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Sensory attributes of e-cigarette flavours and nicotine as mediators of interproduct differences in appeal among young adults

Adam Leventhal, **Junhan Cho**, **Jessica Barrington-Trimis**, **Raina Pang**, **Sara Schiff**, **Matthew Kirkpatrick**
Preventive Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, California, USA

Abstract

Objective—To estimate the extent to which specific sensory attributes, for example, smoothness, mediate differences in electronic cigarette (e-cigarette) appeal between products in non-tobacco versus tobacco flavours and varying nicotine content in young adults.

Method—E-cigarette users (n=100; aged 18–34 years) administered standardised two-puff e-cigarette doses of different products varying in a flavour (fruit, menthol, tobacco) × nicotine (nicotine-containing (6 mg/mL freebase), nicotine-free) with in-subject design. Participants rated sensory attributes (sweetness, bitterness, smoothness and harshness) and appeal on 100-unit visual analogue scales after administering each product. Sensory ratings were tested as simultaneous mediators of flavour, nicotine and flavour × nicotine effects on appeal.

Results—Appeal preferences for fruit versus tobacco flavours were mediated by sweetness-enhancing ($\beta_{indirect}$=0.092), smoothness-enhancing ($\beta_{indirect}$=0.045) and bitterness-reducing ($\beta_{indirect}$=0.072) effects of fruit flavours. Appeal preferences for menthol versus tobacco flavours were mediated by menthol's smoothness-enhancing ($\beta_{indirect}$=0.039) and bitterness-reducing ($\beta_{indirect}$=0.034) effects. Lower appeal of nicotine-containing versus nicotine-free products was mediated by nicotine's sweetness-reducing ($\beta_{indirect}$=−0.036), smoothness-reducing ($\beta_{indirect}$=−0.156) and bitterness-increasing ($\beta_{indirect}$=0.045) effects. Flavour × nicotine interaction effects on appeal were explained by menthol-related suppression of nicotine's bitterness-enhancing and

Correspondence to: Dr Adam Leventhal, Preventive Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, CA 90032, USA; adam.leventhal@usc.edu.

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sweetness-reducing mediation pathways and fruit-related suppression of nicotine's bitterness-enhancing mediation pathway. Harshness did not mediate appeal after adjusting for other sensory attributes.

Conclusion—Bitterness and smoothness may be cross-cutting mediators of interproduct variation in the effects of types of non-tobacco flavours and nicotine on e-cigarette appeal in young adults. Sweetness may also mediate appeal-enhancing effects of fruit and appeal-reducing effects of nicotine. Non-tobacco flavours may suppress appeal-reducing effects of nicotine in e-cigarettes through attenuation of nicotine's aversive taste attributes.

INTRODUCTION

Flavour and nicotine concentration in electronic cigarettes (e-cigarettes) are focal targets for regulatory policies.[1–5] To guide such policies, evidence of mechanisms mediating differences in e-cigarette appeal across products varying in flavour and nicotine is needed, particularly among young adults who more likely vape non-tobacco flavours (eg, fruit, menthol).[6] Past evidence suggests sensory attributes of e-cigarette flavours and nicotine are germane to their appeal.[7–13] E-cigarettes in non-tobacco (vs tobacco) flavours typically elicit more desired taste perceptions (eg, greater sweetness, lower bitterness) and product appeal.[8–13] Nicotine, which has central nervous system-mediated reinforcing effects,[14] produces instantaneous unpleasant sensory perceptions on exposure (ie, bitterness and harshness/irritation) and reduces appeal of users' puffing experiences.[891112] Menthol and nicotine may have interactive effects, whereby menthol attenuates the harshness or aversive taste of nicotine.[8912]

While past research suggests that sensory attributes and product appeal are affected by e-cigarette flavours and nicotine, three key evidence gaps remain. First, although aversive airway sensations (eg, perceived harshness) have been investigated, certain desirable airway sensations (eg, perceived smoothness) elicited by e-cigarette exposure have not. It is possible perceived smoothness provides information about product appeal not captured by other sensory ratings and may be a useful component of e-cigarette product appeal testing. Second, extant studies of whether flavourings interact with nicotine to alter nicotine's sensory attributes solely compare fruit and menthol flavours to flavourless solutions or to each other,[9111215] without testing head-to-head comparisons to tobacco-flavoured products. Tobacco flavours have bitter properties[1016] and could interact with nicotine's bitter qualities to alter the taste of nicotine–tobacco flavour combinations. Thus, tobacco flavours may be an ideal scientific comparator in tests of nicotine-by-flavour interactions. Further, proposed regulations call for restrictions on all non-tobacco characterising e-cigarette flavours, making tobacco a practical comparator in flavour-by-nicotine interaction tests. Finally, while effects of e-cigarette flavours and nicotine on sensory perceptions are well documented, limited direct empirical evidence of the association between an e-liquid's sensory ratings and its corresponding appeal exists. Appeal-sensory rating associations have been reported in three studies, finding that appeal was positively correlated with sweetness and negatively correlated with bitterness and irritation, and irritation-appeal associations were attenuated after adjustment for other sensory ratings.[71016] Importantly, these studies stratified or amalgamated data across different flavours or nicotine concentrations, reflecting sensory-appeal relations driven by *interindividual* (but not necessarily *interproduct*) differences. Direct empirical evidence of whether sensory properties of e-cigarettes in different flavours or nicotine explain interproduct variation in appeal is lacking.

Mediation is a statistical tool testing the degree to which an independent variable's effect on a dependent variable is explained through an intermediate (ie, mediator) variable.[17] Empirical mediation estimates reflect change in effect magnitude before versus after covarying for mediator variables.[17] When interproduct variation in flavour or nicotine are experimentally manipulated and sensory perception ratings are analysed as mediators, mediation elucidates the magnitude through which the causal effect of interproduct differences in flavour or nicotine, per se, on appeal is explained (ie, mediated) through a product's sensory attributes. Yet, mediation has yet to be leveraged for this purpose.

