Original Investigation

Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence

Adam M. Leventhal, PhD; David R. Strong, PhD; Matthew G. Kirkpatrick, PhD; Jennifer B. Unger, PhD; Steve Sussman, PhD; Nathaniel R. Riggs; Matthew D. Stone, BA; Rubin Khoddam, MA; Jonathan M. Samet, MD, MS; Janet Audrain-McGovern, PhD

IMPORTANCE Exposure to nicotine in electronic cigarettes (e-cigarettes) is becoming increasingly common among adolescents who report never having smoked combustible tobacco.

OBJECTIVE To evaluate whether e-cigarette use among 14-year-old adolescents who have never tried combustible tobacco is associated with risk of initiating use of 3 combustible tobacco products (ie, cigarettes, cigars, and hookah).

DESIGN, SETTING, AND PARTICIPANTS Longitudinal repeated assessment of a school-based cohort at baseline (fall 2013, 9th grade, mean age = 14.1 years) and at a 6-month follow-up (spring 2014, 9th grade) and a 12-month follow-up (fall 2014, 10th grade). Ten public high schools in Los Angeles, California, were recruited through convenience sampling. Participants were students who reported never using combustible tobacco at baseline and completed follow-up assessments at 6 or 12 months (N = 2530). At each time point, students completed self-report surveys during in-classroom data collections.

EXPOSURE Student self-report of whether he or she ever used e-cigarettes (yes or no) at baseline.

MAIN OUTCOMES AND MEASURES Six- and 12-month follow-up reports on use of any of the following tobacco products within the prior 6 months: (1) any combustible tobacco product (yes or no); (2) combustible cigarettes (yes or no), (3) cigars (yes or no); (4) hookah (yes or no); and (5) number of combustible tobacco products (range: 0-3).

RESULTS Past 6-month use of any combustible tobacco product was more frequent in baseline e-cigarette ever users (n = 222) than never users (n = 2308) at the 6-month follow-up (30.7% vs 8.1%, respectively; difference between groups in prevalence rates, 22.7% [95% CI, 16.4%-28.9%]) and at the 12-month follow-up (25.2% vs 9.3%, respectively; difference between groups, 15.9% [95% CI, 10.0%-21.8%]). Baseline e-cigarette use was associated with greater likelihood of use of any combustible tobacco product averaged across the 2 follow-up periods in the unadjusted analyses (odds ratio [OR], 4.27 [95% CI, 3.19-5.71]) and in the analyses adjusted for sociodemographic, environmental, and intrapersonal risk factors for smoking (OR, 2.73 [95% CI, 2.00-3.73]). Product-specific analyses showed that baseline e-cigarette use was positively associated with combustible cigarette (OR, 2.65 [95% CI, 1.73-4.05]), cigar (OR, 4.85 [95% CI, 3.38-6.96]), and hookah (OR, 3.25 [95% CI, 2.29-4.62]) use and with the number of different combustible products used (OR, 4.26 [95% CI, 3.16-5.74]) averaged across the 2 follow-up periods.

CONCLUSIONS AND RELEVANCE Among high school students in Los Angeles, those who had ever used e-cigarettes at baseline compared with nonusers were more likely to report initiation of combustible tobacco use over the next year. Further research is needed to understand whether this association may be causal.

JAMA. 2015;314(7):700-707. doi:10.1001/jama.2015.8950

Viewpoint page 663 and **Editorial** page 673

JAMA Report Video and **Author Video Interview** at jama.com

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and **CME Questions** page 724

Author Affiliations: Department of Preventive Medicine, University of Southern California, Keck School of Medicine, Los Angeles (Leventhal, Kirkpatrick, Unger, Sussman, Stone, Khoddam, Samet); Department of Psychology, University of Southern California, Los Angeles (Leventhal, Sussman, Khoddam); Department of Family Medicine and Public Health, University of California–San Diego School of Medicine, La Jolla (Strong); School of Social Work, University of Southern California, Los Angeles (Sussman); Department of Human Development and Family Studies, Colorado State University, Fort Collins (Riggs); Department of Psychiatry, University of Pennsylvania, Perelman School of Medicine, Philadelphia (Audrain-McGovern).

Corresponding Author: Adam M. Leventhal, PhD, University of Southern California, Keck School of Medicine, 2250 Alcazar St, CSC 271, Los Angeles, CA 90033 (adam.leventhal@usc.edu).

