



Published in final edited form as:

Psychol Addict Behav. 2020 March ; 34(2): 303–307. doi:10.1037/adb0000548.

Sex Differences in the Appeal of Flavored E-Cigarettes Among Young Adult E-Cigarette Users

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Abstract

Experimental evidence suggests that females (vs. males) may be more sensitive to and derive greater reinforcement from the sensory aspects of combustible cigarette smoking (e.g., flavor, taste). However, it is unknown if there are similar sex differences in the appeal of flavored e-cigarettes. Young adult male (N=65) and female (N=35) e-cigarette users (Mean Age=25.4; 53% current smokers) attended one laboratory session in which they self-administered standardized e-cigarette doses according to a Flavor (fruit vs. tobacco vs. menthol) × Nicotine (6 mg/mL vs. 0 mg/mL) × Voltage (3.3V vs. 4.3V) within-participant fully crossed factorial design. Following each trial, participants completed ratings of appeal (mean of liking, disliking [reverse scored], and willingness-to-use-again ratings). Sex was tested as a between-subjects moderator of the effects of flavor on appeal. There was a significant interaction between sex and flavor for e-cigarette appeal ($p < 0.001$). In males, fruit-flavored e-cigarettes generated greater appeal than menthol and tobacco ($ps < 0.001$). In females, both fruit- and menthol-flavored e-cigarettes generated greater appeal than tobacco ($ps < 0.001$), but there was no significant difference between fruit- and menthol-flavored e-cigarettes ($p = 0.40$). The findings of this study suggest that males prefer fruit-flavored e-cigarettes, and females prefer both menthol and fruit-flavored e-cigarettes. The impact of regulatory policies targeting e-cigarette flavors in the population may vary by sex.

Keywords

sex differences; female e-cigarette users; e-cigarettes; vaping; menthol

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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.

This work was presented as a poster at the 2017 annual Tobacco Center of Regulatory Science (TCORS) grantee meeting and was presented as part of Dr. Goldenson's PhD dissertation.

Combustible cigarettes are rewarding due to their pharmacological and non-pharmacological properties (e.g., sensorimotor effects; Rose, Salley, Behm, Bates, & Westman, 2010). Experimental evidence suggests that female smokers may be more strongly influenced by the sensory (e.g., flavor, taste) aspects of smoking than males (Perkins et al., 2001). Female smokers rate cigarettes as less appealing and reinforcing than males do when the olfactory and taste stimuli of cigarettes are blocked (Perkins et al., 2001) and experience significantly greater relief from nicotine withdrawal after smoking reduced nicotine or completely denicotinized cigarettes (Faulkner et al., 2018; Perkins & Karelitz, 2015).

The prevalence of flavored electronic cigarette (e-cigarette) use has increased among youth and adults in recent years (Cantrell et al., 2018). Controlled laboratory research in young-adult and adult vapers demonstrates that fruit or dessert-flavored e-cigarettes are more appealing than tobacco-flavored e-cigarettes (Goldenson et al., 2016; Kim et al., 2016). Other studies in adult vapers, dual users, and cigarette smokers have shown that menthol-flavored e-cigarettes increase coolness and reduce airway irritation caused by the harshness of nicotine (Kim et al., 2016; Rosbrook & Green, 2016).

