence on adult smokers and recent quitters from a discrete choice experiment. *Tob Control*. 2018. doi:10.1136/tobaccocontrol-2017-054165
67. Pesko MF, Kenkel DS, Wang H, Hughes JM. The effect of potential electronic nicotine delivery system regulations on nicotine product selection. *Addiction*. 2016;111(4):734-744. doi:10.1111/add.13257
68. Morean ME, Butler ER, Bold KW, et al. Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. *PLoS One*. 2018;13(1). doi:10.1371/journal.pone.0189015
69. Harrell MB, Loukas A, Jackson CD, Marti CN, Perry CL. Flavored Tobacco Product Use among Youth and Young Adults: What if Flavors Didn't Exist? *Tob Regul Sci*. 2017;3(2):168-173. doi:10.18001/TRS.3.2.4
70. Litt MD, Duffy V, Oncken C. Cigarette smoking and electronic cigarette vaping patterns as a function of e-cigarette flavourings. *Tob Control An Int J*. 2016;25(Suppl 2 PG-67-72):67-72.

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doi:10.1136/tobaccocontrol-2016-053223
71. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: An internet survey. *Int J Environ Res Public Health*. 2013;10(12):7272-7282. doi:10.3390/ijerph10127272
72. Etter JF. Characteristics of users and usage of different types of electronic cigarettes: findings from an online survey. *Addiction*. 2016;111(4):724-733. doi:10.1111/add.13240
73. Weaver SR, Huang J, Pechacek TF, Heath JW, Ashley DL, Eriksen MP. Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015-2016. *PLoS One*. 2018;13(7):e0198047. doi:10.1371/journal.pone.0198047
74. Tackett AP, Lechner W V., Meier E, et al. Biochemically verified smoking cessation and vaping beliefs among vape store customers. *Addiction*. 2015;110(5):868-874. doi:10.1111/add.12878
75. Camenga DR, Kong G, Cavallo DA, Krishnan-Sarin S. Current and Former Smokers' Use of Electronic Cigarettes for Quitting Smoking: An Exploratory Study of Adolescents and Young Adults. *Nicotine Tob Res*. 2017;19(12):1531-1535. doi:10.1093/ntr/ntw248
76. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620185.htm. Published 2018. Accessed October 26, 2018.
77. Bomey N. Marlboro maker Altria stops sales of flavored vaping liquid. *USA Today*. https://www.usatoday.com/story/money/2018/10/25/altria-group-flavored-vaping-liquid/1759794002/. Published October 25, 2018. Accessed October 25, 2018.
78. Kaplan S, Hoffman J. Juul Suspends Selling Most E-Cigarette Flavors in Stores. *The New York Times*. https://www.nytimes.com/2018/11/13/health/juul-ecigarettes-vaping-teenagers.html. Published November 13, 2018.
79. Chen JC, Green KM, Chen J, Hoke KS, Borzekowski DLG. Restricting the Sale of Flavored E-cigarettes in the US: An Examination of Local Regulations. *Tob Regul Sci*. 2018;4(4):32-40. doi:10.18001/trs.4.4.4
80. Hoffman J. San Francisco Voters Uphold Ban on Flavored Vaping Products. NY Times. https://www.nytimes.com/2018/06/06/health/vaping-ban-san-francisco.html. Published 2018. Accessed October 9, 2018.
81. Campaign for Tobacco-Free Kids. Brazil's Highest Court Upholds Ban on Flavored Tobacco Products. https://www.tobaccofreekids.org/press-releases/2018_02_01_brazil-court-upholds-flavor-ban. Published 2018. Accessed July 24, 2018.
82. World Health Organization. *Partial Guidelines for Implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control*.; 2012. http://www.who.int/fctc/guidelines/Guideliness_Articles_9_10_rev_240613.pdf.
83. Yingst JM, Veldheer S, Hammett E, Hrabovsky S, Foulds J. A method for classifying user-reported electronic cigarette liquid flavors. *Nicotine Tob Res*. 2017;19(11):1381-1385. doi:10.1093/ntr/ntw383

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Figure Legends:

Figure 1. PRISMA Flow Diagram

Author's Contributions:

Ms. Meernik and Ms. Baker contributed equally to this paper as joint first authors.

Ms. Meernik, Ms. Baker, and Dr. Kowitt conducted data review and analysis, drafted the initial manuscript, and revised and reviewed the full manuscript.

Dr. Ranney and Dr. Goldstein conceptualized the study and provided critical feedback to the intellectual content during drafting and revisions of the manuscript, as well as to the interpretation of data analyses.

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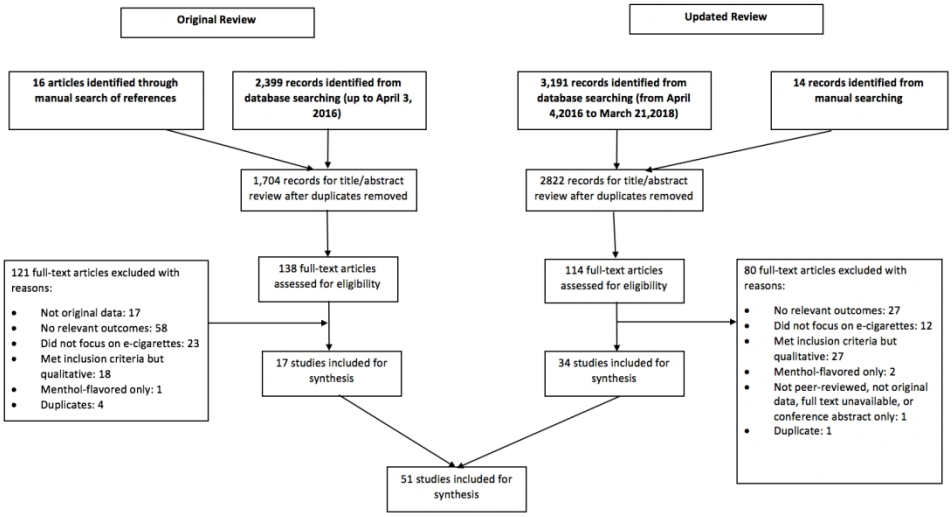

Figure 1. PRISMA Flow Diagram

Supplementary File 1. Search String

Final PubMed search string: (((((smoke OR smoker OR smokers OR smokes OR smokings OR smoking OR cigarette OR cigarettes OR cigar OR cigars OR cigarillos OR cigarillo OR hookahs OR hookah OR waterpipe OR waterpipes OR narghile OR narghiles OR argila OR argiles OR tobacco OR tobaccos OR cigar* OR smoke* OR tobacco* OR ends OR "electronic nicotine delivery system*" OR vape OR vapor OR vapour OR vapours OR vapors OR vapor OR vapors OR vaping OR snus OR pipe OR pipes OR "e-cigarette" OR "e-cigarettes" OR bidi OR bidis OR kretek OR kreteks OR chewing tobacco OR snuff OR shisha OR "water pipe" OR "water pipes" OR goza OR narkeela OR "hubble bubble" OR hukkah OR hukkas OR hukka OR argileh) AND (flavor OR flavor* OR flavour OR flavour* OR flavors OR flavours OR flavoring OR flavouring OR flavorings OR flavourings OR flavoured OR flavoured OR flavoring OR flavorings OR flavouring OR flavourings OR flavouring OR flavoring OR flavourants OR flavorants)) OR (kretek OR kreteks OR bidi OR bidis))) 2016/04/04:2018/03/21 [edat])

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Supplementary Table 1. Main results of all studies (* indicates study was included in original 2016 review)

Study	Study design	Measures / Analysis	Results
Amato, 2015[24] *	Cross-sectional survey Probability sample	Descriptive statistics were used to examine reasons for e-cigarette use.	A greater proportion of current e-cigarette users cited "come in flavors other than menthol" as a reason for their e-cigarette use than past users (55.5% vs. 25.0%).
Audrain-McGovern, 2016[25]	Cross-sectional laboratory experiment Convenience sample	Regression models used to evaluate the effect of flavor on subjective rewarding value, relative reinforcing value, and absolute reinforcing value.	The average subjective rewarding value across the three e-cigarettes included: unflavored (M = 3.11, SD = 1.55), dessert flavored (M = 3.69, SD = 1.78), and fruit flavored (M = 4.22, SD = 1.55). Both the fruit flavored (β = 1.11, CI: 0.58-1.64, p<.0001) and the dessert flavored e-cigarettes (β = 0.57, CI: 0.47-1.11, p=.03) were rated significantly more rewarding than the unflavored e-cigarette. Subjective reward was higher for the flavored e-cigarette compared to unflavored (β = 0.83, CI: 0.35–1.32, p=.001). This group difference meant that participants rated the unflavored e-cigarettes as “a little” and the flavored e-cigarette as “moderately” satisfying and good tasting. Participants took twice as many flavored puffs than unflavored e-cigarette puffs (IRR = 2.03, CI: 1.18-3.47, p=.01).
Barnes, 2017[26]	Cross-sectional laboratory experiment Convenience sample	Linear mixed effects models used to assess abuse liability for tobacco products.	The crossover point (i.e., the largest dollar amount at which participants still choose the tobacco product over the money) for cherry flavored e-cigarettes was significantly higher than for e-cigarettes without a flavor ($0.71 vs $0.51, p<.05).
Berg, 2016[27]*	Cross-sectional survey	ANOVAs were used to compare continuous variables across	32% of nonusers included ‘‘they come in appealing flavors’’ as a reason for possible future e-cigarette use.

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	Convenience sample	groups, and Chi-square tests were used to compare categorical variables.	39% of current smokers, who were non-e-cigarette users, chose “they come in appealing flavors” as a reason for possible e-cigarette use; this is compared to <31% of nonsmokers and former smokers, p<0.001. 60.2% of current e-cigarette users chose “they come in appealing flavors” as a reason for e-cigarette use; 59.5% of those same users chose “I like experimenting with various flavors” as a reason for e-cigarette use. 69.7% of never cigarette smokers who use e-cigarettes chose “they come in appealing flavors” as a reason for e-cigarette use; 61.4% of former cigarette smokers who use e-cigarettes chose “I like experimenting with various flavors” as a reason for e-cigarette use. 20.3% of former e-cigarette users reported no recent use of e-cigarettes because they ‘‘don’t like the flavor(s)’’.
Bold, 2016[28]	Longitudinal survey Convenience sample	Logistic regression models used to examine reasons for trying e-cigarettes at wave 1 as predictors of continuing e-cigarette use at wave 2; linear regression models used to examine reasons for trying e-cigarettes at wave 1 as predictors of e-cigarette frequency at wave 2 among those who continued e-cigarette use.	"Good flavors" was endorsed by 41.8% of students as a reason for first trying e-cigarettes among ever e-cigarette users, the second most highly endorsed reason for trying behind curiosity (reasons not exclusive). In univariate models, good flavors as a reason for first trying e-cigarettes predicted continued e-cigarette use, though it was no longer significant after adjusting for cigarette smoking status. In univariate models, good flavors a reason for first trying e-cigarettes predicted more frequent use, though it was no longer significant after adjusting for other covariates.

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Brozek, 2017[29]	Cross-sectional survey Convenience sample	Descriptive statistics used to describe attitudes and motivations for e-cigarette use.	28.3% of e-cigarette users decided to start using e-cigarettes because of the unique flavors, the fourth most cited reason behind other reasons such as desire to quit traditional cigarettes (58.7%) and less harmful effect on health (43.5%).
Buckell, 2018[30]	Cross-sectional discrete choice experiment Convenience sample	Exploded multinomial logit models used to analyze respondents' preferences.	Adult smokers prefer the following e-cigarette flavors, from most to least: tobacco, fruit/sweet, and menthol. Adult smokers with at least one quit attempt in the past year preferred all flavored (including tobacco) e-cigarettes, relative to tobacco cigarettes.
Camenga, 2017[31]	Cross-sectional survey Convenience sample	Multivariable logistic regression used to evaluate association between using e-cigarettes to quit smoking and age, gender, race, e-cigarette frequency, cigarette smoking status, preferred e-cigarette flavor, and risk perceptions.	Having a preference for "a combination of 2 or more flavors mixed together" predicted increased likelihood of using e-cigarettes to quit smoking, relative to not having a preferred flavor (aOR = 1.92, 95% CI: 1.31-2.81; p=.0008).
Chen, 2017[32]	Cross-sectional survey Probability sample	Logistic regression used to estimate association between cigarette susceptibility and e-cigarette use status, demographic characteristics, and risk factors for cigarette smoking. Multivariate logistic regression used to explore moderating variables	Among those who used e-cigarettes, youth who used the product 3 days or more were more likely to be flavored e-cigarette users than those who used e-cigarettes 1 or 2 days in the past 30 days (p<.05). The unadjusted odds ratio of being susceptible to cigarette smoking was the largest for flavored e-cigarette use (OR = 6.6, CI: 3.8-9.1, p <.0001), followed by nicotine dependence and cigarette experimentation. In the adjusted regression analysis, flavored e-cigarette users had higher

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		influencing direction and strength of association between e-cigarette use and smoking susceptibility.	odds of being susceptible to cigarette smoking than plain e-cigarette users (AOR = 1.7, CI: 1.3-2.4, p<.001) and non-users (AOR = 3.8, CI: 2.8-5.3, p<.0001), the largest effect across all demographic characteristics and smoking risk factors. In stratified analyses, the association between smoking susceptibility and flavored e-cigarette use was significantly higher for females (AOR = 6.5, CI: 4.2-9.9, p<.01) than males (AOR = 2.5, CI: 1.5-4.1, p<.01). The association between smoking susceptibility and flavored e-cigarette use was significantly higher for those who were not receptive to tobacco marketing (AOR = 5.0, CI: 3.5-7.0, p<.01) than those who were receptive (AOR = 2.5, CI: 1.2-3.1, p<.05).
Chen, 2018[33]	Longitudinal survey Probability sample	Univariate and multivariate regressions used to examine associations between past-year smoking reduction and cessation and current e-cigarette flavor use at wave 2.	Users of one non-tobacco/menthol flavor (37.1%) were more likely than non-e-cigarette users (24.7%) to adopt smoking cessation methods (p<.001). In adjusted analysis, wave 2 e-cigarette users who used one (AOR = 2.5, p<.001) or multiple (AOR = 3.0, p<.001) non-tobacco/menthol flavors were more likely to have reduced or quit smoking cigarettes in the past year than non-e-cigarette users. The third most endorsed reason for using e-cigarettes among current users (subsample of 844 respondents) were that e-cigarettes “come in flavors I like” (80.2%), behind “might be less harmful to people around me than cigarettes” (85.4%) and “can be used where smoking cigarettes is not allowed” (82.2%).

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			Compared to users of tobacco/menthol flavors, users of non-tobacco/menthol flavors were more likely to enjoy e-cigarette flavors (p<.001) and to vape daily (p<.001). E-cigarette users who said that e-cigarettes "come in flavors I like" (OR = 2.1, p=.007) were more than twice as likely to have reduced or quit smoking in the past year compared to those who did not endorse e-cigarette use for this reason.
Clarke, 2017[34]	Cross-sectional survey Convenience sample	Sequential hierarchical multiple regression used to identify predictors of adolescents' willingness to try flavored and tobacco-flavored e-cigarettes.	The majority of cigarette smokers (90.6%) were more willing to try flavored e-cigarettes than tobacco-flavored products (73.4%), with around one-third (33.9%) of non-smoking participants willing to try flavored e-cigarettes, as opposed to tobacco-flavored (12.0%). The more positively adolescents perceived a smoker, the more willing they were to try a flavored e-cigarette (p<.05), while the more negatively they perceived an e-cigarette user, the less willing they were to try a flavored e-cigarette (p<.05).
Coleman, 2017[35]	Cross-sectional survey Probability sample	Poisson regression used to examine association between everyday versus someday e-cigarette use and demographic, tobacco use, and product characteristics.	Never smokers were more likely to endorse appealing flavors as a reason for e-cigarette use (75.3%) compared with current (63.7%, p<.0001) and former (60.1%, p<.0001) smokers. Daily e-cigarette users were more likely to report that their first e-cigarette was non-tobacco flavored (65.2%) than moderate (60.7%) or infrequent (54.8%) e-cigarette users (p<.0001).
Cooper, 2016[36]	Cross-sectional survey Probability sample	Logistic regression models used to investigate relationship between perceptions of	27.0% of youth reported that flavored e-cigarettes were "less harmful" than non-flavored e-cigarettes. Youth who currently used e-cigarettes had higher odds (OR = 2.84, 95% CI:

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		harm and addictiveness and e-cigarette use.	1.91–4.21) of reporting flavored e-cigarettes as "less harmful" than non-flavored e-cigarettes compared to non-current users, after adjusting for covariates. Youth who had ever used e-cigarettes had higher odds (OR = 2.88, 95% CI: 2.42–3.42) of reporting that flavored e-cigarettes were "less harmful" than non-flavored products compared to never users, after adjusting for covariates.
Czoli, 2015[37]*	Cross-sectional discrete choice experiment Convenience sample	Multinomial logit regression was used to analyze the effect of attributes on consumer choice for each outcome in a discrete choice experiment.	Participants were significantly more interested in trying e-cigarettes with cherry ($p<0.0001$, $r=0.2$) and menthol ($p=0.01$, $r=0.1$) flavors. Younger smokers expressed interest in trying e-cigarettes with a preference for products with cherry flavor ($p<.001$, $r=0.2$) while younger nonsmokers indicated interest in trying cherry ($p<.0001$, $r=0.3$), menthol ($p<.0001$, $r=0.2$) and coffee flavor ($p<.001$, $r=0.2$); Older smokers indicated greater interest in trying tobacco-flavored e-cigarettes ($p<0.0001$, $r=0.6$). E-cigarettes with the following characteristics were perceived as less harmful and greater quit efficacy: menthol ($p<0.0001$, $r=0.6$; $p<0.0001$, $r=0.2$) and coffee flavors ($p<0.0001$, $r=0.3$; $p<0.001$, $r=0.2$). Younger non-smokers were more likely to perceive coffee-flavored ($p=0.02$, $r=0.1$) e-cigarettes as less harmful while younger smokers held these beliefs about products with cherry flavor ($p=0.03$, $r=0.1$); Older smokers perceived products with tobacco flavor ($p<0.001$, $r=0.2$) as less harmful.

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			Compared to other attributes, flavor accounted for 24% of the relative importance on intention to try, 36% for perceptions of reduced product harm, and 25% on perceptions of enhanced product quit efficacy.
Dai, 2016[38]	Cross-sectional survey Probability sample	Logistic regression model used to examine associations between flavored e-cigarette use and tobacco use and perception of tobacco's danger.	Among all respondents, students who reported using flavored e-cigarettes were least likely to perceive tobacco's danger compared with those who reported not using e-cigarettes (74.8% vs 91.3%; aOR = 0.5; p<.0001) or with those who reported using non-flavored e-cigarettes (74.8% vs 77.1%). Among never smokers, the use of flavored e-cigarettes was associated with a higher prevalence of intention to initiate cigarette use compared with those who had not used e-cigarettes in the past 30 days (58.3% vs 20.1%; aOR = 5.7; p<.0001) or with those who had used non-flavored e-cigarettes (58.3% vs 47.4%; aOR = 1.7; p=.02). Among current smokers, students who reported using flavored e-cigarettes were less likely to quit tobacco use compared with those who reported not using e-cigarettes (24.1% vs 32.7%; aOR = 0.6; p=.006) or with those who had used non-flavored cigarettes (24.1% vs 33.5%).
Elkalmi, 2016[39]	Cross-sectional survey Convenience sample	Descriptive statistics used to report frequencies.	66.7% of respondents who had tried e-cigarettes in the past reported that variety of flavors contribute to better enjoyment of e-cigarettes compared to traditional cigarettes.
Etter, 2010[40]*	Cross-sectional survey Convenience sample	Open-ended questions about the most positive and negative points about e-cigarettes were analyzed.	The most frequently cited positive feature of e-cigarettes was that respondents liked the taste and variety of flavors (18% of total open-ended comments).

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Etter, 2016[41]	Cross-sectional survey Convenience sample	T-tests used to compare means, Mann-Whitney U-tests and Wilcoxon's signed-ranks test to compare medians between or within groups, and chi-square tests to compare proportions.	Tobacco flavor e-cigarettes were used by 44% of users who had recently started vaping (i.e. those who had used e-cigarettes for 0–3 months) versus 25% of long-term users (who had used e-cigarettes for ≥ 4 months, $\chi 2 = 79.0$, $p<.001$). Most participants (80%) said that the e-cigarette flavors helped them either to quit smoking or reduce their cigarette consumption, while 18% said that the flavors had no impact on their smoking and 2% said that the flavors made them want to smoke.
Farsalinos, 2013[42]*	Cross-sectional survey Convenience sample	X^2 tests compared categorical variables (e.g., type of e-cigarette flavors regularly used) between current and former smokers. A stepwise binary logistic regression analysis was used with smoking status (former vs current smoker) as the independent variable and age, gender, education level, smoking duration, number of flavorings used regularly, and e-cigarette consumption as covariates.	More current smokers were using tobacco flavors compared to former smokers ($X^2=14.6$, $p<.001$), while more former smokers were using fruit ($X^2=14.0$, $p<.001$) and sweet flavors ($X^2=21.8$, $p<.001$). The average score for importance of flavors variability in reducing or quitting smoking was 4 ("very important") on a 5-point scale. 39.7% of participants reported that restricting variability of flavors would make reducing or completely substituting smoking less likely. Binary logistic regression analysis showed that number of flavors regularly used ($\beta=0.089$, $p=0.038$) was associated with complete smoking abstinence among dedicated long-term users.
Farsalinos, 2014[43]*	Cross-sectional survey Convenience sample	Descriptive statistics examined reasons for initiating e-cigarette use.	Initiating e-cigarette use to enjoy the variability of flavors in e-cigarettes was ranked as 3 on a 5-point scale from 1 (not important) to 5 (most important).