Nicotine is addictive when delivered in tobacco smoke, which provides a significant dose that travels quickly to the brain after inhalation.[1] Combustible tobacco, which has well-known health consequences, has long been the dominant nicotine-delivering product used in the population. Electronic cigarettes (e-cigarettes), which are devices that deliver inhaled aerosol generally containing nicotine, are becoming increasingly popular, particularly among adolescents, including teens who have never used combustible tobacco.[2,3] According to 2014 US estimates, 16% of 10th graders reported use of e-cigarettes within the past 30 days, of whom 43% reported never having tried combustible cigarettes.[3]

Whether use of e-cigarettes is associated with risk of initiating combustible tobacco use is unknown. Enjoyment of the sensations and the pharmacological effects of inhaling nicotine via e-cigarettes could increase the propensity to try other products that similarly deliver inhaled nicotine, including combustible tobacco products.

If e-cigarette use is a risk factor for initiation of combustible tobacco use, the high prevalence of e-cigarette use in the adolescent population could ultimately perpetuate and potentially enlarge the epidemic of tobacco-related illness. Because the first year of high school is a vulnerable period for initiating risky behaviors,[4] this study investigated whether adolescents entering the 9th grade in Los Angeles, California, who reported ever using e-cigarettes were more likely to initiate the use of combustible tobacco during the subsequent year.

Methods

Participants and Procedures

Data were collected as part of a longitudinal survey of substance use and mental health among high school students. Approximately 40 public high schools in the Los Angeles metropolitan area were approached about participating in this study. These schools were chosen because of their diverse demographic characteristics and proximity. Ten schools agreed to participate in the study (school characteristics appear in eTable 1 in the Supplement).

To enroll in the study, students were required to provide active written or verbal assent and their parents were required to provide active written or verbal consent. Data collection involved 3 assessment waves that took place approximately 6 months apart: baseline (fall 2013 during 9th grade), 6-month follow-up (spring 2014 also during 9th grade), and 12-month follow-up (fall 2014 during 10th grade).

At each wave, paper-and-pencil surveys were administered in students' classrooms onsite. Students not in class during data collections completed telephone or Internet surveys. The University of Southern California institutional review board approved the study.

Measures

Each study measure has shown adequate psychometric properties in previous youth samples.[5-9]

e-Cigarette and Combustible Tobacco Product Use

At each wave, items based on the Youth Behavior Risk Surveillance[5] and Monitoring the Future[6] surveys assessed lifetime and past 6-month use (yes or no) of e-cigarettes, combustible cigarettes (described as even a few puffs), full-size cigars, little cigars or cigarillos, hookah water pipe, and blunts (marijuana rolled in a tobacco leaf or cigar casing). Response to the lifetime e-cigarette use question at baseline was the primary exposure variable.

Outcomes were any use during the prior 6 months of (1) any combustible tobacco product (yes or no); (2) combustible cigarettes (yes or no); (3) cigars (full-size cigars, little cigars, or blunts; yes or no); (4) hookah (yes or no); and (5) the total number of combustible tobacco products used among the cigarette, cigar, and hookah categories (range, 0-3). A composite cigar variable was used because of the infrequent use of individual cigar products. Blunt use was included given the high prevalence in this sample, association with adolescent e-cigarette use in past work,[10] and evidence that there are significant tobacco smoke toxicants in blunt smoke.[11]

A sensitivity analysis was conducted that compared the rates of nonblunt cigar use at the 6- and 12-month follow-up assessments by baseline e-cigarette use. The terms *ever smokers* and *never smokers* are used to refer to adolescents who ever and never, respectively, used at least 1 of the combustible tobacco products.

Covariates

Variables peripheral to a putative pathway by which e-cigarette use may be directly associated with risk of combustible tobacco use initiation, yet potentially overlapping with both e-cigarette and combustible tobacco use, were selected a priori as covariates based on previous literature.[10,12-16] Covariates were selected from the following 3 domains.

Sociodemographics | Sociodemographic characteristics, including age, sex, race/ethnicity, and highest parental education level, were assessed using self-report responses to investigator-defined forced-choice items (**Table 1**).

Environmental Factors | Indicators of the proximal environment included family living situation, measured with the question, "Who do you live with most of the time?" (both biological parents vs other).[12] Family history of smoking was measured using the question, "Does anyone in your immediate family (brothers, sisters, parents, or grandparents) have a history of smoking cigarettes?" (yes or no). Peer smoking was assessed by responses to the question, "In the last 30 days, how many of your 5 closest friends have smoked cigarettes?" (range, 0-5).[17]

Intrapersonal Factors | Mental health, personality traits, and psychological processes linked with experimentation, risky behavior, and smoking were assessed. Depressive symptoms were measured using the 20-item Center for Epidemiologic Studies Depression Scale[8] composite sum past week frequency rating (score range for each item: 0 [rarely or none of the time; 0-1 day] to 3 [most or all of the time; 5-7 days]). Impulsivity was measured with the 5-item Temperament and Character In-