Studies in non-treatment seeking smokers have found that female (vs. male) menthol smokers vaped less when presented with tobacco-flavored e-cigarettes and rated flavorless and tobacco-flavored e-cigarettes as less rewarding and appealing than menthol-flavored e-cigarettes (Mead, Duffy, Oncken, & Litt, 2018; Oncken, Litt, McLaughlin, & Burki, 2015). One study found that female (vs. male) cigarette smokers preferred menthol-flavoring in the absence of nicotine and reported stronger sensory effects at lower menthol concentrations (Rosbrook & Green, 2016). Surveys in adolescent and adult samples suggest that female (vs. male) e-cigarette users may prefer e-cigarettes in flavors other than tobacco (Kong, Kuguru, & Krishnan-Sarin, 2017; Piñeiro et al., 2016) and that the relationship between flavored e-cigarettes and smoking susceptibility may be greater in females compared to males (Chen, Das, Mead, & Borzekowski, 2017). However, little experimental work has been conducted to investigate sex differences in e-cigarette flavor preference in young adult e-cigarette users. In this secondary analysis of a laboratory experiment in which young adult e-cigarette users were provided e-cigarettes of varying flavors and nicotine levels (Leventhal, Goldenson, Barrington-Trimis, Pang, & Kirkpatrick, 2019), we tested the hypothesis that the difference in appeal between non-tobacco flavors (i.e., fruit and menthol) and tobacco flavors would be amplified in females relative to males. As an exploratory analysis, we also compared differences in appeal between nicotine and nicotine-free e-cigarette solutions by sex.

Method

Participants

Young adult e-cigarette users (N=100, 35% female) were recruited in Los Angeles, CA (Leventhal, Goldenson, et al., 2019). Inclusion criteria were: (1) 18–35 years of age; (2) e-cigarette use 1 day/week for 1 month; and (3) English fluency. Exclusion criteria included: (1) desire to immediately reduce e-cigarette use; (2) smoking cessation medication use; and (3) pregnancy or breastfeeding. All participants who met eligibility criteria and completed the single experimental session were included in the analyses. All participants

provided written informed consent and the University of Southern California Institutional Review Board approved the study protocol.

Research Design

This double-blind study used a Flavor (5 fruit vs. 2 menthol vs. 2 tobacco) \times Nicotine (6 mg/mL vs. 0 mg/mL) \times Voltage (3.3V vs. 4.3V) within-participant fully crossed factorial design. Each participant self-administered 36 experimental e-cigarette administrations (i.e., 9 flavors in 2 nicotine strengths at 2 voltage levels) plus 4 filler trials in a flavorless solution. This design provided 3600 observations (36 administrations \times 100 participants) that were included in our analyses.

Procedure

Following eligibility confirmation via telephone, participants attended a single four-hour laboratory session based on the product appeal testing procedure developed in a previous study (Goldenson et al., 2016). Participants were instructed to deprive themselves of all nicotine products (e.g., e-cigarettes, combustible cigarettes) for two-hours before attending the laboratory session. Before beginning the vaping evaluation portion of the experiment, participants completed carbon monoxide and salivary cotinine assessments. Then participants completed 4 blocks of 10 administrations (i.e., each flavor [including flavorless] in each nicotine concentration and each voltage). Order of trials was randomly assigned for each participant. Each administration included 2 standardized puffs, which were cued via an animated video. Within each block, administrations were separated by a one-minute period in which participants were prompted to drink water to prevent conflating prior administrations. Each block was separated by a 30-minute rest period. During this rest period, participants completed surveys assessing demographics, health information and e-cigarette and combustible cigarette use characteristics.

Materials

E-cigarette solutions were loaded into Joyetech “Delta 23 Atomizer” tanks that were connected to a Joyetech “eVic Supreme” battery (i.e., a tank device) with atomizer resistance of 1.5 Ω (Ohms). All e-cigarette solutions (Dekang Biotechnology Co., Ltd.) were composed of 50/50 propylene glycol/vegetable glycerin; nicotine concentration was either 6 or 0 mg/mL (free-base formulation) and were prepared prior to the study visit to keep conditions blind to the staff administering the protocol. The 9 experimental flavorings included 5 fruit-flavored solutions (i.e., blueberry, strawberry, peach, watermelon, blackberry), 2 tobacco-flavored solutions (i.e., red USA, desert ship), and 2 menthol solutions (i.e., triple menthol, portal blend). Flavorings were analyzed by flavor group type (i.e., fruit, menthol, tobacco) as previous work demonstrated limited variability within flavor groups (Goldenson et al., 2016). Device voltage was set to 3.3V or 4.3V for each administration to increase the generalizability of the findings across devices varying in power available on the market.