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Ford, 2016[44]*	Cross-sectional survey Probability sample	Paired t-tests were run on weighted data to produce mean scores; the Friedman test was used on ordinal data, then post hoc tests were conducted using the Wilcoxon signed rank test	Perceptions of harm from the different flavors ranged from a mean of 3.00 (SD = 1.35) for candy floss flavor to 3.06 (SD = 1.29) for cherry, 3.47 (SD = 1.22) for coffee and 3.99 (SD = 1.14) for tobacco flavor. Perceptions of harm differed depending on the flavor, χ^2 (4) = 851.59, p<0.001. Post hoc analysis showed that, when compared against perceptions of harm of e-cigarettes in general, tobacco flavor e-cigarettes were perceived as being more harmful (p<0.001) while cherry and candy floss flavors were each perceived as less harmful (p<0.001). Coffee flavor e-cigarettes were perceived as having the same level of harm as e-cigarettes in general. Perceptions of likelihood of an adult smoker using each differed depending on the flavor, χ^2 (3) = 153.9, p <0.001 as did perceptions of likelihood of a never smoker of their age, χ^2 (3) = 879.01, p<0.001. Post hoc analysis showed that, when compared with tobacco flavor e-cigarettes, adult smokers who were trying to give up smoking were perceived by youth to be less likely to use cherry, candy floss or coffee flavors (p<0.001). Conversely, a never smoker of their age was perceived to be more likely to try cherry (p<0.001), candy floss (p<0.001) or coffee flavor (p<0.01) than a tobacco flavor e-cigarette. An adult smoker was perceived by youth to be more likely than a never smoker of their age to use tobacco (p<0.001) and coffee (p<0.001) flavors whereas a never smoker of their age was perceived to be more likely than an

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			adult smoker to try candy floss (p<0.001) and cherry (p<0.01) flavors.
Goldenson, 2016[45]	Cross-sectional laboratory experiment Convenience sample	Multilevel linear models used to examine associations between each sensory rating (sweetness or throat hit) and appeal outcomes.	A significant main effect of e-liquid flavor was found for each appeal outcome (i.e., liking, willingness to use again, and amount willing to pay) and sweetness (ps<.0001). Sweet-flavored e-liquids resulted in higher appeal ratings than non-sweet and flavorless solutions (ps<.0001). Ratings of sweetness were positively associated with each appeal outcome (ps<.0001). For instance, each one-point increase in sweetness rating (0-100) was associated with a 0.51 increase in liking, a 0.51 increase in willingness to use again, and a $0.04 increase in amount willing to pay for a day's worth of the solution.
Gubner, 2017[46]	Cross-sectional survey Convenience sample	Bivariate analyses and logistic regression used to examine factors associated with daily vs. weekly e-cigarette use.	Daily and weekly e-cigarette users both reported similar reasons for use of e-cigarettes, including because they have good flavors (41.1% overall). Daily e-cigarette users reported using more types of e-juice flavors (2.2 ± 1.3 vs. 1.8 ± 1.4), t(168) = 2.15, p=.03), and were more likely to have used tobacco flavor, fruit/berry flavor, or select "other" flavor compared to weekly users.
Harrell, 2017a[47]	Cross-sectional survey Probability and convenience sample	Proportions and 95% confidence intervals used to examine percentage of flavored e-cigarette use at initiation and current use; Chi-square tests used to examine differences in flavored e-cigarette use by combustible	The proportion of current e-cigarette users who initiated with an e-cigarette flavored with something other than tobacco was considerably higher in Texas youth (98.6%) and young adults in Texas (95.2%) and nationwide (71.2%) compared to older adults nationwide (44.1%). At initiation, the use of tobacco-flavored e-cigarettes was more common among current dual users (e-cigarette and combustible tobacco product users)

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		tobacco product use and demographic characteristics.	than exclusive e-cigarette users (i.e., former combustible tobacco product users), for both age groups (p<.05). Among adults nationwide, 43.5% of current combustible users said their first e-cigarette was flavored to taste like tobacco, compared to 27.8% of former combustible product users. The proportion of current users whose "usual" e-cigarette was flavored with something other than tobacco was higher for Texas youth (97.9%) and young adults (96.7%) in Texas and nationwide (82.2%) compared to older adults nationwide (69.3%). Among current e-cigarette users, more Texas youth (72.9%) than young adult college students in Texas (57.4%) and young adults (64.8%) and adults (54.0%) nationwide cited using e-cigarettes because they "come in flavors I like."
Harrell, 2017b[48]	Cross-sectional survey Probability sample (youth) and convenience sample (young adults)	Chi-square tests used to test for differences between subgroups (sex and school/age level).	Roughly 3 out of every 4 youth (78%) and young adult (74%) flavored e-cigarette users said that they would not use an e-cigarette if it was not available in a flavored form (e.g., candy, fruit, mint/menthol). Significantly more young adult females than males reported that they would not use e-cigarettes if it were not flavored (77% vs 69%, p=.03).
Kim, 2016[49]	Cross-sectional laboratory experiment Convenience sample	One-way analysis of variance (ANOVA) used to examine differences between e-cigarette flavors in hedonic ratings and sensory attribute ratings; regression models used to examine	In terms of mean hedonic (liking/disliking) ratings of the 6 e-cigarette flavors, Pina Colada was liked significantly more than Classic Tobacco (p<.05). One-way ANOVAs found a significant main effect of e-cigarette flavors on sweetness (F = 14.56, p<.0001), coolness (F = 11.96, p<.00001), and bitterness (F = 3.56, p<.01), but not on

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		relative effects of flavor attributes on hedonic ratings.	harshness and own flavor. The four non-tobacco flavored e-cigarette samples were rated significantly sweeter than Classic Tobacco. Pina Colada was perceived as sweetest and liked the most; Classic Tobacco was perceived as least sweet and liked the least. Hedonic ratings were significantly positively correlated for sweetness for Pina Colada ($r = 0.36$, $p<.05$) and Peach Schnapps ($r= 0.56$, $p<.05$). Hedonic ratings were significantly positively correlated with coolness for Classic Tobacco, Magnificent Menthol, and Vivid Vanilla ($r = 0.41–0.52$, $p<.05$). Harshness ratings were significantly negatively correlated with hedonic ratings for Cherry Crush, Pina Colada, and Peach Schnapps ($r = 0.37–0.40$, $p<.05$). When regressing sensory attributes on hedonic ratings, sweetness and coolness had a positive contribution to liking and disliking of the six e-cigarette flavors, while bitterness and harshness had a negative contribution.
Kinouani, 2017[50]	Cross-sectional survey Convenience sample	Descriptive statistics used to describe reasons for trying e-cigarettes among current and former e-cigarette users, stratified by smoking status.	24.6 % of respondents reporting trying e-cigarettes because of the flavor, behind reasons of curiosity (77.4%) and because someone offered one to try (63.5%); there was no significant difference between men and women using for this reason (20.7% and 26.0%, respectively; $p=.07$). 28.6% of former smokers, 25.1% of current smokers, and 17.8% of never smokers tried e-cigarettes because of flavors.

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Kong, 2014[51]*	Cross-sectional survey Convenience sample	X^2 tests evaluated school level differences (middle school, high school, college) on all variables. Multinomial logistic regression analyses evaluated the extent to which reasons for e-cigarette experimentation differed based on cigarette smoking status.	43.8% of respondents reported the availability of flavors as a reason for experimentation with e-cigarettes. School level differences were observed ($X^2(2,N=1,157)=18.63$, $p\leq.001$), with high school students more likely to experiment with e-cigarettes because of appealing flavors compared to college students (47.0% vs 32.8%, $X^2(1,N=1,116)=13.61$, $p\leq.001$).
Krishnan-Sarin, 2014[52]*	Cross-sectional survey Convenience sample	Descriptive statistics explored flavors of e-cigarettes that had been tried and preferred.	Most lifetime e-cigarette users in middle school and high school, across cigarette smoking status, reported that they had tried and preferred sweet flavors compared to menthol and tobacco flavors.
Lee, 2017[53]	Cross-sectional survey Convenience sample	Multinomial logistic regression models and Heckman two-step selection procedures used to examine determinants that promote e-cigarette use acceptability.	A higher preference for the availability of flavors in e-cigarettes increased intention to use e-cigarettes (OR = 1.49) and likelihood of currently using e-cigarettes (OR = 1.82).
Lee, 2017b[54]	Cross-sectional survey Probability sample	Chi-square tests used to assess association between reason for using e-cigarettes and frequency of use.	9.3% of respondents reported using e-cigarettes “since they have good flavor,” behind reasons of curiosity (22.9%), being potentially less harmful (18.9%), for smoking cessation (13.1%), for indoor use (10.7%), or being better tasting (9.6%).
Litt, 2016[55]	Two-phase longitudinal laboratory study	Multilevel modelling with maximum likelihood estimation used to evaluate effects of	The largest drop in cigarette smoking occurred among those assigned menthol e-cigarettes (smoking 4.0 per day by week 7), and the smallest drop in smoking occurred among those assigned cherry and chocolate flavors

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	Convenience sample	assigned e-cigarette flavor on use of usual cigarettes and e-cigarettes over 6-week study period.	(smoking 9.8 per day by week 7) (contrast: menthol vs all others: F(1, 3143) = 2.48; p<.05). E-cigarette vaping rates differed significantly by flavor assigned, with the highest vaping rates (about 12.3 vaping episodes per day) for tobacco e-cigarettes and the lowest rates for those assigned to chocolate (8.6 episodes per day) (contrast: tobacco vs chocolate: F(1, 3143) = 3.86; p<.001).
Maglalang, 2016[56]	Cross-sectional survey Convenience sample	Frequencies reported for preferred e-cigarette flavors and reasons for e-cigarette use.	Among current e-cigarette users who responded to the question (n=39), 8% cited “enjoying the flavor” as a reason for using e-cigarettes. This ranked the lowest behind use as a cessation aid or healthier alternative to conventional cigarettes; use for recreational/social reasons; use for stress relief/coping; and use for nicotine's highs.
Morean, 2018[57]	Cross-sectional survey Convenience sample	Chi-squares and independent samples t-tests used to examine differences in sex, age, smoking status, e-cigarette nicotine content, e-liquid flavor preferences, the total number of e-liquid flavors preferred, and e-cigarette use frequency; univariate general linear modeling used to examine associations between flavor preferences and total number of flavors preferred with e-cigarette use frequency	The most commonly preferred flavors among adults were fruit (40.0%), tobacco (32.0%) and menthol/mint (27.6%). Compared to adolescents, a larger percentage of adult e-cigarette users preferred tobacco, menthol/mint, coffee (16.6%), and spice (12.2%) flavor e-liquids. Adults preferred a greater total number of e-liquid flavors than did adolescents (M = 15.56, SD = 12.48 among adults compared to M = 9.98, SD = 10.52 among adolescents). The most commonly preferred flavors among adolescents were fruit (52.3%), candy/dessert (16.2%), and vanilla (11.4%). Compared to adults, more adolescents preferred fruit, alcohol (9.8%), and “other” flavored (2.0%) e-liquids or reported not knowing what their preferred flavor was (15.4%).

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		among adolescents and adults separately.	Adolescents who preferred to use fruit (ηp2 = 0.02, p = .003), dessert (ηp2 = 0.02, p=.007), and/or alcohol flavored e-liquids (ηp2 = 0.02, p=.002) reported using e-cigarettes more frequently. Among adolescents, the total number of e-cigarette flavors preferred was associated with e-cigarette frequency; preferring to use a greater number of e-cigarette flavors was associated with using e-cigarette on more days in the past month (ηp2 = 0.04, p<.001).
Nonnemaker, 2016[58]*	Cross-sectional survey Convenience sample	Calculated coefficients and corresponding 95% CIs for a series of multivariate linear regression models; regressed indicators for each characteristic on respondents' reported willingness to pay for an e-cigarette with a specific set of attributes	Among the full sample, removing the attribute "coming in flavors" significantly reduced the price respondents were willing to pay for an e-cigarette (p<0.05). Among cigarette-only users, losing the attribute "coming in flavors" significantly reduced the price respondents were willing to pay for an e-cigarette (p<.01); this relationship was not significant for dual users.
Patel, 2016[59]	Cross-sectional survey Probability sample	Wald tests and multivariate Poisson regressions used to assess differences in reasons for e-cigarette use across respondent characteristics.	Flavoring was the 5th most reported reason for using e-cigarettes (34.4%), behind cessation/health, consideration of others, convenience, and curiosity. Current e-cigarette users aged 18 to 24 years (adjusted prevalence ratio [aPR] = 2.02, 95% CI: 1.60–2.55), 25 to 34 years (aPR = 1.61, 95% CI: 1.30–2.01), and 35 to 54 years (aPR = 1.29, 95% CI: 1.08–1.54) were more likely to cite flavoring as a reason for use than those aged 55 years or older. The prevalence of citing flavoring as a reason for use was greater among current e-cigarette users living in the

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			South than those in the Northeast (aPR = 1.36, 95% CI: 1.01–1.83). Compared with current e-cigarette users who used disposables the most, tank users had a greater odds of citing flavoring as reason for use (aPR = 2.55, 95% CI: 1.97–3.32).
Pepper, 2013[60]*	Cross-sectional survey Probability sample	Logistic regression examined willingness to try any kind of e-cigarette (plain, flavored, or both).	The same proportion of respondents were willing to try plain e-cigarettes or to try flavored e-cigarettes (p=.15).
Pepper, 2014[61]*	Cross-sectional survey Probability and convenience sample	Descriptive statistics assessed reasons for first trying e-cigarettes.	Less than 10% of respondents reported starting e-cigarette use because "e-cigarettes come in flavors they like."
Pepper, 2016[63]	Cross-sectional survey Probability sample	Logistic regression models used to examine the effects of flavor condition on interest in trying e-cigarettes; linear regression models used to assess association between flavor and perceived harm.	Adolescents perceived fruit-flavored e-cigarettes to be less harmful than tobacco-flavored ones (mean 2.71 vs. 2.87, $\beta = -0.08$, $p<.05$). Adolescents reported that, if offered by a friend, they were more likely to try menthol-flavored (8.3%, OR = 4.00, 95% CI 1.46-10.97), candy-flavored (9.3%, OR = 4.53, 95% CI: 1.67-12.31) or fruit-flavored e-cigarettes (12.8%, OR = 6.49, 95% CI: 2.48-17.01) compared with tobacco-flavored e-cigarettes (2.2%). Perceptions of e-cigarette harm partly mediated the relationship between flavor and interest in trying e-cigarettes. Adolescents believed that menthol-flavored, candy-flavored or fruit-flavored e-cigarettes were less harmful than tobacco-flavored or alcohol flavored ones ($\beta = -0.15$, $p<.01$). Greater perceived harmfulness was

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			associated with less interest in trying e-cigarettes (OR = 0.31, 95% CI: 0.22-0.43).
Pesko, 2016[63]	Cross-sectional discrete choice experiment Convenience sample	Linear probability model estimated probability of choosing the e-cigarette option as a function of indicator variables for each attribute level.	Increased flavor availability increased e-cigarette selection for younger adults, from 17.5% to 21.9% (p<.001) but was not associated with a significant increase for older adults. Increased flavor availability increased e-cigarette selection for individuals that have not used vaping devices in the past month (p<.001) but was not associated with a significant increase in e-cigarette selection for individuals that have. Regardless of interest in quitting cigarettes, greater flavor availability increased e-cigarette selection. In linear probability models, greater flavor availability was associated with a 2.1 percentage point increase in e-cigarette selection (p<.001). In the interaction model, young adults were 3.7 percentage points more likely to choose e-cigarettes when multiple flavors were available compared to older adults (p<.001).
Russell, 2018[64]	Cross-sectional survey Convenience sample	Chi-square tests used to compare prevalence of first e-cigarette flavor purchased for each time period of first e-cigarette purchase; logistic regression analysis used to examine association between current use of tobacco-flavored e-liquids and fruit/fruit beverage flavored	Switchers (from regular cigarette smoking to regular e-cigarette use) (OR = 4.03, 95% CI: 3.26-4.97), dual users (OR = 4.14, 95% CI: 3.26-5.26), and former smokers (OR = 2.33, 95% CI: 1.85-2.93) were more likely than never smoker e-cigarette users to have initiated e-cigarette use with a tobacco-flavored product. Switchers (OR = 0.43, 95% CI: 0.38-0.49), dual users (OR = 0.41, 95% CI: 0.34-0.48), and former smoker (OR = 0.58, 95% CI: 0.50-0.67) e-cigarette users were all significantly less likely than never smoker e-cigarette users to

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		e-liquids and Tobacco Use Pathway Group and time of first e-cigarette purchase.	have initiated e-cigarette use with fruit-flavored products. The highest rate of current use of tobacco-flavored e-liquid was reported by those who initiated e-cigarette use ≥ 5 years ago; the lowest rate of current use of tobacco flavor was reported by those who initiated e-cigarette use in the past 12 months. The highest rate of current use of fruit/fruit beverage e-liquid flavors was among those who initiated e-cigarette use in the past 12 months, while the lowest rate was among those who initiated e-cigarette use ≥5 years ago; a similar effect of time since first e-cigarette purchase was found for current use of dessert/pastry flavors and for candy/chocolate/sweets flavors. As was observed for tobacco-flavored first e-cigarette purchases, switchers (OR = 2.18, 95% CI: 1.69-2.81), dual users (OR = 2.63, 95% CI: 1.97-3.51), and former smoker (OR = 1.54, 95% CI: 1.16-2.03) e-cigarette users all had significantly higher odds of current use of tobacco-flavored e-liquid compared to never smoker e-cigarette users. Switchers (OR = 0.64, 95% CI: 0.54-0.75), dual users (OR = 0.70, 95% CI: 0.57-0.86), and former smoker (OR = 0.70, 95% CI: 0.59-0.85) e-cigarette users were significantly less likely than never smoker e-cigarette users to be current users of fruit-flavored products.
Rutten, 2015[65]	Cross-sectional survey Probability sample	Logistic regression models used to assess association between reasons for use of e-cigarettes smoking	14.7% of smokers who also used e-cigarettes reported using e-cigarettes because of appealing flavors, behind eight other reasons including to quit smoking (58.4%), reduce smoking (57.9%), and to reduce the health risks of smoking (51.9%).

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		reduction behaviors.	Smoking reduction behaviors (i.e., decreased use of cigarettes or considered quitting) did not vary among those reporting using e-cigarettes because of appealing flavors vs. those that did not report using e-cigarettes because of appealing flavors.
Shang, 2017[66]	Cross-sectional discrete choice experiment Probability sample	Conditional logit regressions used to analyze the effects of flavors, warnings, and device types on the choice of using e-cigarettes.	For both e-cigarette ever and never users, fruit/sweets/beverage flavors marginally significantly increased ($p<.01$) the probability of choosing an e-cigarette product compared to tobacco flavor.
Shiffman, 2015[67]*	Cross-sectional survey Convenience sample	Comparisons of teen and adult respondents' ratings of their interest by flavor and comparisons of ratings by flavor within the adult sample by e-cigarette use status (recent user, past user, never user).	Adult smokers' e-cigarette ratings (overall mean=1.73±1.0 on a 0-10 scale) were significantly higher ($p<.0001$) than non-smoking teens' (overall mean=0.41±0.14) for each e-cigarette flavor. For each of the 15 flavors, adult smokers' interest in trying e-cigarettes was significantly higher than non-smoking teens' interest (all p values<.05, most p values<.0001).
Shiplo, 2015[68]*	Cross-sectional survey Convenience sample	Logistic regression models examined factors associated with use of flavors	Among current e-cigarette users, a common reason for use was taste (32.3% of younger non-smokers, 18.4% of younger smokers, 6.5% of older smokers).
Spears, 2018[69]	Cross-sectional survey Probability sample	Rao-Scott chi-square tests, independent samples t-tests of mean differences, and ordinal logistic regression used to examine associations between mental health condition	Compared to former smokers without mental health conditions, former smokers with mental health conditions gave higher importance ratings for appealing flavors as a reason for use ($t[79] = 3.83$, $p=.0001$).

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		and variables of interest.	
Tackett, 2015[70]*	Cross-sectional survey Convenience sample	Descriptive statistics examined preferred e-liquid flavors. Logistic regression, controlling for age and sex, was performed to assess associations between flavor (traditional tobacco/menthol vs non-traditional e.g., fruity, coffee, candy) on participants' biochemically verified smoking status.	E-cigarette users who reported using non-tobacco and non-menthol flavors were more likely to have quit smoking compared to those who vaped traditional (tobacco/menthol) flavors (OR=2.626, 95% CI=1.133-6.085, p=.024).
Tsai, 2018[71]	Cross-sectional survey Probability sample	Chi-square tests used to assess differences in reasons for e-cigarette use across groups.	Among students who reported ever using e-cigarettes, the second most commonly selected reason for use was availability of flavors such as mint, candy, fruit, or chocolate (31.0%), behind use by friend or family member (39.0%). High school students were more likely than middle school students to report the availability of flavors as a reason for e-cigarette use (32.3% vs. 26.8%, respectively; p<.05).
Vasiljevic, 2015[72]*	Cross-sectional survey Convenience sample	Mann-Whitney tests and logistic regression were used to assess exposure to advertisements and increase in ratings of appeal, interest in buying and trying e-cigarettes.	Exposure to the flavored e-cigarette ads increased interest in buying and trying e-cigarettes (Mann-Whitney test, U=9140.000, Z=−3.949, p<0.001), whereby those who saw the flavored e-cigarette ads expressed greater interest in buying and trying e-cigarettes (mean rank=176.44) than those who saw the non-flavored e-cigarette ads (mean rank=136.26).

