



Initial e-cigarette flavoring and nicotine exposure and e-cigarette uptake among adolescents

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ABSTRACT

Objective: E-cigarettes are the most prevalent tobacco product used by adolescents. We sought to determine whether the presence of flavoring and/or the presence of nicotine at the first e-cigarette exposure predicted progression to current e-cigarette use (use in past 30 days) as well as escalation in use (number of days in the past 30 days) among adolescents.

Methods: Adolescents from public high schools outside of Philadelphia, PA completed in-classroom surveys at baseline (9th grade) and at 6-month intervals for the following 18 months (fall 2018, beginning of 11th grade). Adolescents who reported ever having used e-cigarettes at baseline ($N = 354$) comprised the analytical sample.

Results: We employed a two-part Latent Growth Curve Model including flavor, nicotine, and other covariates. Initial use of a flavored (vs unflavored) e-cigarette was associated with progression to current e-cigarette use ($\beta = 0.54$, $z = 2.09$, $p = 0.04$) and escalation in the number of days of e-cigarette use ($\beta = 0.35$, $z = 2.58$, $p = 0.01$) across the following 18 months. Initial use of an e-cigarette with nicotine (vs without nicotine) was associated with a greater number of days of e-cigarette use at baseline ($\beta = 0.49$, $z = 2.16$, $p = 0.03$).

Conclusions: The findings underscore the risk that flavoring and nicotine pose for progression beyond initial e-cigarette use. Regulations addressing flavoring and nicotine in e-cigarettes have the potential to reduce the number of adolescents who become current as well as frequent e-cigarette users.

1. Introduction

Electronic or e-cigarettes are the most commonly used tobacco product among adolescents (Jamal et al., 2017). In 2018, 21% of adolescents in high school reported currently using e-cigarettes (Gentzke et al., 2019). Initial exposure to substances of abuse, such as e-cigarettes typically occurs during adolescence when the brain is most vulnerable to reinforcing effects (de Wit and Phillips, 2012). As such, the process of becoming a regular e-cigarette user likely begins at the initial e-cigarette exposure. Similar to combustible tobacco products, e-cigarette characteristics associated with positive initial subjective effects may discriminate between those adolescents who progress beyond initial e-cigarette use to regular e-cigarette use (Mantey et al., 2017; Rodriguez and Audrain-McGovern, 2004; Sartor et al., 2010; Urban, 2010).

The presence of characterizing flavors – a taste or aroma other than tobacco (Family Smoking Prevention and Tobacco Act, 2009; Russell et al., 2018) – in e-liquids may help ensure that the first e-cigarette

exposure is pleasurable, thereby increasing the likelihood of subsequent use. Adolescents report that flavors are critical in their choice to use e-cigarettes (Ambrose et al., 2015). Eighty-one percent of adolescents who have ever used an e-cigarette report that their first e-cigarette was flavored (Ambrose et al., 2015). While there are no published prospective studies establishing an association between initial flavored e-cigarette exposure and escalation in adolescent e-cigarette use, research has shown that adolescents who initially tried menthol cigarettes reported fewer negative subjective experiences, which predicted persistent cigarette smoking into adulthood as well as nicotine dependence (Nonnemaker et al., 2013).

Unlike combustible tobacco products, e-cigarette e-liquid may or may not contain nicotine. About 41% of adolescents report that there was no nicotine in the first e-cigarette that they tried, 20% were uncertain, and 39% reported that there was nicotine (Krishnan-Sarin et al., 2015). Given that nicotine is the primary reinforcing component in tobacco (Henningfield et al., 2009), adolescents who have a nicotine-free initial e-cigarette exposure may not progress to subsequent e-

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cigarette use or progress more slowly than adolescents who were exposed to nicotine with their first use. It is important to examine these relationships as research has shown that almost one- to two-thirds of adolescents currently use e-cigarettes without nicotine (Miech et al., 2017; Morean et al., 2016).

The purpose of the present study was to determine whether the presence of characterizing flavors and/or the presence of nicotine at the first e-cigarette exposure predicted progression to current e-cigarette use as well as escalation in use among adolescents. Given the growing number of adolescents who are using e-cigarettes, it is important to understand how initial e-cigarette experiences set the stage for subsequent use (Drazen et al., 2019).