Measures

Outcome measures—After each 2-puff administration, participants answered three questions that assessed the appeal of the preceding e-cigarette condition (“How much did

you like it?"; "How much did you dislike it?" [reverse scored; and "Would you use it again?"). All questions were rated on visual analogue scales (VAS) from 0–100 with anchors of "Not at all" to "Extremely"—with the exception of willingness-to-use-again, which used anchors of "Not at all" to "Definitely." Confirmatory factor analysis of the three appeal measures indicated a single factor with well-balanced loadings of 0.95 for "Liking", 0.89 for Willingness to use again," and 0.78 for "Disliking (reverse scored)." The three appeal measures were subsequently combined to form one composite appeal measure that was the mean of "Liking," "Willingness to use again," and "Disliking" (reverse-scored; $\alpha=.93$).

Participant Characteristics—All participants completed investigator-created questionnaires that assessed demographics and e-cigarette use characteristics. The Penn State Electronic Cigarette Dependence Index (Foulds et al., 2015) is a 10-item measure of current e-cigarette dependence (range 0–20). Participants self-reported whether they were "female" or "male". Participants also reported their preferred e-cigarette flavor, selecting their top choice from a list of six options (i.e., fruit, candy, chocolate or other sweets, menthol, mint, tobacco). E-cigarette device type (i.e., first-, second- or third-generation) was coded by model type/generation. Participants who reported smoking more than 100 cigarettes in their lifetime ($N=78$) were administered the Smoking History Questionnaire and the Fagerstroöm Test of Cigarette dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) a well-validated 6-item measure of combustible cigarette dependence (range 0–10). For smoking history, participants were classified as never smokers (smoked <100 lifetime cigarettes), former smokers (smoked >100 lifetime cigarettes without smoking in the past 30 days), and current smokers (smoked >100 lifetime cigarettes and smoked in the past 30 days).

Data Analysis

Preliminary analyses calculated descriptive statistics for all demographic and smoking and vaping characteristics, stratified by sex. Fixed effects of flavor group (i.e., fruit vs. menthol vs. tobacco), nicotine (i.e., nicotine vs. placebo), and sex (i.e., male vs. female) were included in multilevel linear (mixed) models with appeal serving as the dependent variable.

Sex was tested as a between-subjects moderator (i.e., interaction terms were created for sex \times flavor and sex \times nicotine interactions) of all main effects for the three composite outcomes. For significant interactions, post-hoc pairwise tests assessed differences between flavor (i.e., fruit vs. tobacco, fruit vs. menthol, tobacco vs. menthol) and nicotine (i.e., nicotine vs. placebo) conditions within females and males. Participant characteristics that significantly differed by sex (i.e., e-cigarette dependence and usual nicotine concentration; see Table 1) or are likely to influence e-cigarette appeal (i.e., device type, baseline e-cigarette flavor preference, smoking history) were included as main effect covariates (additional tests including the sex \times covariate interaction for each covariate yielded identical results and are not shown). Data were analyzed using IBM SPSS Statistics Version 24 with alpha set to 0.05 (IBM Corp., Armonk, NY).

Results

Sample Characteristics

See Table 1 for Sample Characteristics. On average, females (vs. males) reported greater e-cigarette dependence and using e-cigarettes with higher nicotine concentrations (Table 1).

Sex × Flavor Interaction Effects on Product Appeal

After adjusting for smoking history, e-cigarette dependence, nicotine concentration, e-cigarette device type, and baseline reported preference for menthol-flavored and sweet-flavored e-cigarettes, there was a significant interaction between sex and flavor condition for appeal (F-statistic = 9.34; $p < 0.001$). Males rated the fruit-flavored e-cigarettes as significantly more appealing than both the menthol and tobacco conditions and menthol more appealing than tobacco (Figure 1; p -values < 0.001). Among females, there were no significant differences in appeal between the menthol and fruit-flavored e-cigarettes ($p = 0.40$), which were both rated as more appealing than the tobacco condition (p -values < 0.001 ; Figure 1).

