Flavored E-cigarette Use and Progression of Vaping in Adolescents

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abstract

OBJECTIVES: Electronic cigarettes (e-cigarettes) are available in nontraditional flavors (eg, fruit and candy) that are banned in combustible cigarettes in the United States. Whether adolescent use of e-cigarettes in nontraditional flavors prospectively predicts continuation of vaping and progression to more frequent vaping is unknown.

METHODS: High school students in Los Angeles, California, completed 5 semiannual surveys (2014–2017 [10th grade to 12th grade]). Among past-6-month e-cigarette users at survey waves 1 to 4 (N = 478), e-cigarette flavor (or flavors) used was coded into 2 mutually exclusive categories at each wave (use of ≥1 nontraditional flavors [fruit, candy, sweet or dessert, buttery, blends or combinations, and other] versus exclusive use of tobacco, menthol or mint, or flavorless). Flavor used during waves 1 to 4 was modeled as a time-varying, time-lagged regressor of vaping status and frequency outcomes 6 months later at waves 2 to 5.

RESULTS: Across waves 1 to 4, there were 739 (93.8%) observations of nontraditional-flavor use and 49 (6.2%) observations of exclusive use of tobacco, mint or menthol, or flavorless e-cigarettes. Use of e-cigarettes in nontraditional flavors (versus only tobacco, mint or menthol, or flavorless) was positively associated with vaping continuation (64.3% vs 42.9%; adjusted odds ratio = 3.76 [95% confidence interval 1.20 to 10.31]) and past-30-day number of puffs per nicotine vaping episode (mean: 3.1 [SD 5.5] vs 1.5 [SD 3.8]; adjusted rate ratio = 2.41 [95% confidence interval 1.08 to 5.92]) 6 months later. Flavor used was not associated with the subsequent number of past-30-day vaping days or episodes per day.

CONCLUSIONS: Adolescents who vaped e-cigarettes in nontraditional flavors, compared with those who exclusively vaped tobacco-flavored, mint- or menthol-flavored, or flavorless e-cigarettes, were more likely to continue vaping and take more puffs per vaping occasion 6 months later.

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WHAT'S KNOWN ON THIS SUBJECT: Electronic cigarettes (e-cigarettes) in nontraditional flavors (eg, fruit and candy) are commonly used at e-cigarette use initiation by youth. Whether exposure to e-cigarettes in nontraditional flavors after youth start vaping prospectively predicts persistence and progression of vaping is unknown.

WHAT THIS STUDY ADDS: This study provides the first prospective longitudinal evidence indicating that among youth who vape e-cigarettes, use of e-cigarettes in nontraditional flavors is positively associated with subsequent persistence of vaping and puffs per vaping episode.

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The US Food and Drug Administration (FDA) prohibits the sale of combustible cigarettes in flavors other than menthol or tobacco.[1,2] These policies do not currently extend to electronic cigarettes (e-cigarettes), which are available in flavors not traditionally found in combustible cigarettes.[3]

E-cigarettes in nontraditional flavors (eg, fruit and candy) are commonly used at e-cigarette use initiation by youth.[4–8] Prospective longitudinal evidence of whether exposure to e-cigarettes in nontraditional flavors after youth start vaping predicts future continuation of e-cigarette use and progression to more frequent vaping patterns is lacking. Greater frequency and chronicity of vaping may be dose-dependently associated with increased risk of addiction, behavioral conditions resulting from nicotine neuroexposure, combustible tobacco use, and other adverse health effects.[9,10] Flavors may compound these risks; exposure to e-cigarettes in nontraditional (versus traditional) flavors is associated with increased combustible cigarette smoking susceptibility,[11] abuse liability,[9,10] and toxic emissions caused by aerosolization of flavoring compounds.[9]

