



Effects of non-tobacco flavors and nicotine on e-cigarette product appeal among young adult never, former, and current smokers

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ABSTRACT

Background: E-cigarette regulations targeting products that disproportionately appeal to never-smokers may optimize population health. This laboratory study of young adults tested whether differences in appeal between e-cigarettes with non-tobacco-flavored (vs. tobacco-flavored) and nicotine-containing (vs. nicotine-free) solutions varied by smoking history.

Methods: Current (N = 53), former (N = 25), and never (N = 22) cigarette smokers who vape (Mean[SD] age = 25.4[4.4] years) administered standardized e-cigarette doses varied by a Flavor (fruit, menthol, tobacco) × Nicotine (nicotine-containing [6 mg/mL], nicotine-free) within-subject double-blind design. Participants rated each dose's appeal (0–100 scale). Covariate-adjusted interactions tested whether smoking history moderated flavor and nicotine effects.

Results: Appeal was higher for fruit and menthol than tobacco flavors in each group. The fruit vs. tobacco appeal difference was greater in never smokers (fruit–tobacco estimate = 19.6) than current smokers (estimate = 12.1) but not former smokers (estimate = 12.6). The menthol vs. tobacco difference was greater in never smokers (menthol–tobacco estimate = 17.3) than former (estimate = 6.0) and current (estimate = 7.2) smokers. Appeal was lower for nicotine-containing than nicotine-free solutions in each group; this difference was greater in never smokers (nicotine–nicotine-free estimate = –17.3) than former (estimate = –7.0) and current (estimate = –10.6) smokers. Compared to tobacco flavors, nicotine's appeal-reducing effects were suppressed by fruit and menthol flavors in never smokers.

Conclusions: Higher appeal of non-tobacco-flavored (vs. tobacco-flavored) and lower appeal of nicotine-containing (vs. nicotine-free) e-cigarettes may be widespread in young adults but disproportionately amplified in never smokers. Non-tobacco flavors may suppress nicotine's appeal-lowering qualities in never smokers. The impact of regulating non-tobacco flavors in e-cigarettes may vary by smoking history.

1. Introduction

Product standards prohibiting the manufacture, marketing, and sales of electronic cigarettes (e-cigarettes) with specific product characteristics can substantially affect prevalence of vaping in the population and in turn markedly impact public health (Food and Drug Administration, 2018). E-cigarettes currently on the market are available in numerous non-tobacco flavors, such as menthol and a variety of fruit flavors (e.g., candy, fruit), and are sold in various nicotine concentration levels, including nicotine-free solutions (Camenga et al., 2018; Zare et al., 2018). Non-tobacco flavors and nicotine concentration have been targeted in existing or proposed product standards by

the U.S. Food and Drug Administration (2018), European Union Tobacco Product Directive (Berteletti et al., 2017; European Commission Public Health, 2018), and other regulatory agencies (Canada House of Commons' Standing Committee on Health, 2015; Tulsieram et al., 2017).

Differences in user-reported product appeal in response to systematic administration of tobacco products that vary in flavor or nicotine content in the laboratory under double-blind conditions can guide product standards (Carter et al., 2009; Carter and Griffiths, 2009). Such experiments can isolate causal effects of flavorings, nicotine, and other product constituents on appeal while experimentally controlling exogenous influences common to observational research

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(e.g., marketing, pre-existing beliefs about products, social influences). Evidence from previous laboratory experiments demonstrate that product appeal is higher for e-cigarettes with fruit-flavored or dessert-flavored (Audrain-McGovern et al., 2016; Bono et al., 2018; Goldenson et al., 2016; Kim et al., 2016; DeVito et al., 2019) or menthol-flavored (Krishnan-Sarin et al., 2017; Rosbrook and Green, 2016) solutions than tobacco-flavored or flavorless solutions. Nicotine concentration in e-cigarettes produce counterpoising effects. In addition to increasing neuropharmacological-mediated reinforcement due to nicotine absorption, products with higher nicotine concentration produce aversive acute sensory effects (i.e., perceptions of harshness or bitterness) that may reduce immediate subjective appeal (Etter, 2016; Goldenson et al., 2016; Hajek et al., 2018; Rosbrook and Green, 2016; DeVito et al., 2019). Nicotine concentration may interact with menthol flavorings such that menthol-related cooling sensations suppress nicotine's unappealing sensory qualities (Krishnan-Sarin et al., 2017; Rosbrook and Green, 2016).

While observational research suggests that use and appeal of non-tobacco flavored e-cigarettes is greater in never smokers than smokers (Berg, 2015; Bonhomme et al., 2016; Farsalinos et al., 2013; Harrell et al., 2016; Patel et al., 2016; Rodu and Plurphanswat, 2018; Russell et al., 2018), prior controlled laboratory product appeal experiments have aggregated results across never, former, and current combustible cigarette smokers, leaving unclear whether product preferences in experimental research vary by smoking history. Translating this literature into actionable evidence to base regulations that benefit the entire population is difficult because smokers and non-smokers garner divergent health effects from exposure to e-cigarette products they find appealing.