Table 1. Sample Characteristics by e-Cigarette Use Status Among Never Smokers at Baseline[a]

	Total (N = 2530)[b]	Never Use of e-Cigarettes (n = 2308)	Ever Use of e-Cigarettes (n = 222)	*P* Value
Sociodemographics				
Sex (n = 2524)[c]				
Male	1181 (46.8)	1052 (45.7)	129 (58.6)	<.001[d]
Female	1343 (53.2)	1252 (54.3)	91 (41.4)	
Age, mean (95% CI), y (n = 2519)[c]	14.06 (14.04-14.07)	14.05 (14.04-14.07)	14.10 (14.05-14.15)	.11[e]
Race/ethnicity (n = 2487)[c]				
American Indian/Alaska Native	21 (0.8)	19 (0.8)	2 (0.9)	.02[d]
Asian	472 (19.0)	432 (19.0)	40 (18.7)	
Black	119 (4.8)	107 (4.7)	12 (5.6)	
Hispanic	1099 (44.2)	998 (43.9)	101 (47.2)	
Native Hawaiian/Pacific Islander	89 (3.6)	74 (3.3)	15 (7.0)	
White	404 (16.2)	383 (16.9)	21 (9.8)	
Other[f]	142 (5.7)	134 (5.9)	8 (3.7)	
Multiethnic or multiracial	141 (5.7)	126 (5.5)	15 (7.0)	
Highest parental education level (n = 2200)[c]				
≤8th grade	72 (3.3)	69 (3.4)	3 (1.6)	.03[g]
Some high school	171 (7.8)	151 (7.5)	20 (10.4)	
High school graduate	334 (15.2)	298 (14.8)	36 (18.8)	
Some college	428 (19.5)	384 (19.1)	44 (22.9)	
College graduate	741 (33.7)	683 (34.0)	58 (30.2)	
Graduate degree	454 (20.6)	423 (21.1)	31 (16.2)	
Environmental Factors				
Lives with both biological parents (n = 2510)[c]	1688 (67.3)	1563 (68.3)	125 (56.6)	<.001[d]
Family history of smoking (n = 2430)[c]	1487 (61.2)	1337 (60.3)	150 (70.8)	.003[d]
Peer smoking, mean (95% CI) (n = 2484)[c]	0.22 (0.19-0.25)	0.20 (0.17-0.23)	0.46 (0.32-0.59)	<.001[d]
Intrapersonal Factors, Mean (95% CI)				
CESD Scale for depressive symptoms (n = 2490)[c,h]	13.49 (13.06-13.93)	13.37 (12.91-13.82)	14.80 (13.27-16.33)	.07[e]
TCI subscale for impulsivity (n = 2481)[c,i]	2.39 (2.33-2.45)	2.35 (2.29-2.41)	2.76 (2.58-2.94)	<.001[e]
Substance use, No. (%)	454 (17.9)	345 (15.0)	109 (49.1)	<.001[d]
Delinquent behavior (n = 2496)[c]	14.64 (14.50-14.79)	14.43 (14.29-14.57)	16.88 (16.12-17.64)	<.001[e]
Smoking susceptibility (n = 2506)[c]	1.11 (1.10-1.12)	1.10 (1.09-1.11)	1.22 (1.16-1.27)	<.001[e]
Smoking expectancies (n = 2502)[c,j]	1.39 (1.37-1.41)	1.38 (1.36-1.40)	1.48 (1.40-1.55)	.02[e]

Abbreviations: CESD, Center for Epidemiologic Studies Depression; TCI, Temperament and Character Inventory.

[a] Data are expressed as No. (%) unless otherwise indicated. Never smokers at baseline defined as those who have never used any of the 3 combustible tobacco products (ie, combustible cigarettes, cigars, hookah).

[b] Indicates No. of students who completed follow-up assessments at 6 or 12 months.

[c] The denominator is for the data in column 2 and is provided due to missing data for this variable in each column in this row (or rows; the denominators for columns 3 and 4 are not provided).

[d] Calculated using the χ^2 test.

[e] Calculated using the independent samples *t* test.

[f] Students selected "other" in response to the forced-choice race/ethnicity question because they did not self-identify with any of the categories provided.

[g] Calculated using the Spearman ρ test.

[h] Score range: 0 (rarely or none of the time; 0-1 day) to 3 (most or all of the time; 5-7 days) for each symptom × 20 symptoms.

[i] Score range: 0-5 (example item: "I often do things based on how I feel at the moment"; score based on the sum of true or false responses to 5 items).