The FDA was considering a policy to limit sales of e-cigarettes in nontraditional flavors to only specialty stores that sell tobacco products.[12,13] In September 2019, the FDA announced that it intends to finalize a compliance policy that would prioritize the agency's enforcement of the premarket authorization requirements for non-tobacco-flavored e-cigarettes, which would clear the market of flavored e-cigarette products until manufacturers obtained premarket authorization for their products or until a new policy is issued.[14] Ordinances prohibiting sales of e-cigarettes in nontraditional flavors within city or town boundaries have been introduced in several locations[15] and could be adopted elsewhere. Prospective data on the relation of adolescent use of flavored e-cigarettes with subsequent vaping patterns could help policy makers forecast whether future regulations that prevent youth exposure to flavored e-cigarettes would improve pediatric population health. This prospective cohort study tested whether adolescents who used e-cigarettes in nontraditional flavors, compared with those who only used traditional-flavored (tobacco and menthol or mint) or flavorless e-cigarettes, were more likely to continue vaping and progress to more frequent vaping patterns 6 months later.

METHODS

Participants and Study Design

Students from 10 Los Angeles County, California, high schools enrolled in a longitudinal cohort study of behavioral health beginning in fall 2013 (their ninth-grade year).[16] Of 4100 eligible students, 3396 (82.8%) provided assent and parental consent and enrolled in the cohort. Paper-and-pencil surveys were administered on-site at participating high schools every 6 months through 12th grade in spring 2017.

Flavored e-cigarette use was first assessed during the spring 2015 10th-grade assessment wave, the initial time point in the current study (wave 1; total surveyed = 3251 [96.0% of cohort enrollees]). Data from the fall 2015 11th-grade (wave 2; N = 3232 [95.6%]), spring 2016 11th-grade (wave 3; N = 3078 [91.0%]), fall 2016 12th-grade (wave 4; N = 3168 [93.8%]), and spring 2017 12th-grade (wave 5; N = 3140 [93.1%]) assessments were also included in this study. The analytic sample (N = 478 [14.1% of cohort enrollees]; Supplemental Fig 1) included students with ≥1 exposure wave–outcome wave pairings that met the following criteria: (1) across waves 1 to 4, students reported vaping e-cigarettes with or without nicotine in the past 6 months and at that same wave indicated which e-cigarette flavor they used (designated as exposure waves), and (2) vaping outcome data were available at the wave immediately after the exposure wave (waves 2–5; outcome waves). Individual students could contribute multiple exposure–outcome wave pairings to the analysis.

The University of Southern California Institutional Review Board approved this study. Written or verbal parental consent was obtained. All students assented to participation.

Measures

Flavored E-cigarette Use

At waves 1 to 4, participants were provided with a checklist of 9 different flavors identified in previous work[17,18] preceded by the headings "Vaping" or "Vaping in the Past 30 Days" and the instructional stem, "Which flavors did you usually use in your e-cigarette (select all that apply)?" Responses were coded to generate the study's exposure variable that had 2 mutually exclusive categories: (1) use of tobacco-flavored, menthol- or mint-flavored, or flavorless products only (unexposed to nontraditional flavors) and (2) use of ≥1 nontraditional flavors, which included fruit, candy, sweet or dessert, buttery, blends or combinations, or other flavors (exposed to nontraditional flavors; either with or without concomitant use of tobacco, menthol or mint, or flavorless products).[17,18]

Vaping Outcomes

Self-reported past-6-month use of e-cigarettes (with or without nicotine; yes or no) indicated whether youth continued vaping during the 6 months after the flavored e-cigarette exposure assessment.[19] At all waves, students completed vaping frequency items measuring

past-30-day number of days vaped nicotine (range: 0–30), number of nicotine vaping episodes (range: 0–20), and puffs per nicotine vaping episode (range: 0–20) per vaping day, as in previous work (see the Supplemental Information for detailed item descriptions, data coding, and preliminary psychometric data suggesting convergent validity across frequency measures).[20]

Covariates

On the basis of the literature,[20–28] we identified a priori covariates considered to be conceptually peripheral to the putative risk pathway, which could increase exposure to flavored e-cigarettes as well as alter vaping patterns and could therefore confound associations.