2. Method

2.1. Participants and procedures

Participants were adolescents in the 9th grade taking part in a longitudinal cohort study of e-cigarette and other tobacco use. Participants were enrolled in one of four public high schools in suburban Philadelphia, PA. The cohort participants were drawn from 2198 students identified through class rosters at the start of 9th grade. Adolescents were ineligible to participate if they had a severe learning disability or if they did not speak fluent English. Based on the selection criteria, a total of 2017 of the 2198 (92%) students were eligible to participate.

Parents were mailed a study information letter (active information) with a telephone number to call to obtain answers to any questions and to decline consent for their adolescent to participate (passive consent). Of the 2017 eligible adolescents, 2000 (99%) had a parent's consent to participate. Adolescents who were absent on the assent/baseline survey days ($n = 124$, 6%) were not enrolled in the cohort. Adolescents who declined to provide assent ($n = 41$, 2%) due to lack of interest in participation ($n = 41$) were asked to complete a brief, anonymous 7-item information form. This form assessed gender, race, ethnicity, as well as lifetime use and 30-day e-cigarette and combustible cigarette use. Adolescents who provided assent did not significantly differ from those who did not with respect to gender, race, ethnicity, lifetime/past 30-day cigarette smoking or lifetime/past 30-day e-cigarette use. Thus, 1835 of the 2000 adolescents with consent (92%) provided their assent to participate and completed a 40-min paper and pencil baseline survey. The baseline survey was completed on-site during compulsory classes in November and December of 2016.

Adolescents completed three paper and pencil follow-up surveys at 6-month intervals with 92% completing a survey at wave 2 ($N = 1687$, May/June 2017), 90% completing a survey at wave 3 ($N = 1658$, November/December of 2017), 89% completing a survey at wave 4 ($N = 1637$, May/June 2018), and 87% completing a survey at wave 5 ($N = 1601$, November/December of 2018). Adolescents were assigned a unique ID at the baseline survey. A cover page with the adolescents name connected to their ID on the follow-up survey was removed at the time of survey receipt. The participants included in this study are adolescents who reported ever trying an e-cigarette at the 9th grade assessments (wave 1 and wave 2, $N = 368$), and who had completed data on the covariates ($N = 354$ of 368 9th graders), which is required for statistical modeling. The Institutional Review Board of the University of Pennsylvania and the administration of each of the four high schools approved the study.

2.2. Measures

2.2.1. E-cigarette use

The surveys included an introduction explaining what e-cigarettes are, and the types of products or devices that are labeled as e-cigarettes. Images of different e-cigarette devices were provided to facilitate clarity (Conway et al., 2018). At baseline, these images included e-cigarettes,

e-hookah, vape pens and mods for waves 1-3. Images of USB-style pod vaporizers were added at wave 4. Excluding using an e-cigarette device for vaping marijuana, adolescents were asked: "Have you ever used an e-cigarette like the ones pictured above, even 1 or 2 times?" Adolescents who reported ever using e-cigarettes were then prompted to answer a series of standard epidemiological questions assessing lifetime use (i.e., number of times used e-cigarettes in lifetime, age at first use) and current use (i.e., number of days e-cigarette used in the past 30 days) (Audrain-McGovern et al., 2018). As is standard, current use was defined as using an e-cigarette on at least one day in the past 30 days (Jamal et al., 2017). Progression to current e-cigarette was defined as progressing beyond initial trying to using an e-cigarette in the past 30 days. Escalation in e-cigarette use among those adolescents who reported current use (past 30 days) at baseline was defined as an increase in the number of days in the past 30 days in which an e-cigarette was used. E-cigarette use was measured in all waves.

2.2.2. E-cigarette flavoring and E-Cigarette nicotine

The presence of flavoring in the first e-cigarette used was measured with the question "Was the first e-cigarette you used flavored to taste like menthol, mint, candy, fruit, dessert, alcoholic beverages, or other sweets?" Response options were either yes or no (Ambrose et al., 2015). For "yes" responses, adolescents indicated which flavor and for "no" responses adolescents indicated whether their first e-cigarette did not contain any flavoring and was thus unflavored ($N = 27$) or tobacco flavored ($N = 14$) (Schneller et al., 2018). The presence of nicotine in the first e-cigarette used was measured with the question "When you first tried an e-cigarette, did it have nicotine in it?" Response options were either yes, no, or not sure (Krishnan-Sarin et al., 2015; Morean et al., 2016).