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		Logistic regression was also used to examine exposure to advertisements and effects on susceptibility to smoking.	
Weaver, 2018[73]	Longitudinal survey Probability sample	Weighted logistic regression or weighted general linear models used to assess associations between e-cigarette use and outcomes, such as making a smoking quit attempt and 30-day smoking abstinence; both a complete-case analysis and a multiple-imputation approach used to account for missing data.	Among baseline daily smokers, both menthol/wintergreen/mint users and other flavor e-cigarette users were more likely to report a quit attempt (AORs = 6.0 and 2.4, respectively) than non-users of e-cigarettes, and menthol/wintergreen/mint users were more likely to report a quit attempt than tobacco/unflavored e-cigarette users in the past year ($p<.05$). Users of other e-cigarette flavors (e.g., fruit, dessert, spice; 8.8%; AOR = 0.22, 95% CI: 0.08–0.59) had significantly lower adjusted odds of quitting than non-users of e-cigarettes in the past year, which remained significant in multiple imputation analysis.
Yingst, 2015[74]*	Cross-sectional survey Convenience sample	T-tests and X^2 tests were used to identify differences between current first generation device (FGD) and advanced generation device (AGD) users. Descriptive statistics examined how respondents transitioned between devices.	Participants using an AGD were more likely to rate variety of flavor choices as important (FGD 54.6% vs AGD 94.9%, $p<.0001$).

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Supplementary Table 2. Risk of bias assessed by Quality Assessment Tool (QATSDD) (* indicates study was included in original 2016 review)

Note. [a] Percentage = the total score of a study / the full score 42 (14 items x 3 per item)

Study ID (Author, Year)	Amato, 2015[24]*	Audrain-McGovern 2016[25]	Barnes 2017[26]	Berg, 2016[27]*	Bold 2016[28]	Brozek, 2017[29]	Buckell, 2018[30]	Camenga 2017[31]	Chen 2017[32]	Chen 2018[33]	Clarke, 2017[34]	Coleman 2017[35]	Cooper 2016[36]	Czoli, 2016[37]*
Total score	35	22	27	29	26	24	31	26	25	29	31	28	37	31
%[a]	83%	52%	64%	69%	62%	57%	74%	62%	60%	69%	74%	67%	88%	74%
Explicit theoretical framework	0	1	0	0	0	0	0	0	0	0	3	0	2	3
Statement of aims/objectives in main body of report	3	2	3	3	3	3	3	3	3	3	3	3	3	3
Clear description of research setting	3	1	1	3	2	3	3	2	2	3	3	3	3	3
Evidence of sample size considered in terms of analysis	3	0	1	3	1	1	1	1	1	1	0	0	1	0
Representative sample of target group of a reasonable size	3	1	1	2	2	2	3	1	3	3	1	3	2	2
Description of procedure for data collection	3	3	3	3	3	1	3	3	1	3	2	3	3	3
Rationale for choice of data collection tool(s)	3	3	2	2	1	0	2	1	3	2	3	1	3	2
Detailed recruitment data	3	1	3	3	2	0	1	3	1	2	1	3	3	1
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	1	1	1	0	0	2	3	0	0	0	1	0	2	0
Fit between stated research question and method of data collection (Quantitative)	3	3	3	2	3	3	3	3	3	3	3	3	3	2
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Good justification for analytical method selected	1	3	3	2	3	3	3	3	2	3	3	3	3	3
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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Evidence of user involvement in design	3	0	0	0	0	1	0	0	0	0	2	0	3	3
Strengths and limitations critically discussed	3	0	3	3	3	2	3	3	3	3	3	3	3	3

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Study ID (Author, Year)	Dai 2016[38]	Elkami 2016[39]	Etter, 2010[40]*	Etter 2016[41]	Farsalinos, 2013[42]*	Farsalinos, 2014[43]*	Ford, 2016[44]*	Goldenson 2016[45]	Gubner 2018[46]	Harrell 2017a[47]	Harrell 2017b[48]	Kim 2016[49]	Kinouani 2017[50]	Kong, 2014[51]*	Krishnan-Sarin, 2014[52]*
Total score	31	33	20	27	16	19	32	22	28	31	27	28	27	31	26
% [a]	74%	79%	48%	64%	38%	45%	76%	52%	67%	74%	64%	67%	64%	74%	62%
Explicit theoretical framework	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Statement of aims/objectives in main body of report	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Clear description of research setting	3	3	3	3	3	3	3	2	3	3	3	3	3	3	3
Evidence of sample size considered in terms of analysis	0	2	1	3	0	0	3	1	0	1	0	1	0	1	1
Representative sample of target group of a reasonable size	3	1	2	1	1	2	3	1	2	2	2	1	1	3	3
Description of procedure for data collection	3	3	2	2	1	2	3	3	3	3	2	3	3	3	3
Rationale for choice of data collection tool(s)	2	3	1	2	1	1	2	2	2	3	2	3	2	3	0
Detailed recruitment data	3	3	1	1	1	1	1	1	3	3	2	1	3	3	3
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	1	2	0	0	0	0	0	0	0	1	1	1	0	0	0
Fit between stated research question and method of data collection (Quantitative)	3	3	2	3	1	2	3	3	3	3	3	3	3	2	2
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	2	3	2	2	3	3	3	3	3	3	3	3	3
Good justification for analytical method selected	3	2	1	3	1	1	3	3	3	3	3	3	3	3	3
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Evidence of user involvement in design	0	3	0	0	0	0	2	0	1	0	0	0	0	2	0
Strengths and limitations critically discussed	3	2	2	3	2	2	3	0	2	3	3	3	3	2	2

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Study ID (Author, Year)	Lee 2017a[53]	Lee 2017b[54]	Litt 2016[55]	Maglalang 2016[56]	Morean 2018[57]	Nonnemaker, 2016[58]*	Patel 2017[59]	Pepper, 2013[60]*	Pepper, 2014[61]*	Pepper 2016[62]	Pesko 2016[63]	Russell 2018[64]	Rutten 2015[65]	Shang 2017[66]
Total score	32	28	27	27	26	24	34	35	34	28	29	24	32	27
% [a]	76%	67%	64%	64%	62%	57%	81%	83%	81%	67%	69%	57%	76%	64%
Explicit theoretical framework	3	0	0	0	0	0	3	3	2	0	0	0	0	0
Statement of aims/objectives in main body of report	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Clear description of research setting	3	3	3	3	3	3	3	3	3	3	3	2	3	1
Evidence of sample size considered in terms of analysis	0	0	0	1	0	0	1	1	1	0	0	1	1	3
Representative sample of target group of a reasonable size	2	3	1	1	1	2	3	2	3	3	2	1	3	3
Description of procedure for data collection	3	3	3	3	3	3	3	3	2	3	3	3	3	2
Rationale for choice of data collection tool(s)	3	3	2	1	1	0	3	2	3	1	2	0	2	3
Detailed recruitment data	3	3	3	3	3	1	3	3	3	3	2	3	3	1
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	0	0	0	0	0	0	0	3	0	0	2	0	0	0
Fit between stated research question and method of data collection (Quantitative)	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Good justification for analytical method selected	3	2	3	3	3	3	3	3	3	3	3	2	3	3
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Evidence of user involvement in design	0	0	0	0	0	0	0	0	2	0	0	0	2	0
Strengths and limitations critically discussed	3	2	3	3	3	3	3	3	3	3	3	3	3	2

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Study ID (Author, Year)	Shiffman, 2015[67]*	Shiplo, 2015[68]*	Spears 2018[69]	Tackett, 2015[70]*	Tsai 2018[71]	Vasiljevic, 2016[72]*	Weaver 2018[73]	Yingst, 2015[74]*
Total score	26	27	29	26	22	33	30	21
% [a]	62%	64%	69%	62%	52%	79%	71%	50%
Explicit theoretical framework	0	0	0	0	0	2	0	0
Statement of aims/objectives in main body of report	3	3	3	3	2	3	3	3
Clear description of research setting	3	3	3	3	3	3	3	2
Evidence of sample size considered in terms of analysis	2	3	0	3	1	3	1	0
Representative sample of target group of a reasonable size	1	2	3	1	3	2	3	2
Description of procedure for data collection	3	3	2	2	2	2	3	2
Rationale for choice of data collection tool(s)	2	0	2	2	0	3	2	1
Detailed recruitment data	3	3	3	2	0	1	3	3
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	1	0	1	0	0	3	0	0
Fit between stated research question and method of data collection (Quantitative)	1	2	3	3	3	2	3	3
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	3	3	3	3	3	2
Good justification for analytical method selected	1	2	3	2	2	1	3	1
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-
Evidence of user involvement in design	0	0	0	0	0	2	0	0
Strengths and limitations critically discussed	3	3	3	2	3	3	3	2

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

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The Impact of Non-Menthol Flavors in E-Cigarettes on Perceptions and Use: An Updated Systematic Review

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The Impact of Non-Menthol Flavors in E-Cigarettes on Perceptions and Use: An Updated Systematic Review

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Objectives: Given the exponential increase in the use of e-cigarettes among younger age groups and in the growth in research on e-cigarette flavors, we conducted a systematic review examining the impact of non-menthol flavored e-cigarettes on e-cigarette perceptions and use among youth and adults.

Design: PubMed, Embase, PyscINFO, and CINAHL were systematically searched for studies published and indexed through March 2018.

Eligibility criteria: Quantitative observational and experimental studies that assessed the effect of non-menthol flavors in e-cigarettes on perceptions and use behaviors were included. Specific outcome measures assessed are: appeal, reasons for use, risk perceptions, susceptibility, intention to try, initiation, preference, current use, quit intentions, and cessation.

Data Extraction and Synthesis: Three authors independently extracted data related to the impact of flavors in tobacco products. Data from a previous review were then combined with those from the updated review for final analysis. Results were then grouped and analyzed by outcome measure.

Results: The review included 51 articles for synthesis, including 17 published up to 2016, and an additional 34 published between 2016-2018. Results indicate non-tobacco flavors in e-cigarettes decrease harm perceptions (5 studies) and increase willingness to try and initiation of e-cigarettes (6 studies). Among adults, e-cigarette flavors increase product appeal (7 studies) and are a primary reason many adults use the product (5 studies). The role of flavored e-cigarettes on smoking cessation remains unclear (6 studies).

Conclusions: This review provides summary data on the role of non-menthol flavors in e-cigarette perceptions and use. Consistent evidence shows that flavors attract both youth and adults to use e-cigarettes. Given the clear findings that such flavors increase product appeal, willingness to try, and initiation among youth, banning non-menthol flavors in e-cigarettes may reduce youth e-cigarette use. Longitudinal research is needed to examine any role flavors may play in quit behaviors among adults.

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Strengths and Limitations of the Study

- This large comprehensive review that included 51 final articles for synthesis, including 17 published up to 2016, and an additional 34 published between 2016-2018.
- The majority of studies were cross-sectional and were from convenience samples, limiting the ability to make causal inferences as well as the generalizability of findings from these articles.
- We used a quality assessment tool (QATSDD) to rate the quality of articles included in the review.
- Qualitative data, while excluded, could have provided additional contextual information to the conclusions.

Funding Statement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: The authors have no competing interests to disclose.

Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

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INTRODUCTION

Despite a ban on non-menthol flavors in cigarettes, current regulations in the United States allow for the sale of non-menthol flavors in other tobacco products, including e-cigarettes.[1] However, The FDA continues to seek out and prioritize research that explores the issue of non-menthol flavors in tobacco products other than cigarettes, and as such has issued an advance notice of proposed rulemaking seeking comments on the role that flavors play in tobacco product use.[2] Similarly, in fall of 2018 the FDA proposed a policy framework that would only allow non-menthol flavored e-cigarettes to be sold in age-restricted locations or online under heightened age verification standards.[3]

Some studies have shown that flavors are particularly appealing to youth and are cited as a primary reason for use among this age group.[4] The use of e-cigarettes among youth may be a gateway to future cigarette use,[5,6] and nicotine (which is found in most e-cigarettes) is especially harmful to developing adolescent brains.[7–9] This makes the recent precipitous increase in e-cigarette use among youth particularly alarming.[7] Policymakers, including the FDA, are increasingly concerned about the rise in popularity of pod-type e-cigarette devices (e.g. Juul), which now own a large market share and deliver more nicotine than older generations of e-cigarettes.[10,11]

E-cigarettes are also regarded by many experts in tobacco control as a potential means of harm reduction among adult smokers if they use e-cigarettes to transition away from combustible tobacco products.[12] A few studies have suggested a positive association between e-cigarettes and quitting behaviors, including a recent randomized controlled trial.[13–16] Unraveling the relationship between potential harms or benefits of e-cigarette use among adult smokers is important in the development of regulations for e-cigarettes, and in particular, regulations regarding product flavors.

It is well known that recent years have seen a precipitous increase in the use of e-cigarettes in the US and other countries among both youth and adults.[17] Recent data suggest that 20.8% of US youth[18] and 4.5% of US adults are current e-cigarette users.[19] These numbers vary globally, with 5.9% of adults and 8.2% of adolescents in Poland but only 0.3% of adults in Indonesia reporting current use.[20] However, upward trajectories of use have been noted globally,[20] and this increase in use has coincided with an exponential rise in e-cigarette flavors, with over 7,000 flavors existing.[21] Many of these flavors utilize names that may appeal to younger populations such as cotton candy, gummy bear, cookies ‘n cream, and other sweet-flavored brands.[21] The intense public health interest in e-cigarettes’ impact on the tobacco control landscape and population health has resulted in a sharp increase in research conducted on flavors and e-cigarettes. Given this changing landscape, we conducted a systematic review of non-menthol flavored e-cigarettes that extends previous research[4] by providing evidence specific to e-cigarettes about the role of non-menthol flavors in appeal, harm perceptions, intentions, use, and cessation among youth and adults in the US and globally.

METHODS

We used methods similar to previously published research,[4] and implemented two alterations: 1) updated the range of eligible publication dates (with the original including articles ever published until April 4, 2016, and the current review including articles published and indexed on or after April 4, 2016), and 2) focused this review specifically on e-cigarettes rather than all tobacco products, based on the precipitous increase in literature on e-cigarettes, as well as the increase in use of these products among youth and adults. All data relevant to the study are included in the article or uploaded as supplementary information.

Eligibility criteria

We included observational and experimental studies that assessed the impact of non-menthol flavors in e-cigarettes on perceptions and use behaviors such as initiation, preference, and cessation. We did not

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exclude studies based on participant characteristics. Studies included populations of any age, race, sex, ethnicity, or country.

We excluded the following types of articles: those that were not English-language; were not peer-reviewed (e.g., dissertations, technical reports); did not contain original data about flavored e-cigarettes (e.g., editorials, commentaries, literature reviews); did not address the impact of flavors on e-cigarette perceptions and use behaviors (e.g., biological/medical/chemical toxicology/animal studies, sales trends, effects of flavor bans); were related to smoking marijuana; or limited findings to menthol flavored e-cigarettes only. In order to maintain a semblance of consistency across studies examined, we chose to exclude articles that used qualitative study designs. Additionally, because menthol and tobacco are often treated differently as it relates to policy implementation (e.g., in 2009, FDA banned characterizing flavors except for tobacco and menthol in cigarettes) and is also often viewed separately from other flavors in the literature, this review excludes articles that examine just menthol as a flavor.[22] We do include tobacco in this review because despite the regulatory differences, some literature chooses to include tobacco as a characterizing flavor and we wanted to explore any potential relationships produced by the literature.

Type of outcome measures and intervention

Outcome measures include perceptions about appeal, reasons for use, and risk perceptions; susceptibility and intentions to try; and use behaviors, including initiation, preference, current use, quit intentions, and cessation.

Data sources and study selection

Literature search. One author (HMB) conducted searches of PubMed, Embase, PsycINFO and CINAHL for studies published and indexed in a database between April 4, 2016 and March 21, 2018. To maintain consistency with the previous systematic review, we maintained the same search string rather than modifying the search to include only e-cigarettes. We used Boolean language to connect variants of words related to tobacco products, use, and flavor for PubMed, which was translated to match the search string requirements for other databases. A total of 3,191 articles resulted from searching the four databases during the initial search (March 21, 2018). After authors removed duplicates, 2,822 articles remained for title and abstract review, including 14 articles identified through manual search of references.

Study selection. Two authors (CM and HMB) reviewed the titles and abstracts of all 2,822 articles. A third author (SDK) resolved any discrepancies. Following this step, two authors (CM and HMB) reviewed the full text of all 114 articles eligible for full-text screening. A third author (SDK) resolved any discrepancies. 80 articles were excluded for the following reasons: they did not have data on the specified outcomes (n=27), used qualitative methodologies (n=27), focused on a tobacco product other than e-cigarettes (n=12), were only focused on menthol flavor (n=2), was a duplicate (n=1), or were not peer-reviewed, did not include original data, did not include full-text, or included only a conference abstract (n=11). Articles that addressed e-cigarettes from the original systematic review (n=17) were then added to the 34 articles identified from this current review, combining for a total of 51 articles included in the final analysis. The study selection processes, which approximate but do not exactly follow the PRISMA methodology, are illustrated in Figure 1.[23]

Data extraction and synthesis

For the articles identified in the most current review, three authors (CM, HMB, SDK) independently extracted data using a data extraction sheet, which assessed study aim, type of flavored tobacco product, characteristics of study populations and study design, and main results and findings related to the impact of flavors in tobacco products. We used a validated quality assessment tool (QATSDD) to examine the quality of quantitative studies with a diverse range of research designs.[24] Studies were scored on a 4-point scale from 0 (did not address criteria at all) to 3 (completely addressed criteria), with specified guidance to inform scorers based on the level of detail provided by study authors.[24] Specific scores

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were not used for inclusion/exclusion or used in any analysis. Rather, the tool was used to provide a valuable overall assessment of the general quality of included studies from which our conclusions are based. To ensure agreement in data extraction and quality assessment, three authors (CM, HMB, SDK) reviewed and extracted the same three articles, then compared results of review and extraction, resolving discrepancies through an iterative approach of discussion. Once mutual standards were decided upon based on this process, each of the three authors then split up the remainder of articles to extract and assess on their own. We created evidence tables using pertinent information extracted from each study, and we grouped the results by outcome measures. A similar procedure was conducted in the previous review, and all data were combined for final data analysis. A meta-analysis was not conducted due to the heterogeneity in outcomes across studies.

Patient and public involvement

This research did not include input from patients or the public.

RESULTS

The review included 51 final articles for synthesis, including 17 published up to 2016 and 34 published between 2016-2018. Most studies included adults only (n=30), though 13 included youth and eight included both youth and adults (Table 1).

Table 1. Characteristics of included studies (N=51)

Sample characteristics		**N (%)**	**US Studies (N=37), N (%)**	**International Studies (N=14), N (%)**
Population	Youth only	13 (25)	9 (24)	4 (29)
	Adults only	30 (59)	22 (59)	8 (57)
	Both youth and adults	8 (16)	6 (16)	2 (14)
Design	Cross-sectional	47 (92)	33 (89)	14 (100)
	Longitudinal	4 (8)	4 (11)	0 (0)
Sampling (not mutually exclusive)	Convenience	35 (69)	23 (62)	12 (86)
	Probability	19 (37)	17 (46)	2 (14)
Outcome measure (not mutually exclusive)	Taste, appeal, perceived risk	14 (27)	10 (27)	4 (29)
	Reasons for use	13 (25)	11 (30)	2 (14)
	Susceptibility, intention to try/initiation	17 (33)	11 (30)	6 (43)
	Preference	9 (18)	7 (19)	2 (14)
	Current use behaviors	12 (24)	10 (27)	2 (14)
	Quit intention/quitting behavior	10 (20)	7 (19)	3 (21)

Results of this review are broken out into three age categories: youth, adults, and youth and adults combined. Studies defined these age groups differently, and we therefore used the age groups as defined by the study authors. Most youth were defined as anyone below age 18 (though some went up to age 19[25]), and most adults were defined as 18+. Additionally, though young adults are an important population and were included as a separate age group in some studies in the review, the variability in definitions of this age group made it difficult to separate for purposes of the results, (some defining as

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ages 19-34, some as ages 18-29, etc.) and we therefore included all young adults in the adult category. Specific age groups used by authors can be found in Table 2.