[j] Assessed using the average of the 2 responses for "I think I might enjoy ... smoking" and (reversed) "I think I might feel bad ... from smoking." Score range: 1-4; a response of strongly disagree, 1; disagree, 2; agree, 3; and strongly agree, 4.

ventory impulsivity subscale, which assesses tendency toward acting on instinct without conscious deliberation (eg, "I often do things based on how I feel at the moment." true or false items summed to total score with a score range of 0-5).[18]

Use of non-nicotine or tobacco substances was measured using items from the Youth Behavior Risk Surveillance and Monitoring the Future surveys assessing ever use of alcohol and 13 separate illicit and prescription substances of abuse (use of ≥1 vs 0 substances). Delinquent behavior was measured with a sum of frequency ratings for engaging in 11 different behaviors (eg, stealing, lying to parents; score range: 1 [never] to 6 [≥10 times]) within the past 6 months.[19]

Susceptibility to smoking was measured using a 3-item index,[9] averaging responses to the following 3 questions: "Would you try smoking a cigarette if one of your best friends offered it to you?" "Do you think you would smoke in the next 6 months?" "Are you curious about smoking?" Responses corresponded to the following scores: a response of definitely not received a score of 1; probably not, 2; probably yes, 3; and definitely yes, 4. Smoking outcome expectancies were assessed using the average of the 2 responses[20] for "I think I might enjoy ... smoking" and (reversed) "I think I might feel bad ... from smoking." Responses corresponded to the following scores: a response of strongly disagree received a score of 1; disagree, 2; agree, 3; and strongly agree, 4.

Data Analysis

The prevalence and association of e-cigarette and combustible tobacco use in the overall baseline sample are reported first. Then, in the sample of baseline never smokers, corre-

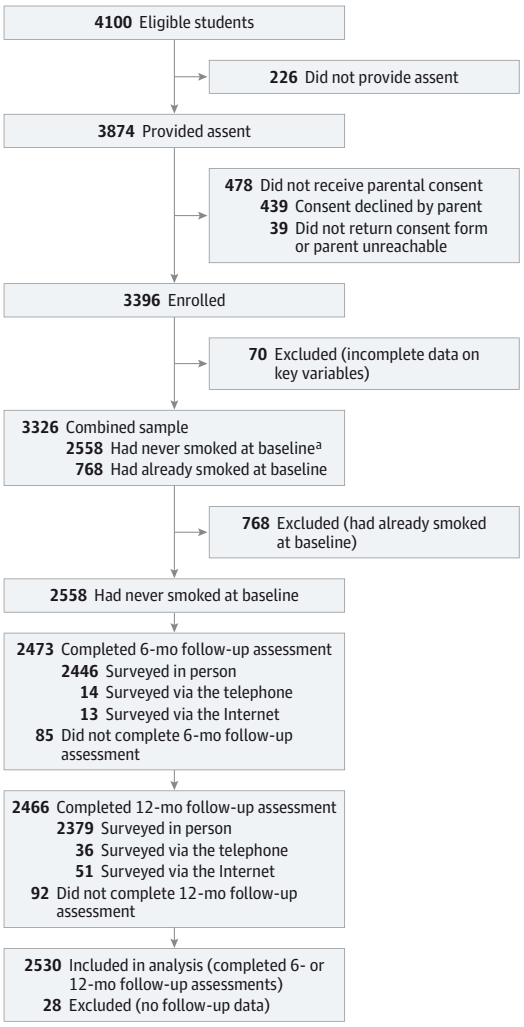
lates of study attrition and descriptive statistics are reported. Primary analyses used repeated-measures, generalized-linear mixed models,[21] an extension of logistic regression, in which each participant had 2 time points of follow-up data (at 6 and 12 months). Separate models were constructed for each binary outcome (ie, any combustible tobacco product, cigarettes, cigars, hookah) and the ordinal number of combustible products (cumulative logit) outcome at the 6- and 12-month follow-up periods.

All models included baseline e-cigarette use, school, and time (6-month vs 12-month follow-up) as fixed effects and were fit with and without adjustment for all covariates. The parameter estimate from each regressor or covariate reflected the association with the outcome averaged across the 2 follow-up periods. To explore whether the association between baseline e-cigarette and combustible tobacco use differed across the follow-up periods, the baseline e-cigarette × time interaction term was added to each model in a subsequent step. Participants with missing data on baseline e-cigarette use or the respective outcome variable were not included in the models.

Missing data on covariates were accounted for using a multiple-imputation approach,[22] which replaces each missing value with a set of plausible values that represent the uncertainty about the correct value to impute. Using the Markov-chain Monte Carlo method for missing at random assumptions and the available covariate data, 5 multiply-imputed data sets were created. The parameter estimates from the models tested in each imputed data set were pooled and presented as a single estimate. The amount of missing data for each covariate is indicated in Table 1. Continuous variables were rescaled (mean = 0, SD = 1) for the models to facilitate interpretation.

Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc).[23] Significance was set to .05 and all tests were 2-tailed. A Bonferroni-Holm correction[24] for multiple tests was applied.

Figure. Flow of Adolescent Students in Study to Assess e-Cigarette Use at Baseline and Later Use of Combustible Tobacco Products



[a] Includes all 3 combustible tobacco products (ie, combustible cigarettes, cigars, hookah).

Results

Study Sample

All 9th-grade, English-speaking students not enrolled in special education classes (ie, those with severe learning disabilities) were eligible to participate (N = 4100). Of the 3874 assenting students (94.5%), 3396 parents (87.7%) provided consent. Data were collected for 3383 participants (99.6%) at baseline, 3293 (97.0%) at the 6-month follow-up, and 3282 (96.6%) at the 12-month follow-up. The analytic samples available for the analyses appear in the **Figure**.

Descriptive Analyses

In the combined sample of ever smokers (n = 768) and never smokers (n = 2558), baseline e-cigarette ever use was positively associated with baseline ever use of each combustible tobacco product; prevalence ranged from 10.5% to 15.2% for the combustible tobacco products and the prevalence of ever use of e-cigarettes was 18.6% (**Table 2**).

Baseline never smokers with (N = 2530) vs without (n = 28) follow-up data did not differ by baseline e-cigarette use or any sociodemographic characteristic except for age in which participants without data were older (P = .006). There were positive associations of e-cigarette use with male sex, Native Hawaiian/Pacific Islander ethnicity, lower parental education level, and most environmental and intrapersonal factors (Table 1).

Associations Between Baseline e-Cigarette Use and Combustible Tobacco Use at Follow-up Assessments

In the sample of students who were never smokers of combustible tobacco products at baseline, baseline e-cigarette ever users were more likely to report past 6-month use of any combustible tobacco product at the 6-month follow-up (30.7% vs 8.1% in never users; difference between groups in prevalence rates, 22.7% [95% CI, 16.4%-28.9%]) and at the 12-month follow-up (25.2% vs 9.3%, respectively; difference between groups, 15.9% [95% CI, 10.0%-21.8%]) (**Table 3**).

Table 2. Prevalence and Cross-sectional Association of Baseline e-Cigarette Use and Combustible Tobacco Use[a]

	Combined Sample (n = 3326)[b]	Never Use of e-Cigarettes (n = 2709)	Ever Use of e-Cigarettes (n = 617)	Difference in Prevalence Rates, % (95% CI)
Ever Use				
Any combustible tobacco product	768 (23.1)	376 (13.9)	392 (63.5)	49.7 (45.6-53.7)
Combustible cigarettes (n = 3320)[c]	349 (10.5)	153 (5.7)	196 (32.0)	26.4 (22.6-30.2)
Cigars (n = 3324)[c]	419 (12.6)	168 (6.2)	251 (40.8)	34.6 (30.6-38.6)
Hookah (n = 3304)[c]	501 (15.2)	220 (8.2)	281 (46.5)	38.3 (34.2-42.4)
No. of different combustible tobacco products				
0	2558 (76.9)	2333 (86.1)	225 (36.5)	
1	401 (12.1)	245 (9.0)	156 (25.3)	
2	233 (7.0)	97 (3.6)	136 (22.0)	
3	134 (4.0)	34 (1.3)	100 (16.2)	

[a] Data are expressed as No. (%) unless otherwise indicated. All *P* value comparisons yielded values <.001 and were calculated using the χ^2 test.

[b] Total is larger than 2530 participants because it includes students who did not have data from follow-up assessments at 6 or 12 months and includes both ever and never smokers at baseline.

[c] The denominator is for the data in column 2 and is provided due to missing data for this variable in each column in this row (the denominators for columns 3 and 4 are not provided).

Table 3. Prevalence of Combustible Tobacco Product Use During Past 6 Months at 2 Follow-up Periods[a]