Restricting the sale of products that appeal to never smokers could prevent nicotine addiction and reduce exposure to toxins in e-cigarette aerosols in a population who garners no health benefits from vaping (National Academies of Sciences et al., 2018; U.S. Department of Health and Human Services, 2016). Prohibiting the sale of products that appeal to smokers could discourage transition to e-cigarettes and perhaps encourage former smokers who vape to resume smoking. Optimal regulatory restrictions would target particular products with greater appeal in never smokers than former or current smokers. By doing so, regulations could reduce the appeal of e-cigarettes among never smokers without discouraging smokers from transitioning to e-cigarette use. Consequently, it is critical to identify e-cigarette product characteristics that disproportionately appeal to never smokers relative to current or former smokers to inform regulatory policies that optimize health impact to the population as a whole.

Although most middle-aged and older adults who vape are current or former smokers, never-smoking is common among young adult vapers (Centers for Disease Control and Prevention and National Center on Health Statistics, 2016). This laboratory study of young adult e-cigarette users tested whether smoking history moderated the individual and interactive effects of fruit and menthol (vs. tobacco) flavors and nicotine-containing (vs. nicotine-free) e-cigarette solutions on product appeal ratings. Given past observational research results (Berg, 2015; Bonhomme et al., 2016; Farsalinos et al., 2013; Patel et al., 2016), we hypothesized that the relative preference of fruit or menthol (vs. tobacco) flavors would be heightened in never smokers relative to former and current smokers. No a priori hypotheses were made regarding whether nicotine concentration's main effects or interactive effects with flavor differed by smoking history.

2. Methods

2.1. Participants

Participants (N = 101) in Los Angeles, CA, USA responded to advertisements about a study on reasons for e-cigarette use in 2015. Inclusion criteria were: 1) 18–35 years old; 2) current e-cigarette

use > 1 day/week for > 1 month; 3) use nicotine-containing (> 0 mg/mL) e-cigarettes; and 4) English fluency. Exclusion criteria were: 1) plan to immediately reduce or quit vaping; 2) current smoking cessation medication use; or 3) pregnancy or breastfeeding. One participant who did not complete the entire procedure after enrollment was excluded from analytic sample (N = 100). Participants provided written informed consent. The University of Southern California Institutional Review Board approved the protocol.

2.2. Design

A flavor (fruit, menthol, tobacco) × nicotine concentration (nicotine-containing vs. nicotine-free) within-participant fully crossed factorial design was applied using a double-blind product appeal testing procedure. In previous work, this methodology showed sensitivity to flavor manipulations and successful upholding of study blind (Goldenson et al., 2016). This single-visit procedure involved multiple controlled puffing trials administered via experimenter-provided e-cigarette devices loaded with solutions that systematically varied by flavor and nicotine according to the design. Devices were pre-prepared prior to study visits to keep conditions blind to staff administering the protocol. Nine flavors (5 fruit, 2 menthol, 2 tobacco) each in nicotine and nicotine-free formulations were used (18 total solutions). Each solution was administered at 3.3 and 4.3 V power settings to provide greater generalizability of the findings across devices of varying power available on the market. There were 36 total experimental trials (plus 4 filler trials in a flavorless solution) appearing in a randomly assigned order for each participant. Appeal ratings were collected following each trial.

2.3. Procedure

After eligibility confirmation, participants attended a 4 h laboratory session before which they were told to avoid use of all nicotine/tobacco products for 2 hs prior to arrival. After informed consent and breath carbon monoxide (CO) and salivary cotinine assessment, participants completed the product appeal testing procedure following previous work (Goldenson et al., 2016) in four 9-trial blocks. During each 30-minute inter-block interval, participants completed questionnaires assessing tobacco product use and other characteristics (see below).

At study outset, participants were informed that they would be vaping different e-cigarettes of various flavors, nicotine concentrations, and voltage settings. Participants then viewed an animated video tutorial depicting the controlled puffing parameters. The video cued participants when to inhale and exhale to standardize puffing parameters across trials and was played each trial. A cycle of a 10-s preparation interval, 4 s inhalation interval, 1 s hold interval, and 2 s exhale interval was repeated twice per trial (i.e., 2-puffs per trial). These puff parameters approximate typical e-cigarette use patterns (Helen et al., 2016; Yip and Talbot, 2013) and were used previously (Goldenson et al., 2016). Each trial was separated by a one-minute rest period during which participants were provided with drinking water to reduce cross-trial carryover of olfactory and gustatory sensations. The visible window portion of the atomizer was concealed to prevent unblinding of participants and staff from seeing the color of the e-cigarette solution in each trial. The laboratory was equipped with ventilation to clear aerosol, which reduced staff unblinding due to exposure to the scent of aerosols between trials.

2.4. Materials

Solutions were loaded into Joyetech “Delta 23 Atomizer” tanks with “eVic Supreme” batteries (i.e., tank style device), which allowed voltage to be varied with constant resistance (i.e., 1.5Ω [Ohms]). Solutions (Dekang Biotechnology Co., Ltd.) included those used in our previous study with this paradigm (Goldenson et al., 2016) and were labeled as

containing 50/50 propylene glycol/vegetable glycerin (PG/VG) and either 6 mg/mL free-base nicotine or no nicotine. Five fruit-flavored (Blueberry, Strawberry, Peach, Watermelon, Blackberry), 2 menthol-flavored (Triple Menthol, Portal Blend), and 2 tobacco-flavored (Red USA, Desert Ship) solutions were used in addition to the flavorless solution.