This secondary analysis of a laboratory experiment in young adult e-cigarette users[18] examined sensory ratings as mediators of the independent and interactive influences of flavour and nicotine on e-cigarette product appeal. The primary outcomes paper reported effects of flavour, nicotine and their interaction on product appeal ratings stratified by smoking history; sensory rating data were excluded.[18] Four sensory ratings of each product were collected, encompassing both taste (sweetness, bitterness) and airway (smoothness, harshness) sensations. We hypothesised that appeal preferences for fruit versus tobacco flavours would be mediated by desirable taste perceptions, preferences for menthol versus tobacco flavours by desirable airway sensations, and nicotine's lower appeal by both undesired taste and airway sensory perceptions. We also hypothesised that fruit and menthol flavours would suppress nicotine's undesirable sensory attributes, mediating the interactive effects of flavour and nicotine on appeal.

METHODS

Participants

Young adult e-cigarette users (n = 100) meeting inclusion (18–35 years old; current nicotine-containing e-cigarette use ≥1 day/week for ≥1 month)—but not exclusion (plan to quit vaping during the study; use of smoking cessation medications; pregnancy or breastfeeding)—criteria were recruited. Participants provided written informed consent.

Design and materials

A single-visit double-blind product procedure was used, which applied a flavour (fruit, menthol, tobacco) × nicotine content (nicotine-containing (6 mg/mL free base nicotine) vs nicotine-free) within-subject fully crossed factorial design.[18] Given the device's wattage, 6 mg/mL generates a nicotine flux comparable to products used in the general population[19,20] and has been previously well-tolerated in this paradigm.[7] We used nine flavours—five fruit (Blueberry, Strawberry, Peach, Watermelon, Blackberry), two menthol (Triple Menthol, Portal Blend) and two tobacco (Red USA, Desert Ship)—in nicotine-containing and nicotine-free solutions (Dekang Biotechnology Co.). The 18 solutions' mean PG/VG ratio was 51/49 (SD=4.3/4.3). The nine nicotine-containing solutions' mean nicotine concentration was 6.1 mg/mL (SD=0.53). Solutions were loaded in a Joyetech 'Delta 23

Atomizer' tank device and 'eVic Supreme' battery and administered in two separate trials at 3.3V and 4.3V (1.5 Ohms) settings. There were 36 trials presented in random order.

Procedure

Participants were told to avoid nicotine/tobacco products for 2 hours prior to arrival. The study visit included informed consent, product appeal testing procedure (beginning with practice trials to familiarise to the device and puffing procedure) and questionnaires. Per previous application of this paradigm,[7] each trial consisted of a guided controlled puffing procedure involving two-puff cycles (10 s preparation, 4 s inhalation, 1 s hold, 2 s exhale intervals) per product, followed by sensory and appeal ratings, with 1 m intertrial intervals.

Measures

Appeal and sensory ratings—Immediately after each two-puff trial, participants provided three appeal ('How much did you like it?', 'How much did you dislike it?', 'Would you use it again?') and four sensory ('How sweet was it?', 'How bitter was it?', 'How smooth was it?', 'How harsh was it?') ratings of the product on 100-unit visual analogue scales with 'Not at all'—'Extremely' as anchors; willingness to use again used Not at all—'Definitely' anchors. No additional instructions or benchmarks were provided to interpret the anchor labels. Based on factor analyses reported in the online supplement, the three appeal ratings were combined into a composite appeal score (mean of 'Liking', 'Willingness to use again' and 'Disliking' (reverse-scored); ratings; Cronbach's α=0.93) and the four sensory ratings were analysed separately.

Participant characteristics—Demographic and tobacco product use history questionnaires were administered (table 1). Participants completed the Penn State Electronic Cigarette Dependence Index,[21] a 10-item measure of e-cigarette dependence (range: 0–20). NicAlert test strips (LiveWellTesting.com, San Diego, California, USA) were used to yield a semi-quantitative index of salivary cotinine—providing descriptive data on the extent of nicotine exposure.[22] Carbon monoxide was assessed using Smokelyzer breath monitors (Bedfont Scientific) at study outset, providing descriptive data.

Analytic plan

Analyses used data from each trial nested by participant (36 per participant). Sensory ratings were tested as simultaneous mediators of the main effects of flavour and nicotine content on appeal using path analysis, including correlational paths among the sensory ratings. Flavour was modelled with tobacco as the referent, providing fruit versus tobacco and menthol versus tobacco contrasts. The analysis yielded estimates on: (1) total effects—flavour and nicotine effects on appeal; (2) indirect effects—mediation of flavour and nicotine effects on appeal through each sensory rating; (3) direct effects—flavour and nicotine effects on appeal adjusted for the four mediators, indicating the portion of flavour and nicotine effects that were not mediated by sensory ratings, and (4) the proportion mediated—the amount of flavour and nicotine total effects that were empirically explained by the four mediators. We report flavour and nicotine effects on each sensory rating (figure 1), and the association of each sensory rating with appeal adjusted for the three other sensory ratings.

We tested whether sensory attributes mediated flavour × nicotine interaction effects on appeal using moderated mediation by calculating the indirect effects of nicotine on appeal via mediators stratified by flavour. Moderated mediation was significant when the 95% CIs surrounding the nicotine→sensory rating→appeal indirect effect did not overlap between the tobacco and fruit or menthol flavour conditions.

Analyses were conducted in MPLUS.[23] Results are reported as standardised regression weights (βs) with 95% CIs with two-tailed tests. A Benjamini-Hochberg multiple test correction was used to maintain a 0.05 study-wise false discovery rate.[24]

RESULTS

Descriptive analyses

The sample (mean (SD) age 25.4 (4.4) years) was 35% female, racially/ethnically heterogenous, and exhibited, on average, moderate e-cigarette dependence severity and salivary cotinine levels translating to ~100 ng/mL, similar to prior samples of current regular tobacco users.[2125] Most participants used tank/pen or advanced personal vaporizer mod devices and fruit or dessert flavours. All were current e-cigarette users per study eligibility criteria; 53% were also current combustible cigarette smokers (ie, dual product users), 25% were former smokers and 22% were never smokers (table 1). Correlations between sensory ratings were in expected directions (eg, positive sweetness-smoothness association, negative sweetness-bitterness association; online supplementary table S1).

Figure 1 illustrates M(SE) of appeal and sensory ratings by study conditions. Fruit (vs tobacco) flavours increased appeal, smoothness, and sweetness and reduced bitterness. Menthol (vs tobacco) flavours increased appeal and smoothness and reduced bitterness. Nicotine-containing (vs nicotine-free) solutions reduced appeal, sweetness, and smoothness and increased harshness and bitterness. Fruit × nicotine interactions showed fruit (vs tobacco) attenuated nicotine's appeal-reducing, sweetness-reducing and bitterness-enhancing effects. Menthol × nicotine interactions showed menthol (vs tobacco) attenuated nicotine's appeal-reducing, smoothness-reducing, sweetness-reducing, bitterness-enhancing and harshness-enhancing effect.