Time-Invariant Covariates

Demographics, including age (years; continuous variable), sex, and parental education (≥1 parent obtained a college degree [yes or no]), were assessed with self-report questionnaires. Forced choice of 1 of 8 race and/or ethnicity categories (American Indian and/or Alaskan native, Asian American, Black and/or African American, Hispanic and/or Latino, Native Hawaiian and/or Pacific Islander, white, multiethnic and/or multiracial, or other) was recoded into a 4-level variable (Hispanic, white, Asian American, and other race and/or ethnicity).[21,22] Because chronicity of vaping and device type may be associated with vaping patterns and e-cigarette flavors used,[26,27] additional covariates included age of vaping onset[25] (years; continuous variable) and e-cigarette device type[26,27] (forced choice: cigalike [appearance similar to combustible cigarette, nonrefillable, low power], midsize tank [appearance similar to a large pen, refillable, rechargeable, moderate to high power], or advanced personal vaporizer or modified electronic cigarette or "Mod" [similar in size to a smartphone, high power, modifiable, refillable]; assessed only at wave 2). Sensation seeking, assessed with the 12-item subscale of the urgency, perseverance, premeditation, and sensation seeking (UPPS) Impulsive Behavior Scale[28] (eg, "I generally seek new and exciting experiences and sensations"; Cronbach's $\alpha = 0.93$)[29] at wave 1, was included because it could influence the pursuit of flavors and vaping pattern.[30]

Time-Varying Covariates

All nicotine vaping frequency variables at each exposure wave were included as time-varying covariates to adjust for a propensity toward frequent vaping patterns that may precede use of flavors and subsequent vaping outcomes. To address confounding of vaping patterns and flavor choice with exposure to nicotine, other tobacco products, and social elements, we also included exposure wave self-report measures of past-month e-cigarette nicotine concentration typically used (0, 1–5, 6–17, or ≥18 mg/mL; recoded continuously [range: 0–3]),[20] number of smoking days (range: 0–30) and cigarettes smoked per smoking day (range: 0–20), past-6-month noncigarette tobacco product use (hookah, cigars, or smokeless tobacco [yes or no]) and peer vaping ([0 vs ≥1 friends who vaped in the past 30 days]).[24]

Statistical Analysis

Random-effect repeated-measures regression can increase statistical power in cases with low frequency exposures that are spread across multiple time points.[31] We used logistic random-effect repeated-measures regression models in which e-cigarette flavor used (any nontraditional versus only tobacco, menthol or mint, or flavorless) at the exposure waves (waves 1–4) was modeled as a time-varying and time-lagged regressor. Dependent variables were either any past-6-month vaping (yes or no; modeled with binary logit link distributions) or 1 of the past-30-day nicotine vaping frequency count variables (number of vaping days, episodes per day, and puffs per episode; negative binomial distributions) at the immediately subsequent outcome wave (waves 2–5).

Models were fit with and without adjustment for all time-invariant and time-varying covariates described above and included exposure wave time point (continuous variable: 1–4) random effects. Flavor–by–exposure-wave time point interactions were also tested. Analyses were conducted in Mplus version 7.[32] Because students could contribute multiple observations to the analysis (by providing ≥2 exposure–outcome wave pairings) and because of clustering of data within schools, 2-level random effects (time nested within students) and school-level random effects were included. Missing data were managed with full information maximum likelihood estimation. Regression coefficients were exponentiated to obtain odds ratios (ORs) or rate ratios (RRs) with 95% confidence intervals (CIs). Significance was set to 0.05 (2 tailed). For flavor regressor estimates, Benjamini-Hochberg multiple testing corrections were applied to control the study-wide false-discovery rate at 0.05.[33] For exploratory purposes, vaping outcome descriptive statistics for exclusive use of tobacco, menthol or mint, or flavorless products were compared with exposure to each of the 6 individual nontraditional flavors. Additional sensitivity analyses are summarized below and detailed in the Supplemental Information.