2.5. Measures

2.5.1. Appeal

After each 2-puff trial, ratings using visual analogue scales [VAS; 0–100 range] included three appeal questions used previously (Goldenson et al., 2016): 1) “How much did you like it?” (“Not at all” - “Extremely” as anchors); 2) “How much did you dislike it?” (“Not at all” - “Extremely”); and 3) “Would you use it again?” (“Not at all” - “Definitely”). For each trial, composite mean scores of “Liking,” “Disliking” (reverse-scored), and “Willingness to use again” ratings were calculated.

2.5.2. Combustible cigarette smoking history and other participant characteristics

Participants completed a demographic and tobacco product use history questionnaire to characterize the sample and identify covariates (see Table 1). As in prior work (Berg, 2015; Rodu and Plurphanswat, 2018; Russell et al., 2018; Villanti et al., 2017), lifetime and past 30-day

smoking questions were used to classify participants who smoked < 100 cigarettes lifetime as never smokers, > 100 cigarettes lifetime without past 30-day smoking as former smokers, and > 100 cigarettes lifetime and past 30-day smoking as current smokers.

All participants were administered the Penn State Electronic Cigarette Dependence Index (Foulds et al., 2015), a 10-item measure of current e-cigarette use and dependence, that assesses frequency of use, prior quit attempts, difficulty quitting, experience of craving, withdrawal symptoms, and urge use e-cigarettes (range: 0–20). Current smokers completed the Fagerström Test of Cigarette Dependence (FTCD) (Heatherton et al., 1991), a 6-item measure of combustible cigarette dependence severity (range: 0–10). CO was assessed using Smokelyzer breath monitor (Bedfont Scientific Ltd.). Salivary cotinine was measured with NicAlert™ test strips (LiveWellTesting.com, San Diego, CA), which provided a semi-quantitative index (0 = 0–10, 1 = 10–30, 2 = 30–100, 3 = 100–200, 4 = 200–500, 5 = 500–1000, 6 = > 1000 ng/mL) (Cooke et al., 2008).

2.5.3 Chemical Assay of e-Cigarette Solutions. The solutions were analyzed for nicotine, PG, and VG concentrations, and presence of constituents that are known flavorants via gas chromatography with nitrogen-phosphorous detector using previously-published methods (Leigh et al., 2016).

Table 1

Descriptive statistics of participant characteristics, by smoking history.

| | Pooled Sample (N = 100) | Stratified by Smoking History | | | P-Value for Test of Group Differences |
|--|----------------------------|-------------------------------|----------------------------|-----------------------------|---------------------------------------|
| | | Never Smokers (N = 22) | Former Smokers (N = 25) | Current Smokers (N = 53) | |
| Demographics | | | | | |
| Female Gender, N (%) | 35 (35.0%) | 6 (27.3%) | 9 (36.0%) | 20 (37.7%) | .68 |
| Age, mean (SD), years | 25.4 (4.4) | 22.7 (4.0) ^a | 25.6 (4.0) ^b | 26.5 (4.4) ^b | .003 |
| Race/Ethnicity, N (%) | | | | | .14 |
| Hispanic Ethnicity | 22 (22.0%) | 6 (27.3%) | 6 (24.0%) | 10 (18.9%) | |
| White | 29 (29.0%) | 6 (27.3%) | 11 (44.0%) | 12 (22.6%) | |
| Black | 25 (25.0%) | 3 (13.6%) | 3 (12.0%) | 19 (35.8%) | |
| Asian | 15 (15.0%) | 6 (27.3%) | 3 (12.0%) | 6 (11.3%) | |
| Other | 9 (9.0%) | 1 (4.5%) | 2 (8.0%) | 6 (11.3%) | |
| Tobacco Product Use Characteristics | | | | | |
| Biomarkers, mean (SD) | | | | | |
| Carbon monoxide, ppm | 5.00 (5.51) | 3.05 (4.73) ^a | 2.40 (3.04) ^a | 7.04 (5.95) [§] | .001 |
| Salivary cotinine semi-quantitative level [§] | 2.85 (1.22) | 2.14 (0.89) ^a | 3.00 (1.41) [§] | 3.08 (1.15) [§] | .007 |
| Combustible cigarettes | | | | | |
| Age started smoking everyday, mean (SD), years | 18.46 (4.11) | N/A | 18.83 (1.17) | 18.42 (4.33) | .82 |
| Current cigarettes/day, mean (SD) | 5.89 (5.67) | N/A | N/A | 5.89 (5.67) | N/A |
| Cigarettes/day when smoking heaviest, mean (SD) | 11.60 (7.35) | N/A | 12.20 (5.40) | 11.55 (7.54) | .85 |
| FTCD, mean (SD) | 2.45 (1.94) | N/A | N/A | 2.45 (1.94) | N/A |
| Smoke(d) Mentholated Cigarettes, N (%) | 25 (43.1%) | N/A | N/A | 23 (43.4%) | N/A |
| e-Cigarettes | | | | | |
| PSECD, mean (SD) | 7.01 (4.51) | 4.73 (3.82) ^a | 8.32 (4.89) ^b | 7.34 (4.32) ^b | .02 |
| Puffs per day, mean (SD) | 74.3 (124.3) | 49.7 (53.3) | 123.0 (205.6) | 61.5 (84.8) | .07 |
| Nicotine concentration typically used, mean (SD) | 8.77 (13.92) | 5.76 (6.23) | 6.57 (5.35) | 11.1 (18.1) | .22 |
| Duration of e-cigarette use, mean (SD), months | 19.8 (14.4) | 20.6 (13.3) | 21.9 (13.2) | 18.4 (15.4) | .59 |
| e-Cigarette device type typically used, N (%) | | | | | |
| Cig-a-like | 12 (12%) | 2 (9.1%) ^{ab} | 0 (0%) ^a | 10 (18.9%) ^b | .03 |
| Tank/pen | 30 (30%) | 3 (13.6%) ^a | 8 (32.0%) ^a | 19 (35.8%) ^a | |
| Advanced personal vaporizer/mod | 58 (58%) | 17 (77.3%) ^a | 17 (68.0%) ^{ab} | 24 (45.3%) ^b | |
| Preferred e-cigarette flavor, N (%) | | | | | |
| Fruit | 80 (80.0%) | 20 (90.9%) | 19 (76.0%) | 41 (77.4%) | .58 |
| Menthol | 13 (13.0%) | 2 (9.1%) | 4 (16.0%) | 7 (13.2%) | |
| Tobacco | 7 (7.0%) | 0 (0%) | 2 (8.0%) | 5 (9.4%) | |