2.2.3. Covariates

Variables that potentially overlapped with the risk for e-cigarette use were selected a priori as covariates based on previous studies (Leventhal et al., 2015; Pentz et al., 2015; Primack et al., 2015). Demographic characteristics including sex and race were assessed using self-report items. Peer e-cigarette use was measured by asking adolescents how many of their four best male and four best female friends use e-cigarettes (Audrain-McGovern et al., 2009), with scores ranging from 0 to 8. Family e-cigarette use was measured by asking whether family members in the household used e-cigarettes (Audrain-McGovern et al., 2004). Age at first e-cigarette use was assessed by asking, "How old were you when you first tried an e-cigarette, even 1 or 2 times?" Sensation-seeking was measured with the 8-item Brief Sensation-Seeking Scale (1 = strongly disagree to 5 = strongly agree) (Hoyle et al., 2002). Combustible cigarette smoking was assessed by a series of standard epidemiological questions assessing lifetime (i.e., ever tried smoking a cigarette), past 6-month (i.e., last time smoked a cigarette), and current use (i.e., number of days in past 30 days) (Audrain-McGovern et al., 2018; Jamal et al., 2017). Current cigarette smoking was included in the model.

2.3. Statistical analysis

A two-part Latent Growth Curve Model (LGCM) evaluated the association between the presence of flavoring and nicotine in the first e-cigarette used, and progression to current e-cigarette use as well as escalation in use across the following 18 months (Audrain-McGovern et al., 2012; Petras et al., 2010). The first part of the model examined whether an adolescent used an electronic cigarette in the past 30 days at baseline and/or progressed to 30-day use at follow-up (current use, binary outcome, yes or no). The second part of the model examined the frequency of e-cigarette use at baseline (number of days in past 30 days) and escalation in the number of days used at follow-up among adolescents who reported using an e-cigarette in the past 30 days (continuous outcome).

Increases in e-cigarette use was modeled across four repeated measures of e-cigarette use with the two-part model, measured six months apart, with latent variables (factors) representing baseline e-cigarette use (level factors) and change from baseline (trend factors) for the binary and continuous parts. A crude model without covariates was first estimated to test growth form (e.g., linear or quadratic) for the continuous part of the model. The crude model was followed by the model including flavoring, nicotine, and covariates. Means and standard deviations were used to describe continuous variables. Frequency distributions and proportions were used to describe categorical variables. Model parameter estimation for the two-part growth model employed maximum likelihood estimation with robust standard errors (Muthén and Muthén, 1998-2017; Muthén and Muthén, 1998-2017).

We used *Mplus* 8.2 software for our analyses. To account for missing data, *Mplus* uses a Full Information Maximum Likelihood (FIML) estimating procedure, which employs the Expectation Maximization (EM) algorithm, assuming data are missing at random for the continuous part of the model (Muthén and Muthén, 1998-2017; Muthén and Muthén, 1998-2017). For the binary part, individuals with missing data are treated as missing on both the binary and continuous model part.

To account for the possibility of a school effect on initial and subsequent e-cigarette use, we created a set of three dummy school variables, with the fourth school arbitrarily set as the comparison school. Although *Mplus* 8.2 software includes a Type = complex analysis strategy that is frequently employed in multi-level modeling, this procedure is best used when there are at least 20 levels (Huang, 2018). Given that we had only four schools, we tested for a school effect by including the three dummy school variables in our multivariate model.

3. Results

3.1. Study sample

The sample characteristics are presented in Table 1. The flavored category reflected flavoring other than tobacco (N = 313) (Harrell et al., 2017). As such, we combined unflavored (n = 27) and tobacco flavored (n = 14) into one group (N = 41). Twenty-four percent (n = 84) of adolescents reported that the first e-cigarette that they tried contained nicotine, while 45% (n = 160) reported that the first e-cigarette that they tried did not have nicotine in it, and 31% (n = 110) were unsure. The following is a breakdown of the adolescents in this sample by school (1 = 113, 2 = 132, 3 = 53, 4 = 56). The number of participants from each school in this sample represented 21% 18% 20% and 19% of the total adolescents enrolled at each school, respectively.