RESULTS

Sample

Cohort enrollees included versus excluded from analyses were more likely to be boys, reported higher

sensation-seeking scores, and differed in racial and/or ethnic distribution (Supplemental Table 4).

Descriptive Analyses

The analytic sample (N = 478; wave 1 mean age = 16.1 [SD 0.4]) was demographically heterogeneous (47.5% girls; 46.7% Hispanic; 47.5% had ≥1 parent with a college degree). The mean age of vaping initiation was 15.3 (SD = 0.9) years. Most students reported using advanced personal vaporizers or Mods (52.2%; Table 1).

Pooled across waves 1 to 4, there were 739 (93.8%) total exposure wave observations involving the use of e-cigarettes in nontraditional flavors constituted by 454 unique students. There were 49 (6.22%) exposure wave observations involving exclusive use of traditional flavors (tobacco and mint or menthol) or flavorless products constituted by 47 unique students. Of these 47 students, 23 also reported using a nontraditional flavor on ≥1 other exposure wave.

Illustrated in the left column of Table 2, fruit (total observations = 561 [71.2%]) and candy (N = 299 [37.9%]) were the most common nontraditional flavors used pooled across exposure waves. Supplemental Table 5 reports wave-by-wave frequencies of nontraditional-flavor use and exclusive traditional-flavor or flavorless use. Supplemental Table 6 reports detailed frequencies of the use of each e-cigarette flavor in the overall sample and shows that the use of menthol or mint (18.3%) was more common than flavorless (6.3%) and tobacco-flavored (3.0%) products.

TABLE 1 Descriptive Statistics for Study Covariates

Variable	Result	Available, No.[a]
Time-invariant covariates (total students: N = 478)		
Female sex, No. (%)	227 (47.5)	478
Age, y, mean (SD)	16.1 (0.4)	472
Race and/or ethnicity, No. (%)		465
Hispanic ethnicity	217 (46.7)	
White	102 (21.9)	
Asian American	92 (19.8)	
Other	54 (11.6)	
Parents graduated college, No. (%)	196 (47.5)	413
Age of vaping onset, y, mean (SD)	15.3 (0.9)	440
E-cigarette device type, No. (%)		205
Cigalike, mini e-cigarette, or slim model	19 (9.3)	
Midsize or vape pen	79 (38.5)	
Advanced personal vaporizer or Mod	107 (52.2)	
Sensation-seeking score,[b] mean (SD)	33.0 (9.7)	400
Time-varying covariates at exposure waves 1–4 (total observations: N = 788)		
No. d vaped nicotine in past 30 d, mean (SD)	6.4 (8.9)	780
No. d smoked cigarettes in past 30 d, mean (SD)	2.6 (6.7)	783
Cigarettes smoked per d, mean (SD)	0.9 (3.2)	784
No. nicotine vaping episodes per d, mean (SD)	4.9 (6.5)	784
No. puffs per nicotine vaping episode, mean (SD)	5.9 (6.4)	786
E-cigarette nicotine concentration, mg/mL, No. (%)		619
0	157 (25.4)	
1–5	245 (39.6)	
6–17	162 (26.2)	
≥18	55 (8.9)	
Past-6-mo other tobacco product use,[c] No. (%)	371 (47.9)	775
Past-30-d peer e-cigarette use,[d] No. (%)	570 (80.1)	712

[a] The number of students or observations with (nonmissing) data available for the respective variable and denominators for percentages reported for categorical variables.

[b] UPPS Impulsive Behavior Scale sensation-seeking score range: 0 to 48.

[c] Use of hookah, smokeless tobacco, cigars, and cigarillos (yes or no).

[d] One or more close friends vaped in past 30 days (yes or no).