Exploratory Analysis of Nicotine Effects

There were not significant two-way sex and nicotine or three-way sex, flavor and nicotine interaction effects on product appeal (p -values > 0.15).

Discussion

In this laboratory e-cigarette administration study, we found sex differences in the appeal of flavored e-cigarettes among young adult e-cigarette users. Male participants rated fruit-flavored e-cigarettes as more appealing than menthol and tobacco flavored products. However, among female e-cigarette users there were no significant differences in the appeal of the menthol- and fruit-flavored e-cigarettes, which were both more appealing than the tobacco e-cigarettes. These findings expand prior laboratory studies showing that young adult and adult vapers prefer sweet flavored compared to tobacco flavored e-cigarettes (Goldenson et al., 2016; Kim et al., 2016) to demonstrate that young adult female vapers may also prefer menthol flavored e-cigarettes.

Menthol may be a particularly important e-cigarette flavoring to consider among females, as preclinical evidence suggests that females may have a biological preference for the analgesic effects of menthol, possibly as a result of a propensity to experience bitter taste sensations (Oncken, Feinn, et al., 2015). Studies in cigarette smokers have shown that females (vs. males) prefer menthol-flavoring in the absence of nicotine, report stronger sensory effects at lower menthol concentrations (Rosbrook & Green, 2016) and that menthol smokers rate tobacco-flavored e-cigarettes as less rewarding and appealing than menthol-flavored e-cigarettes (Mead et al., 2018; Oncken, Litt, et al., 2015).

This study also found that female compared to male vapers reported greater e-cigarette dependence and using higher nicotine concentrations. This is in contrast to prior studies that found that females compared to male adult vapers report using lower nicotine concentrations (Piñeiro et al., 2016) and no gender differences in e-cigarette dependence (Dawkins, Turner,

Roberts, & Soar, 2013). Prior studies in cigarette smokers are suggestive that nicotine may be less important in maintaining smoking in females compared to males. Specifically, studies have shown that reduced nicotine cigarettes relieve nicotine withdrawal to a greater extent in female smokers compared to male smokers (Faulkner et al., 2018; Perkins & Karelitz, 2015) and that nicotine replacement therapy may be less effective in female smokers compared to male smokers (Smith et al., 2016; Smith, Zhang, Weinberger, Mazure, & McKee, 2017). Vapers report the ability to control nicotine concentrations and the use of flavors as appealing qualities of e-cigarettes (Zare, Nemati, & Zheng, 2018) and it is unclear whether sex differences in the role of nicotine in maintaining cigarette use extends to vaping. There is some evidence that female smokers may show greater susceptibility to increasing nicotine intake via vaping when using preferred flavors (Oncken, Litt, et al., 2015). Thus, it is possible that the ability to modulate nicotine levels and alter flavors may result in differences in use of nicotine in e-cigarettes compared to cigarettes.

The current study has implications for two key issues that fall under the regulatory purview of the US Food and Drug Administration and other public health agencies, including regulations that impact: (1) the popularity of flavored e-cigarettes among non-smoking adolescents and young adults; and (2) availability of less harmful nicotine delivery products that may aid adult combustible cigarette smokers in smoking reduction and cessation. Our findings suggest that fruit may promote appeal in both male and female young adult e-cigarette users, and menthol could facilitate e-cigarette use particularly in females. This may be of importance as a prior study found that the association between flavored e-cigarettes and smoking susceptibility may be increased in females compared to males (Chen et al., 2017). Thus, it is possible that females may be particularly susceptible to liking non-tobacco flavored e-cigarettes, which may increase their overall susceptibility to transitioning to smoking.