Mediation results

Flavour and nicotine main effects—Sensory mediators explained 91% of the fruit (vs tobacco) total effect on appeal ($\beta_{\text{total effect}}$=0.22). Fruit's appeal-enhancing effect was mediated through its sweetness-increasing ($\beta_{\text{indirect effect}}$=0.092), smoothness-increasing (β_{indirect}=0.045) and bitterness-reducing (β_{indirect}=0.072) effects but not harshness (figure 2A). Sensory mediators explained 58% of the menthol (vs tobacco) effect on appeal ($\beta_{\text{total effect}}$=0.12). Menthol's appealenhancing effect was mediated through its smoothness-increasing (β_{indirect}=0.039) and bitterness-reducing (β_{indirect}=0.034) effects but not sweetness or harshness (figure 2B). Mediators explained 85% of the appeal-reducing effect of nicotine-containing (vs nicotine-free) solutions ($\beta_{\text{total effect}}$= −0.20). Nicotine's appeal-reducing effect was mediated through its bitterness-increasing (β_{indirect}= −0.067), sweetness-reducing (β_{indirect}= −0.156) and smoothness-reducing (β_{indirect}= −0.036) effects but not harshness (figure 2C). Direct effects of fruit, menthol and nicotine on appeal after adjusting for mediators were non-significant. Online supplementary tables S2–S3 present each estimate's p value and 95% CIs.

Flavour × nicotine effects—Moderated mediation tests showed that the weakening of nicotine's appeal-reducing effects by fruit versus tobacco flavours ($\beta_{\text{nicotine total effect}} = -0.19$ vs -0.29) was explained by significantly greater attenuation of the nicotine-induced bitterness enhancement mediation pathway in fruit versus tobacco ($\beta_{\text{indirect}} = -0.034$ vs -0.141) flavours (figure 3). Weakening of nicotine's appeal-reducing effects by menthol versus tobacco flavours ($\beta_{\text{nicotine total effect}} = -0.19$ vs -0.29) was explained by significantly greater attenuation of nicotine-induced bitterness enhancement ($\beta_{\text{indirect}} = -0.04$ vs -0.141) and sweetness reduction ($\beta_{\text{indirect}} = -0.007$ vs -0.072) mediation pathways in menthol versus tobacco conditions. Significant moderated mediation was not observed for other pathways (figure 3).

Moderation by smoking status

Given variability in smoking status, we conducted moderated mediation analyses as a supplemental test of generalisability of study results across smoking statuses. These analyses showed each indirect effect for fruit, menthol and nicotine exhibited overlapping 95% CIs across current, former and never smokers, suggesting no substantial moderation of effects by smoking status (online supplementary table S4).

DISCUSSION

Previously, three key gaps in e-cigarette appeal testing research existed, including data: (1) on desirable airway sensations, (eg, smoothness); (2) comparing how fruit and menthol flavours interact with nicotine, altering nicotine's sensory attributes as compared with tobacco flavours; and (3) on associations between sensory ratings of e-cigarettes and their corresponding appeal, including estimates of mediation of flavour and nicotine effects on appeal. By addressing these, this study showed smoothness may be an important sensory perception to measure in e-cigarette product testing research and found that differences in sensory attributes exist when fruit and tobacco flavours are compared with one another, in the context of interactions with nicotine. Additionally, it showed interproduct variation in flavour and nicotine content on e-cigarette appeal is mediated by sensory attributes in young adults. Specifically, fruit-flavoured e-cigarette solutions were perceived as sweeter, smoother and less bitter than tobacco-flavoured solutions, mediating appeal preferences for fruit over tobacco-flavoured products. Menthol solutions were rated smoother and less bitter than tobacco-flavoured solutions, mediating preferences for menthol over tobacco-flavoured products. Solutions with versus without nicotine were perceived as more bitter, less smooth and less sweet, mediating lower appeal of nicotine-containing than nicotine-free products. Flavour-by-nicotine interaction effects on appeal were explained by menthol-induced suppression of nicotine's bitterness-enhancing and sweetness-reducing mediation pathways and by fruit-induced suppression of nicotine's bitternessenhancing mediation pathway.

These findings advance previous e-cigarette administration research, which has found: (1) fruit flavourings increase appeal and sweetness, reduce bitterness and have null effects on harshness; (2) nicotine reduces sweetness and appeal and increases irritation/harshness and bitterness; (3) menthol suppresses nicotine's harshness; (4) higher sweetness and lower bitterness predict higher appeal; and (5) harshness does not predict appeal after adjusting for other sensory perceptions.[7–911–1326] Our results are largely concordant with extant findings and advance knowledge about sensory attributes of e-cigarettes and their role in product appeal in three ways.

First, because smoothness had not been previously measured in e-cigarette product testing, whether smoothness ratings provide unique information about product appeal and sensory profile was unclear. The empirical independence of smoothness and harshness in this study suggest participants did not solely perceive these airway sensations as inverse descriptors of a redundant sensation. Smoothness consistently mediating the effects of both fruit and menthol flavours on appeal and nicotine's appeal-reducing effects further suggests that smoothness may represent a cross-cutting sensory attribute of various products with high user appeal. Measuring smoothness in future e-cigarette product appeal testing warrants consideration.

Second, this study provides the first evidence that fruit (vs tobacco) flavours may attenuate nicotine's bitterness-enhancing (and corresponding appeal-reducing) effects. Prior tests of flavour-by-nicotine interactions compared fruit flavours to only flavourless or menthol-flavoured products, finding no evidence that fruit flavours were capable of suppressing nicotine's undesirable sensory qualities.[1112] Absence of head-to-head comparisons of fruit and tobacco flavours may explain previous null fruit-by-nicotine interaction results. The flavourants in some e-cigarette solutions used to simulate tobacco taste could have bitter qualities, which may explain why tobacco flavours increased perceived bitterness in this study and previous experiments.[1016] Given the 'baseline' bitterness of tobacco-flavoured products, using a tobacco comparison flavour may increase sensitivity for detecting whether certain flavours, including fruit, are capable of suppressing nicotine's bitter qualities. Furthermore, using tobacco as a reference flavour is relevant to forecasting impacts of regulatory restrictions on all non-tobacco flavours, including menthol, which the US Food and Drug Administration (FDA) has recently proposed.[27] The current results suggest products exempt to such regulations would be available in only tobacco flavours that, when combined with nicotine, might be perceived as bitter and unappealing in young populations.