Association of Flavored E-cigarette Use With Subsequent Vaping Outcomes

Table 2 reports descriptive results of study outcomes. Table 3 reports regression modeling results. With or without adjusting for the 15 covariates listed in Table 1, use of e-cigarettes in nontraditional flavors (versus exclusive use of tobacco, menthol or mint, or flavorless products) at waves 1 to 4 was associated with greater odds of continuing versus discontinuing vaping during the 6 months after exposure in waves 2 to 5 (64.3% vs 42.9%; adjusted OR = 3.76 [95% CI 1.20 to 10.31]). Use of e-cigarettes in nontraditional flavors (versus exclusive use of tobacco-flavored, mint- or menthol-flavored, or flavorless products) was also associated with a greater number of puffs per nicotine vaping episode 6 months later (mean: 3.1 [SD 5.5] vs 1.5 [SD 3.8]; adjusted RR = 2.41 [95% CI 1.08 to 5.92]). Use of nontraditional flavors (versus exclusively tobacco, mint or menthol, or flavorless products) was not significantly associated with the number of past-30-day nicotine vaping days (mean: 4.6 [SD 8.8] vs 2.9 [SD 7.3]) or episodes per day (mean: 3.5 [SD 6.3] vs 2.5 [SD 5.9]).

Flavor-by-time interactions were not significant in all models ($P > .15$), suggesting flavor–vaping outcome associations did not differ by study wave. Estimates of association for covariates in the adjusted model are reported in Supplemental Table 7 and show that peer vaping, use of an advanced personal vaporizer (versus a cigalike), vaping a higher nicotine concentration, cigarette smoking, use of other tobacco products, and exposure wave vaping frequency were positively associated with some vaping outcomes 6 months later.

TABLE 2 Descriptive Statistics of Vaping Outcomes in Combined Sample and Stratified by Flavor of E-cigarette Used

Flavor E-cigarette Used, Pooled Across Waves 1–4	Vaping Outcomes 6 mo After Flavor Assessment, Pooled Across Waves 2–5							
	Any Vaping		No. d Vaped Nicotine in Past 30 d		No. Nicotine Vaping Episodes Per d		No. Puffs per Nicotine Vaping Episode	
	% (SE)	Difference[a] (95% CI)	Mean (SD)	Difference[a] (95% CI)	Mean (SD)	Difference[a] (95% CI)	Mean (SD)	Difference[a] (95% CI)
Combined sample (N = 788)	62.9 (1.7)	—	4.5 (8.7)	—	3.5 (6.3)	—	3.0 (5.5)	—
Primary study exposure variable (mutually exclusive categories)								
Traditional flavor or flavorless only (N = 49)[b]	42.9 (7.1)	Reference	2.9 (7.3)	Reference	2.5 (5.9)	Reference	1.5 (3.8)	Reference
Any nontraditional flavor (N = 739)[c]	64.3 (1.8)	21.4 (7.5 to 35.3)	4.6 (8.8)	1.7 (−0.9 to 4.2)	3.5 (6.3)	1.0 (−0.9 to 2.8)	3.1 (5.5)	1.6 (0.04 to 3.2)
Individual nontraditional flavors (not mutually exclusive)								
Fruit (N = 561)[d]	62.5 (2.0)	19.6 (5.6 to 33.6)	4.2 (8.3)	1.3 (−1.0 to 3.7)	3.4 (6.1)	0.9 (−0.8 to 2.7)	2.8 (5.2)	1.3 (−0.2 to 2.8)
Candy (N = 299)[d]	63.0 (2.7)	20.1 (5.5 to 34.7)	3.8 (7.8)	0.9 (−1.4 to 3.2)	3.2 (6.0)	0.7 (−1.1 to 2.5)	2.8 (5.2)	1.3 (−0.2 to 2.8)
Blends or combinations (N = 260)[d]	70.4 (2.8)	27.5 (13.4 to 41.6)	4.9 (8.7)	2.0 (−0.4 to 4.6)	4.2 (6.9)	1.7 (0.05 to 3.5)	4.0 (6.2)	2.5 (0.7 to 4.3)
Sweets or desserts (N = 229)[d]	71.1 (2.9)	28.2 (14.0 to 42.4)	5.0 (8.8)	2.1 (−0.5 to 4.7)	4.3 (7.0)	1.8 (−0.04 to 3.7)	4.3 (6.4)	2.8 (0.9 to 4.7)
Other flavor (N = 73)[d]	72.7 (5.1)	29.8 (11.5 to 48.1)	6.5 (11.0)	3.6 (0.1 to 7.1)	4.9 (7.5)	2.4 (−0.1 to 4.9)	4.5 (6.8)	3.0 (0.9 to 5.1)
Buttery (N = 54)[d]	71.4 (6.1)	28.5 (10.0 to 47.0)	7.5 (11.2)	4.6 (0.9 to 8.3)	5.8 (7.8)	3.3 (0.6 to 6.0)	5.3 (7.1)	3.8 (1.6 to 6.1)