Table 2. Sample characteristics and objectives of included articles (* indicates study was included in original 2016 review)

Study ID (Country)	Sample size and study population	Study aim	Main findings on flavors' impact
Amato, 2015[26] (US)*	n=9,301 Adults (18+) Tobacco users and non-users	Investigate patterns of e-cigarettes' use in order to establish a standard definition of e-cigarette current use prevalence for the purpose of population surveillance.	Current e-cigarette users cited flavors as a reason for use more often than past users.
Audrain-McGovern, 2016[27] (US)	n=32 Young adults (18-30) Current cigarette smokers and had ever used an e-cigarette	Determine whether flavoring enhances the subjective rewarding value, relative reinforcing value, and absolute reinforcing value of an e-cigarette with nicotine compared to an unflavored e-cigarette with nicotine.	E-cigarette flavoring enhanced the rewarding and reinforcing value of e-cigarettes with nicotine compared to unflavored e-cigarettes with nicotine.
Barnes, 2017[28] (US)	n=36 Adults (18+) Current cigarette smokers naïve to e-cigarettes	Examine e-cigarettes' abuse liability compared to conventional tobacco cigarettes that varied in e-cigarette flavor and modified-risk message.	Cherry flavor increased abuse liability relative to unflavored e-cigarettes (i.e., increased the degree to which e-cigarettes led to physical/psychological dependence).
Berg, 2016[29] (US)*	n=1,567 Young adults (18-34) E-cigarette users, non-users; cigarette	Compare (1) e-cigarette never, current, and former users; (2) never, current, and former traditional cigarette smokers in relation to e-cigarette use characteristics, flavors	Flavors were frequently indicated as reason for use across smoking and non-smoking e-cigarette users

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	users, non-users	preferred and reasons for use; and (3) reasons for discontinued use among former e-cigarette users across never, current, and former smokers.	
Bold, 2016[30] (US)	n=340 Youth (middle school and high school students) Ever e-cigarette users	Investigate whether certain reasons for trying e-cigarettes would predict continued use over time.	Good flavors were highly endorsed by youth as a reason for trying e-cigarettes; in univariate models, endorsing good flavors as a reason for trying e-cigarettes predicted continued e-cigarette use and e-cigarette frequency, but was no longer a significant predictor after adjusting for other covariates including cigarette smoking status.
Brozek, 2017[31] (Poland)	n=46 Adults (18-35) E-cigarette users	Assess prevalence of e-cigarette and tobacco cigarette use; to compare the patterns of smoking; and to assess the attitudes and motivations for e-cigarette use.	More than one-fourth of e-cigarette users started using e-cigarettes because of the unique flavors.
Buckell, 2018[32] (US)	n=2,031 Adults (18-64) Current cigarette smokers or recent quitters	Estimate preferences for flavors in cigarettes and e-cigarettes while controlling for other attributes of both products, and study how these preferences vary with individual characteristics.	Among e-cigarette flavors, adult smokers preferred tobacco flavor over fruit/sweet and menthol flavors; younger adult smokers, those with a higher education, and those with a recent quit attempt prefer all flavors of e-cigarettes compared to tobacco cigarettes.
Camenga, 2017[33] (US)	n=189 Youth (14-18) and young adults (18-24)	Examine the prevalence and predictors of current and former smokers' use of e-cigarettes for smoking cessation.	Preference for using a combination of two or more e-cigarette flavors mixed together was associated with increased odds of using e-cigarettes for smoking

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	Lifetime cigarette smokers and ever e-cigarette users		cessation, relative to e-cigarette users without a preferred flavor.
Chen, 2017[34] (US)	n=18,392 Youth (11-18) Non-smokers	Explore association between e-cigarette use and smoking susceptibility among non-smoking youth.	Flavored e-cigarette use was associated with increased smoking susceptibility among non-smoking youth, particularly among females and those not susceptible to tobacco marketing.
Chen, 2018[35] (US)	n=4,645 Young adults (18-34) Current cigarette smokers at Wave 1	Examine differences in smoking reduction and cessation among young adult smokers who did not use e-cigarettes, who used e-cigarettes with tobacco and menthol/mint flavors, and who used e-cigarettes with one or multiple non-tobacco and non-menthol flavors.	Compared to non-e-cigarette users, users of non-tobacco/menthol e-cigarette flavors were more likely to have reduced or quit smoking cigarettes in the past year; current e-cigarette users highly endorsed using e-cigarettes because of appealing flavors, with those endorsing this reason for use more than twice as likely to have reduced or quit smoking in the past year than e-cigarette users who did not endorse this reason for use.
Clarke, 2017[25] (UK)	n=256 Youth (16-19) Tobacco users and non-users	Investigate factors that lead to willingness to try e-cigarettes among UK youth.	Youth reported a preference for non-tobacco flavored e-cigarettes, regardless of smoking status; youth with a more positive prototype of smokers were more willing to try flavored e-cigarettes, while youth with a more negative prototype of e-cigarette users were less willing to try flavored e-cigarettes.
Coleman, 2017[36] (US)	n=3,373 Adults (18+)	Examine patterns of current e-cigarette use among daily and non-daily adult users.	Appealing flavors were highly cited as a reason for e-cigarette use, particularly among never smokers; more

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	Current e-cigarette users		frequent e-cigarette users (daily vs. moderate or infrequent) were more likely to initiate with a non-tobacco flavored e-cigarette.
Cooper, 2016[37] (US)	n=3,704 Youth (grades 6, 8, and 10) Tobacco users and non-users	Evaluate harm perceptions and perceived addictiveness of e-cigarettes among youth.	Youth who were ever or current e-cigarette users had higher odds of reporting flavored e-cigarettes as less harmful than non-e-cigarette users.
Czoli, 2015[38] (Canada)*	n=915 Youth and young adults (16-24) and adults (25+) Users and non-users (youth and young adults) and users (adults)	Determine the effect of distinct attributes of e-cigarettes (flavors, nicotine content, health warnings, price) and attribute levels on consumer choice.	Flavors in e-cigarettes significantly predicted lower perceptions of product harm and ability to help someone quit smoking.
Dai, 2016[39] (US)	n=21,491 Youth (middle and high school students) Tobacco users and non-users	Examine the 1) association between flavored e-cigarette use and intention to initiate cigarette smoking among never-smoking youth, 2) association between flavored e-cigarette use and intention to quit tobacco use in the next 12 months among current youth smokers, and 3) association between flavored e-cigarette use and youth	Compared with not using e-cigarettes, flavored e-cigarette use was associated lower perceived harm of tobacco, higher intention to initiate cigarette use among never smoking youth, and lower quit intentions among current smoking youth.

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		perception of the danger of tobacco.	
Elkalmi, 2016[40] (Malaysia)	n=277 Primarily adults (18+) but 7.2% of sample was 17 or younger Tobacco users and non-users	Determine the prevalence of current e-cigarette use and identify sociodemographic factors, motivators, attitudes, and perceptions that are associated with current e-cigarette use.	The majority of respondents who had tried e-cigarettes reported that the variety of flavors contributed to more enjoyment of the product compared to conventional cigarettes.
Etter, 2010[41] (France, Belgium, and other countries)*	n=81 Adults (18+) Current e-cigarette users	Assess usage patterns of e-cigarettes, reasons for use and users' opinions of these products.	Adult e-cigarette users reported flavors as being the most positive feature of the product.
Etter, 2016[42] (France, US, Switzerland, UK, and other countries)	n=1,685 Adults (18+) Current e-cigarette users	Describe personal characteristics of vapers, their utilization patterns, any modifications of the devices, and compare users of pre-filled cartridges, refillable tanks, and modified models for their patterns of use, reasons for use, satisfaction, and perceived effects on smoking.	Tobacco flavor was reported to be the most preferred e-cigarette flavor among current users, particularly among those who had recently started vaping; most respondents reported that flavors helped them to either quit smoking or reduce their smoking consumption.
Farsalinos, 2013[43] (Online survey in 10 languages)*	n=4,618 Adults (18+) E-cigarette users	Examine the patterns and perceptions of flavoring use in e-cigarettes among dedicated users.	E-cigarette users who were former smokers were more likely to prefer fruit and sweet flavors compared to current smokers. E-cigarette users reported that the variability of e-cigarette flavors is an important factor in reducing or quitting cigarette smoking and a

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			greater number of flavors used was associated with smoking abstinence.
Farsalinos, 2014[44] (Online survey in 10 languages)*	n=19,441 Adults (18+) E-cigarette users	Assess the characteristics and experiences of a large, worldwide sample of e-cigarette users and examine the differences between those who partially and completely substituted smoking with e-cigarette use.	The variability of flavors was cited as one of the reasons for initiating e-cigarette use, though it was not a primary reason.
Ford, 2016[45] (UK)*	n=1,205 Youth (11-16) Tobacco users and non-users	Examine adolescents' awareness of e-cigarette marketing and investigate the impact of e-cigarette flavor descriptors on perceptions of product harm and user image.	Fruit and sweet flavors were perceived as more likely to be tried by young never smokers than adult smokers trying to quit. The perceived harmfulness of e-cigarettes was moderated by product flavors.
Goldenson 2016[46] (US)	n=20 Young adults (19-34) Current e-cigarette users	Assess whether sweet flavorings and nicotine affect e-cigarette appeal; sweet flavorings increase perceived sweetness; nicotine increases throat hit; and perceived sweetness and throat hit are associated with appeal.	Sweet-flavored e-cigarette solutions increased appeal (including liking, willingness to use again, and amount willing to pay) and perceived sweetness ratings.
Gubner 2017[47] (US)	n=168 Adults (18+) Weekly or daily e-cigarette users	Examine e-cigarette use by individuals in treatment for substance abuse.	A large proportion of daily and weekly e-cigarette users reported using e-cigarettes because they have good flavors; daily e-cigarette users were more likely to use more types of flavors compared to weekly users.
Harrell, 2017a[48] (US)	n=3,907 youth n=5,482 young adults	Investigate whether the use of flavored e-cigarettes varies	Initiation with and current use of flavored e-cigarettes was higher among youth and young adults compared to

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	n=6,051 adults Youth (12-17), young adults (18-29), and adults (30+) Tobacco users and non-users	between youth, young adults, and adults.	older adults, and citing flavor availability as a reason for use was higher among youth current users relative to young adults and older adults.
Harrell, 2017b[49] (US)	n=143 youth and n=1,325 young adults Youth (12-17) and young adults (18-29) Current tobacco product users	Determine the potential for reductions in the prevalence of young people's e-cigarette and tobacco use if characterizing flavors were not present.	The large majority of youth and young adult current tobacco users reported use of flavored e-cigarettes, and about three-fourths of flavored e-cigarette users reported they would no longer use the product if it was not flavored.
Kim, 2016[50] (US)	n=31 Adults (18+) Current e-cigarette users	Examine the extent to which the perception of sweet and other flavors is associated with liking and disliking of flavored e-cigarettes.	Flavors influenced hedonic ratings of e-cigarettes, such that, in general, sweetness and coolness were positively associated with liking while bitterness and harshness were negatively associated with liking of e-cigarettes.
Kinouani, 2017[51] (France)	n=1,086 University students (18+; more than 90% 18-24) Ever e-cigarette users	Describe the relationship between e-cigarette use and tobacco smoking and describe reasons for experimenting with e-cigarettes.	The third most cited reason for trying e-cigarettes was because of attractive flavors, behind reasons of curiosity and offered to try by someone.
Kong, 2014[52] (US)*	n=1,157	Assess reasons for e-cigarette experimentation and	Availability of flavors was a primary reason for experimentation with e-

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	Youth and young adults E-cigarette users	discontinuation and examine whether these reasons differed by school level (MS, HS, college) and cigarette smoking status.	cigarettes, and appealing flavors were particularly important to high school students.
Krishnan-Sarin, 2014[53] (US)*	n=4,780 Youth (middle school and high school students) Tobacco users and non-users	Examine e-cigarette awareness, use patterns, susceptibility to future use, preferences, product components used, and sources of marketing and access among youth.	Use and preference for sweet e-cigarette flavors was high among adolescents regardless of cigarette smoking status.
Lee, 2017a[54] (US)	n=1,185 Young adults (18-25) Tobacco users and non-users	Investigate the characteristics of potential and current e-cigarette users based on four different levels of use acceptability and determinants that promote e-cigarette acceptability.	A higher preference for the availability of flavors in e-cigarettes was associated with experimentation and current use of e-cigarettes among college students.
Lee, 2017b[55] (South Korea)	n=6,656 Youth (13-18) Ever e-cigarette users	Determine the relation between frequency of e-cigarette use and the frequency and intensity of conventional cigarette smoking; and identify the association between reasons for e-cigarette use and frequency of use.	Nearly 1 in 10 youth cited good flavors as the main reason for using e-cigarettes, though this reason ranked behind five others, including curiosity and potentially being less harmful.
Litt, 2016[56] (US)	n=88 Adults (18-55) Cigarette smokers	Examine the influence of flavoring on the smoking and vaping behavior of cigarette smokers asked to adopt e-cigarettes for 6 weeks.	Cigarette smoking frequency was most reduced in participants assigned to menthol-flavored e-cigarettes, while it was least reduced in those assigned to cherry and chocolate flavors; participants

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			assigned to tobacco-flavored e-cigarettes had the highest rates of vaping, while those assigned to chocolate had the lowest rates of vaping.
Maglalang, 2016[57] (US)	n=56 Asian American and Pacific Islander young adults (18-25) Current e-cigarette users	Characterize e-cigarette use and risk perceptions among Asian American and Pacific Islander young adults in California.	Fruit and candy/sweet flavors were most preferred by current e-cigarette uses, though citing flavors as a reason for using e-cigarettes was reported by a low percentage of respondents, behind a variety of other reasons.
Morean, 2018[58] (US)	n=396 adolescents and n=590 adults Adolescents (high school students) and adults (18+) Past-month e-cigarette users	Examine differences in adolescents' and adults' preferences for e-liquid flavors and whether their preferences or the total number of flavors preferred were associated with number of days of e-cigarette use in the past month.	Compared to adults, adolescents were more likely to prefer e-liquid flavors such as fruit, candy/dessert, and vanilla, while adults were more likely to prefer tobacco, menthol/mint, coffee, and spice flavors. Among adolescents (though not adults), preferences for particular e-liquid flavors (i.e., fruit, dessert, or alcohol flavored) and the total number of flavors preferred were associated with more frequent e-cigarette use.
Nonnemaker, 2016[59] (US)*	n=765 Adults (18+) Current or former smokers	Examines how e-cigarette attributes influence willingness to pay for e-cigarettes.	Losing flavors significantly reduced the price participants are willing to pay for e-cigarettes, though this relationship was not found for dual users of cigarettes and e-cigarettes.
Patel, 2016[60] (US)	n=2,448 Adults (18+)	Assess reasons for e-cigarette use among current e-cigarette users.	Reasons for e-cigarette use among current adult users varied by sociodemographic and user characteristics; notably, flavorings were more

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	Current e-cigarette users		likely to be cited as a reason for use among younger age groups (ages 18-24, 25-34, and 35-54).
Pepper, 2013[61] (US)*	n=228 Youth (11-19), males Tobacco users and non-users	Sought to understand awareness of and willingness to try e-cigarettes among adolescent males.	Flavored e-cigarettes did not increase male adolescents' willingness to try e-cigarettes compared to plain varieties.
Pepper, 2014[62] (US)*	n=3,878 Adults (18+) Tobacco users and non-users	Explore reasons for starting and then stopping e-cigarettes use and examine differences in discontinuation by reason for trying among population-based sample of US adults.	Few adult e-cigarette users reported starting e-cigarette use because of the available flavors.
Pepper, 2016[63] (US)	n=1,125 Youth (13-17) Tobacco users and non-users	Examine the impact of flavor on interest in trying e-cigarettes and harm beliefs.	Adolescents were more interested in trying menthol, candy, or fruit-flavored e-cigarettes than tobacco or alcohol flavors; belief that these particular flavors were less harmful than tobacco or alcohol flavors party mediated this relationship.
Pesko, 2016[64] (US)	n=1,020 Adults (18+) Current cigarette smokers	Determine the preferences and relative importance placed on e-cigarette warning labels, flavor regulation, and prices.	Restriction of flavor availability in e-cigarettes to tobacco and menthol was associated with a significant reduction in e-cigarette selection, particularly among young adults compared to older adults.
Russell, 2018[65] (US)	n=20,836 Adults (18+) Frequent e-cigarette users	Examine flavor preferences of frequent e-cigarette users.	Adults are increasingly initiating e-cigarette use with non-tobacco flavors, particularly fruit and dessert flavors; never smoker e-cigarette users were more likely to initiate with and

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			currently use fruit/fruit beverage-flavored e-cigarettes compared to switchers, dual users, and former smoker e-cigarette users.
Rutten, 2015[66] (US)	n=582 Adults (18+) Current dual users of cigarettes and e-cigarettes	Assess attitudes, beliefs, and behaviors relating to e-cigarette use among current cigarette smokers.	Dual users of cigarettes and e-cigarettes ranked appealing flavors relatively low on the list of reasons for using e-cigarettes; no differences in smoking quit intentions or reduction in the use of cigarettes was observed for those reporting using e-cigarettes because of flavors compared to those not reporting using e-cigarettes because of the flavors.
Shang, 2017[67] (US)	n=515 Youth (14-17) Tobacco users and non-users	Understand how different attributes (flavors, health warnings, device types) influence youth's decisions to choose e-cigarettes.	Among youth ever and never e-cigarette users, fruit/sweet/beverage flavors increased the probability that a youth chose an e-cigarette product.
Shiffman, 2015[68] (US)*	n=216 (youth) n=432 (adults) Youth (13-17) Adults (19-80) Non-users (youth) and users (adult)	Compare e-cigarettes interest between nonsmoking teens and adult smoker, across flavors and assess differences in flavor preferences among adult smokers based on e-cigarettes use history.	The interest of nonsmoking teens in trying flavored e-cigarettes was very low, and interest was not influenced by flavor descriptors. Though adult smokers' interest was also modest, their interest was significantly higher than that of nonsmoking teens for each flavor.
Shiplo, 2015[69] (Canada)*	n=1,095 Youth and young adults (16-24)	Examines e-cigarette ever and current use, types of products used, and reasons for use.	Use of flavored e-cigarettes varies by smoking status, with smokers being more likely to try flavors than non-smokers. A common reason

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	Adults (25+) Non-smokers and smokers (youth and young adults) and smokers (adults)		for e-cigarette use is for the taste.
Spears, 2018[70] (US)	n=550 Adults (18+) Current e-cigarette users	Examine reasons for e-cigarette use and related risk perceptions among individuals with and without mental health conditions.	Compared to former smokers without mental health conditions, former smokers with mental health conditions placed higher importance on appealing flavors as a reason for e-cigarette.
Tackett, 2015[71] (US)*	n=215 Adults (18+) E-cigarette users	Estimate e-cigarettes preference, e-cigarettes use behaviors, perceived harm and health beliefs of various smoking cessation medications, nicotine replacement therapies and nicotine/tobacco products, and smoking history and current biochemically verified smoking status.	Most e-cigarette users reported a preference for vaping non-traditional flavors. Those who reported vaping non-tobacco and non-menthol flavors were more likely to have quit smoking compared to those who vaped traditional (tobacco/menthol) flavors.
Tsai, 2018[72] (US)	n=4,049 Youth (grades 6-12) Ever e-cigarette users	Assess self-reported reasons for e-cigarette use among middle school and high school student e-cigarette users.	One of the primary reasons for e-cigarette use by middle school and high school students was the availability of flavors, particularly among high school students.
Vasiljevic, 2015[73] (UK)*	n=471 Youth (11-16) Non-e-cigarette users	Assess the impact on appeal of tobacco smoking after exposure to advertisements for e-cigarettes with and without candy-like flavors.	Flavored, compared to non-flavored, e-cigarette advertisements elicited greater interest in buying and trying e-cigarettes.

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Weaver, 2018[74] (US)	n=858 Adults (18+) Current cigarette smokers	Assess the effect of "real world" e-cigarette use on population quit rates of adult smokers, accounting for frequency of use, device type, e-liquid flavor, and reasons for use.	Compared to non-e-cigarette users, users of menthol/wintergreen/mint or other non-tobacco/menthol flavor e-cigarettes (e.g., fruit, dessert, spice) were more likely to report a quit attempt, but users of other non-tobacco/menthol e-cigarette flavors had significantly lower odds of quitting smoking than non-users of e-cigarettes in the past year.
Yingst, 2015[75] (US and other countries)*	n=421 (87% in US; 13% outside US) Adults (18+) E-cigarette users	Examine the frequency with which e-cigarette users transition between device types and identify device characteristics and user preferences that may influence such transitions.	Most e-cigarette users began use with a device shaped like a cigarette (first generation devices) and transitioned to a larger advanced generation device with a more powerful battery and a wider choice of liquid flavors. Advanced generation device e-cigarette users report the variety of flavors as being important characteristic of e-cigarettes.

72% (n=37) of included studies were conducted in the US. While four studies used longitudinal designs, most (n=47; 92%) were cross-sectional. Study populations, aims, and relevant outcomes are provided in Table 2, with more detailed descriptions of analytical methods and results included in Supplementary Table 1.