Third, this study confirms sensory attributes account for *interproduct* differences in user appeal over and above interindividual differences. Importantly, prior studies of the relation between sensory attributes and appeal clustered or stratified data across different flavours,[71016] not controlling for interindividual influences. Consequently, previously identified associations may be driven by interindividual differences, whereby people who perceive most e-cigarette products as appealing (regardless of product flavour or nicotine content) may also typically experience desirable sensations while vaping (regardless of product flavour or nicotine content). To hold constant interindividual differences, mediation analyses were used, allowing us to isolate sensory attributes that explain interproduct differences in appeal. Using this approach, we found that most interproduct variation in flavour and nicotine was mediated by sweetness, bitterness and smoothness, with the caveat that 32% of the difference in appeal between menthol and tobacco flavours were not explained by the sensory attributes studied here. Thus, measuring additional sensory attributes, such as coolness,[8912] may be useful adjuncts in product appeal tests of menthol flavoured products.

Evidence that flavour-by-nicotine interaction effects were mediated by taste perceptions reveal possible mechanisms through which flavours make nicotine less aversive in e-cigarettes. While nicotine has central nervous system-mediated reinforcing effects once absorbed into the blood stream,[14] nicotine produces instantaneous sensory perceptions on exposure that can be unpleasant, as demonstrated here at 6mg/mL and previously at 6, 12, 18 and 24 mg/mL[78111216] concentrations, due in part to nicotine-related simulation of bitter taste receptors.[28–30] Previous evidence suggests cross-modal gustatory–olfactory system intersections, whereby a sweet odour reduces perception of bitter taste.[31] Thus, constituents in fruit flavours that produce sweet-smelling odours could contribute to the masking of nicotine's bitter qualities observed here. Menthol-related suppression of sweetness and bitterness mediation pathways extends previous findings that menthol improves perceived taste of e-cigarettes with nicotine in youth[9] and adults.[12] There exists evidence that menthol disrupts taste receptor function, which could explain the current findings; however, effects of menthol on taste fibres are neither large nor consistent,[32–34] suggesting further mechanistic work on this topic is warranted.

E-cigarette manufacturers' capability to suppress nicotine's undesirable sensory attributes with non-tobacco flavourings may have critical public health implications. In the USA, 21% of adolescents and 8% of young adults reported last 30-day vaping in 2018[3536] most of whom use e-cigarettes in non-tobacco flavours.[637] The findings reported here and previously consistently demonstrate nicotine causes the user experience of vaping to generate aversive sensory effects.[78111216] Nicotine produces irritating sensations to the airways, colloquially labelled 'throat hit', that may be desirable for long-time adult smokers who desire a sensory substitute for combustible cigarettes[26]; however, previous data in young adults suggest inverse associations between throat hit and appeal.[7] Thus, neuropharmacologically mediated reinforcement may drive young consumers to purchase e-cigarettes with nicotine, rather than acute sensory effects of nicotine, which may actually be a deterrent for youth. With combustible cigarettes, aversive sensory attributes during initial use experiences deter many young people from subsequently continuing to smoke.[38] Menthol and other flavourants added to commercially manufactured combustible cigarettes suppress the aversive sensory attributes of smoking, increasing product appeal, probability of continued use and risk of nicotine dependence.[3940] The current evidence that flavourings also make the sensory experience of vaping e-cigarettes with nicotine more appealing, reinforces hypotheses that regulatory restrictions on non-tobacco flavours in e-cigarettes may prevent young people from continuing use of e-cigarettes with nicotine after initial trial and subsequent vulnerability to tobacco product addiction.[4142]

Limitations

First, associations between sensory and appeal ratings were correlational and measured contemporaneously, restricting inferences regarding the causal sequence from sensory perception to product appeal following e-cigarette exposure. Second, we did not address mechanisms underlying product appeal that operate on slower time courses (eg, nicotine-mediated pharmacological reinforcement). Third, most participants reported typically using non-tobacco flavours, which is representative of flavour preferences in populations of young adult e-cigarette users[6] and explains robust differences in appeal between non-tobacco and tobacco flavours observed here. Thus, these results are most aptly suited to understanding sensory mechanisms underlying considerable preferences for non-tobacco flavours in young adult populations but not necessarily older adults who may prefer tobacco-flavoured products. Fourth, it is unclear whether the current results generalise to other e-cigarette products, including pod-mods, which use salt-based nicotine solutions that may produce fewer unpleasant sensory attributes than the free-base nicotine solutions utilised here.[43] Fifth, interindividual variability in how participants subjectively interpret reference points and labels with visual analogue scales exists. While within-participant designs experimentally control for such variance, additional analyses involving between-person comparisons by smoking status reported in the supplement should be interpreted with caution. Sixth, the nicotine concentration tested was lower in this study than others[8,9,12] and most participants used tank-style devices that may be more powerful than the study device. Consequently, the sensory perceptions elicited by this study's products may be less familiar and appealing than participants' preferred products. Seventh, the sample was heterogenous with regards to smoking status, which may increase variance in study outcomes and reduce statistical power. However, supplemental analyses suggested no evidence of substantial differences in mediation estimates by smoking status.