3.2. Effects of flavoring and nicotine at the first E-Cigarette exposure on subsequent E-cigarette use

We first fit a two-part LGCM without covariates (crude model) to the data, with attention to the shape of the trend in the continuous part of the model (e.g., linear, quadratic). A linear trend fit the data for the average level of change in the number of days (in the past 30 days) that e-cigarettes were used. The model likelihood and the Bayesian Information Criterion (BIC) for the linear model was -1531.07 and 3132.19, respectively. The model likelihood was -1530.39 and the BIC increased to 3137.19 with the addition of a quadratic trend. Further, the -2loglikelihood difference (chi square = 1.374) was not significant, $p = 0.24$. Thus, the results suggest a two-part model with a linear trend was the best model representing days of e-cigarette use.

Next, flavor, nicotine, and the covariates were added to the model with pathways predicting the binary level (30-day e-cigarette use at baseline), binary trend (progression to 30-day e-cigarette use at follow-up), continuous level (number of days e-cigarettes used/past 30 days at baseline) and continuous trend (escalation in the number of days e-cigarettes used/past 30 days across follow-up). Inclusion of the covariates decreased the Log likelihood to -890.88 and the BIC to 2175.00

Table 1
Sample Characteristics.

Baseline Characteristic	N = 354
Sex	
Female	171 (48.0%)
Male	183 (52.0%)
Race	
White	257 (72.0%)
Black	62 (18.0%)
Other	35 (10.0%)
Family e-cigarette use	
Yes	120 (34.0%)
No	234 (66.0%)
Flavoring	
Yes	313 (88.0%)
No	41 (12.0%)
Nicotine	
Yes	84 (24.0%)
No	160 (45.0%)
Not Sure	110 (31.0%)
Smoking (past 30 days)	
Yes	33 (9.0%)
No	321 (91.0%)
Baseline e-cigarette use	
Tried once	180 (51.0%)
Used > once, not in past 30 days	73 (21.0%)
Used > once, and in past 30 days	101 (29.0%)
Follow-up e-cigarette use*	
Tried once	146 (46.0%)
Used > once, not in past 30 days	75 (23.0%)
Used > once, and in past 30 days	100 (31.0%)
Continuous Variables	Mean SD
Baseline e-cigarette use (past 30 days)	6.97 7.75
Follow-up e-cigarette use (past 30 days)	16.84 11.64
Peer e-cigarette use	2.26 2.79
Sensation seeking	17.19 7.26
Age first used	13.23 1.26

* Does not add up to 354 due to missing data; missing data not significantly related to baseline e-cigarette use ($\chi^2 = 2.03, p = 0.57$).

indicating that the model was improved with the inclusion of these variables. The non-standardized path coefficients, standard errors, z-values and probabilities are presented in Table 2.

3.2.1. Progression to current use of E-Cigarettes

Fig. 1 depicts the LGCM with standardized coefficients for significant paths only. Several covariates had a significant and positive effect on the binary e-cigarette level factor, representing effects on current e-cigarette use at baseline. Having a greater number of peers and household members who use e-cigarettes was associated with current e-cigarette use at baseline ($\beta = 0.19, z = 3.33, p = 0.001$; $\beta = 0.69, z = 2.17, p = 0.03$, respectively). Smoking a combustible cigarette in the past 30 days at baseline was also associated with current e-cigarette use at baseline ($\beta = 1.63, z = 3.41, p = 0.001$). Neither flavoring nor nicotine at the first e-cigarette exposure were associated with current e-cigarette use at baseline.

Considering change from baseline, flavoring in the initial e-cigarette used had a significant and positive effect on the binary e-cigarette trend factor. This indicated that initial use of a flavored e-cigarette was associated with progression to current e-cigarette use across the following 18 months compared to initial use of an unflavored e-cigarette ($\beta = 0.54, z = 2.09, p = 0.04$). Using standardized coefficients, flavoring was associated with a 1.09 standard deviation increase in the rate of progression to current e-cigarette use compared to no flavoring.