Taste, appeal, and risk perceptions

Youth

Four studies surveyed probability samples of youth and assessed harm perceptions of e-cigarettes, all observing similar results. Three studies of youth in the US (two national samples and one state-wide sample) and one national sample of youth in the UK found that perceptions of e-cigarette harm differed depending on the product flavoring. Specifically, fruit and candy-flavored e-cigarettes were perceived as less harmful than tobacco-flavored e-cigarettes,[45,63] and ever or current e-cigarette users were less likely than non-users to perceive flavored e-cigarettes or tobacco as harmful.[37,39]

Adults

Eight studies were conducted among adults, including three laboratory experiments and one discrete choice experiment that examined the effect of e-cigarette flavors on factors such as ratings of taste and appeal.[27,28,46,50] Four studies included relatively small convenience samples of adults, each finding similar results: flavors in e-cigarettes enhanced the rewarding and reinforcing value of e-cigarettes compared to unflavored e-cigarettes,[27] and the appealing sensory characteristics of flavors (i.e.,

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sweetness and coolness) were positively associated with liking of the product,[46,50] the willingness to use again, and an increase in amount willing to pay for the product.[28,46] Similarly, in a cross-sectional survey of 765 current or former adult smokers, removal of flavors significantly reduced the price respondents were willing to pay for e-cigarettes, though this association was not observed among dual users of cigarettes and e-cigarettes.[59] One study in the US and two international studies likewise found that among ever or current e-cigarette users, the taste and variety of flavors were positive features of e-cigarettes and contributed to increased enjoyment of the product.[35,40,41]

Youth and Adults

Two studies examined appeal and harm perceptions in convenience samples of youth and adults. A sample of 216 youth and 432 adults in the US found that adult smokers rated interest toward e-cigarettes significantly higher than non-smoking teens for each e-cigarette flavor examined (note: study was funded by an e-cigarette company).[68] One discrete choice experiment in Canada (n=915) found that e-cigarette flavor significantly predicted lower perceptions of product harm; specifically, in the overall sample, menthol and coffee flavors were perceived as less harmful; among younger non-smokers, coffee-flavored was perceived as less harmful, while younger smokers perceived cherry flavor as less harmful and older smokers perceived tobacco-flavored as less harmful.[38]

Reasons for use

Youth

Two national probability samples of youth examining reasons for e-cigarette use found varied results. Less than 10% of South Korean youth who ever used e-cigarettes reported using the product because of good flavors,[55] compared to roughly a third of US students reporting ever using e-cigarettes because of the availability of flavors, with high school students more likely than middle school students to report flavors as a reason for use.[72]

Adults

Nine studies in the US examined reasons for using e-cigarettes among adults, also finding varied results. Three probability samples (two national and one state-wide) found that a majority of current e-cigarette users cited appealing flavors as a reason for using e-cigarettes,[26,35] particularly among never cigarette smokers compared to current and former smokers.[36] Another national probability sample in the US (n=550) found that former smokers with mental health conditions placed a higher importance on appealing flavors as a reason for use compared to former smokers without mental health conditions.[70] Further, about 40% of daily and weekly e-cigarette users (n=168) at substance use treatment centers reported good flavors as a reason for using e-cigarettes.[47] Among a convenience sample of 1,567 young adults, roughly a third of those who were non-e-cigarette users reported appealing flavors as a reason for possible e-cigarette use in the future, while a majority of current e-cigarette users reported appealing flavors and the ability to experiment with a variety of flavors as reasons for use.[29] Three other studies in the US (two national probability samples and one small convenience sample) observed relatively low proportions of current adult e-cigarette users reporting using e-cigarettes because of product flavorings, behind a variety of other reasons for use,[57,60,66] though flavors were more likely to be cited as a reason for use among younger age groups, particularly young adults ages 18-24, and among users of tank devices compared to disposables.[60]

Youth and Adults

Two studies in the US and Canada among youth and adults found that citing flavor availability or taste as a reason for e-cigarette use was higher among younger e-cigarette users compared to older users.[48,69]

Susceptibility, intention to try, and initiation

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Youth

Seven studies in the US and the UK examined susceptibility, intention to try, or initiation of e-cigarettes among youth. One study of a national probability sample of 228 adolescent males in the US found no differences in willingness to try flavored e-cigarettes compared to plain e-cigarettes.[61] However, the other six studies reported positive associations between flavors and e-cigarette use intentions. In a convenience sample of 340 youth in the US who were ever e-cigarette users, more than 40% endorsed good flavors as a reason for first trying e-cigarettes, the second highest endorsed reason.[30] Similarly, in a convenience sample of 256 UK youth, cigarette smokers and non-smokers were more willing to try flavored e-cigarettes than tobacco-flavored e-cigarettes (90% vs. 73% and 34% vs. 12%, respectively); further, having a positive prototype of smokers was associated with increased willingness to try flavored e-cigarettes.[25] Three different studies using national probability samples of US youth found similar relationships between flavors and e-cigarette use susceptibility and intentions to use. Adolescents were more likely to try menthol-, candy-, or fruit-flavored e-cigarettes compared to tobacco-flavored e-cigarettes;[63] and flavored e-cigarette use among non-smoking youth was associated with increased intention to initiate cigarette use[39] and smoking susceptibility, particularly among females and those not susceptible to tobacco marketing.[34] Finally, a convenience sample of 471 non-e-cigarette using youth in the UK found that exposure to flavored e-cigarette ads, compared to non-flavored e-cigarette ads, increased interest in buying and trying e-cigarettes.[73]

Adults

Six studies conducted in the US and internationally examined intention to try or initiation of e-cigarettes among adults. Two studies using convenience samples of young adults in Poland (n=46) and France (n=1,086) both found roughly 25-30% of e-cigarette users tried or started using e-cigarettes because of the variability of flavors, though other reasons for initiation were rated more highly than flavors.[31,51] Similarly, among an online convenience sample of international e-cigarette users (n=19,441) (note: study was funded by an e-cigarette advocacy group) and among a combined probability and non-probability sample of US adults (n=3,878), the availability of appealing flavors was not frequently cited as a reason for e-cigarette initiation.[44,62] However, two convenience samples of US adults found that the availability of flavors in e-cigarettes was associated with increased intention to use the product among young adult college students,[54] and never smoker e-cigarette users were more likely to have initiated e-cigarette use with a fruit-flavored product compared to switchers (from regular cigarette smoking to regular e-cigarette use), dual users, and former smoker e-cigarette users.[65]

Youth and Adults

Four studies examined interest in trying and initiation of e-cigarettes among youth and adults. One study of 648 youth and adults in the US observed that adult smokers' interest in trying e-cigarettes was significantly higher than non-smoking teens' interest for all 15 e-cigarette flavors investigated (note: study was funded by an e-cigarette company).[68] However, the three other studies conducted found similar results in that youth and younger adults in Canada expressed more interest in trying non-tobacco-flavored e-cigarettes than older adults;[38] high school students in the US were more likely to experiment with e-cigarettes because of flavors compared to college students, with 40% of the overall sample (n=1,157) reporting the availability of flavors as a reason for experimentation with e-cigarettes;[52] and youth and young adults reported higher initiation with flavored e-cigarette use compared to tobacco-flavored e-cigarettes.[48]

Preference

Youth

In three studies of youth, one discrete choice experiment of 515 e-cigarette ever and never users in the US found that fruit, sweet, and beverage flavors increased the probability (relative to tobacco flavor) of choosing an e-cigarette product.[67] A national probability sample of 1,205 UK youth examined how youth perceive others to use e-cigarettes; youth perceived adult smokers who were trying to quit smoking

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as less likely to prefer cherry, candy floss, or coffee flavored e-cigarettes, whereas youth perceived adolescents their age to be more likely to try flavored e-cigarettes compared to tobacco-flavored.[45] Further, a convenience sample of 4,780 middle school and high school students in the US found that most ever e-cigarette users—regardless of cigarette smoking status—had tried and preferred sweet flavors compared to menthol and tobacco flavors.[53]

Adults

Four studies examined preference among adults in relation to e-cigarette flavors. One international study of 421 e-cigarette users found that those using an advanced generation e-cigarette device were more likely to rate a variety of flavor choices as important, relative to users of first-generation devices.[75] A laboratory experiment of a small convenience sample of adults in the US observed that ever e-cigarette users took twice as many puffs from flavored e-cigarettes compared to unflavored e-cigarettes.[27] Further, a discrete choice experiment of 2,031 adults in the US found that adult smokers preferred tobacco-flavored e-cigarettes to fruit/sweet and menthol flavors,[32] while another discrete choice experiment of 1,020 adults observed that increased flavor availability increased e-cigarette selection for younger cigarette smokers, but not for older smokers.[64] Additionally, regardless of interest in quitting cigarettes, greater flavor availability increased e-cigarette selection.[64]

Youth and Adults

Two convenience samples of US youth and adults found that, compared to adult e-cigarette users, adolescent users were more likely to prefer e-cigarette flavors such as fruit and alcohol, while adults were more likely to prefer tobacco, menthol/mint, coffee, and spice flavors; further, adult users preferred a greater number of e-cigarette flavors than adolescents.[58] Among 1,468 youth and young adults currently using tobacco, most reported use of flavored e-cigarettes, and roughly three-quarters of those reported they would not use e-cigarettes if they were not available in a flavored form, such as candy, fruit, or mint/menthol.[49]

Current use behaviors

Youth

Two studies among US youth examined e-cigarette use behaviors. In a longitudinal study of 340 ever e-cigarette users, youth who initiated e-cigarette use because of good flavors were more frequent users of e-cigarettes, though this association was no longer significant after adjustment for other covariates.[30] Additionally, in a national probability sample of 18,395 never smoking youth, those who used e-cigarettes three or more days in the past 30 days were more likely to be flavored e-cigarette users than those who had used e-cigarettes only one or two days in the past 30 days.[34]

Adults

Eight studies among adults examined current e-cigarette use behaviors in relation to flavors. A two-phase longitudinal laboratory study of 88 current cigarette smokers in the US assigned e-cigarettes to participants as substitution for cigarettes; the highest vaping rates were observed for those assigned to tobacco flavored e-cigarettes, and the lowest rates were observed for those assigned to chocolate-flavored.[56] A convenience sample of 168 e-cigarette users found that daily e-cigarette users reported using more types of flavors and were more likely to have used tobacco flavor or fruit/berry flavor compared to weekly users,[47] while a national probability sample of 4,645 young adults in the US found that users of non-tobacco/menthol flavors were more likely to vape daily compared to tobacco/menthol flavored e-cigarette users,[35] Another national probability sample of 3,373 current e-cigarette users in the US found that daily e-cigarette users were more likely to have initiated with a non-tobacco flavored e-cigarette, compared to moderate or infrequent e-cigarette users.[36] A convenience sample of 1,185 college students in the US found that a higher preference for the availability of flavors in e-cigarettes was associated with a higher likelihood of currently using e-cigarettes.[54] One international survey of 4,618 e-cigarette users showed that users who were former smokers were more likely to prefer fruit and sweet

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flavors compared to current smokers (note: study was promoted by an e-cigarette advocacy group).[43] Another survey of 1,685 e-cigarette users found that tobacco flavor was used by nearly half of the respondents who had started vaping the past three months, compared to only a quarter of those who had been vaping for at least four months.[42] Lastly, a convenience sample of 20,836 frequent e-cigarette users in the US found that the highest rate of current tobacco-flavored e-cigarette use was reported by those who initiated e-cigarettes five or more years ago, while the lowest rate of tobacco-flavored e-cigarette use was reported by those who initiated within the past year; those who initiated in the past year had the highest rate of fruit, dessert, and candy/sweet flavored e-cigarette use, and never smoker e-cigarette users were more likely to use fruit-flavored products and less likely to use tobacco-flavored products compared to ever cigarette smokers.[65]

Youth and Adults

Two studies of youth and adults in the US reported similar findings related to a preference for flavors among younger e-cigarette users. Nearly all youth and young adult current users (a probability and convenience sample in Texas and nationwide) reported a usual e-cigarette that was flavored with something other than tobacco (97-98%), compared to roughly 70% of older adults.[48] Similarly, a survey of 986 adolescents and adults in the US found that adolescents who preferred to use fruit, dessert, or alcohol-flavored e-cigarettes reported using e-cigarettes more frequently, and preferring to use a greater number of flavors was associated with using the product more frequently in the past month, though these relationships were not seen among adult e-cigarette users.[58]

Quit intentions and quitting behavior

Youth

In regards to smoking cessation, one national probability sample of 21,491 youth in the US found that among current smokers, students who reported using flavored e-cigarettes were less likely to quit tobacco use compared with those who reported not using e-cigarettes or with those who had used non-flavored e-cigarettes.[39]

Adults

Seven studies examined the relation between flavors in e-cigarettes and quit intentions and quitting behavior among adults, finding varied results. One longitudinal study of 4,645 young adult cigarette smokers in the US found that e-cigarette users who used at least one non-tobacco/menthol flavor were more likely to have reduced or quit smoking cigarettes in the past year compared to non-e-cigarette users, and e-cigarette users who reported using e-cigarettes because of appealing flavors were more than twice as likely to have reduced or quit smoking compared to those who did not endorse using e-cigarettes for that reason.[35] Another longitudinal study of 858 cigarette smokers in the US similarly found that users of non-tobacco flavor e-cigarettes (e.g., fruit, dessert, spice) were more likely than non-e-cigarette users to report a quit attempt in the past 12 months; however, users of non-tobacco/menthol flavors were less likely to have quit smoking compared to non-e-cigarette users.[74] In a two-phase longitudinal laboratory study among 88 cigarette smokers, cigarette smoking frequency was most reduced in participants assigned to menthol-flavored e-cigarettes, while it was least reduced in those assigned to cherry or chocolate flavored e-cigarettes.[56] Two international surveys of current e-cigarette users both found that e-cigarette flavors were an important factor in helping to reduce or quit cigarette smoking,[42,43] and the number of e-cigarette flavors used was associated with smoking abstinence (note: study was promoted by an e-cigarette advocacy group).[43] Further, a convenience sample of 215 e-cigarette users in the US found that e-cigarette users reporting use of non-tobacco/menthol flavors were more likely to have quit smoking compared to those vaping tobacco/menthol flavors,[71] while a national probability sample of 582 dual users in the US found no differences in smoking quit intentions or smoking reduction for those reporting using e-cigarette because of the flavors compared to e-cigarette users not endorsing use of e-cigarettes for that reason.[66]

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Youth and Adults

Two studies among youth and adults examined quit intentions and behaviors. A discrete choice experiment of 915 Canadian tobacco users and non-users observed that menthol and coffee flavored e-cigarettes were perceived as having a greater quit efficacy.[38] In a convenience sample of 189 youth and young adult ever e-cigarette users in the US, preference for using a combination of at least two e-cigarette flavors mixed together was associated with increased likelihood of using e-cigarettes to quit smoking, relative to not having a preferred e-cigarette flavor.[33]

Quality assessment

We used a validated quality assessment tool (QATSDD) to examine the quality of studies with a diverse range of research designs.[24] In this quality assessment tool, there are 14 criteria and each criterion is rated on a 4-point scale (0-3), with a maximum score of 42. Because the studies examined in this review use a variety of methodological approaches, the QATSDD tool was chosen as it was developed specifically for this purpose and has been shown to provide valid, reliable assessments of study quality.[24] Studies were scored on the criteria listed below, and all scores and criteria can be found in Supplementary Table 2. Quality assessment scores relative to the maximum score possible ranged from 38% to 88% with a mean score of 66%. Nearly all studies sufficiently detailed their aims and objectives, the research setting, recruitment and data collection, the fit between their research question and method of data collection and analysis, justification for their analytical method, and the study strengths and limitations (see QATSDD scores in Supplementary Table 2). However, few studies reported an explicit theoretical framework, user involvement in study design (e.g., cognitive interviewing of survey measures), evidence of sample size consideration, or statistical assessment of reliability and validity of measurement tools. A low score on these criteria do not necessarily mean that the study authors did not consider it (e.g., power calculations that were not reported); rather, the criteria was not sufficiently described in the manuscript. Of note, three studies were funded or promoted by the e-cigarette industry or e-cigarette user advocacy groups.[43,44,68]

DISCUSSION

Given the sharp increase in both the use of e-cigarettes (particularly among youth) and the amount of new research related to e-cigarettes and flavors published from 2016-2018 alone, this systematic review provides a necessary update of a previous review that included research on e-cigarettes and non-menthol flavors among youth and adults.[4] This synthesis of evidence regarding the role of non-menthol flavors in e-cigarettes on product perceptions and use is particularly relevant to the FDA's recently proposed policy framework that seeks to place additional regulations on the sale of non-menthol flavored e-cigarettes to youth.[3] 17 studies examining flavors in e-cigarettes were published up to 2016; from 2016-2018, 34 new studies were published, *doubling* the research in just two years.

This new review significantly expands earlier findings about e-cigarettes and flavor among youth and adults. The previous review showed initial evidence that flavors in e-cigarettes were primary reasons for willingness to try or use the products. This expanded systematic review includes emerging longitudinal data and adds evidence on the role of flavors in e-cigarettes among youth and adults. Among youth, flavors increase not only preferences for e-cigarettes, but they also increase e-cigarette product appeal, willingness to use, susceptibility to use, and initiation, as well as decrease e-cigarette product harm perceptions. Among adults, the expanded research now shows that e-cigarette flavors increase product appeal and enjoyment, and the availability of flavors are a primary reason for use for many adults. Further, our quality review process provides important insight for researchers in this field to improve the rigor of e-cigarette research and includes essential information on study sample size and the reliability or validity of measures.

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Findings highlight the following: youth prefer non-tobacco flavored e-cigarettes;[49,53,58,67] flavors—particularly sweet flavors such as fruit and candy—decreased perceived product harm;[37–39,45,63] and the availability of appealing flavors is associated with an increased willingness to try e-cigarettes, initiation of e-cigarettes, and susceptibility to cigarette smoking.[25,30,34,39,63,73] Findings specific to adults are more varied, but demonstrate that non-menthol flavors in e-cigarettes increase appeal, enjoyment, and the price users are willing to pay for the product[27,35,40,41,46,50,59] and are a primary reason many adults use e-cigarettes.[26,29,35,36,47,70] Evidence on whether non-menthol flavored e-cigarettes promote or disrupt cessation among adult smokers remains unclear.[35,42,43,56,71,74]

Given that non-menthol flavors available in e-cigarettes attract youth to use these products, the impetus for policymakers to address the issue is strong. Results from the current review make it clear that banning flavors in e-cigarettes would discourage youth use of these products; however, doing so may also discourage adult smokers from using e-cigarettes for smoking cessation.[76] It is also important to consider the context in which each of these studies was conducted; because this review included results from both US and global studies, policies may differ and individual cultural contexts around e-cigarette use may have affected the outcomes.

Policy action at the federal level regarding flavored tobacco products has recently been undertaken, with the FDA seeking to limit the sale of non-menthol flavored e-cigarettes to age-restricted locations and heightening age verification practices for products sold online.[3] Also of note in that same announcement is FDA's consideration of banning menthol in cigarettes, which would significantly impact the tobacco control landscape.[3] FDA's recent proposed action appears to be affecting manufacturers; the tobacco company Altria recently announced they would halt the sale of multiple e-cigarette products they produce, including flavored products,[77] and Juul Labs also announced a suspension of its non-menthol flavored e-cigarettes in retail stores.[78] In the meantime, states and localities have the authority to restrict the sale of flavored tobacco products, including flavored e-cigarettes. A comprehensive review of flavored e-cigarette regulations from 2017 showed that at the time, over 100 localities had implemented restrictions on the sale of flavored e-cigarettes.[79] Movement has continued to be made on this topic since that review; for instance, San Francisco passed a measure to ban the sale of all flavored tobacco products,[80] including e-cigarettes, in 2018. Jurisdictions globally have taken steps to more broadly regulate flavors in all tobacco products, recognizing their impact on youth.[17,81] This is in accordance with the 2010 WHO Framework Convention on Tobacco Control guidelines that recommends restricting or banning flavors in all tobacco products.[82]

Based on the results of this review, it is important to consider deficits in the literature that would assist policymakers in developing the most impactful regulations. For one, it is important to note that the literature does not have a consistent and standardized way to categorize flavors. Yingst and colleagues (2017) have attempted to identify such a classification system, which, if used by researchers, would allow results to be more easily compared across studies.[83] This would also assist policymakers in regulating flavors more easily, as it is possible that some categories of flavors may be more appealing to youth than others. Similarly, because much of the research uses varying categories to examine age, it makes it difficult to disaggregate the effects flavors have on different age groups. Doing so would especially be helpful to policymakers who are trying to create regulations that would have the most impact on youth initiation while maintaining the potential for adult harm reduction, though more research is needed to explore the latter. Furthermore, use of the QATSDD tool reveals deficits in the existing literature. Few studies provided evidence of sample size consideration or commented on the reliability or validity of their measurement tools. Reviewing these types of parameters before publishing may ensure that researchers are providing the most rigorous explanation of their research as possible. Finally, since so few longitudinal studies are present, it may be beneficial for researchers to use such data sets as PATH to show longitudinal trends in the outcomes presented in this review, in an effort to strengthen the existing body of literature with longitudinal data.

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Limitations

Our review is limited in several ways. First, relevant articles may have been missed due to the exclusion of grey literature, doctoral dissertations, and non-English language articles; articles published within the search period (before March 2018) may also have been missed if they were not indexed in one of the searched databases by the time of the search. Similarly, we excluded qualitative articles in order to maintain consistency in data reviewed, though we recognize that qualitative data could potentially provide important contextual information on this topic. Second, a minimum threshold for study quality was not set, though only three studies received a score lower than 50% on the quality assessment (with scores of 48%, 45%, and 38%), and the mean score of all studies was 66%. Further, three studies were funded or supported by the e-cigarette industry or user advocacy groups.[43,44,68] Findings from these studies, and studies scoring lower in study quality, should be interpreted with caution. Third, more than 90% of studies were cross-sectional in nature, preventing us from making causal inferences between flavors and the perceptions and use of flavored e-cigarettes. Future research using longitudinal designs could further elucidate the role of flavors, particularly their effect on behavioral outcomes such as initiation among youth and cessation among adult smokers. Fourth, nearly half of all studies were conducted with convenience samples in the US, limiting the generalizability of findings, though nearly 40% of all studies did use probability-based sampling. Lastly, as research on e-cigarette flavors continues to evolve and additional research is regularly published, periodic updates of this review will be needed.

Conclusions

This systematic review provides a necessary update and extension of all evidence published to date on the role of flavors in e-cigarette perceptions and use behaviors. The increasing evidence among youth is clear: flavors in e-cigarettes (particularly sweet flavors) increase product appeal, decrease product harm perceptions, and increase willingness to use and initiation of e-cigarettes. Similarly, findings among adults demonstrate that flavors increase product appeal and enjoyment, and the availability of flavors are a primary reason for use for many adults. As the role of e-cigarettes in smoking cessation—and particularly how flavors impact this relationship—remains unclear, longitudinal studies of adult smokers are needed to assess the effect that e-cigarettes may have promoting or disrupting efforts to reduce or quit cigarette use. Regardless, findings are clear that banning flavors in e-cigarettes would discourage youth use of these products.

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REFERENCES

1 U.S. Food and Drug Administration. Menthol and Other Flavors in Tobacco Products. 2018.https://www.fda.gov/tobaccoproducts/labeling/productsingredientscomponents/ucm2019416.htm (accessed 24 Jul 2018).

2 U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to reduce tobacco use, especially among youth, by exploring options to address the role of flavors – including menthol – in tobacco products. 2018.https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM601690.htm?utm_source=Eloqua&utm_medium=email&utm_term=StratComms&utm_content=pressrelease&utm_campaign=CTP News%26Connect%26SOS%3A ANPRM Flavors—32018 (accessed 9 Oct 2018).

3 U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on proposed new steps to protect youth by preventing access to flavored tobacco products and banning menthol in cigarettes. 2018.https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-proposed-new-steps-protect-youth-preventing-access (accessed 3 May 2019).

4 Huang L-L, Baker HM, Meernik C, *et al.* Impact of non-menthol flavours in tobacco products on perceptions and use among youth, young adults and adults: A systematic review. *Tob Control* 2017;**26**. doi:10.1136/tobaccocontrol-2016-053196

5 Bold KW, Kong G, Camenga DR, *et al.* Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth. *Pediatrics* 2018;**141**.