CONCLUSIONS AND IMPLICATIONS

Based on the current findings, bitterness and smoothness may be cross-cutting mediators of interproduct variation in the effects of multiple types of non-tobacco flavours and nicotine on e-cigarette product appeal in young adults. Thus, bitterness and smoothness may warrant prioritisation in further e-cigarette product testing research. To provide more precise regulation targets, future research should link bitterness, smoothness and other specific sensory attributes to particular e-cigarette product constituents and elucidate how constituents interact with nicotine and each other to influence sensory perception. While needed, research of specific constituents is challenging because the e-cigarette industry constantly produces new products with novel constituents. The current findings may address this by providing direct empirical evidence that sensory attributes could be common mediators of interproduct differences in e-cigarette appeal due to various dimensions of product diversity. Given these results, sensory perceptions could be considered proxy indicators of the presence of various types of constituents (either known or unknown) that enhance a product's appeal. Consequently, premarket regulatory review of new e-cigarette products—including those with novel constituents—could be optimised if sensory perception data on new products were available. Sensory attributes should continue to be stable foci for tobacco regulatory science and policy as the e-cigarette product landscape continues to evolve.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Food and Drug Administration. Statement from FDA commissioner Scott Gottlieb MD, on new enforcement actions and a youth tobacco prevention plan to stop youth use of, and access to, JUUL and other e-cigarettes, 2018 Available: https://wwwfdagov/NewsEvents/Newsroom/PressAnnouncements/ucm605432htm [Accessed 10 May 2018].
2. European tobacco products Directive 2014/14/EU (TPD). 2018.
3. Berteletti F, King J, Burch J, et al. Campaign for a revised tobacco products Directive in the European Union: lessons learnt. Tob. Control 2017;26:464–7. [PubMed: 27432913]
4. Canada House of Commons' Standing Committee on Health. Vaping: toward a regulatory framework for e-cigarettes. 2015, 41st Parliament, second session, 2015.
5. Tulsieram KL, Rinaldi S, Shelley JJ. Recommendations: will the tobacco and Vaping products act go far enough? Can J Public Health 2017; 108:e328–30. [PubMed: 28910258]
6. Bonhomme MG, Holder-Hayes E, Ambrose BK, et al. Flavoured non-cigarette tobacco product use among US adults: 2013-2014. Tob Control 2016;25:ii4–13. [PubMed: 27794065]
7. 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. [PubMed: 27676583]
8. Rosbrook K, Green BG. Sensory effects of menthol and nicotine in an e-cigarette. Nicotine Tob Res 2016;18:1588–95. [PubMed: 26783293]
9. Krishnan-Sarin S, Green BG, Kong G, et al. Studying the interactive effects of menthol and nicotine among youth: an examination using e-cigarettes. Drug Alcohol Depend 2017;180:193–9. [PubMed: 28915478]
10. 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. [PubMed: 27708124]
11. Pullicin AJ, Kim H, Brinkman MC, et al. Impacts of nicotine and flavoring on the sensoiy perception of e-cigarette aerosol. Nicotine Tob Res 2019. doi:10.1093/ntr/ntz058. [Epub ahead of print: 17 Apr 2019],
12. DeVito EE, Jensen KP, O'Malley SS, et al. Modulation of 'Protective' Nicotine Perception and Use Profile by Flavorants: Preliminary Findings in E-Cigarettes. Nicotine Tob Res 2019. doi:10.1093/ntr/ntz057. [Epub ahead of print: 17 Apr 2019].
13. Hajek P, Przulj D, Phillips-Waller A, et al. Initial ratings of different types of e-cigarettes and relationships between product appeal and nicotine delivery. Psychopharmacology 2018;235:1083–92. [PubMed: 29306962]
14. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol 2009;49:57–71. [PubMed: 18834313]
15. Rosbrook K, Erythropel HC, DeWinter TM, et al. The effect of sucralose on flavor sweetness in electronic cigarettes varies between delivery devices. PLoS One 2017;12:e0185334. [PubMed: 28968411]
16. Mead EL, Duffy V, Oncken C,et al. E-Cigarette palatability in smokers as a function of flavorings, nicotine content and propylthiouracil (ProP) taster phenotype. Addict Behav 2019;91:37–44. [PubMed: 30470456]
17. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. Annu Rev Psychol 2007;58:593–614. [PubMed: 16968208]
18. Leventhal AM, Goldenson NI, Barrington-Trimis JL, et al. Effects of non-tobacco flavors and nicotine on e-cigarette product appeal among young adult never, former, and current smokers. Drug Alcohol Depend. 2019;203:99–106. [PubMed: 31434028]

19. Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. Nicotine Tob Res 2015;17:158–62. [PubMed: 25180079]

20. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery SystemsEaton DL, Kwan LY, Stratton K, eds. Public health consequences of e-cigarettes. Washington (DC): National Academies Press (US), 2018 https://www.ncbi.nlm.nih.gov/books/NBK507171/

21. Foulds J, Veldheer S, Yingst J, et al. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking e-cigarette users. Nicotine Tob Res 2015;17:186–92. [PubMed: 25332459]

22. Cooke F, Bullen C, Whittaker R, et al. Diagnostic accuracy of NicAlert cotinine test strips in saliva for verifying smoking status. Nicotine Tob Res 2008;10:607–12. [PubMed: 18418783]

23. Muthén LK, Muthen B. Mplus user’s guide: statistical analysis with latent variables, user’s guide. Muthén & Muthén, 2017.

24. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B 1995;57:289–300.

25. Kim S Overview of cotinine cutoff values for smoking status classification. Int J Environ Res Public Health 2016; 13:1236.

26. Etter J-F. Throat hit in users of the electronic cigarette: an exploratory study. Psychol Addict Behav 2016;30:93–100. [PubMed: 26653150]

27. U.S. Food and Drug Administration. Trump administration combating epidemic of youth e-cigarette use with plan to dear market of Unauthorized, Non-Tobacco-Flavored e-dgarette products. Available: https://www.fda.gov/news-events/press-announcements/trump-administration-combating-epidemic-youth-e-cigarette-use-plan-clear-market-unauthorized-non [Accessed 10 Feb 2019].

28. Maus AD, Pereira EF, Karachunski PI, et al. Human and rodent bronchial epithelial cells express functional nicotinic acetylcholine receptors. Mol Pharmacol 1998;54:779–88. [PubMed: 9804613]

29. West KA, Brognard J, Clark AS, et al. Rapid Akt activation by nicotine and a tobacco carcinogen modulates the phenotype of normal human airway epithelial cells. J Clin Invest 2003;111:81–90. [PubMed: 12511591]

30. Hummel T, Livermore A, Hummel C, et al. Chemosensoiy event-related potentials in man: relation to olfactory and painful sensations elicited by nicotine. Electroencephalogr Clin Neurophysiol 1992;84:192–5. [PubMed: 1372235]

31. Isogai T, Wise PM. The effects of odor quality and temporal asynchrony on modulation of taste intensity by retronasal odor. Chem Senses 2016; 14:bjw059–66.