^aNicAlert Strip (Range 1–6). P-value for omnibus group differences from χ^2 (categorical variable) or ANOVA (continuous variable) test. Groups that do not share superscripts are significantly different without correction for multiple testing ($p < .05$). FTCD = Fagerström Test for Cigarette Dependence; PSECD = Penn State Electronic Cigarette Dependence Index; ppm = parts per million.

2.6. Data analyses

Following descriptive comparisons of participant characteristics by smoking history groups, the primary analysis used multilevel linear models (MLMs) of trial-level appeal outcome data nested within participants (36 observations per participant). MLMs included the independent categorical variables of flavor (fruit, menthol, and tobacco [reference category]) and nicotine concentration (nicotine and nicotine-free [reference]) fixed effects. Flavor × nicotine concentration interaction effects were also tested to determine whether nicotine effects differed with fruit and menthol flavors compared to tobacco flavor. The MLMs were first tested separately in three subsamples separated into never (n = 22), former (n = 25), and current (n = 53) smokers. Then, to determine whether effects were moderated by smoking history, the subsamples were pooled into a combined dataset (N = 100) to test interactions with the categorical smoking history variable (never [reference], former, current smokers). Flavor × smoking history interactions indicated whether flavor effects differed by smoking history, nicotine × smoking history interactions tested differences in nicotine effects by smoking history, and flavor × nicotine × smoking history interactions indicated whether flavor × nicotine interaction effects varied by smoking history. To address confounds associated with smoking history that could moderate flavor and nicotine effects on appeal, all relevant participant characteristics that significantly differed by smoking history were selected as covariates and adjusted for in the pooled sample moderation by smoking history tests. Four covariate constructs differed by smoking history (i.e., age, e-cigarette device type, e-cigarette dependence, salivary cotinine; see Table 1). Adjustment involved simultaneous inclusion of each covariate construct’s main effect and corresponding interactions with flavor and nicotine (e.g., tests of flavor × smoking history interactions included age, Electronic Cigarette Dependence Index score, cotinine, device type, age × flavor, Electronic Cigarette Dependence Index × flavor, cotinine × flavor, and device type × flavor terms as covariates). The three-way interaction tests included all two-way and three-way interaction term covariates for the 4 covariate constructs (e.g., adjustment for age involved inclusion of age, age × flavor, age × flavor, and age × flavor × nicotine effects).

Primary results are reported as unstandardized effect estimates (differences in outcomes by condition in 0–100 VAS units; Table 2). To correct for multiple testing, the Benjamini-Hochberg method was used to identify two-tailed raw P-values that were significant with a study-wide false discovery rate of 0.05 (see Table 2; Benjamini and Hochberg, 1995). Data were analyzed using IBM SPSS Statistics Version 24 (IBM Corp., Armonk, NY). Additional supplementary analyses are described below.