6 Chaffee BW, Watkins SL, Glantz SA. Electronic Cigarette Use and Progression From Experimentation to Established Smoking. *Pediatrics* 2018;**141**. doi:10.1542/peds.2017-3594

7 U.S. Department of Health and Human Services. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta, GA: 2016. https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf (accessed 27 Jul 2018).

8 Yuan M, Cross SJ, Loughlin SE, *et al.* Nicotine and the adolescent brain. *J Physiol* 2015;**593**:3397–412. doi:10.1113/JP270492

9 England LJ, Bunnell RE, Pechacek TF, *et al.* Nicotine and the Developing Human: A Neglected Element in the Electronic Cigarette Debate. *Am J Prev Med* 2015;**49**:286–93. doi:10.1016/j.amepre.2015.01.015

10 Goniewicz ML, Boykan R, Messina CR, *et al.* High exposure to nicotine among adolescents who use Juul and other vape pod systems ('pods'). *Tob Control* 2018;**0**:1–2. doi:10.1136/tobaccocontrol-2018-054565

11 Huang J, Duan Z, Kwok J, *et al.* Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tob Control* 2018;:1–6. doi:10.1136/tobaccocontrol-2018-054382

12 Warner KE, Mendez D. E-cigarettes: Comparing the Possible Risks of Increasing Smoking Initiation with the Potential Benefits of Increasing Smoking Cessation. *Nicotine Tob Res* 2018;:1–7. doi:10.1093/ntr/nty062

13 Hajek P, Phillips-Waller A, Przulj D, *et al.* A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N Engl J Med* 2019;**380**:629–37. doi:10.1056/NEJMoa1808779

14 Beard E, West R, Michie S, *et al.* Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *BMJ* 2016;**354**:i4645. doi:10.1136/bmj.i4645

15 Bullen C, Knight-West O. E-cigarettes for the management of nicotine addiction. *Subst Abuse Rehabil* 2016;**7**:111–8. doi:10.2147/SAR.S94264

16 McRobbie H, Bullen C, Hartmann-Boyce J, *et al.* Electronic cigarettes for smoking cessation and reduction (Review). *Cochrane Libr* 2014;**12**.

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doi:10.1002/14651858.CD010216.pub2.www.cochranelibrary.com
17 Kennedy RD, Awopegba A, De León E, *et al.* Global approaches to regulating electronic cigarettes. *Tob Control* 2017;**26**:440–5. doi:10.1136/tobaccocontrol-2016-053179
18 Cullen KA, Ambrose BK, Gentzke AS, *et al.* Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students — United States, 2011–2018. *Morb Mortal Wkly Rep* 2018;**67**:1276–7. doi:10.15585/mmwr.mm6745a5
19 Mirbolouk M, Charkhchi P, Kianoush S, *et al.* Prevalence and Distribution of E-Cigarette Use Among U.S. Adults: Behavioral Risk Factor Surveillance System, 2016. *Ann Intern Med* 2018;**169**:429. doi:10.7326/M17-3440
20 Breland A, Soule E, Lopez A, *et al.* Electronic cigarettes: what are they and what do they do? *Ann N Y Acad Sci* 2017;**1394**:5–30. doi:10.1111/nyas.12977
21 Zhu SH, Sun JY, Bonnevie E, *et al.* Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. *Tob Control* 2014;**23**:iii3–9. doi:10.1136/tobaccocontrol-2014-051670
22 U.S. Food and Drug Administration. Family Smoking Prevention and Tobacco Control Act - An Overview. 2018.https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/family-smoking-prevention-and-tobacco-control-act-overview (accessed 24 Jul 2019).
23 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009;**6**:e1000097. doi:doi:10.1371/journal.pmed.1000097
24 Sirriyeh R, Lawton R, Gardner P, *et al.* Reviewing studies with diverse designs: The development and evaluation of a new tool. *J Eval Clin Pract* 2012;**18**:746–52. doi:10.1111/j.1365-2753.2011.01662.x
25 Clarke TN, Lusher JM. Willingness to Try Electronic Cigarettes Among UK Adolescents. *J Child Adolesc Subst Abuse* 2017;**26**:175–82. doi:10.1080/1067828x.2016.1242098
26 Amato MS, Boyle RG, Levy D. How to define e-cigarette prevalence? Finding clues in the use frequency distribution. *Tob Control* 2016;**25**:e24–9. doi:10.1136/tobaccocontrol-2015-052236
27 Audrain-McGovern J, Strasser AA, Wileyto EP. The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers. *Drug Alcohol Depend* 2016;**166**:263–7. doi:10.1016/j.drugalcdep.2016.06.030
28 Barnes AJ, Bono RS, Lester RC, *et al.* Effect of Flavors and Modified Risk Messages on E-cigarette Abuse Liability. *Tob Regul Sci* 2017;**3**:374–87. doi:10.18001/trs.3.4.1
29 Berg CJ. Preferred Flavors and Reasons for E-cigarette Use and Discontinued Use Among Never, Current, and Former Smokers. *Int J Public Health* 2016;**61**:225–36. doi:10.1007/s00038-015-0764-x
30 Bold KW, Kong G, Cavallo DA, *et al.* Reasons for Trying E-cigarettes and Risk of Continued Use. *Pediatrics* 2016;**138**:e20160895–e20160895. doi:10.1542/peds.2016-0895
31 Brozek G, Jankowski M, Zejda J, *et al.* E-smoking among students of medicine-frequency, pattern and motivations. *Adv Respir Med* 2017;**85**:8–14. doi:10.5603/arm.2017.0003
32 Buckell J, Marti J, Sindelar J. Should flavours be banned in cigarettes and e-cigarettes? Evidence on adult smokers and recent quitters from a discrete choice experiment. *Tob Control* Published Online First: 2018. doi:10.1136/tobaccocontrol-2017-054165
33 Camenga DR, Kong G, Cavallo DA, *et al.* Current and Former Smokers' Use of Electronic Cigarettes for Quitting Smoking: An Exploratory Study of Adolescents and Young Adults. *Nicotine Tob Res* 2017;**19**:1531–5. doi:10.1093/ntr/ntw248
34 Chen JC, Das B, Mead EL, *et al.* Flavored E-cigarette Use and Cigarette Smoking Susceptibility among Youth. *Tob Regul Sci* 2016;**3**:68–80. doi:10.18001/trs.3.1.7
35 Chen JC. Flavored E-cigarette Use and Cigarette Smoking Reduction and Cessation—A Large National Study among Young Adult Smokers. *Subst Use Misuse* 2018;**53**:2017–31. doi:10.1080/10826084.2018.1455704
36 Coleman BN, Rostron B, Johnson SE, *et al.* Electronic cigarette use among US adults in the

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Population Assessment of Tobacco and Health (PATH) Study, 2013-2014. *Tob Control* 2017;**26**:e117–26. doi:10.1136/tobaccocontrol-2016-053462

37 Cooper M, Harrell MB, Perez A, *et al.* Flavorings and Perceived Harm and Addictiveness of E-cigarettes among Youth. *Tob Regul Sci* 2016;**2**:278–89. doi:10.18001/trs.2.3.7

38 Czoli CD, Goniewicz M, Islam T, *et al.* Consumer preferences for electronic cigarettes: Results from a discrete choice experiment. *Tob Control* 2016;**25**:e30–6. doi:10.1136/tobaccocontrol-2015-052422

39 Dai H, Hao J. Flavored electronic cigarette use and smoking among youth. *Pediatrics* 2016;**138**:e2016513. doi:10.1542/peds.2016-2513

40 Elkalmi RM, Bhagavathul AS, Ya'u A, *et al.* Familiarity, perception, and reasons for electronic-cigarette experimentation among the general public in Malaysia: Preliminary insight. *J Pharm Bioallied Sci* 2016;**8**:240–7. doi:10.4103/0975-7406.180768

41 Etter J-F. Electronic cigarettes: a survey of users. *BMC Public Health* 2010;**10**. doi:10.1186/1471-2458-10-231

42 Etter JF. Characteristics of users and usage of different types of electronic cigarettes: findings from an online survey. *Addiction* 2016;**111**:724–33. doi:10.1111/add.13240

43 Farsalinos KE, Romagna G, Tsiapras D, *et al.* Impact of flavour variability on electronic cigarette use experience: An internet survey. *Int J Environ Res Public Health* 2013;**10**:7272–82. doi:10.3390/ijerph10127272

44 Farsalinos KE, Romagna G, Tsiapras D, *et al.* Characteristics, perceived side effects and benefits of electronic cigarette use: A worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health* 2014;**11**:4356–73. doi:10.3390/ijerph110404356

45 Ford A, MacKintosh AM, Bauld L, *et al.* Adolescents' responses to the promotion and flavouring of e-cigarettes. *Int J Public Health* 2016;**61**:215–24. doi:10.1007/s00038-015-0769-5

46 Goldenson NI, Kirkpatrick MG, Barrington-Trimis JL, *et al.* Effects of sweet flavorings and nicotine on the appeal and sensory properties of e-cigarettes among young adult vapers: Application of a novel methodology. *Drug Alcohol Depend* 2016;**168**:176–80. doi:10.1016/j.drugalcdep.2016.09.014

47 Gubner NR, Pagano A, Tajima B, *et al.* A comparison of daily versus weekly electronic cigarette users in treatment for substance abuse. *Nicotine Tob Res* 2018;**20**:636–42. doi:10.1093/ntr/ntx116

48 Harrell MB, Weaver SR, Loukas A, *et al.* Flavored e-cigarette use: Characterizing youth, young adult, and adult users. *Prev Med Reports* 2017;**5**:33–40. doi:10.1016/j.pmedr.2016.11.001

49 Harrell MB, Loukas A, Jackson CD, *et al.* Flavored Tobacco Product Use among Youth and Young Adults: What if Flavors Didn't Exist? *Tob Regul Sci* 2017;**3**:168–73. doi:10.18001/TRS.3.2.4

50 Kim H, Lim J, Buehler SS, *et al.* Role of sweet and other flavours in liking and disliking of electronic cigarettes. *Tob Control* 2016;**25**:ii55–61. doi:10.1136/tobaccocontrol-2016-053221

51 Kinouani S, Pereira E, Tzourio C. Electronic cigarette use in students and its relation with Tobacco-Smoking: A Cross-Sectional analysis of the I-Share study. *Int J Environ Res Public Health* 2017;**14**:1345. doi:10.3390/ijerph14111345

52 Kong G, Morean ME, Cavallo DA, *et al.* Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;**17**:847–54. doi:10.1093/ntr/ntu257

53 Krishnan-Sarin S, Morean ME, Camenga DR, *et al.* E-cigarette use among high school and middle school adolescents in Connecticut. *Nicotine Tob Res* 2015;**17**:810–8. doi:10.1093/ntr/ntu243

54 Lee H-Y, Lin H-C, Seo D-C, *et al.* Determinants associated with E-cigarette adoption and use intention among college students. *Addict Behav* 2017;**65**:102–10. doi:10.1016/j.addbeh.2016.10.023

55 Lee JA, Lee S, Cho HJ. The Relation between Frequency of E-Cigarette Use and Frequency and Intensity of Cigarette Smoking among South Korean Adolescents. *Int J Env Res Public Heal* 2017;**14**. doi:10.3390/ijerph14030305

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

56 Litt MD, Duffy V, Oncken C. Cigarette smoking and electronic cigarette vaping patterns as a function of e-cigarette flavourings. *Tob Control An Int J* 2016;**25**:67–72. doi:10.1136/tobaccocontrol-2016-053223

57 Maglalang DD, Brown-Johnson C, Prochaska JJ. Associations with E-cigarette use among Asian American and Pacific Islander young adults in California. *Prev Med Rep* 2016;**4**:29–32. doi:10.1016/j.pmedr.2016.05.011

58 Morean ME, Butler ER, Bold KW, *et al.* Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. *PLoS One* 2018;**13**. doi:10.1371/journal.pone.0189015

59 Nonnemaker J, Kim AE, Lee YO, *et al.* Quantifying how smokers value attributes of electronic cigarettes. *Tob Control An Int J* 2016;**25**:e37–43. doi:10.1136/tobaccocontrol-2015-052511

60 Patel D, Davis KC, Cox S, *et al.* Reasons for current E-cigarette use among U.S. adults. *Prev Med (Baltim)* 2016;**93**:14–20. doi:10.1016/j.ypmed.2016.09.011

61 Pepper JK, Reither PL, McRee A-L, *et al.* Adolescent Males' Awareness of and Willingness to Try Electronic Cigarettes. *J Adolesc Heal* 2013;**52**:144–50. doi:10.1016/j.jadohealth.2012.09.014

62 Pepper JK, Ribisl KM, Emery SL, *et al.* Reasons for starting and stopping electronic cigarette use. *Int J Environ Res Public Health* 2014;**11**:10345–61. doi:10.3390/ijerph111010345

63 Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tob Control An Int J* 2016;**25**:ii62–6. doi:10.1136/tobaccocontrol-2016-053174

64 Pesko MF, Kenkel DS, Wang H, *et al.* The effect of potential electronic nicotine delivery system regulations on nicotine product selection. *Addiction* 2016;**111**:734–44. doi:10.1111/add.13257

65 Russell C, McKeganey N, Dickson T, *et al.* Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. *Harm Reduct J* 2018;**15**:33. doi:10.1186/s12954-018-0238-6

66 Rutten LJ, Blake KD, Agunwamba AA, *et al.* Use of E-Cigarettes Among Current Smokers: Associations Among Reasons for Use, Quit Intentions, and Current Tobacco Use. *Nicotine Tob Res* 2015;**17**:1228–34. doi:10.1093/ntr/ntv003

67 Shang C, Huang J, Chaloupka FJ, *et al.* The impact of flavour, device type and warning messages on youth preferences for electronic nicotine delivery systems: evidence from an online discrete choice experiment. *Tob Control* 2017;**0**:1–8. doi:10.1136/tobaccocontrol-2017-053754

68 Shiffman S, Sembower MA, Pillitteri JL, *et al.* The impact of flavor descriptors on nonsmoking teens' and adult smokers' interest in electronic cigarettes. *Nicotine Tob Res* 2015;**17**:1255–62. doi:10.1093/ntr/ntu333

69 Shiplo S, Czoli CD, Hammond D. E-cigarette use in Canada: Prevalence and patterns of use in a regulated market. *BMJ Open* 2015;**5**:1–7. doi:10.1136/bmjopen-2015-007971

70 Spears CA, Jones DM, Weaver SR, *et al.* Motives and perceptions regarding electronic nicotine delivery systems (ENDS) use among adults with mental health conditions. *Addict Behav* 2018;**80**:102–9. doi:10.1016/j.addbeh.2018.01.014

71 Tackett AP, Lechner W V, Meier E, *et al.* Biochemically verified smoking cessation and vaping beliefs among vape store customers. *Addiction* 2015;**110**:868–74. doi:10.1111/add.12878

72 Tsai J, Walton K, Coleman BN, *et al.* Reasons for Electronic Cigarette Use Among Middle and High School Students - National Youth Tobacco Survey, United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018;**67**:196–200. doi:10.15585/mmwr.mm6706a5

73 Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: An experimental study. *Tob Control* 2016;**25**:e107–12. doi:10.1136/tobaccocontrol-2015-052593

74 Weaver SR, Huang J, Pechacek TF, *et al.* Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015-2016. *PLoS One* 2018;**13**:e0198047. doi:10.1371/journal.pone.0198047

75 Yingst JM, Veldheer S, Hrabovsky S, *et al.* Factors associated with electronic cigarette users' device preferences and transition from first generation to advanced generation devices. *Nicotine*

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Tob Res 2015;**17**:1242–6. doi:10.1093/ntr/ntv052

76 U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use. 2018.https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620185.htm (accessed 26 Oct 2018).

77 Bomey N. Marlboro maker Altria stops sales of flavored vaping liquid. USA Today. 2018.https://www.usatoday.com/story/money/2018/10/25/altria-group-flavored-vaping-liquid/1759794002/ (accessed 25 Oct 2018).

78 Kaplan S, Hoffman J. Juul Suspends Selling Most E-Cigarette Flavors in Stores. New York Times. 2018.https://www.nytimes.com/2018/11/13/health/juul-ecigarettes-vaping-teenagers.html

79 Chen JC, Green KM, Chen J, *et al.* Restricting the Sale of Flavored E-cigarettes in the US: An Examination of Local Regulations. *Tob Regul Sci* 2018;**4**:32–40. doi:10.18001/trs.4.4.4

80 Hoffman J. San Francisco Voters Uphold Ban on Flavored Vaping Products. NY Times. 2018.https://www.nytimes.com/2018/06/06/health/vaping-ban-san-francisco.html (accessed 9 Oct 2018).

81 Campaign for Tobacco-Free Kids. Brazil's Highest Court Upholds Ban on Flavored Tobacco Products. 2018.https://www.tobaccofreekids.org/press-releases/2018_02_01_brazil-court-upholds-flavor-ban (accessed 24 Jul 2018).

82 World Health Organization. Partial guidelines for implementation of articles 9 and 10 of the WHO Framework Convention on Tobacco Control. 2012. http://www.who.int/fctc/guidelines/Guideliness_Articles_9_10_rev_240613.pdf

83 Yingst JM, Veldheer S, Hammett E, *et al.* A method for classifying user-reported electronic cigarette liquid flavors. *Nicotine Tob Res* 2017;**19**:1381–5. doi:10.1093/ntr/ntw383

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Figure Legends:

Figure 1. PRISMA Flow Diagram

Author's Contributions:

Ms. Meernik and Ms. Baker contributed equally to this paper as joint first authors.

Ms. Meernik, Ms. Baker, and Dr. Kowitt conducted data review and analysis, drafted the initial manuscript, and revised and reviewed the full manuscript.

Dr. Ranney and Dr. Goldstein conceptualized the study and provided critical feedback to the intellectual content during drafting and revisions of the manuscript, as well as to the interpretation of data analyses.

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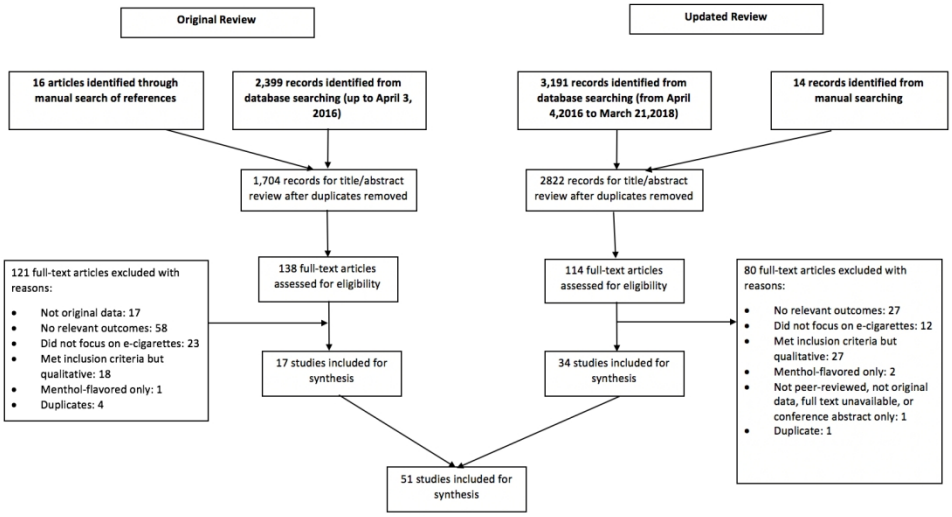

Figure 1. PRISMA Flow Diagram

Supplementary File 1. Search String

Final PubMed search string: (((((smoke OR smoker OR smokers OR smokes OR smokings OR smoking OR cigarette OR cigarettes OR cigar OR cigars OR cigarillos OR cigarillo OR hookahs OR hookah OR waterpipe OR waterpipes OR narghile OR narghiles OR argila OR argiles OR tobacco OR tobaccos OR cigar* OR smoke* OR tobacco* OR ends OR "electronic nicotine delivery system*" OR vape OR vapor OR vapour OR vapours OR vapors OR vapor OR vapors OR vaping OR snus OR pipe OR pipes OR "e-cigarette" OR "e-cigarettes" OR bidi OR bidis OR kretek OR kreteks OR chewing tobacco OR snuff OR shisha OR "water pipe" OR "water pipes" OR goza OR narkeela OR "hubble bubble" OR hukkah OR hukkas OR hukka OR argileh) AND (flavor OR flavor* OR flavour OR flavour* OR flavors OR flavours OR flavoring OR flavouring OR flavorings OR flavourings OR flavoured OR flavoured OR flavoring OR flavorings OR flavouring OR flavourings OR flavouring OR flavoring OR flavourants OR flavorants)) OR (kretek OR kreteks OR bidi OR bidis))) 2016/04/04:2018/03/21 [edat])

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Supplementary Table 1. Main results of all studies (* indicates study was included in original 2016 review)

Study	Study design	Measures / Analysis	Results
Amato, 2015[26] *	Cross-sectional survey Probability sample	Descriptive statistics were used to examine reasons for e-cigarette use.	A greater proportion of current e-cigarette users cited "come in flavors other than menthol" as a reason for their e-cigarette use than past users (55.5% vs. 25.0%).
Audrain-McGovern, 2016[27]	Cross-sectional laboratory experiment Convenience sample	Regression models used to evaluate the effect of flavor on subjective rewarding value, relative reinforcing value, and absolute reinforcing value.	The average subjective rewarding value across the three e-cigarettes included: unflavored (M = 3.11, SD = 1.55), dessert flavored (M = 3.69, SD = 1.78), and fruit flavored (M = 4.22, SD = 1.55). Both the fruit flavored (β = 1.11, CI: 0.58-1.64, p<.0001) and the dessert flavored e-cigarettes (β = 0.57, CI: 0.47-1.11, p=.03) were rated significantly more rewarding than the unflavored e-cigarette. Subjective reward was higher for the flavored e-cigarette compared to unflavored (β = 0.83, CI: 0.35–1.32, p=.001). This group difference meant that participants rated the unflavored e-cigarettes as “a little” and the flavored e-cigarette as “moderately” satisfying and good tasting. Participants took twice as many flavored puffs than unflavored e-cigarette puffs (IRR = 2.03, CI: 1.18-3.47, p=.01).
Barnes, 2017[28]	Cross-sectional laboratory experiment Convenience sample	Linear mixed effects models used to assess abuse liability for tobacco products.	The crossover point (i.e., the largest dollar amount at which participants still choose the tobacco product over the money) for cherry flavored e-cigarettes was significantly higher than for e-cigarettes without a flavor ($0.71 vs $0.51, p<.05).
Berg, 2016[29]*	Cross-sectional survey	ANOVAs were used to compare continuous variables across	32% of nonusers included ‘‘they come in appealing flavors’’ as a reason for possible future e-cigarette use.