	Combustible Tobacco Use During Past 6 mo			
	Total (N = 2530)[b]	Never Use of e-Cigarettes (n = 2308)	Ever Use of e-Cigarettes (n = 222)	Difference in Prevalence Rates, % (95% CI)
6-mo Follow-up				
Any combustible tobacco product (n = 2473)[c]	249 (10.1)	182 (8.1)	67 (30.7)	22.7 (16.4-28.9)
Combustible cigarettes (n = 2468)[c]	89 (3.6)	68 (3.0)	21 (9.7)	6.7 (2.7-10.7)
Cigars (n = 2443)[c]	107 (4.4)	70 (3.1)	37 (17.3)	14.2 (9.0-19.3)
Hookah (n = 2434)[c]	160 (6.6)	122 (5.5)	38 (17.8)	12.3 (7.1-17.5)
No. of different combustible tobacco products (n = 2472)[c]				
0	2223 (89.9)	2072 (91.9)	151 (69.3)	
1	166 (6.7)	122 (5.4)	44 (20.2)	
2	59 (2.4)	42 (1.9)	17 (7.8)	
3	24 (1.0)	18 (0.8)	6 (2.8)	
12-mo Follow-up				
Any combustible tobacco product (n = 2463)[c]	264 (10.7)	210 (9.3)	54 (25.2)	15.9 (10.0-21.8)
Combustible cigarettes (n = 2462)[c]	91 (3.7)	74 (3.3)	17 (7.9)	4.7 (1.0-8.4)
Cigars (n = 2374)[c]	126 (5.3)	93 (4.3)	33 (16.2)	11.9 (6.8-17.0)
Hookah (n = 2371)[c]	152 (6.4)	127 (5.9)	25 (12.3)	6.4 (1.8-11.0)
No. of different combustible tobacco products (n = 2462)[c]				
0	2198 (89.3)	2038 (90.7)	160 (74.8)	
1	181 (7.4)	143 (6.4)	38 (17.8)	
2	61 (2.5)	50 (2.2)	11 (5.1)	
3	22 (0.9)	17 (0.8)	5 (2.3)	

[a] Data are expressed as No. (%) unless otherwise indicated. All *P* value comparisons yielded values <.001 and were calculated using the χ^2 test.

[b] Indicates No. of students who completed follow-up assessments at 6 or 12 months.

[c] The denominator is for the data in column 2 and is provided due to missing data for this variable in each column in this row (or rows; the denominators for columns 3 and 4 are not provided).

The unadjusted estimate for the association of baseline use of e-cigarettes with use of any combustible tobacco product averaged across the 2 follow-up periods was statistically significant (odds ratio [OR], 4.27 [95% CI, 3.19-5.71]; **Table 4**). In this model, the estimate for time of data collection was not significant (OR, 1.09 [95% CI, 0.90-1.32]), indicating no change in the prevalence of use of any combustible tobacco product across the 6- and 12-month follow-up periods. The e-cigarette × time interaction was not significant (OR, 0.64 [95% CI, 0.39-1.04]), indicating that the strength of association between baseline e-cigarette use and use of any combustible tobacco product did not significantly differ between the 6-month and 12-month follow-up periods.

In the adjusted model, baseline e-cigarette ever use was associated with use of any combustible tobacco product averaged across the 2 follow-up periods over and above the covariates (OR, 2.73 [95% CI, 2.00-3.73]). Parameter estimates for covariates in the adjusted models indicated that lower parental education and baseline peer smoking, impulsivity, ever use of non-nicotine or tobacco substances, delinquent behavior, and smoking expectancies were positively associated with any combustible tobacco use averaged across the 2 follow-up periods (Table 4 and eTable 2 in the Supplement). These particular covariates also were associated with baseline e-cigarette ever use (Table 1).

At both follow-up periods, the prevalence of combustible cigarette smoking, cigar use, and hookah use was higher among

Table 4. Association of Baseline e-Cigarette Ever Use and Covariates With Combustible Tobacco Product Use Outcomes at 6- and 12-Month Follow-up Periods Among Never Smokers at Baseline