—, not applicable.

a Difference in vaping outcome between respective flavor category and traditional flavor or flavorless only category.

b Use of tobacco-flavored, mint- or menthol-flavored, or flavorless e-cigarettes only.

c Use of e-cigarettes in ≥1 nontraditional flavor (ie, fruit, candy, blends, sweets or desserts, other, or buttery).

d Subset of any nontraditional-flavor category that used respective individual flavor (not mutually exclusive with use of the 5 other individual nontraditional flavors).

Exploratory Analyses of Use of Individual Nontraditional Flavors

Relative to exclusive use of tobacco, menthol or mint, or flavorless products, the prevalence of vaping continuation was higher 6 months after use of each of the 6 individual nontraditional flavors (ie, fruit, candy, blends, sweets or desserts, other, or buttery; Table 2). The mean number of puffs per nicotine vaping episode was higher 6 months after use of 4 of the 6 individual nontraditional flavors than after exclusive use of tobacco, menthol or mint, or flavorless products. The number of past-30-day nicotine vaping days or episodes per vaping day did not uniformly differ by flavor used at exposure waves (Table 2).

Sensitivity Analyses

Sensitivity analyses found that the 3 vaping frequency items were moderately to strongly correlated with one another, providing preliminary evidence of their convergent validity (Supplemental Information, Supplemental Table 8). Sensitivity analyses suggested that the likelihood of unmeasured confounding was low and results were unchanged on the basis of past-30-day vaping at exposure (Supplemental Information). Analysis of alternative exposure variables suggested (1) possible graded (dose-responselike) associations between vaping a greater number of different nontraditional flavors and subsequent vaping patterns across most outcomes and (2) no differences in vaping outcomes between youth who used only nontraditional flavors and those who used both traditional and nontraditional flavors during concurrent or sequential waves (Supplemental Information, Supplemental Tables 9–12). To determine if graded associations were observed with traditionally flavored or flavorless products, models including the total number of traditionally flavored or flavorless

TABLE 3 Association of Flavored E-cigarette Use With Vaping Outcomes 6 Months Later

	Any Vaping in Past 6 mo, OR (95% CI)	Past-30-d Nicotine Vaping Frequency Outcomes		
		No. d Vaped, RR (95% CI)	No. Vaping Episodes per Vaping d, RR (95% CI)	No. Puffs per Vaping Episode, RR (95% CI)
Unadjusted models[a]				
Use of e-cigarettes in any nontraditional flavor[b]	4.86 (2.11 to 9.86)[c]	2.54 (0.94 to 6.77)	2.06 (0.98 to 4.31)	3.00 (1.46 to 6.17)[c]
Time[d]	1.14 (0.91 to 1.42)	1.15 (0.98 to 1.36)	1.14 (0.97 to 1.32)	1.09 (0.93 to 1.26)
Adjusted models[e]				
Use of e-cigarettes in any nontraditional flavor[b]	3.76 (1.20 to 10.31)[c]	1.47 (0.56 to 4.91)	1.65 (0.70 to 5.36)	2.41 (1.08 to 5.92)[c]
Time[d]	1.23 (0.96 to 1.56)	1.13 (0.93 to 1.38)	1.04 (0.87 to 1.25)	1.14 (0.98 to 1.34)

Estimates are of association of time-varying, time-lagged regressors at waves 1 to 4 and time-invariant covariates with vaping outcomes 6 mo postexposure assessment at waves 2 to 5 from logistic repeated-measures random-effect regression models including school random effects (total observations: range 768–788; totals for each outcome are presented in Supplemental Fig 1). Flavor-by-time interaction terms were tested in separate models and were not significant in all models ($P > .15$).