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	Convenience sample	groups, and Chi-square tests were used to compare categorical variables.	39% of current smokers, who were non-e-cigarette users, chose “they come in appealing flavors” as a reason for possible e-cigarette use; this is compared to <31% of nonsmokers and former smokers, p<0.001. 60.2% of current e-cigarette users chose “they come in appealing flavors” as a reason for e-cigarette use; 59.5% of those same users chose “I like experimenting with various flavors” as a reason for e-cigarette use. 69.7% of never cigarette smokers who use e-cigarettes chose “they come in appealing flavors” as a reason for e-cigarette use; 61.4% of former cigarette smokers who use e-cigarettes chose “I like experimenting with various flavors” as a reason for e-cigarette use. 20.3% of former e-cigarette users reported no recent use of e-cigarettes because they ‘‘don’t like the flavor(s)’’.
Bold, 2016[30]	Longitudinal survey Convenience sample	Logistic regression models used to examine reasons for trying e-cigarettes at wave 1 as predictors of continuing e-cigarette use at wave 2; linear regression models used to examine reasons for trying e-cigarettes at wave 1 as predictors of e-cigarette frequency at wave 2 among those who continued e-cigarette use.	"Good flavors" was endorsed by 41.8% of students as a reason for first trying e-cigarettes among ever e-cigarette users, the second most highly endorsed reason for trying behind curiosity (reasons not exclusive). In univariate models, good flavors as a reason for first trying e-cigarettes predicted continued e-cigarette use, though it was no longer significant after adjusting for cigarette smoking status. In univariate models, good flavors a reason for first trying e-cigarettes predicted more frequent use, though it was no longer significant after adjusting for other covariates.

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Brozek, 2017[31]	Cross-sectional survey Convenience sample	Descriptive statistics used to describe attitudes and motivations for e-cigarette use.	28.3% of e-cigarette users decided to start using e-cigarettes because of the unique flavors, the fourth most cited reason behind other reasons such as desire to quit traditional cigarettes (58.7%) and less harmful effect on health (43.5%).
Buckell, 2018[32]	Cross-sectional discrete choice experiment Convenience sample	Exploded multinomial logit models used to analyze respondents' preferences.	Adult smokers prefer the following e-cigarette flavors, from most to least: tobacco, fruit/sweet, and menthol. Adult smokers with at least one quit attempt in the past year preferred all flavored (including tobacco) e-cigarettes, relative to tobacco cigarettes.
Camenga, 2017[33]	Cross-sectional survey Convenience sample	Multivariable logistic regression used to evaluate association between using e-cigarettes to quit smoking and age, gender, race, e-cigarette frequency, cigarette smoking status, preferred e-cigarette flavor, and risk perceptions.	Having a preference for "a combination of 2 or more flavors mixed together" predicted increased likelihood of using e-cigarettes to quit smoking, relative to not having a preferred flavor (aOR = 1.92, 95% CI: 1.31-2.81; p=.0008).
Chen, 2017[34]	Cross-sectional survey Probability sample	Logistic regression used to estimate association between cigarette susceptibility and e-cigarette use status, demographic characteristics, and risk factors for cigarette smoking. Multivariate logistic regression used to explore moderating variables	Among those who used e-cigarettes, youth who used the product 3 days or more were more likely to be flavored e-cigarette users than those who used e-cigarettes 1 or 2 days in the past 30 days (p<.05). The unadjusted odds ratio of being susceptible to cigarette smoking was the largest for flavored e-cigarette use (OR = 6.6, CI: 3.8-9.1, p <.0001), followed by nicotine dependence and cigarette experimentation. In the adjusted regression analysis, flavored e-cigarette users had higher

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		influencing direction and strength of association between e-cigarette use and smoking susceptibility.	odds of being susceptible to cigarette smoking than plain e-cigarette users (AOR = 1.7, CI: 1.3-2.4, p<.001) and non-users (AOR = 3.8, CI: 2.8-5.3, p<.0001), the largest effect across all demographic characteristics and smoking risk factors. In stratified analyses, the association between smoking susceptibility and flavored e-cigarette use was significantly higher for females (AOR = 6.5, CI: 4.2-9.9, p<.01) than males (AOR = 2.5, CI: 1.5-4.1, p<.01). The association between smoking susceptibility and flavored e-cigarette use was significantly higher for those who were not receptive to tobacco marketing (AOR = 5.0, CI: 3.5-7.0, p<.01) than those who were receptive (AOR = 2.5, CI: 1.2-3.1, p<.05).
Chen, 2018[35]	Longitudinal survey Probability sample	Univariate and multivariate regressions used to examine associations between past-year smoking reduction and cessation and current e-cigarette flavor use at wave 2.	Users of one non-tobacco/menthol flavor (37.1%) were more likely than non-e-cigarette users (24.7%) to adopt smoking cessation methods (p<.001). In adjusted analysis, wave 2 e-cigarette users who used one (AOR = 2.5, p<.001) or multiple (AOR = 3.0, p<.001) non-tobacco/menthol flavors were more likely to have reduced or quit smoking cigarettes in the past year than non-e-cigarette users. The third most endorsed reason for using e-cigarettes among current users (subsample of 844 respondents) were that e-cigarettes “come in flavors I like” (80.2%), behind “might be less harmful to people around me than cigarettes” (85.4%) and “can be used where smoking cigarettes is not allowed” (82.2%).

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			Compared to users of tobacco/menthol flavors, users of non-tobacco/menthol flavors were more likely to enjoy e-cigarette flavors (p<.001) and to vape daily (p<.001). E-cigarette users who said that e-cigarettes "come in flavors I like" (OR = 2.1, p=.007) were more than twice as likely to have reduced or quit smoking in the past year compared to those who did not endorse e-cigarette use for this reason.
Clarke, 2017[25]	Cross-sectional survey Convenience sample	Sequential hierarchical multiple regression used to identify predictors of adolescents' willingness to try flavored and tobacco-flavored e-cigarettes.	The majority of cigarette smokers (90.6%) were more willing to try flavored e-cigarettes than tobacco-flavored products (73.4%), with around one-third (33.9%) of non-smoking participants willing to try flavored e-cigarettes, as opposed to tobacco-flavored (12.0%). The more positively adolescents perceived a smoker, the more willing they were to try a flavored e-cigarette (p<.05), while the more negatively they perceived an e-cigarette user, the less willing they were to try a flavored e-cigarette (p<.05).
Coleman, 2017[36]	Cross-sectional survey Probability sample	Poisson regression used to examine association between everyday versus someday e-cigarette use and demographic, tobacco use, and product characteristics.	Never smokers were more likely to endorse appealing flavors as a reason for e-cigarette use (75.3%) compared with current (63.7%, p<.0001) and former (60.1%, p<.0001) smokers. Daily e-cigarette users were more likely to report that their first e-cigarette was non-tobacco flavored (65.2%) than moderate (60.7%) or infrequent (54.8%) e-cigarette users (p<.0001).
Cooper, 2016[37]	Cross-sectional survey Probability sample	Logistic regression models used to investigate relationship between perceptions of	27.0% of youth reported that flavored e-cigarettes were "less harmful" than non-flavored e-cigarettes. Youth who currently used e-cigarettes had higher odds (OR = 2.84, 95% CI:

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		harm and addictiveness and e-cigarette use.	1.91–4.21) of reporting flavored e-cigarettes as "less harmful" than non-flavored e-cigarettes compared to non-current users, after adjusting for covariates. Youth who had ever used e-cigarettes had higher odds (OR = 2.88, 95% CI: 2.42–3.42) of reporting that flavored e-cigarettes were "less harmful" than non-flavored products compared to never users, after adjusting for covariates.
Czoli, 2015[38]*	Cross-sectional discrete choice experiment Convenience sample	Multinomial logit regression was used to analyze the effect of attributes on consumer choice for each outcome in a discrete choice experiment.	Participants were significantly more interested in trying e-cigarettes with cherry ($p<0.0001$, $r=0.2$) and menthol ($p=0.01$, $r=0.1$) flavors. Younger smokers expressed interest in trying e-cigarettes with a preference for products with cherry flavor ($p<.001$, $r=0.2$) while younger nonsmokers indicated interest in trying cherry ($p<.0001$, $r=0.3$), menthol ($p<.0001$, $r=0.2$) and coffee flavor ($p<.001$, $r=0.2$); Older smokers indicated greater interest in trying tobacco-flavored e-cigarettes ($p<0.0001$, $r=0.6$). E-cigarettes with the following characteristics were perceived as less harmful and greater quit efficacy: menthol ($p<0.0001$, $r=0.6$; $p<0.0001$, $r=0.2$) and coffee flavors ($p<0.0001$, $r=0.3$; $p<0.001$, $r=0.2$). Younger non-smokers were more likely to perceive coffee-flavored ($p=0.02$, $r=0.1$) e-cigarettes as less harmful while younger smokers held these beliefs about products with cherry flavor ($p=0.03$, $r=0.1$); Older smokers perceived products with tobacco flavor ($p<0.001$, $r=0.2$) as less harmful.

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			Compared to other attributes, flavor accounted for 24% of the relative importance on intention to try, 36% for perceptions of reduced product harm, and 25% on perceptions of enhanced product quit efficacy.
Dai, 2016[39]	Cross-sectional survey Probability sample	Logistic regression model used to examine associations between flavored e-cigarette use and tobacco use and perception of tobacco's danger.	Among all respondents, students who reported using flavored e-cigarettes were least likely to perceive tobacco's danger compared with those who reported not using e-cigarettes (74.8% vs 91.3%; aOR = 0.5; p<.0001) or with those who reported using non-flavored e-cigarettes (74.8% vs 77.1%). Among never smokers, the use of flavored e-cigarettes was associated with a higher prevalence of intention to initiate cigarette use compared with those who had not used e-cigarettes in the past 30 days (58.3% vs 20.1%; aOR = 5.7; p<.0001) or with those who had used non-flavored e-cigarettes (58.3% vs 47.4%; aOR = 1.7; p=.02). Among current smokers, students who reported using flavored e-cigarettes were less likely to quit tobacco use compared with those who reported not using e-cigarettes (24.1% vs 32.7%; aOR = 0.6; p=.006) or with those who had used non-flavored cigarettes (24.1% vs 33.5%).
Elkalmi, 2016[40]	Cross-sectional survey Convenience sample	Descriptive statistics used to report frequencies.	66.7% of respondents who had tried e-cigarettes in the past reported that variety of flavors contribute to better enjoyment of e-cigarettes compared to traditional cigarettes.
Etter, 2010[41]*	Cross-sectional survey Convenience sample	Open-ended questions about the most positive and negative points about e-cigarettes were analyzed.	The most frequently cited positive feature of e-cigarettes was that respondents liked the taste and variety of flavors (18% of total open-ended comments).

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Etter, 2016[42]	Cross-sectional survey Convenience sample	T-tests used to compare means, Mann-Whitney U-tests and Wilcoxon's signed-ranks test to compare medians between or within groups, and chi-square tests to compare proportions.	Tobacco flavor e-cigarettes were used by 44% of users who had recently started vaping (i.e. those who had used e-cigarettes for 0–3 months) versus 25% of long-term users (who had used e-cigarettes for ≥ 4 months, $\chi 2 = 79.0$, $p<.001$). Most participants (80%) said that the e-cigarette flavors helped them either to quit smoking or reduce their cigarette consumption, while 18% said that the flavors had no impact on their smoking and 2% said that the flavors made them want to smoke.
Farsalinos, 2013[43]*	Cross-sectional survey Convenience sample	X^2 tests compared categorical variables (e.g., type of e-cigarette flavors regularly used) between current and former smokers. A stepwise binary logistic regression analysis was used with smoking status (former vs current smoker) as the independent variable and age, gender, education level, smoking duration, number of flavorings used regularly, and e-cigarette consumption as covariates.	More current smokers were using tobacco flavors compared to former smokers ($X^2=14.6$, $p<.001$), while more former smokers were using fruit ($X^2=14.0$, $p<.001$) and sweet flavors ($X^2=21.8$, $p<.001$). The average score for importance of flavors variability in reducing or quitting smoking was 4 ("very important") on a 5-point scale. 39.7% of participants reported that restricting variability of flavors would make reducing or completely substituting smoking less likely. Binary logistic regression analysis showed that number of flavors regularly used ($\beta=0.089$, $p=0.038$) was associated with complete smoking abstinence among dedicated long-term users.
Farsalinos, 2014[44]*	Cross-sectional survey Convenience sample	Descriptive statistics examined reasons for initiating e-cigarette use.	Initiating e-cigarette use to enjoy the variability of flavors in e-cigarettes was ranked as 3 on a 5-point scale from 1 (not important) to 5 (most important).

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Ford, 2016[45]*	Cross-sectional survey Probability sample	Paired t-tests were run on weighted data to produce mean scores; the Friedman test was used on ordinal data, then post hoc tests were conducted using the Wilcoxon signed rank test	Perceptions of harm from the different flavors ranged from a mean of 3.00 (SD = 1.35) for candy floss flavor to 3.06 (SD = 1.29) for cherry, 3.47 (SD = 1.22) for coffee and 3.99 (SD = 1.14) for tobacco flavor. Perceptions of harm differed depending on the flavor, χ^2 (4) = 851.59, p<0.001. Post hoc analysis showed that, when compared against perceptions of harm of e-cigarettes in general, tobacco flavor e-cigarettes were perceived as being more harmful (p<0.001) while cherry and candy floss flavors were each perceived as less harmful (p<0.001). Coffee flavor e-cigarettes were perceived as having the same level of harm as e-cigarettes in general. Perceptions of likelihood of an adult smoker using each differed depending on the flavor, χ^2 (3) = 153.9, p <0.001 as did perceptions of likelihood of a never smoker of their age, χ^2 (3) = 879.01, p<0.001. Post hoc analysis showed that, when compared with tobacco flavor e-cigarettes, adult smokers who were trying to give up smoking were perceived by youth to be less likely to use cherry, candy floss or coffee flavors (p<0.001). Conversely, a never smoker of their age was perceived to be more likely to try cherry (p<0.001), candy floss (p<0.001) or coffee flavor (p<0.01) than a tobacco flavor e-cigarette. An adult smoker was perceived by youth to be more likely than a never smoker of their age to use tobacco (p<0.001) and coffee (p<0.001) flavors whereas a never smoker of their age was perceived to be more likely than an

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			adult smoker to try candy floss (p<0.001) and cherry (p<0.01) flavors.
Goldenson, 2016[46]	Cross-sectional laboratory experiment Convenience sample	Multilevel linear models used to examine associations between each sensory rating (sweetness or throat hit) and appeal outcomes.	A significant main effect of e-liquid flavor was found for each appeal outcome (i.e., liking, willingness to use again, and amount willing to pay) and sweetness (ps<.0001). Sweet-flavored e-liquids resulted in higher appeal ratings than non-sweet and flavorless solutions (ps<.0001). Ratings of sweetness were positively associated with each appeal outcome (ps<.0001). For instance, each one-point increase in sweetness rating (0-100) was associated with a 0.51 increase in liking, a 0.51 increase in willingness to use again, and a $0.04 increase in amount willing to pay for a day's worth of the solution.
Gubner, 2017[47]	Cross-sectional survey Convenience sample	Bivariate analyses and logistic regression used to examine factors associated with daily vs. weekly e-cigarette use.	Daily and weekly e-cigarette users both reported similar reasons for use of e-cigarettes, including because they have good flavors (41.1% overall). Daily e-cigarette users reported using more types of e-juice flavors (2.2 ± 1.3 vs. 1.8 ± 1.4), t(168) = 2.15, p=.03), and were more likely to have used tobacco flavor, fruit/berry flavor, or select "other" flavor compared to weekly users.
Harrell, 2017a[48]	Cross-sectional survey Probability and convenience sample	Proportions and 95% confidence intervals used to examine percentage of flavored e-cigarette use at initiation and current use; Chi-square tests used to examine differences in flavored e-cigarette use by combustible	The proportion of current e-cigarette users who initiated with an e-cigarette flavored with something other than tobacco was considerably higher in Texas youth (98.6%) and young adults in Texas (95.2%) and nationwide (71.2%) compared to older adults nationwide (44.1%). At initiation, the use of tobacco-flavored e-cigarettes was more common among current dual users (e-cigarette and combustible tobacco product users)

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		tobacco product use and demographic characteristics.	than exclusive e-cigarette users (i.e., former combustible tobacco product users), for both age groups (p<.05). Among adults nationwide, 43.5% of current combustible users said their first e-cigarette was flavored to taste like tobacco, compared to 27.8% of former combustible product users. The proportion of current users whose "usual" e-cigarette was flavored with something other than tobacco was higher for Texas youth (97.9%) and young adults (96.7%) in Texas and nationwide (82.2%) compared to older adults nationwide (69.3%). Among current e-cigarette users, more Texas youth (72.9%) than young adult college students in Texas (57.4%) and young adults (64.8%) and adults (54.0%) nationwide cited using e-cigarettes because they "come in flavors I like."
Harrell, 2017b[49]	Cross-sectional survey Probability sample (youth) and convenience sample (young adults)	Chi-square tests used to test for differences between subgroups (sex and school/age level).	Roughly 3 out of every 4 youth (78%) and young adult (74%) flavored e-cigarette users said that they would not use an e-cigarette if it was not available in a flavored form (e.g., candy, fruit, mint/menthol). Significantly more young adult females than males reported that they would not use e-cigarettes if it were not flavored (77% vs 69%, p=.03).
Kim, 2016[50]	Cross-sectional laboratory experiment Convenience sample	One-way analysis of variance (ANOVA) used to examine differences between e-cigarette flavors in hedonic ratings and sensory attribute ratings; regression models used to examine	In terms of mean hedonic (liking/disliking) ratings of the 6 e-cigarette flavors, Pina Colada was liked significantly more than Classic Tobacco (p<.05). One-way ANOVAs found a significant main effect of e-cigarette flavors on sweetness (F = 14.56, p<.0001), coolness (F = 11.96, p<.00001), and bitterness (F = 3.56, p<.01), but not on

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		relative effects of flavor attributes on hedonic ratings.	harshness and own flavor. The four non-tobacco flavored e-cigarette samples were rated significantly sweeter than Classic Tobacco. Pina Colada was perceived as sweetest and liked the most; Classic Tobacco was perceived as least sweet and liked the least. Hedonic ratings were significantly positively correlated for sweetness for Pina Colada ($r = 0.36$, $p<.05$) and Peach Schnapps ($r= 0.56$, $p<.05$). Hedonic ratings were significantly positively correlated with coolness for Classic Tobacco, Magnificent Menthol, and Vivid Vanilla ($r = 0.41–0.52$, $p<.05$). Harshness ratings were significantly negatively correlated with hedonic ratings for Cherry Crush, Pina Colada, and Peach Schnapps ($r = 0.37–0.40$, $p<.05$). When regressing sensory attributes on hedonic ratings, sweetness and coolness had a positive contribution to liking and disliking of the six e-cigarette flavors, while bitterness and harshness had a negative contribution.
Kinouani, 2017[51]	Cross-sectional survey Convenience sample	Descriptive statistics used to describe reasons for trying e-cigarettes among current and former e-cigarette users, stratified by smoking status.	24.6 % of respondents reporting trying e-cigarettes because of the flavor, behind reasons of curiosity (77.4%) and because someone offered one to try (63.5%); there was no significant difference between men and women using for this reason (20.7% and 26.0%, respectively; $p=.07$). 28.6% of former smokers, 25.1% of current smokers, and 17.8% of never smokers tried e-cigarettes because of flavors.