Table 2
Effect estimates of fruit, menthol and tobacco-flavored e-cigarettes by smoking history group.

| | Never Smokers (N = 22) | | Former Smokers (N = 25) | | Current Smokers (N = 53) | | Comparisons of Effects by Smoking History | |
|--|------------------------|---------|-------------------------|---------|--------------------------|---------|---|-------------------|
| | M (SE) | P | M (SE) | P | M (SE) | P | Former vs. Never | Current vs. Never |
| Main Effects | | | | | | | | |
| Fruit vs. Tobacco | 19.6 (2.1) | < .001* | 12.6 (2.3) | < .001* | 12.1 (1.5) | < .001* | .05 | .006* |
| Menthol vs. Tobacco | 17.3 (2.5) | < .001* | 6.0 (2.7) | .03* | 7.2 (1.8) | < .001* | < .001* | .001* |
| Nicotine vs. Nicotine-free | −17.3 (1.7) | < .001* | −7.0 (1.8) | < .001* | −10.6 (1.2) | < .001* | .002* | .01* |
| Interactions | | | | | | | | |
| Fruit vs. Tobacco × Nicotine vs. Nicotine-free | 9.0 (4.2) | .03* | 4.6 (4.5) | .31 | 6.0 (3.0) | .05 | .78 | .62 |
| Menthol vs. Tobacco × Nicotine vs. Nicotine-free | 18.0 (5.0) | < .001* | 4.0 (5.4) | .46 | 13.0 (3.6) | < .001* | .16 | .99 |

Note. Smokers = smoked cigarette in past 30-days and smoked > 100 cigarettes in lifetime and; Former Smokers = Did not smoke in past 30-days but smoked > 100 cigarettes in lifetime; Never Smokers = did not smoke in past 30-days and did not smoke > 100 cigarettes in lifetime. Nicotine = 6 mg/mL; Nicotine-Free = 0 mg/mL. Appeal = Average of “liking,” “willingness-to-use-again” and “disliking” (reverse-scored) (range 0–100). *Significant effect after Benjamini-Hochberg correction to maintain study-wide false discovery rate of 0.05.

3. Results

3.1. Sample characteristics

Descriptive statistics of demographics and tobacco product use characteristics, by smoking history, are reported in Table 1. The pooled sample had a mean age of 25.4 (SD = 4.4) years, was 35% female, was racially/ethnically diverse, and reported, on average, moderate e-cigarette dependence levels on the Electronic Cigarette Dependence Index. Never smokers were younger on average than former and current smokers. E-cigarette dependence was lower in never smokers than former and current smokers. Salivary cotinine levels were higher in current and former (vs. never) smokers. The sample majority (80%) reported preferring fruit-flavored e-cigarette solutions, which did not differ by smoking status. A greater proportion of current smokers used cig-a-like devices than former smokers. Personal vaporizers/mods were used by a greater proportion of never than current smokers (Table 1).

3.2. Chemical assay of e-cigarette solutions

All 9 nicotine-free solutions had nicotine levels below limits of quantitation. The 9 nicotine-containing solutions had a mean nicotine concentration of 6.08 mg/mL (SD = 0.53, range: 5.08–6.72). The mean PG/VG ratio of the 18 solutions was 49.2/50.8 (SD = 4.3/4.3; range: 39.2/60.8 – 56.4/43.6). Numerous flavoring compounds consistent with the labeled flavor were detected in the study e-cigarette solutions detailed in the Online Supplement.

3.3. Effects of flavor and nicotine on product appeal

Table 2 depicts flavor, nicotine, and flavor × nicotine interaction effect estimates in the form of difference scores, stratified by smoking history (middle columns), and interaction tests of moderation by smoking history (right-hand columns).

3.3.1. Flavor effects, by smoking history

Flavor main effects averaged across nicotine conditions showed that appeal ratings were significantly higher for fruit vs. tobacco flavored solutions in each smoking history group (Table 2, Fig. 1). Covariate-adjusted fruit vs. tobacco × smoking history interaction tests indicated that the magnitude of difference in appeal ratings favoring fruit (vs. tobacco) solutions was significantly greater in never smokers (estimate [i.e., fruit – tobacco difference score]: 19.6) compared to current smokers (estimate: 12.1) but was not different from former smokers (estimate: 12.6).

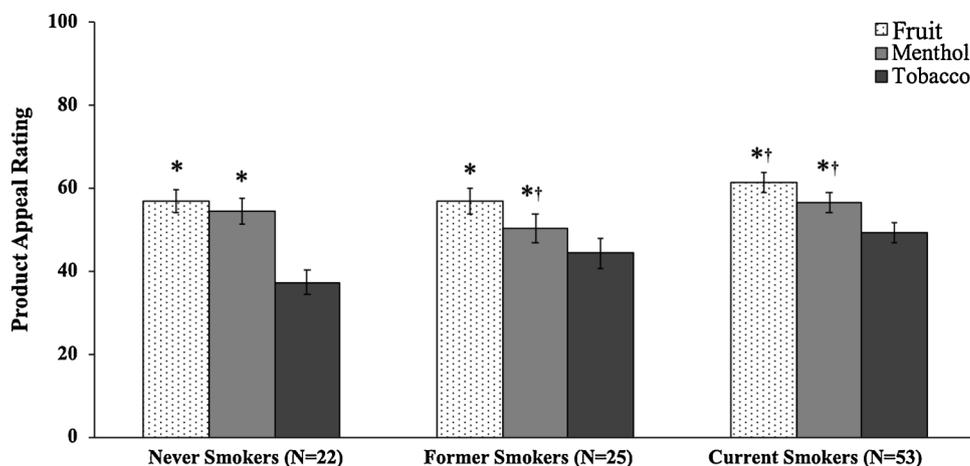


Fig. 1. Product appeal of e-cigarettes with fruit, menthol, and tobacco flavored solutions, by smoking history ($M \pm SE$).
 *Appeal rating significantly different between respective flavor and tobacco flavor within smoking history group ($P_{corr} < 0.05$).
 †Extent of difference in appeal between respective flavor and tobacco flavor significantly differs between respective group and never smokers ($P_{corr} < 0.05$).
 Appeal = Average of “liking,” “willingness-to-use-again” and “disliking” (reverse-scored) (range 0–100).
 P_{corr} = P-value corrected for multiple tests to control study-wise false discovery rate of .05.