Females had a slower rate of progression to current e-cigarette users across the 18 month follow-up than males ($\beta = -0.46, z = -2.44, p = 0.02$), translating to a .93 standard deviation decrease in the rate of progression. Higher levels of sensation-seeking at baseline was associated with progression to current e-cigarette use across the following 18 months ($\beta = 0.03, z = 2.16, p = 0.03$). Higher scores translated to a

Table 2
Effects of Flavoring and Nicotine at the First E-Cigarette Exposure on Subsequent E-cigarette Use.

	Binary e-cigarette level (used in past 30 days Yes/No)				Binary e-cigarette trend (used in past 30 days Yes/No)			
	beta	SE	z	p-value	beta	SE	z	p-value
Sex	-0.13	0.29	-0.45	0.65	-0.46	0.19	-2.44	0.02
Race Black	-0.47	0.40	-1.19	0.23	-0.27	0.25	-1.08	0.28
Race Other	0.16	0.50	0.32	0.75	-0.02	0.37	-0.05	0.96
Family E-cig Use	0.69	0.32	2.17	0.03	-0.16	0.19	-0.83	0.41
Peer E-cig Use	0.19	0.06	3.33	0.001	-0.03	0.03	-0.93	0.35
Cigarette Smoking	1.63	0.48	3.41	0.001	-0.49	0.29	-1.67	0.10
Sensation-seeking	-0.03	0.02	-1.21	0.23	0.03	0.02	2.16	0.03
Age First Used E-cig	-0.07	0.12	-0.61	0.54	0.07	0.08	0.91	0.36
School 1	-0.73	0.44	-1.67	0.10	-0.15	0.25	-0.62	0.54
School 2	-0.20	0.41	-0.49	0.62	-0.10	0.24	-0.40	0.69
School 3	0.44	0.48	0.91	0.36	0.41	0.31	1.31	0.19
Flavored	-0.14	0.43	-0.32	0.75	0.54	0.27	2.09	0.04
Nicotine Not Sure	-0.52	0.36	-1.46	0.15	0.13	0.21	0.61	0.55
Nicotine Yes	0.07	0.35	0.21	0.83	0.39	0.25	1.58	0.11

	Continuous e-cigarette level (number of days used)				Continuous e-cigarette trend (number of days used)			
	beta	SE	z	p-value	beta	SE	z	p-value
Sex	-0.61	0.20	-3.12	0.002	0.07	0.09	0.77	0.44
Race Black	-0.64	0.25	-2.60	0.01	0.19	0.10	1.88	0.06
Race Other	0.25	0.29	0.87	0.38	-0.17	0.19	-0.91	0.37
Family E-cig Use	0.10	0.21	0.47	0.64	0.05	0.10	0.49	0.63
Peer E-cig Use	0.09	0.03	2.74	0.01	-0.02	0.02	-0.96	0.34
Cigarette Smoking	0.27	0.28	0.95	0.34	0.08	0.12	0.68	0.50
Sensation-seeking	-0.01	0.01	-0.79	0.43	0.02	0.01	2.56	0.01
Age First Used E-cig	-0.25	0.07	-3.85	< 0.0001	0.09	0.03	2.50	0.01
School 1	0.14	0.31	0.46	0.65	-0.01	0.14	-0.07	0.94
School 2	-0.36	0.27	-1.33	0.19	0.11	0.13	0.85	0.40
School 3	0.02	0.33	0.07	0.95	0.27	0.16	1.72	0.10
Flavored	-0.01	0.26	-0.02	0.98	0.35	0.14	2.58	0.01
Nicotine Not Sure	0.01	0.25	0.01	0.99	-0.08	0.11	-0.72	0.47
Nicotine Yes	0.49	0.23	2.16	0.03	-0.18	0.10	-1.81	0.07

Note: Gender (0 = male, 1 = female), Race (Black versus White; Other versus White), Household E-cigarette Use (0 = no, 1 = yes), Peer E-cigarette Use (number of peers who use e-cigarettes from 0 to 8), Nicotine (Not Sure vs No; Yes vs No), and Flavored (0 = no, 1 = yes). Model includes School dummy coded as 1 through 3 versus 4.