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Kong, 2014[52]*	Cross-sectional survey Convenience sample	X^2 tests evaluated school level differences (middle school, high school, college) on all variables. Multinomial logistic regression analyses evaluated the extent to which reasons for e-cigarette experimentation differed based on cigarette smoking status.	43.8% of respondents reported the availability of flavors as a reason for experimentation with e-cigarettes. School level differences were observed ($X^2(2,N=1,157)=18.63$, $p\leq.001$), with high school students more likely to experiment with e-cigarettes because of appealing flavors compared to college students (47.0% vs 32.8%, $X^2(1,N=1,116)=13.61$, $p\leq.001$).
Krishnan-Sarin, 2014[53]*	Cross-sectional survey Convenience sample	Descriptive statistics explored flavors of e-cigarettes that had been tried and preferred.	Most lifetime e-cigarette users in middle school and high school, across cigarette smoking status, reported that they had tried and preferred sweet flavors compared to menthol and tobacco flavors.
Lee, 2017[54]	Cross-sectional survey Convenience sample	Multinomial logistic regression models and Heckman two-step selection procedures used to examine determinants that promote e-cigarette use acceptability.	A higher preference for the availability of flavors in e-cigarettes increased intention to use e-cigarettes (OR = 1.49) and likelihood of currently using e-cigarettes (OR = 1.82).
Lee, 2017b[55]	Cross-sectional survey Probability sample	Chi-square tests used to assess association between reason for using e-cigarettes and frequency of use.	9.3% of respondents reported using e-cigarettes “since they have good flavor,” behind reasons of curiosity (22.9%), being potentially less harmful (18.9%), for smoking cessation (13.1%), for indoor use (10.7%), or being better tasting (9.6%).
Litt, 2016[56]	Two-phase longitudinal laboratory study	Multilevel modelling with maximum likelihood estimation used to evaluate effects of	The largest drop in cigarette smoking occurred among those assigned menthol e-cigarettes (smoking 4.0 per day by week 7), and the smallest drop in smoking occurred among those assigned cherry and chocolate flavors

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	Convenience sample	assigned e-cigarette flavor on use of usual cigarettes and e-cigarettes over 6-week study period.	(smoking 9.8 per day by week 7) (contrast: menthol vs all others: F(1, 3143) = 2.48; p<.05). E-cigarette vaping rates differed significantly by flavor assigned, with the highest vaping rates (about 12.3 vaping episodes per day) for tobacco e-cigarettes and the lowest rates for those assigned to chocolate (8.6 episodes per day) (contrast: tobacco vs chocolate: F(1, 3143) = 3.86; p<.001).
Maglalang, 2016[57]	Cross-sectional survey Convenience sample	Frequencies reported for preferred e-cigarette flavors and reasons for e-cigarette use.	Among current e-cigarette users who responded to the question (n=39), 8% cited “enjoying the flavor” as a reason for using e-cigarettes. This ranked the lowest behind use as a cessation aid or healthier alternative to conventional cigarettes; use for recreational/social reasons; use for stress relief/coping; and use for nicotine's highs.
Morean, 2018[58]	Cross-sectional survey Convenience sample	Chi-squares and independent samples t-tests used to examine differences in sex, age, smoking status, e-cigarette nicotine content, e-liquid flavor preferences, the total number of e-liquid flavors preferred, and e-cigarette use frequency; univariate general linear modeling used to examine associations between flavor preferences and total number of flavors preferred with e-cigarette use frequency	The most commonly preferred flavors among adults were fruit (40.0%), tobacco (32.0%) and menthol/mint (27.6%). Compared to adolescents, a larger percentage of adult e-cigarette users preferred tobacco, menthol/mint, coffee (16.6%), and spice (12.2%) flavor e-liquids. Adults preferred a greater total number of e-liquid flavors than did adolescents (M = 15.56, SD = 12.48 among adults compared to M = 9.98, SD = 10.52 among adolescents). The most commonly preferred flavors among adolescents were fruit (52.3%), candy/dessert (16.2%), and vanilla (11.4%). Compared to adults, more adolescents preferred fruit, alcohol (9.8%), and “other” flavored (2.0%) e-liquids or reported not knowing what their preferred flavor was (15.4%).

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		among adolescents and adults separately.	Adolescents who preferred to use fruit (ηp2 = 0.02, p = .003), dessert (ηp2 = 0.02, p=.007), and/or alcohol flavored e-liquids (ηp2 = 0.02, p=.002) reported using e-cigarettes more frequently. Among adolescents, the total number of e-cigarette flavors preferred was associated with e-cigarette frequency; preferring to use a greater number of e-cigarette flavors was associated with using e-cigarette on more days in the past month (ηp2 = 0.04, p<.001).
Nonnemaker, 2016[59]*	Cross-sectional survey Convenience sample	Calculated coefficients and corresponding 95% CIs for a series of multivariate linear regression models; regressed indicators for each characteristic on respondents' reported willingness to pay for an e-cigarette with a specific set of attributes	Among the full sample, removing the attribute "coming in flavors" significantly reduced the price respondents were willing to pay for an e-cigarette (p<0.05). Among cigarette-only users, losing the attribute "coming in flavors" significantly reduced the price respondents were willing to pay for an e-cigarette (p<.01); this relationship was not significant for dual users.
Patel, 2016[60]	Cross-sectional survey Probability sample	Wald tests and multivariate Poisson regressions used to assess differences in reasons for e-cigarette use across respondent characteristics.	Flavoring was the 5th most reported reason for using e-cigarettes (34.4%), behind cessation/health, consideration of others, convenience, and curiosity. Current e-cigarette users aged 18 to 24 years (adjusted prevalence ratio [aPR] = 2.02, 95% CI: 1.60–2.55), 25 to 34 years (aPR = 1.61, 95% CI: 1.30–2.01), and 35 to 54 years (aPR = 1.29, 95% CI: 1.08–1.54) were more likely to cite flavoring as a reason for use than those aged 55 years or older. The prevalence of citing flavoring as a reason for use was greater among current e-cigarette users living in the

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			South than those in the Northeast (aPR = 1.36, 95% CI: 1.01–1.83). Compared with current e-cigarette users who used disposables the most, tank users had a greater odds of citing flavoring as reason for use (aPR = 2.55, 95% CI: 1.97–3.32).
Pepper, 2013[61]*	Cross-sectional survey Probability sample	Logistic regression examined willingness to try any kind of e-cigarette (plain, flavored, or both).	The same proportion of respondents were willing to try plain e-cigarettes or to try flavored e-cigarettes (p=.15).
Pepper, 2014[62]*	Cross-sectional survey Probability and convenience sample	Descriptive statistics assessed reasons for first trying e-cigarettes.	Less than 10% of respondents reported starting e-cigarette use because "e-cigarettes come in flavors they like."
Pepper, 2016[63]	Cross-sectional survey Probability sample	Logistic regression models used to examine the effects of flavor condition on interest in trying e-cigarettes; linear regression models used to assess association between flavor and perceived harm.	Adolescents perceived fruit-flavored e-cigarettes to be less harmful than tobacco-flavored ones (mean 2.71 vs. 2.87, $\beta = -0.08$, $p<.05$). Adolescents reported that, if offered by a friend, they were more likely to try menthol-flavored (8.3%, OR = 4.00, 95% CI 1.46-10.97), candy-flavored (9.3%, OR = 4.53, 95% CI: 1.67-12.31) or fruit-flavored e-cigarettes (12.8%, OR = 6.49, 95% CI: 2.48-17.01) compared with tobacco-flavored e-cigarettes (2.2%). Perceptions of e-cigarette harm partly mediated the relationship between flavor and interest in trying e-cigarettes. Adolescents believed that menthol-flavored, candy-flavored or fruit-flavored e-cigarettes were less harmful than tobacco-flavored or alcohol flavored ones ($\beta = -0.15$, $p<.01$). Greater perceived harmfulness was

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			associated with less interest in trying e-cigarettes (OR = 0.31, 95% CI: 0.22-0.43).
Pesko, 2016[64]	Cross-sectional discrete choice experiment Convenience sample	Linear probability model estimated probability of choosing the e-cigarette option as a function of indicator variables for each attribute level.	Increased flavor availability increased e-cigarette selection for younger adults, from 17.5% to 21.9% (p<.001) but was not associated with a significant increase for older adults. Increased flavor availability increased e-cigarette selection for individuals that have not used vaping devices in the past month (p<.001) but was not associated with a significant increase in e-cigarette selection for individuals that have. Regardless of interest in quitting cigarettes, greater flavor availability increased e-cigarette selection. In linear probability models, greater flavor availability was associated with a 2.1 percentage point increase in e-cigarette selection (p<.001). In the interaction model, young adults were 3.7 percentage points more likely to choose e-cigarettes when multiple flavors were available compared to older adults (p<.001).
Russell, 2018[65]	Cross-sectional survey Convenience sample	Chi-square tests used to compare prevalence of first e-cigarette flavor purchased for each time period of first e-cigarette purchase; logistic regression analysis used to examine association between current use of tobacco-flavored e-liquids and fruit/fruit beverage flavored	Switchers (from regular cigarette smoking to regular e-cigarette use) (OR = 4.03, 95% CI: 3.26-4.97), dual users (OR = 4.14, 95% CI: 3.26-5.26), and former smokers (OR = 2.33, 95% CI: 1.85-2.93) were more likely than never smoker e-cigarette users to have initiated e-cigarette use with a tobacco-flavored product. Switchers (OR = 0.43, 95% CI: 0.38-0.49), dual users (OR = 0.41, 95% CI: 0.34-0.48), and former smoker (OR = 0.58, 95% CI: 0.50-0.67) e-cigarette users were all significantly less likely than never smoker e-cigarette users to

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		e-liquids and Tobacco Use Pathway Group and time of first e-cigarette purchase.	have initiated e-cigarette use with fruit-flavored products. The highest rate of current use of tobacco-flavored e-liquid was reported by those who initiated e-cigarette use ≥ 5 years ago; the lowest rate of current use of tobacco flavor was reported by those who initiated e-cigarette use in the past 12 months. The highest rate of current use of fruit/fruit beverage e-liquid flavors was among those who initiated e-cigarette use in the past 12 months, while the lowest rate was among those who initiated e-cigarette use ≥5 years ago; a similar effect of time since first e-cigarette purchase was found for current use of dessert/pastry flavors and for candy/chocolate/sweets flavors. As was observed for tobacco-flavored first e-cigarette purchases, switchers (OR = 2.18, 95% CI: 1.69-2.81), dual users (OR = 2.63, 95% CI: 1.97-3.51), and former smoker (OR = 1.54, 95% CI: 1.16-2.03) e-cigarette users all had significantly higher odds of current use of tobacco-flavored e-liquid compared to never smoker e-cigarette users. Switchers (OR = 0.64, 95% CI: 0.54-0.75), dual users (OR = 0.70, 95% CI: 0.57-0.86), and former smoker (OR = 0.70, 95% CI: 0.59-0.85) e-cigarette users were significantly less likely than never smoker e-cigarette users to be current users of fruit-flavored products.
Rutten, 2015[66]	Cross-sectional survey Probability sample	Logistic regression models used to assess association between reasons for use of e-cigarettes smoking	14.7% of smokers who also used e-cigarettes reported using e-cigarettes because of appealing flavors, behind eight other reasons including to quit smoking (58.4%), reduce smoking (57.9%), and to reduce the health risks of smoking (51.9%).

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		reduction behaviors.	Smoking reduction behaviors (i.e., decreased use of cigarettes or considered quitting) did not vary among those reporting using e-cigarettes because of appealing flavors vs. those that did not report using e-cigarettes because of appealing flavors.
Shang, 2017[67]	Cross-sectional discrete choice experiment Probability sample	Conditional logit regressions used to analyze the effects of flavors, warnings, and device types on the choice of using e-cigarettes.	For both e-cigarette ever and never users, fruit/sweets/beverage flavors marginally significantly increased ($p<.01$) the probability of choosing an e-cigarette product compared to tobacco flavor.
Shiffman, 2015[68]*	Cross-sectional survey Convenience sample	Comparisons of teen and adult respondents' ratings of their interest by flavor and comparisons of ratings by flavor within the adult sample by e-cigarette use status (recent user, past user, never user).	Adult smokers' e-cigarette ratings (overall mean=1.73±1.0 on a 0-10 scale) were significantly higher ($p<.0001$) than non-smoking teens' (overall mean=0.41±0.14) for each e-cigarette flavor. For each of the 15 flavors, adult smokers' interest in trying e-cigarettes was significantly higher than non-smoking teens' interest (all p values<.05, most p values<.0001).
Shiplo, 2015[69]*	Cross-sectional survey Convenience sample	Logistic regression models examined factors associated with use of flavors	Among current e-cigarette users, a common reason for use was taste (32.3% of younger non-smokers, 18.4% of younger smokers, 6.5% of older smokers).
Spears, 2018[70]	Cross-sectional survey Probability sample	Rao-Scott chi-square tests, independent samples t-tests of mean differences, and ordinal logistic regression used to examine associations between mental health condition	Compared to former smokers without mental health conditions, former smokers with mental health conditions gave higher importance ratings for appealing flavors as a reason for use ($t[79] = 3.83$, $p=.0001$).

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		and variables of interest.	
Tackett, 2015[71]*	Cross-sectional survey Convenience sample	Descriptive statistics examined preferred e-liquid flavors. Logistic regression, controlling for age and sex, was performed to assess associations between flavor (traditional tobacco/menthol vs non-traditional e.g., fruity, coffee, candy) on participants' biochemically verified smoking status.	E-cigarette users who reported using non-tobacco and non-menthol flavors were more likely to have quit smoking compared to those who vaped traditional (tobacco/menthol) flavors (OR=2.626, 95% CI=1.133-6.085, p=.024).
Tsai, 2018[72]	Cross-sectional survey Probability sample	Chi-square tests used to assess differences in reasons for e-cigarette use across groups.	Among students who reported ever using e-cigarettes, the second most commonly selected reason for use was availability of flavors such as mint, candy, fruit, or chocolate (31.0%), behind use by friend or family member (39.0%). High school students were more likely than middle school students to report the availability of flavors as a reason for e-cigarette use (32.3% vs. 26.8%, respectively; p<.05).
Vasiljevic, 2015[73]*	Cross-sectional survey Convenience sample	Mann-Whitney tests and logistic regression were used to assess exposure to advertisements and increase in ratings of appeal, interest in buying and trying e-cigarettes.	Exposure to the flavored e-cigarette ads increased interest in buying and trying e-cigarettes (Mann-Whitney test, U=9140.000, Z=−3.949, p<0.001), whereby those who saw the flavored e-cigarette ads expressed greater interest in buying and trying e-cigarettes (mean rank=176.44) than those who saw the non-flavored e-cigarette ads (mean rank=136.26).

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		Logistic regression was also used to examine exposure to advertisements and effects on susceptibility to smoking.	
Weaver, 2018[74]	Longitudinal survey Probability sample	Weighted logistic regression or weighted general linear models used to assess associations between e-cigarette use and outcomes, such as making a smoking quit attempt and 30-day smoking abstinence; both a complete-case analysis and a multiple-imputation approach used to account for missing data.	Among baseline daily smokers, both menthol/wintergreen/mint users and other flavor e-cigarette users were more likely to report a quit attempt (AORs = 6.0 and 2.4, respectively) than non-users of e-cigarettes, and menthol/wintergreen/mint users were more likely to report a quit attempt than tobacco/unflavored e-cigarette users in the past year ($p<.05$). Users of other e-cigarette flavors (e.g., fruit, dessert, spice; 8.8%; AOR = 0.22, 95% CI: 0.08–0.59) had significantly lower adjusted odds of quitting than non-users of e-cigarettes in the past year, which remained significant in multiple imputation analysis.
Yingst, 2015[75]*	Cross-sectional survey Convenience sample	T-tests and X^2 tests were used to identify differences between current first generation device (FGD) and advanced generation device (AGD) users. Descriptive statistics examined how respondents transitioned between devices.	Participants using an AGD were more likely to rate variety of flavor choices as important (FGD 54.6% vs AGD 94.9%, $p<.0001$).

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Supplementary Table 2. Risk of bias assessed by Quality Assessment Tool (QATSDD) (* indicates study was included in original 2016 review)

Note. [a] Percentage = the total score of a study / the full score 42 (14 items x 3 per item)

Study ID (Author, Year)	Amato, 2015[26]*	Audrain-McGovern 2016[27]	Barnes 2017[28]	Berg, 2016[29]*	Bold 2016[30]	Brozek, 2017[31]	Buckell, 2018[32]	Camenga 2017[33]	Chen 2017[34]	Chen 2018[35]	Clarke, 2017[25]	Coleman 2017[36]	Cooper 2016[37]	Czoli, 2016[38]*
Total score	35	22	27	29	26	24	31	26	25	29	31	28	37	31
%[a]	83%	52%	64%	69%	62%	57%	74%	62%	60%	69%	74%	67%	88%	74%
Explicit theoretical framework	0	1	0	0	0	0	0	0	0	0	3	0	2	3
Statement of aims/objectives in main body of report	3	2	3	3	3	3	3	3	3	3	3	3	3	3
Clear description of research setting	3	1	1	3	2	3	3	2	2	3	3	3	3	3
Evidence of sample size considered in terms of analysis	3	0	1	3	1	1	1	1	1	1	0	0	1	0
Representative sample of target group of a reasonable size	3	1	1	2	2	2	3	1	3	3	1	3	2	2
Description of procedure for data collection	3	3	3	3	3	1	3	3	1	3	2	3	3	3
Rationale for choice of data collection tool(s)	3	3	2	2	1	0	2	1	3	2	3	1	3	2
Detailed recruitment data	3	1	3	3	2	0	1	3	1	2	1	3	3	1
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	1	1	1	0	0	2	3	0	0	0	1	0	2	0
Fit between stated research question and method of data collection (Quantitative)	3	3	3	2	3	3	3	3	3	3	3	3	3	2
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Good justification for analytical method selected	1	3	3	2	3	3	3	3	2	3	3	3	3	3
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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Evidence of user involvement in design	3	0	0	0	0	1	0	0	0	0	2	0	3	3
Strengths and limitations critically discussed	3	0	3	3	3	2	3	3	3	3	3	3	3	3

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Study ID (Author, Year)	Dai 2016[39]	Elkami 2016[40]	Etter, 2010[41]*	Etter 2016[42]	Farsalinos, 2013[43]*	Farsalinos, 2014[44]*	Ford, 2016[45]*	Goldenson 2016[46]	Gubner 2018[47]	Harrell 2017a[48]	Harrell 2017b[49]	Kim 2016[50]	Kinouani 2017[51]	Kong, 2014[52]*	Krishnan-Sarin, 2014[53]*
Total score	31	33	20	27	16	19	32	22	28	31	27	28	27	31	26
% [a]	74%	79%	48%	64%	38%	45%	76%	52%	67%	74%	64%	67%	64%	74%	62%
Explicit theoretical framework	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Statement of aims/objectives in main body of report	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Clear description of research setting	3	3	3	3	3	3	3	2	3	3	3	3	3	3	3
Evidence of sample size considered in terms of analysis	0	2	1	3	0	0	3	1	0	1	0	1	0	1	1
Representative sample of target group of a reasonable size	3	1	2	1	1	2	3	1	2	2	2	1	1	3	3
Description of procedure for data collection	3	3	2	2	1	2	3	3	3	3	2	3	3	3	3
Rationale for choice of data collection tool(s)	2	3	1	2	1	1	2	2	2	3	2	3	2	3	0
Detailed recruitment data	3	3	1	1	1	1	1	1	3	3	2	1	3	3	3
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	1	2	0	0	0	0	0	0	0	1	1	1	0	0	0
Fit between stated research question and method of data collection (Quantitative)	3	3	2	3	1	2	3	3	3	3	3	3	3	2	2
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	2	3	2	2	3	3	3	3	3	3	3	3	3
Good justification for analytical method selected	3	2	1	3	1	1	3	3	3	3	3	3	3	3	3
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Evidence of user involvement in design	0	3	0	0	0	0	2	0	1	0	0	0	0	2	0
Strengths and limitations critically discussed	3	2	2	3	2	2	3	0	2	3	3	3	3	2	2

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Study ID (Author, Year)	Lee 2017a[54]	Lee 2017b[55]	Litt 2016[56]	Maglalang 2016[57]	Morean 2018[58]	Nonnemaker, 2016[59]*	Patel 2017[60]	Pepper, 2013[61]*	Pepper, 2014[62]*	Pepper 2016[63]	Pesko 2016[64]	Russell 2018[65]	Rutten 2015[66]	Shang 2017[67]
Total score	32	28	27	27	26	24	34	35	34	28	29	24	32	27
% [a]	76%	67%	64%	64%	62%	57%	81%	83%	81%	67%	69%	57%	76%	64%
Explicit theoretical framework	3	0	0	0	0	0	3	3	2	0	0	0	0	0
Statement of aims/objectives in main body of report	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Clear description of research setting	3	3	3	3	3	3	3	3	3	3	2	3	1
Evidence of sample size considered in terms of analysis	0	0	0	1	0	0	1	1	1	0	0	1	1	3
Representative sample of target group of a reasonable size	2	3	1	1	1	2	3	2	3	3	2	1	3	3
Description of procedure for data collection	3	3	3	3	3	3	3	3	2	3	3	3	3	2
Rationale for choice of data collection tool(s)	3	3	2	1	1	0	3	2	3	1	2	0	2	3
Detailed recruitment data	3	3	3	3	3	1	3	3	3	3	2	3	3	1
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	0	0	0	0	0	0	0	3	0	0	2	0	0	0
Fit between stated research question and method of data collection (Quantitative)	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Good justification for analytical method selected	3	2	3	3	3	3	3	3	3	3	3	2	3	3
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Evidence of user involvement in design	0	0	0	0	0	0	0	0	2	0	0	0	2	0
Strengths and limitations critically discussed	3	2	3	3	3	3	3	3	3	3	3	3	3	2

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Study ID (Author, Year)	Shiffman, 2015[68]*	Shiplo, 2015[69]*	Spears 2018[70]	Tackett, 2015[71]*	Tsai 2018[72]	Vasiljevic, 2016[73]*	Weaver 2018[74]	Yingst, 2015[75]*
Total score	26	27	29	26	22	33	30	21
% [a]	62%	64%	69%	62%	52%	79%	71%	50%
Explicit theoretical framework	0	0	0	0	0	2	0	0
Statement of aims/objectives in main body of report	3	3	3	3	2	3	3	3
Clear description of research setting	3	3	3	3	3	3	3	2
Evidence of sample size considered in terms of analysis	2	3	0	3	1	3	1	0
Representative sample of target group of a reasonable size	1	2	3	1	3	2	3	2
Description of procedure for data collection	3	3	2	2	2	2	3	2
Rationale for choice of data collection tool(s)	2	0	2	2	0	3	2	1
Detailed recruitment data	3	3	3	2	0	1	3	3
Statistical assessment of reliability and validity of measurement tool(s) (Quantitative only)	1	0	1	0	0	3	0	0
Fit between stated research question and method of data collection (Quantitative)	1	2	3	3	3	2	3	3
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	-	-	-	-	-	-	-	-
Fit between research question and method of analysis	3	3	3	3	3	3	3	2
Good justification for analytical method selected	1	2	3	2	2	1	3	1
Assessment of reliability of analytical process (Qualitative only)	-	-	-	-	-	-	-	-
Evidence of user involvement in design	0	0	0	0	0	2	0	0
Strengths and limitations critically discussed	3	3	3	2	3	3	3	2

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

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