[a] Unadjusted models include use of e-cigarettes in nontraditional flavors and time as sole regressors.

[b] Time-varying variable assessed at each exposure wave at waves 1 to 4 involving use of ≥1 nontraditional flavor (fruit, candy, blends, sweets or desserts, other, or buttery [$N = 739$]) versus use of flavorless, tobacco-flavored, or mint- or menthol-flavored e-cigarettes only ($N = 49$).

[c] Statistically significant after Benjamini-Hochberg corrections for multiple testing to control the false-discovery rate at 0.05 for all estimates of e-cigarette flavor used (on the basis of 2-tailed corrected P value).

[d] Time is the continuous variable (scored: wave 1, 0; wave 2, 1; wave 3, 2; wave 4, 3).

[e] Adjusted models include use of e-cigarettes in nontraditional flavors, time, time-invariant covariates (age, sex, race and/or ethnicity, parental education, e-cigarette device type, age started vaping, and sensation-seeking score) and time-varying covariates (days smoked cigarettes in past 30 d, number of cigarettes smoked per day, e-cigarette nicotine concentration, days vaped nicotine in past 30 d, number of nicotine vaping episodes per day, no puffs per vaping episode, past-6-mo use of other tobacco products, and peer vaping) as simultaneous regressors. Association estimates for covariates are provided in Supplemental Table 7.

products used as regressors were tested and found no significant associations with any outcome (Supplemental Information, Supplemental Table 10).

DISCUSSION

This study provides new prospective evidence that adolescent use of e-cigarettes in nontraditional flavors may be associated with greater odds of continuing vaping and progression to more frequent vaping patterns. Previous research on this topic has predominately implicated nontraditional flavors in e-cigarette use initiation.[4–8] Existing youth studies linking e-cigarette flavor used with vaping persistence and progression have primarily been retrospective and cross-sectional,[4–8,34] leaving the temporal ordering of the association unclear. The present investigation addresses this gap by using a rigorous, prospective, longitudinal, 5-wave, time-varying, and time-lagged study design; comprehensive flavored e-cigarette use assessment; and sensitivity analyses that support the robustness and specificity of the identified associations. An additional study strength is the detailed vaping frequency outcome assessment, which permitted the identification of an association of flavored e-cigarette use with taking more puffs per vaping episode, which is notable given that frequent and consecutive puffing patterns can cause some e-cigarette devices to overheat and emit aerosol with greater toxicant concentrations.[35]

Common factors that increase exposure to flavored e-cigarettes and alter vaping trajectories could confound the observed associations. After adjusting for 15 potential confounders, estimates of association were reduced by 20% to 23% but remained statistically significant, suggesting that these factors only partially explained the results. Further increasing the plausibility of the associations was supplementary evidence of graded (dose-responselike) associations between exposure to more nontraditionally flavored e-cigarette products and subsequent vaping patterns, which has been previously reported in cross-sectional research.[34] It is unlikely that these graded associations reflect a nonspecific inclination toward using a greater diversity of e-cigarette products regardless of flavor. Sensitivity analyses found that the number of traditionally flavored or flavorless e-cigarette products used was not associated with vaping outcomes and observed no differences in vaping outcomes between youth using both nontraditional and traditional flavors versus those using nontraditional flavors only.