32. Fan L, Balakrishna S, Jabba SV, et al. Menthol decreases oral nicotine aversion in C57BL/6 mice through a TRPM8-dependent mechanism. Tob Control 2016;25:ii50–4. [PubMed: 27698211]

33. Hellekant G The effect of menthol on taste receptors. Acta Physiol Scand 1969;76:361–8. [PubMed: 5823867]

34. Lundy RF, Contreras RJ. Taste prestimulation increases the chorda tympani nerve response to menthol. Physiol Behav 1993;54:65–70. [PubMed: 8327609]

35. Gentzke AS, Creamer M, Cullen KA, et al. Vital signs: tobacco product use among middle and high school students - United States, 2011–2018. MMWR Morb Mortal Wkly Rep 2019;68:157–64. [PubMed: 30763302]

36. National Center for Health Statistics. Survey description, National health interview survey, 2018. Hyattsville, Maryland: National Center for Health Statistics, 2019.

37. Harrell MB, Weaver SR, Loukas A, et al. Flavored e-dgarette use: characterizing youth, young adult, and adult users. Prev Med Rep 2017;5:33–40. [PubMed: 27896041]

38. Urbán R, Sutfin E. Do early smoking experiences count in development of smoking?: temporal stability and predictive validity of an early smoking experience questionnaire in adolescents. Nicotine Tob Res 2010;12:1265–9. [PubMed: 21036958]

39. Villanti AC, Collins LK, Niaura RS, et al. Menthol cigarettes and the public health standard: a systematic review. BMC Public Health 2017; 17:983. [PubMed: 29284458]

40. Rabinoff M, Caskey N, Rissling A, et al. Pharmacological and chemical effects of cigarette additives. Am J Public Health 2007;97:1981–91. [PubMed: 17666709]

41. Drazen JM, Morrissey S, Campion EW. The dangerous flavors of e-cigarettes. N Engl J Med 2019;380:679–80. [PubMed: 30699053]

42. Chatterjee K, Alzghoul B, Innabi A, et al. Is vaping a gateway to smoking: a review of the longitudinal studies. Int J Adolesc Med Health 2016;30:1972–86.

43. Barrington-Trimis JL, Leventhal AM. Adolescents' use of "pod mod" e-cigarettes - urgent concerns. N Engl J Med 2018;379:1099–102. [PubMed: 30134127]

What this paper adds

What is already known on this subject

- Electronic cigarettes (e-cigarettes) in non-tobacco flavours (eg, fruit and menthol) produce greater user appeal than tobacco-flavoured e-cigarettes, particularly in young populations.
- Nicotine in e-cigarettes generates acute aversive sensory attributes (eg, bitterness, harshness).
- Menthol may suppress the aversive sensory attributes of nicotine in e-cigarettes.

What important gaps in knowledge exist on this topic

- Whether smoothness is an important sensory attribute of e-cigarettes implicated in product appeal is unknown.
- Whether fruit and menthol flavours, as compared with tobacco flavours, interact with nicotine to alter the aversive sensory attributes of nicotine is unknown.
- Whether and which sensory attributes of e-cigarette flavours and nicotine mediate interproduct differences in appeal is unknown.

What this paper adds

- Among various sensory attributes of e-cigarettes that explain interproduct variation in appeal in young adults, bitterness and smoothness appear to be consistent and robust mediators of the effects of multiple flavours and nicotine on e-cigarette appeal, whereas sweetness is a robust mediator of the appeal-enhancing effects of fruit flavours, per se, and harshness does not consistently mediate interproduct differences in appeal.
- Non-tobacco flavours may suppress the appeal-reducing effects of nicotine in e-cigarettes through attenuation of nicotine’s aversive sensory attributes.
- Data on sensory attributes, including smoothness, of e-cigarette products may be useful to inform premarket review and other regulatory actions guided by the appeal of e-cigarette products.