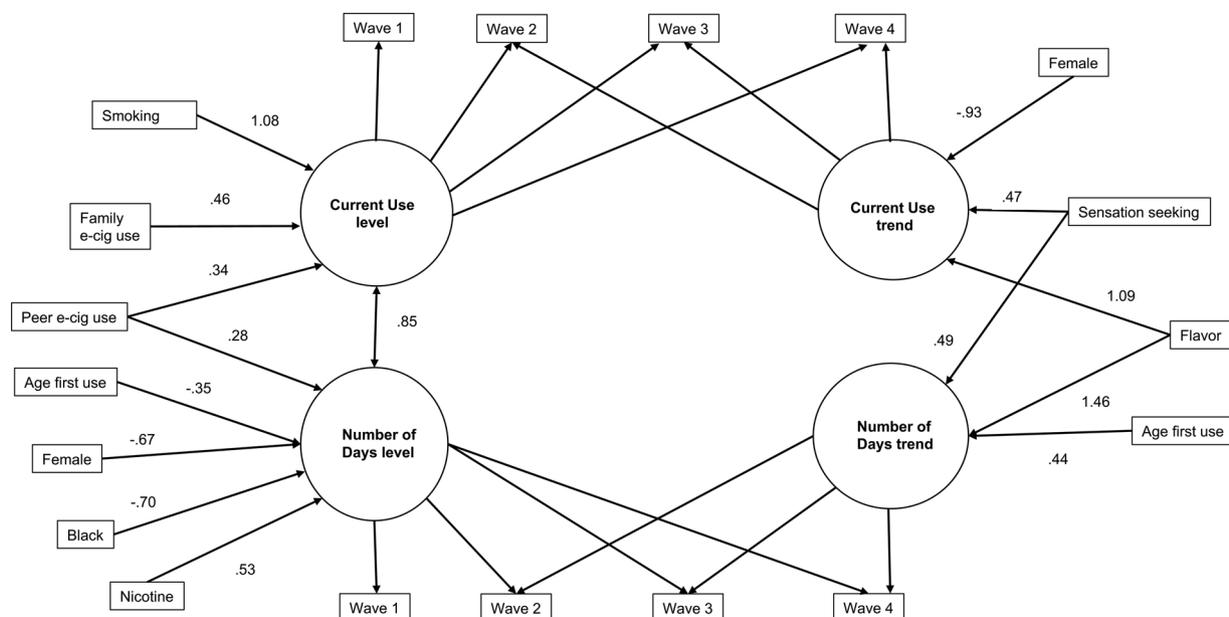


Fig. 1. Two-part latent growth curve model examining the effects of initial e-cigarette flavoring and nicotine exposure on progression to current e-cigarette use and escalation in days used among adolescents. Note: Standardized path coefficients are presented for the significant path effects only.

0.47 standard deviation increase in the rate of progression from baseline. Neither nicotine nor uncertain nicotine at the first e-cigarette exposure were associated with rate of progression to current e-cigarette use across the following 18 months

3.2.2. Escalation in the frequency of E-Cigarette use

Initial use of an e-cigarette with nicotine versus without nicotine was associated with using e-cigarettes on a greater number of days at baseline ($\beta = 0.46$, $z = 2.07$, $p = 0.03$). This translated to a 0.53 standard deviation increase in the number of days of e-cigarette use at baseline among adolescents whose first e-cigarette contained nicotine. Uncertainty about the presence of nicotine in the first e-cigarette exposure was not significantly associated with the numbers of days e-cigarettes were used in the past 30 days at baseline. Flavoring (versus no flavoring) at the first e-cigarette exposure was not significantly associated with the numbers of days e-cigarettes were used in the past 30 days at baseline.

Several covariates had a significant effect on the continuous e-cigarette level factor, representing effects on the frequency (number of days) of e-cigarette use at baseline. Females used e-cigarettes on fewer days than males ($\beta = -0.61$, $z = -3.12$, $p = 0.002$), a .67 standard deviation decrease. Black adolescents used e-cigarettes on fewer days than white adolescents ($\beta = -0.64$, $z = -2.60$, $p = 0.01$), a .70 standard deviation decrease. Having a greater number of peers who use e-cigarettes was associated with more frequent e-cigarette use at baseline ($\beta = 0.09$, $z = 2.74$, $p = 0.01$). Younger age at first e-cigarette use was associated with more frequent e-cigarette use at baseline ($\beta = -0.25$, $z = -3.85$, $p = 0.0001$).