	Any Combustible Tobacco Product		Combustible Cigarettes		Cigars		Hookah		No. of Different Combustible Tobacco Products	
	OR (95% CI)[a]	*P* Value	OR (95% CI)[a]	*P* Value	OR (95% CI)[a]	*P* Value	OR (95% CI)[a]	*P* Value	OR (95% CI)[b]	*P* Value
Unadjusted Models[c]										
Ever e-cigarette use	4.27 (3.19-5.71)	<.001	2.65 (1.73-4.05)	<.001	4.85 (3.38-6.96)	<.001	3.25 (2.29-4.62)	<.001	4.26 (3.16-5.74)	<.001
Time (12- vs 6-mo follow-up)	1.09 (0.90-1.32)	.38	1.03 (0.76-1.39)	.85	1.25 (0.95-1.64)	.11	0.99 (0.78-1.25)	.90	1.08 (0.89-1.30)	.45
Ever e-cigarette use × time[d]	0.64 (0.39-1.04)	.07	0.73 (0.34-1.56)	.41	0.68 (0.36-1.26)	.22	0.60 (0.32-1.12)	.11	0.64 (0.39-1.03)	.07
Adjusted Models[e]										
Categorical covariates[f]										
Female	0.88 (0.70-1.11)	.28	1.50 (1.05-2.15)	.03	1.48 (1.06-2.06)	.02	0.67 (0.51-0.90)	.007	0.92 (0.73-1.17)	.52
Hispanic ethnicity	1.09 (0.82-1.44)	.55	0.91 (0.59-1.39)	.65	0.97 (0.66-1.43)	.87	1.33 (0.97-1.83)	.08	1.11 (0.83-1.48)	.48
Lives with both biological parents	0.80 (0.64-1.01)	.07	0.96 (0.67-1.37)	.80	0.58 (0.42-0.80)	<.001	0.82 (0.62-1.08)	.15	0.80 (0.63-1.01)	.06
Substance use	2.33 (1.81-2.99)	<.001	1.35 (0.91-2.00)	.14	2.42 (1.72-3.42)	<.001	2.25 (1.67-3.01)	<.001	2.24 (1.73-2.90)	<.001
Family history of smoking	1.11 (0.88-1.41)	.37	1.34 (0.91-1.98)	.14	0.95 (0.68-1.32)	.75	0.99 (0.74-1.32)	.94	1.11 (0.87-1.42)	.39
Continuous covariates[g]										
Age	1.07 (0.96-1.20)	.23	1.13 (0.96-1.34)	.15	1.12 (0.95-1.31)	.17	0.97 (0.84-1.11)	.64	1.07 (0.95-1.20)	.27
Parental education	0.83 (0.73-0.94)	.004	0.81 (0.67-0.97)	.03	0.88 (0.72-1.06)	.18	0.86 (0.74-1.01)	.07	0.83 (0.73-0.95)	.007
Peer smoking	1.13 (1.00-1.28)	.05	1.08 (0.90-1.30)	.41	1.18 (1.00-1.38)	.05	1.16 (1.01-1.34)	.03	1.13 (1.00-1.28)	.05
CESD Scale for depressive symptoms	0.95 (0.84-1.08)	.42	1.07 (0.89-1.29)	.45	0.97 (0.81-1.15)	.70	0.99 (0.85-1.14)	.87	0.97 (0.86-1.10)	.66
TCI subscale for impulsivity	1.23 (1.09-1.38)	<.001	1.11 (0.93-1.33)	.25	1.14 (0.97-1.35)	.11	1.28 (1.11-1.46)	<.001	1.22 (1.09-1.38)	<.001
Delinquent behavior	1.38 (1.18-1.61)	<.001	1.35 (1.10-1.66)	.004	1.39 (1.14-1.70)	.001	1.38 (1.14-1.66)	<.001	1.40 (1.20-1.63)	<.001
Smoking susceptibility	1.08 (0.92-1.26)	.37	1.46 (1.18-1.80)	<.001	0.98 (0.79-1.21)	.84	0.94 (0.77-1.14)	.53	1.09 (0.93-1.29)	.28
Smoking expectancies	1.24 (1.10-1.41)	<.001	1.19 (0.98-1.44)	.08	1.43 (1.20-1.69)	<.001	1.26 (1.08-1.46)	.003	1.27 (1.12-1.44)	<.001
Regressors										
Ever e-cigarette use	2.73 (2.00-3.73)	<.001	1.75 (1.10-2.77)	.02	2.96 (2.00-4.38)	<.001	2.26 (1.56-3.29)	<.001	2.73 (1.99-3.75)	<.001
Time (12- vs 6-mo follow-up)	1.09 (0.90-1.33)	.37	1.03 (0.76-1.40)	.85	1.26 (0.95-1.67)	.10	0.98 (0.77-1.24)	.84	1.08 (0.89-1.32)	.42
Ever e-cigarette use × time[d]	0.64 (0.38-1.05)	.08	0.74 (0.34-1.61)	.44	0.68 (0.36-1.29)	.23	0.59 (0.31-1.12)	.11	1.54 (0.94-2.51)	.08

Abbreviations: CESD, Center for Epidemiologic Studies Depression Scale; OR, odds ratio; TCI, Temperament and Character Inventory.

[a] From repeated binary logistic regression model predicting respective outcome from baseline e-cigarette ever use status (yes or no), including school fixed effects.

[b] From repeated ordinal logistic regression model predicting the number of different combustible tobacco products used from baseline e-cigarette ever use status (yes or no), including school fixed effects with the OR reflecting the change in odds of being in a category with use of 1 or more tobacco products (3 vs ≤2; ≥2 vs ≤1; ≥1 vs 0) associated with the covariate or regressor.

[c] For the −2 res log pseudo-likelihood fit indices, the following values are without and with (in parentheses) the interaction term: 24 932.93 (24 946.6) for any tobacco product, 28 391.21 (28 397.11) for combustible cigarettes, 27 019.65 (27 050.36) for cigars, 26 131.31 (26 137.37) for hookah, and 70 339.66 (70 411.89) for No. of tobacco products.