Appeal was greater for menthol-flavored than tobacco-flavored solutions in each group. Menthol \times smoking history interaction tests showed that the magnitude of preference for menthol vs. tobacco was greater in never smokers (estimate: 17.3) as compared to former smokers (estimate: 6.0) and current smokers (estimate: 7.2).

3.3.2. Nicotine concentration effects, by smoking history

Averaged across flavor conditions, main effect analyses showed that appeal was significantly lower for nicotine-containing (vs. nicotine-free) e-cigarette solutions in each group, and the relative magnitude of this effect was amplified in never smokers (estimate [i.e., nicotine – nicotine free difference score]: –17.0) compared to former (estimate: –7.0) and current (estimate: –10.6) smokers (Fig. 2).

3.3.3. Flavor \times Nicotine concentration interaction effects, by smoking history

Among never smokers, the extent to which nicotine-containing solutions produced lower appeal ratings than nicotine-free solutions was suppressed in menthol relative to tobacco flavors (Table 2; Fig. 3). This effect is quantified in the menthol \times nicotine estimate (i.e., nicotine – nicotine-free difference for menthol [–8.3] subtracted by nicotine – nicotine-free difference score for tobacco [–26.3]) of 18.0 in never smokers. Evidence of menthol-induced suppression of nicotine’s unappealing effects was also observed in current smokers (menthol \times nicotine estimate: 13.0) but not former smokers (estimate: 4.0). Head-to-head comparisons in the magnitude of menthol \times nicotine

interaction effects did not significantly vary by smoking history group (i.e., non-significant menthol \times nicotine \times smoking history effects).

Fruit vs. tobacco flavors suppressed the extent to which nicotine produced lower appeal than nicotine-free solutions among never smokers (fruit \times nicotine estimate: 9.0) but not among former (estimate: 4.6) or current (estimate: 6.0) smokers. The magnitude of fruit \times nicotine interaction effects did not significantly vary by smoking history group (i.e., non-significant fruit \times nicotine \times smoking history effects; Fig. 3).

3.4. Supplementary analysis

Given that participants were exposed to numerous products within a single session, it is possible that participants habituated or became fatigued or (de)sensitized during the procedure, which could alter the flavor and nicotine effects on product appeal ratings. To assess for habituation or fatigue effects, we tested the effects of trial order (i.e., continuous variable, range: 1–36) on appeal as well as the trial order \times flavor, order \times nicotine, order \times nicotine \times flavor interactions. None of these effects were significant for each group, providing no evidence that cross-product differences in appeal diminished or increased during the procedure.

4. Discussion

This study provides new experimental evidence indicating that

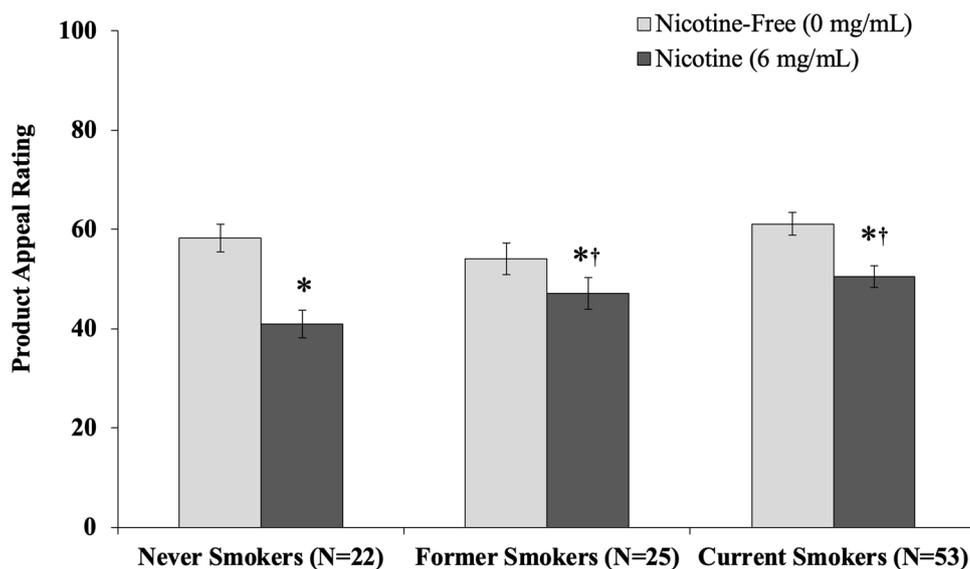


Fig. 2. Product appeal of e-cigarettes with nicotine and nicotine-free solutions, by smoking history ($M \pm SE$).
 *Appeal rating significantly different from nicotine-free within smoking history group ($P_{corr} < 0.05$).
 †Extent of difference in appeal between nicotine and nicotine-free significantly differs between respective group and never smokers ($P_{corr} < 0.05$).
 Appeal = Average of “liking,” “willingness-to-use-again” and “disliking” (reverse-scored) (range 0–100).
 P_{corr} = P-value corrected for multiple tests to control study-wise false discovery rate of .05.