Considering change from baseline, flavoring in the initial e-cigarette used had a significant and positive effect on the continuous e-cigarette trend factor. This indicated that initial use of a flavored versus unflavored e-cigarette was associated with a more rapid rate of escalation in the number of days e-cigarettes were used ($\beta = 0.35$, $z = 2.58$, $p = 0.01$), across the following 18 months. Using standardized coefficients, this translated to a 0.46 standard deviation increase in the rate of escalation in days used from baseline. Higher sensation-seeking scores ($\beta = 0.02$, $z = 2.56$, $p = 0.01$) and older age at first e-cigarette exposure ($\beta = 0.09$, $z = 2.50$, $p = 0.01$) were both significantly associated with a faster rate of escalation in the number of days e-cigarettes were used across the following 18 months.

4. Discussion

The current study offers new evidence for a prospective relationship between e-cigarette flavoring, e-cigarette nicotine content, and an adolescent's e-cigarette use trajectory. Adolescents who initially vaped a flavored e-cigarette progressed to current and more frequent e-cigarette use more rapidly than adolescents who initially vaped an unflavored e-cigarette. Adolescents who initially used an e-cigarette with nicotine tended to use e-cigarettes on a greater number of days during the first year of high school compared to adolescents who initially used an e-cigarette without nicotine. The present findings highlight the importance of policies to prevent e-cigarette use among youth and underscore the risk that flavor and nicotine pose for progression beyond initial use.

The availability of flavoring is the primary reason adolescents give for using e-cigarettes (Ambrose et al., 2015). Over 80% of adolescents report that their first e-cigarette was flavored, and over 85% report that they currently use a flavored e-cigarette (Ambrose et al., 2015). To our knowledge, this is the first prospective study to examine the impact of flavoring in the initial e-cigarette exposure on subsequent e-cigarette use among adolescents. Flavoring may foster subsequent e-cigarette use among adolescent in several ways. Flavoring may serve to reduce the risk perceptions associated with e-cigarette use (Dai and Hao, 2016; Ford et al., 2016), encouraging initial use as well as continued use. Flavoring also may help mitigate irritation of the "throat hit" associated

with propylene glycol in e-liquid, allowing adolescents to more easily become accustomed to inhaling vapor (Rosbrook and Green, 2016). If the first exposure to e-cigarettes is not aversive, adolescents may be more likely to engage in subsequent use (Chen et al., 2003; DiFranza et al., 2007; Mantey et al., 2017; Rodriguez and Audrain-McGovern, 2004; Sartor et al., 2010; Urban, 2010).

Additionally, flavoring may be pleasurable to vape as some adolescents report only vaping flavor without nicotine (Krishnan-Sarin et al., 2015; Miech et al., 2017; Morean et al., 2016). Similar to food flavoring, flavoring in tobacco products can activate reward pathways in the brain (Rolls, 2016; Touzani et al., 2010). The rewarding effects of flavoring is evidenced by the finding that 78% of youth would cease use of e-cigarettes if flavors were unavailable (Harrell et al., 2017). Flavoring also appears to enhance the rewarding and reinforcing effects of nicotine (Palmatier et al., 2013; Touzani et al., 2010). For example, young adult smokers deprived of nicotine for 12 h found flavored e-cigarettes with nicotine were more rewarding and reinforcing than an unflavored e-cigarette with nicotine, and vaped a flavored e-cigarette with nicotine twice as much as an unflavored e-cigarette with nicotine in an ad-libitum session (Audrain-McGovern et al., 2016).

Many youth report only vaping flavors, perhaps assuming that this practice is safe and without harmful effects (Gorukanti et al., 2017). Recent adolescent research challenges the notion that e-cigarette vapor is safe. Carcinogenic volatile organic compounds were up to three times higher in adolescent e-cigarette users compared to adolescents who never used e-cigarettes (Rubinstein et al., 2018). Likewise, adolescent e-cigarette use is associated with increased rates of chronic bronchitis symptoms (McConnell et al., 2017). Flavored e-cigarette use has also been associated with an increased risk of combustible cigarette smoking among adolescents (Dai and Hao, 2016).