Limitations include the use of binary sex and only acute dimensions of appeal, as well as use of self-reported measures. Future research should assess more diverse outcomes (e.g., self-administration and physiological effects) indicative of appeal. The study's sample did not contain adult e-cigarette users over the age of 35 or e-cigarette-naïve smokers, and the results of this study should be extended to these populations. Lastly, this study only focused on menthol flavor and did not assess for mint, which is an important limitation given the popularity of mint e-cigarettes among youth (Leventhal, Miech, et al., 2019).

We found sex differences in the appeal effects of flavored e-cigarettes among young adult e-cigarette users, with females equally liking menthol and fruit-flavored e-cigarettes. This study reinforces the need for researchers to study sex-stratified effects in tobacco regulatory science. This study also raises the possibility that the population health impact of regulatory policies addressing the availability of flavored e-cigarettes could differ by sex.

Acknowledgments

This project was supported by the National Cancer Institute (NCI) and the Food and Drug Administration (FDA) funded Tobacco Centers of Regulatory Science (TCORS) award U54CA180908 (mPI: Pentz & Leventhal), and National Institute of Drug Abuse grants K01DA040043 (PI: Pang) and K01DA042950 (PI: Barrington-Trimis).

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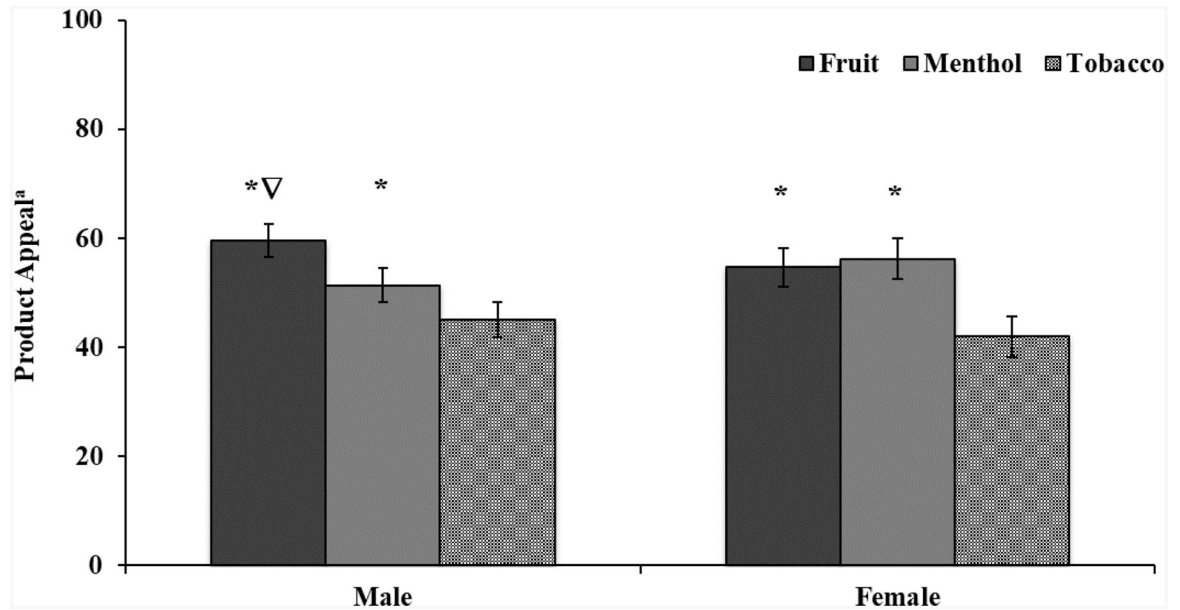


Figure 1. Sex Differences in the Appeal of Flavored e-Cigarettes

Note. $N = 100$ (35 female). Adjusted for e-cigarette dependence, nicotine concentration, e-cigarette device type, smoking history, baseline preference for menthol-flavored e-cigarettes, and baseline preference for sweet-flavored e-cigarettes.