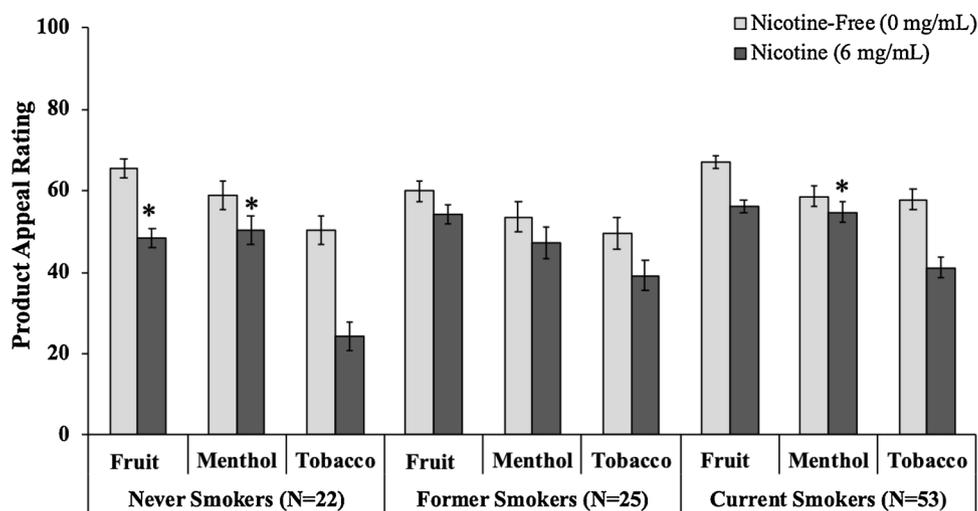


Fig. 3. Product appeal of e-cigarettes with nicotine and nicotine-free solutions, by flavor and smoking history ($M \pm SE$).

*Extent of difference in appeal between nicotine and nicotine-free significantly differs between respective flavor and tobacco flavor within smoking history group ($P_{\text{corr}} < 0.05$). Appeal = Average of “liking,” “willingness-to-use-again” and “disliking” (reverse-scored) (range 0–100).

P_{corr} = P-value corrected for multiple tests to control study-wise false discovery rate of .05.

while most young adult e-cigarette users preferred fruit and menthol over tobacco flavors and found nicotine-containing solutions less appealing than nicotine-free solutions, these effects were amplified in never smokers relative to current and former smokers. We also found that menthol and fruit flavors suppressed nicotine’s appeal-reducing qualities among never smokers. In doing so, this study provides some of the most rigorous experimental evidence to date indicating that the appeal of non-tobacco e-cigarette flavors in young adult vapers may be disproportionately augmented in a subpopulation—never smokers—who garner no health benefits and only risks from vaping.

There are several explanations for differences in product appeal by smoking history. Perhaps inter-individual factors that differ between never, former, and current smokers directly influence product preferences and could confound the findings. The likelihood of quitting smoking increases with age (Lee and Kahende, 2007), and a developmentally-normative propensity toward preferring fruit tastes and disliking bitter tastes declines with age (Hoffman et al., 2016). Thus, mere differences in age, rather than smoking history, could drive younger people toward fruit-flavored products and away from bitter-tasting products; nicotine is a bittering agent (Hummel et al., 1992). Never, former, and current smokers may also differ in their nicotine dependence and access to retailers that sell e-cigarette products that sensitize or habituate the user to certain flavors or nicotine concentrations.

To address such alternative explanations, we considered numerous potential confounds as covariates. Given that results were robust to control of the four covariates that differed by group, it is unlikely that these variables or other characteristics reported in Table 1 that did not differ across groups explain differences in flavor and nicotine concentration effects by smoking history. While it remains possible that other unmeasured factors may explain the pattern of findings, such confounds (whether measured or unmeasured) have ambiguous implications for regulatory policies. Even if, for example, age drives preference for non-tobacco flavors regardless of smoking history, because most never smokers who vape are adolescents and young adults (Centers for Disease Control and Prevention and National Center on Health Statistics, 2016), regulations of non-tobacco flavors might still target never smokers more than smokers.

The current findings may also reflect the possibility that smoking combustible cigarettes directly alters preferences for certain e-cigarette flavors and nicotine concentrations. Repeated exposure to the taste of tobacco and the bitter qualities of nicotine from combustible cigarettes could habituate smokers to the aversiveness of these types of orosensory effects and, through associative conditioning with nicotine’s rewarding pharmacological effects, may cause these sensations to become reinforcing in their own right (Pritchard et al., 1996). When similar

orosensory perceptions are encountered in tobacco-flavored and nicotine-laden e-cigarette solutions, they may be perceived as more appealing (or less aversive) in current or former smokers than never smokers who may be naive to such orosensory effects. This explanation concurs with the current pattern of findings. Group-by-flavor interactions appear to be driven by never smokers’ low appeal of tobacco flavors, especially tobacco-flavored nicotine-containing solutions. Appeal of fruit flavors was similar across groups.