Adolescents who reported that the first e-cigarette that they tried contained nicotine reported using e-cigarettes more frequently during the initial year of high school than adolescents who reported no nicotine content. More frequent use mid-adolescence likely reflects greater vulnerabilities associated with an earlier age at first nicotine exposure (Jordan and Andersen, 2017). Younger age at first e-cigarette exposure was associated with greater days of use among adolescents 14–15 years old. This is concerning as studies have shown that nicotine has adverse effects on the developing adolescent brain, impacting executive functions such as working memory (Jacobsen et al., 2005), attention (Dwyer et al., 2009; Musso et al., 2007), and decision-making (DeBry and Tiffany, 2008). A recent study showed that current use of e-cigarettes with higher nicotine content at age 16 was associated with increased frequency and intensity of e-cigarette use 6 months later (Goldenson et al., 2017). The present study shows that this trajectory of increased use may begin with nicotine in the first e-cigarette used.

It is important to note that the popularity of pod-based e-cigarettes, such as Juul increased substantially after our baseline data collection. As such, these findings may underestimate the number of adolescents who are initially exposed to nicotine given that Juul contains nicotine. In addition, adolescents who initiate e-cigarette use with nicotine free e-liquid may transition to e-liquid with nicotine (Krishnan-Sarin et al., 2015). Comparable to other studies reporting past 30-day use, 31% percent of adolescents in the current study were unsure if the first e-cigarette that they used contained nicotine while 45% indicated that the first e-cigarette that they tried did not contain nicotine (Krishnan-Sarin et al., 2015; Miech et al., 2017; Morean et al., 2016). These adolescents were not likely to become a current or frequent e-cigarette user.

It is always possible that unmeasured risk factors could explain the observed associations between flavoring, nicotine, and subsequent e-cigarette use. While we cannot eliminate this possibility, we attempted to minimize potential confounding by including other factors important to e-cigarette use (e.g., peer and family e-cigarette use, sensation-seeking, combustible cigarette smoking) in our statistical model. After controlling for these variables, we can conclude that flavoring and

nicotine have independent effects on e-cigarette uptake.

The study has several strengths, including having a demographically diverse sample that was measured during a developmentally vulnerable period for tobacco use. We also used repeated measures of e-cigarette use, analyzing the data in a longitudinal fashion across four time points spanning two years. The present study was also able to limit recall bias as the time interval between initial e-cigarette use and an assessment of experiences related to initial use was relatively short in our adolescent sample.

While one limitation of this study is that the relatively smaller unflavored group may have lessened the power to detect some effects, it highlights the overwhelming preference for flavoring among adolescents. The Population Assessment of Tobacco and Health, the largest nationally-representative prospective cohort study that examines flavored e-cigarette use, has only 42 (11%) adolescents who have not been exposed to e-cigarette flavors (Schneller et al., 2018). A potential limitation of this study is that we did not measure the type of e-cigarette device used at the first e-cigarette exposure. This may have affected the initial subjective effects of vaping through the amount of nicotine delivered and the hedonics of the flavoring. An assessment of the type of e-cigarette typically used among adolescents who currently use e-cigarettes revealed that 52% of adolescents were using mods at baseline, while 83% were using pods at follow-up. Unfortunately, we were not able to assess the interacting effects of flavoring and nicotine on e-cigarette use due to the small number of adolescents who reported nicotine, but no flavoring at the initial exposure. An alternative analytic strategy may have been to examine the role of sweet characterizing flavors compared to all other flavors and unflavored e-liquid. However, the majority of the sample reported that their first e-cigarette was sweet-flavored. Future research with larger samples is necessary to delineate further synergistic effects of nicotine and flavoring on e-cigarette uptake.

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Contributors

Dr. Audrain-McGovern led the conceptualization and design of the study, wrote the majority of the manuscript text, and provided input on the analyses and the interpretation of the data. Stephen Pianin and Emily Alexander oversaw data management and processing, drafted portions of the methods, and provided feedback on manuscript drafts. Dr. Rodriguez conducted the analyses, drafted the interpretation of the analysis, and provided feedback on drafts of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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