^aProduct Appeal = Mean ($M \pm SE$) of “Like,” “Use Again” and “Dislike” (reverse-scored).

*Significantly greater than tobacco ($p < 0.01$); ∇Significantly greater than menthol ($p < 0.01$).

Table 1

Sample Descriptive Characteristics by Sex

Variable	Total (N=100) ^a	Male (N=65) ^a	Female (N=35) ^a	Test of Difference ^b
	N (%) / M (SD)	N (%) / M (SD)	N (%) / M (SD)	P
Demographic Characteristics				
Age (years), <i>M</i> (<i>SD</i>)	25.4 (4.4)	25.3 (4.5)	25.6 (4.3)	.77
Race/Ethnicity, N (%)				.47
Hispanic	22 (22.0%)	16 (24.6%)	6 (17.1%)	
White	29 (29.0%)	15 (23.1%)	14 (40.0%)	
Black	25 (25.0%)	17 (26.2%)	8 (22.9%)	
Asian	15 (15.0%)	10 (15.4%)	5 (14.3%)	
Other	9 (9.0%)	7 (10.8%)	2 (5.7%)	
Smoking Characteristics				
Smoking Status, N (%)				.68
Never-Smoker	22 (22.0%)	16 (24.6%)	6 (17.1%)	
Past Smoker	25 (25.0%)	16 (24.6%)	9 (25.7%)	
Current Smoker	53 (53.0%)	33 (50.8%)	20 (57.1%)	
Smoke Menthol Cigarettes, N (%)	23 (43.4%)	16 (48.5%)	7 (35.0%)	.35
Carbon monoxide, <i>M</i> (<i>SD</i>) ^c	5.0 (5.5)	5.4 (6.0)	4.2 (4.5)	.29
Salivary cotinine, <i>M</i> (<i>SD</i>) ^d	2.9 (1.2)	2.8 (1.4)	2.9 (0.9)	.70
Age smoke everyday, <i>M</i> (<i>SD</i>)	18.5 (4.1)	19.2 (3.6)	17.2 (4.7)	.08
FTCD, <i>M</i> (<i>SD</i>) ^e	2.5 (1.9)	2.3 (1.9)	2.8 (2.0)	.36
Vaping Characteristics				
PSECD, <i>M</i> (<i>SD</i>) ^f	7.0 (4.5)	6.3 (4.2)	8.3 (4.8)	.03
Puffs per day, <i>M</i> (<i>SD</i>)	74.3 (124.3)	72.5 (95.6)	77.6 (166.6)	.85
Nicotine Concentration, <i>M</i> (<i>SD</i>)	8.8 (13.9)	6.1 (5.2)	13.8 (21.7)	.01
e-Cigarette Device Type, N (%)				.47
1 st Generation Device	12 (12.0%)	6 (9.2%)	6 (17.1%)	
2 nd Generation Device	30 (30.0%)	21 (32.3%)	9 (25.7%)	
3 rd Generation Device	58 (58.0%)	38 (58.5%)	20 (57.1%)	
e-Cigarette Flavor Preference, N (%)				0.10
Prefer Fruit	80 (80.0%)	55 (84.6%)	25 (71.4%)	
Prefer Menthol	13 (13.0%)	5 (7.7%)	8 (22.9%)	
Prefer Tobacco	7 (7.0%)	5 (7.7%)	2 (5.7%)	

^a Available Ns for the respective variable and denominator for percentage.

^b Tests of differences in sample characteristics by sex were conducted with χ^2 tests for categorical variables and one way analysis of variance for continuous variables.

^c End-tidal carbon monoxide (ppm).

^d NicAlert semi-quantitative cotinine strip (Range: 1–6).

^eFagerström Test of Cigarette Dependence (Range: 0–10) with higher scores indicating greater dependence.

^fPenn. State Electronic Cigarette Dependence Index (Range: 0–20) with higher scores indicating greater dependence.

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