Consistent with previous research in samples with heterogeneous smoking histories (Krishnan-Sarin et al., 2017; Rosbrook and Green, 2016; DeVito et al., 2019), this study found that menthol suppressed the tendency of nicotine-containing (vs. nicotine-free) solutions to be perceived as less appealing but only in never and current smokers. Nicotine’s direct sensory-stimulating effects can be aversive because nicotine causes bitter taste perceptions and irritation to the airways. By suppressing these effects, menthol may make the consumption of e-cigarettes with higher nicotine concentrations more palatable. This study also produced novel evidence that, in never smokers only, fruit flavors also suppressed nicotine’s appeal-reducing effects. For never smokers who were particularly sensitive to nicotine’s appeal-attenuating properties in this study, the suppression of nicotine’s aversive sensory effects by non-tobacco flavors could neutralize a barrier that would otherwise prevent never smokers from vaping e-cigarettes in higher nicotine concentrations.

The premise behind product appeal testing is to provide controlled experimental evidence that may be indicative of the likelihood of continued use after initial exposure to a product. While laboratory product appeal testing may not unequivocally translate to use in the natural ecology, previous research using similar paradigms with other addictive consumer products (e.g., alcoholic beverages) have found laboratory-derived measures predict subsequent use persistence and dependence over long-term follow-up (King et al., 2014). Further, the current results concord with population-based observational research showing that ratios of use of non-tobacco flavored vs. tobacco-flavored e-cigarettes are substantially larger in non-smokers than smokers (Bonhomme et al., 2016). Collectively, there appears to be a triangulation of data from complimentary methodologies implicating non-tobacco flavors as a stronger driver of e-cigarette use in never smokers than smokers.

4.1. Limitations

Limitations of this study’s generalizability warrant consideration in interpreting its policy implications. This study included only 100 vapers, all of whom were young adults from one region. Whether this sample is representative of the entire population of young adult vapers

or generalizes to other age groups is unknown. Only a specific set of e-cigarette solutions with a single device were tested. Pod-mod e-cigarette products, which have recently become popular (Barrington-Trimis and Leventhal, 2018), operate at lower power settings than the tank-style device used in this study. Pod-mods also utilize solutions with salt-based nicotine formulations, which may produce less aversive sensory effects than the free-base nicotine e-cigarette solutions used here (Barrington-Trimis and Leventhal, 2018). Whether similar results are observed with pod-mods and other e-cigarette products warrants future inquiry.

Conclusions drawn from this study's methodology do not address certain drivers of product appeal. This method isolates whether constituents in e-cigarette solutions alter the subjective appeal of the immediate user experience. As ratings are provided immediately following product administration, appeal is likely driven by the momentary smells, tastes, airway sensations, and vapor cloud appearances generated while puffing from the product rather than neuropharmacologically-mediated psychoactive drivers of product appeal. Extraneous factors associated with certain products that may also influence product appeal (e.g., labels, advertising, cultural trends) are intentionally muted in this methodology.

Products were grouped by fruit, menthol, and tobacco classes of flavors rather than the specific constituents. An ideal product standard would identify quantitative limits on particular constituents in e-cigarette products. Like previous constituent analyses of e-cigarette solutions (Leigh et al., 2016), dozens of compounds known to produce certain sensory effects from the food science literature were found in this study's e-cigarette solution. Some constituents may have synergistic effects with one another on taste perceptions, making it difficult to link particular constituents or constituent combinations to specific outcomes. Consequently, classifying flavors into common classes that each have unique defining features, such as what was applied here and previously (Krüsemann et al., 2018; Yingst et al., 2017), makes pragmatic sense.

5. Conclusions

All young adult vapers in this study, regardless of smoking history, found non-tobacco flavors more appealing than tobacco flavored e-cigarettes. Thus, an unfortunate reality is that regulatory policies that reduce the availability of non-tobacco flavors may not benefit the health of every segment of the population, namely smokers who aim to quit smoking with the aid of e-cigarettes and find non-tobacco flavors an appealing alternative to combustible cigarettes (Chen, 2018; Farsalinos et al., 2013; Soule et al., 2019). Yet, findings from the larger literature including those reported here suggest that if tobacco was the primary e-cigarette flavor available, the entire product category would be less appealing (and potentially less addictive) for young never smokers than it would be for smokers interested in transitioning to a lower-harm product.

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The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Contributors

AML was the principal investigator responsible for study conception and directing data collection. AML and NG led the conceptualization of the manuscript and wrote the majority of the manuscript text. NG conducted the analyses and wrote initial drafts of the Results and Analytic Plan and prepared the tables and figures. MK, JBT, and RP aided in study conceptualization and provided feedback on drafts. All

authors contributed to and approved of the final manuscript.

Declaration of Competing Interest

Dr. Goldenson left USC on February 10, 2019 and started as an employee of JUUL Labs as of March 4, 2019. He met criteria for authorship prior to leaving USC, and he had no role in revising the paper after leaving USC and joining JUUL Labs. There are no other interests declared by authors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2019.05.020>.

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