A conservative operationalization of nontraditional-flavor exposure was applied in this study, resulting in a modest prevalence of unexposed cases of e-cigarette use (ie, exclusive use of tobacco-flavored, menthol- or mint-flavored, or flavorless e-cigarettes; $n = 49$ [6.2%]). Youth who use traditionally flavored or flavorless e-cigarettes may represent a unique subgroup of the population that is inherently different from those who use nontraditional flavors, which may directly influence vaping behaviors and is not captured by covariate adjustment. However, the study's

time-varying design mitigates this concern. Approximately half of students who vaped only traditionally flavored or flavorless e-cigarettes during 1 survey wave used nontraditional flavors at another wave during the study and are represented in both exposure categories. Although unmeasured confounding is still possible, the likelihood that unmeasured confounders entirely explain associations was deemed to be low in supplemental analyses reported in the Supplemental Information.

It is possible that the sensory and pharmacologic effects of exposure to flavored e-cigarettes increases the persistence and frequency of vaping in youth. The adolescent brain is particularly sensitive to the pleasurable effects of palatable sweet tastes.[36] Laboratory experiments in young adults indicate that exposure to e-cigarettes in nontraditional flavors that produce sensory perceptions of sweetness (versus menthol and tobacco flavors) generate greater product appeal and willingness to use again.[37] A National Academies of Sciences, Engineering, and Medicine[9] consensus report concluded that that there was moderate evidence that product characteristics, such as nicotine and flavors, may increase the addiction potential of e-cigarettes. Nontraditionally flavored e-cigarette solutions could increase addiction potential because they can contain compounds that decrease product pH, which may increase the bioavailability of nicotine absorbed by the user at equivalent e-cigarette aerosol exposure doses.[38]

This study had limitations. First, exposure data in this study were collected in 2015 and 2016, before the emergence of pod-Mod e-cigarette products with high nicotine concentrations that are currently popular among youth.[39] Replication with more recent data would be useful to explore the generalizability of this study's results to the current milieu, in which youth use of pod-Mod e-cigarettes is ubiquitous. Second, tobacco, menthol or mint, and flavorless categories were collapsed, which is consistent with previous work[22] and past FDA regulatory proposals[12,13] but precluded analyses separating them from each other. Third, some students indicated past-30-day e-cigarette flavor use but did not report past-30-day vaping at certain exposure waves, raising the possibility of inconsistent reporting, although sensitivity analyses comparing these students to the remainder of the sample revealed no differences in flavor–outcome associations. Fourth, although previous work and supplementary analyses provide preliminary evidence of validity for the number of vaping episodes and puffs per episode measures (Supplemental Information),[20] these measures have not yet been extensively validated and may be subject to respondent recall error. Finally, covariate-adjusted association estimates may underestimate risk because certain covariates (eg, other tobacco product use, e-cigarette device, and nicotine concentration) could potentially be mediators along a putative causal pathway.

CONCLUSIONS

Although this study's observational design does not support causal inferences, the results highlight the possibility that regulations that reduce youth exposure to flavored e-cigarettes may aid in preventing young people who try e-cigarettes from becoming frequent and persistent users. Such regulations could also encourage existing adolescents who use flavored e-cigarettes to discontinue vaping. Over the past several years there had been no federal restrictions on the sale of flavored e-cigarettes in the United States. The FDA recently announced plans to enforce premarket authorization requirements for non-tobacco flavored products, and because no flavored products had gone through FDA premarket review, would result in removing flavored e-cigarette products from the market.[14] However, the timeline, parameters, and extent of enforcement of this policy remain unclear, and there are no product standards that would prohibit flavored e-cigarette products from returning to the market pending successful premarket authorization. Some have proposed that the FDA use its authority to set a product standard prohibiting e-cigarettes in nontraditional flavors to be sold anywhere in the United States.[40] Given the health risks associated with frequent and persistent youth use of e-cigarettes, particularly flavored products,[5,6] any regulatory policy that effectively limits youth exposure to flavored e-cigarettes is likely to improve pediatric population health.

ABBREVIATIONS

CI: confidence interval
e-cigarette: electronic cigarette
FDA: Food and Drug Administration
Mod: modified electronic cigarette
OR: odds ratio
RR: rate ratio
UPPS: urgency, perseverance, premeditation, and sensation seeking

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