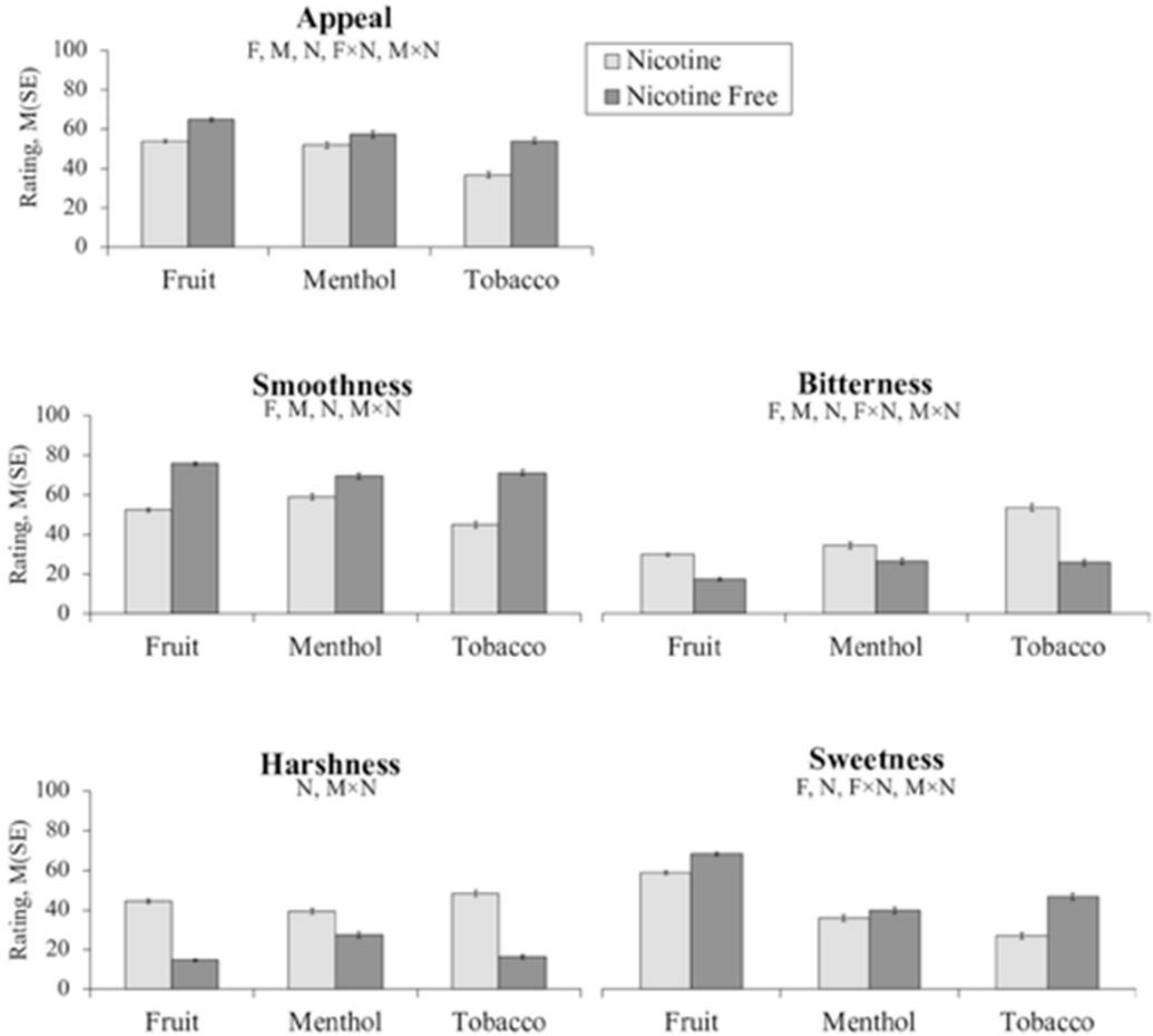

Figure 1.

Mean (SE) of study outcomes by flavour and nicotine content condition. Visual analogue scale with 0–100 range. Appeal=average of 'liking', 'willingness-to-use-again' and 'disliking' (reverse-scored). F=significant effect of fruit. M=significant effect of menthol. N=significant of nicotine. FxN=significant interaction effect of fruit and nicotine. MxN=significant interaction effect of menthol and nicotine.

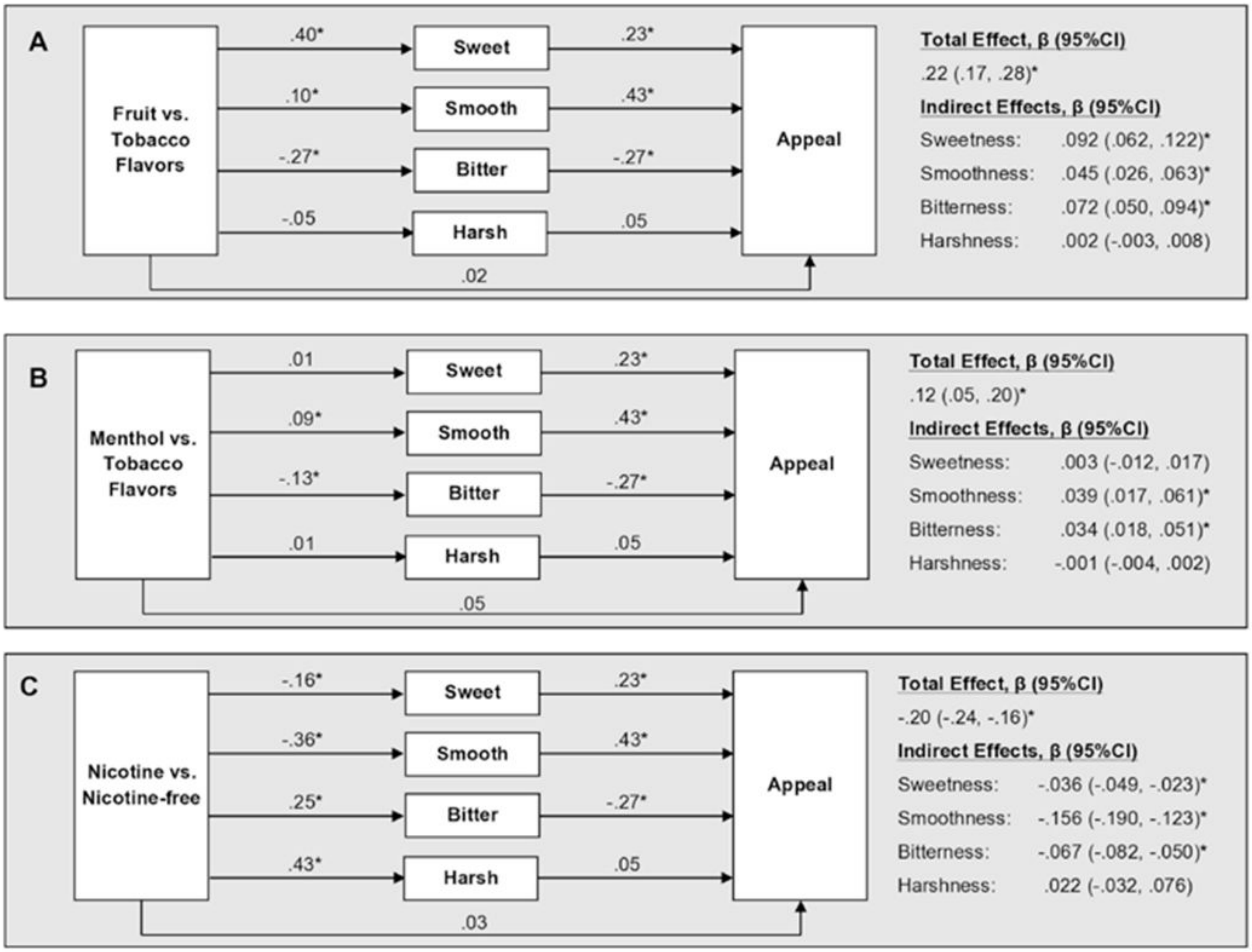

Figure 2.
Indirect effects of flavour and nicotine on appeal through sensory perception ratings. Standardised estimates (βs) of total, direct and indirect effects and component paths from multiple mediator path analysis model, presented separately for fruit (A), menthol (B) and nicotine (C) effects. Correlational paths among sensory effects mediators are not shown. *Statistically significant after Benjamini-Hochberg correction for multiple tests to control study-wise false discovery rate at 0.05. See online supplementary table S2 for p values and 95% CIs of estimates.

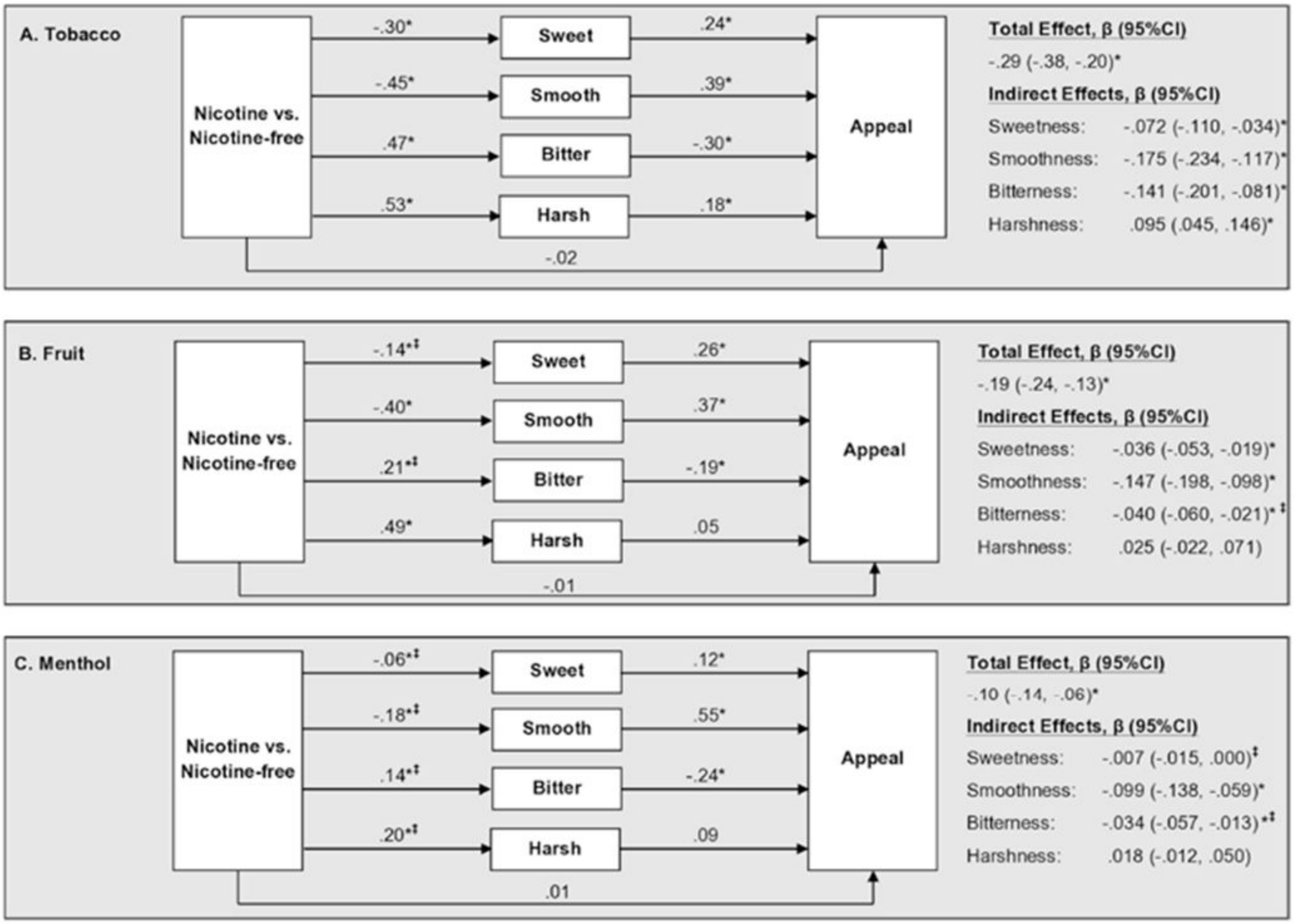

Figure 3.

Indirect effects of nicotine on appeal through sensory perception ratings stratified by flavour condition. Standardised estimates (βs) of total, direct and indirect effects and component paths from three separate multiple mediator path analysis models, stratified by tobacco (A), fruit (B) and menthol (C) flavour conditions. *Statistically significant after Benjamini-Hochberg correction for multiple tests to control study-wise false discovery rate at 0.05. ‡ Effect estimate is significantly different from effect estimate for respective path in tobacco flavour condition.

Table 1

Descriptive statistics of participant characteristics in study sample*

Participant characteristics	N (%) or M (SD)
Demographics	
Female gender, N (%)	35 (35.0)
Age, mean (SD), years	25.4 (4.4)
Race/ethnicity, N (%)	
Hispanic	22 (22.0)
White	29 (29.0)
Black	25 (25.0)
Asian	15 (15.0)
Other	9 (9.0)
Tobacco product use characteristics	
Combustible cigarette smoking status†	
Never smoker	22 (22.0)
Former smoker‡	25 (25.0)
Current smoker§	53 (53.0)
Salivary cotinine semi-guantitative level¶	2.85 (1.22)
Carbon monoxide, ppm**	5.00 (5.51)
PSECDI e-cigarette dependence score, mean (SD)	7.01 (4.51)
Puffs per day, mean (SD)	74.3 (124.3)
Nicotine concentration typically used, mean (SD)	8.77 (13.92)
Duration of e-cigarette use, mean (SD), months	19.8 (14.4)
E-cigarette device type typically used, N (%)	
Cig-a-like	12 (12)
Tank/pen	30 (30)
Advanced personal vaporizer/mod	58 (58)
Preferred e-cigarette flavour, N (%)	
Fruit or dessert	80 (80.0)
Menthol	13 (13.0)
Tobacco	7 (7.0)

*N=100.

†Never smokers: smoked <100 cigarettes lifetime, former smokers: smoked ≥100 cigarettes but did not smoke in last 30 days; current smokers: smoked ≥100 cigarettes lifetime and smoked in last 30 days.

‡Of the former smokers, 10 preferred menthol-flavoured cigarettes and 15 preferred non-mentholated cigarettes when they smoked.

§Of the current smokers, 23 preferred menthol-flavoured cigarettes and 30 preferred non-mentholated cigarettes.

¶NicAlert Strip (range 1–6; 0=0–10,1=10–30, 2=30–100, 3=100–200, 4=200–500, 5=500–1000, 6= >1000 ng/mL).

** Carbon monoxide was significantly higher in participants who were current smokers (M(SD)=7.04 (5.95)) than former (M(SD)=2.40 (3.04)) and never (M(SD)=3.05 (4.73)) smokers (ps<0.001).

e-cigarette, electronic cigarette; PSECDI, Penn State Electronic Cigarette Dependence Index.