[d] Interaction term added in subsequent model; parameter estimates for other regressors or covariates are from the model excluding the interaction term.

[e] For the range of −2 res log pseudo-likelihood fit indices across the 5 imputed data sets for adjusted models, the following values are without and with (in parentheses) the interaction term: 25 701.9-25 743.77 (25 717.24-25 759.27) for any tobacco product, 29 378.05-29 461.92 (29 382.85-29 467.24) for combustible cigarettes, 28 211.45-28 286.11 (28 238.77-28 312.83) for cigars, 27 193.74-27 282.15 (27 209.93-27 297.96) for hookah, and 73 652.58-73 852.15 (73 730.36-73 930.47) for No. of tobacco products.

[f] The prevalence of combustible tobacco use outcomes at the 2 follow-up periods by covariate category membership appears in eTable 2 in the Supplement.

[g] Rescaled (mean = 0, SD = 1) such that the ORs indicate the change in odds in the outcome associated with an increase in 1 SD unit on the covariate continuous scale.

baseline e-cigarette ever users compared with never users (Table 3). Averaged across the 2 follow-up periods in the unadjusted models, there was an association of baseline e-cigarette ever use with use of combustible cigarettes (OR, 2.65 [95% CI, 1.73-4.05]), cigars (OR, 4.85 [95% CI, 3.38-6.96]), and hookah (OR, 3.25 [95% CI, 2.29-4.62]) (Table 4).

In addition, relative to baseline e-cigarette never users, e-cigarette ever users were more likely to be using at least 1 more combustible tobacco product (ie, 3 vs ≤2; ≥2 vs ≤1; and ≥1 vs 0) averaged across the 2 follow-up assessments (OR, 4.26 [95% CI, 3.16-5.74]) (Table 4). Each OR estimate for e-cigarette ever use remained significant in the adjusted models and after applying the Bonferroni-Holm correction for multiple comparisons. The magnitudes of the ORs for e-cigarette ever use were reduced from the unadjusted to adjusted models for each outcome, and a common set of covariates (peer smoking, impulsivity, ever use of non-nicotine or tobacco substances, delinquent behavior, and smoking expectancies) were associated with most outcomes in the adjusted models (Table 4 and eTable 2 in the Supplement). Time and the e-cigarette × time interaction were nonsignificant in all models, suggesting no change in each outcome's prevalence rate or degree of association with baseline e-cigarette use across the 2 follow-up periods. Additional results can be found in the Supplement (eSensitivity Analyses).

Supplementary Analyses

Using the same modeling strategy as applied for the primary analysis, the association between baseline combustible tobacco ever use and past 6-month use (initiation) of e-cigarettes at the 2 follow-up periods was analyzed. These analyses included ever smokers at baseline but excluded ever users of e-cigarettes to model initiation of e-cigarette use. Baseline ever use of each combustible tobacco product was positively associated with e-cigarette use averaged across the 2 follow-up periods in the unadjusted and adjusted models, except for cigars in the adjusted model (P = .06; eTables 3-5 in the Supplement).

Discussion

These data provide new evidence that e-cigarette use is prospectively associated with increased risk of combustible tobacco use initiation during early adolescence. Associations were consistent across unadjusted and adjusted models, multiple tobacco product outcomes, and various sensitivity analyses. Based on these data, it is unlikely that the high prevalence of adolescent dual users of e-cigarettes and combustible tobacco reported in recent national cross-sectional surveys[2,3] is entirely accounted for by adolescent smokers who later initiate e-cigarette use. Supplementary analyses showed that adolescents who ever (vs never) smoked at baseline were more likely to initiate e-cigarette use during the follow-up period. Collectively, these results raise the possibility that the association between e-cigarette and combustible tobacco use initiation may be bidirectional in early adolescence.

During the age period captured in this study (fall 9th grade to fall 10th grade), adolescents adjust to the transition from middle school to high school, which is often accompanied by movement to a school with a larger, more diverse student body, new social contexts, increased exposure to older adolescents, and new academic demands.[4] Early adolescence is also a period of uneven brain development in which the neural circuits that underlie motivation to seek out novel experiences develop more rapidly than circuits involving impulse control and effective decision making.[25] Consequently, the expression of a propensity to initiate combustible tobacco use may be heightened during this age period.

The observed association between e-cigarette use and combustible tobacco use initiation may be explained by several mechanisms. It is possible that common risk factors for both e-cigarette and combustible tobacco use are responsible for the use of these 2 products and the order of onset of e-cigarette use relative to combustible tobacco use may not be determined by a causal sequence. Some teens may be more likely to use e-cigarettes prior to combustible tobacco because of beliefs that e-cigarettes are not harmful or addictive,[16,26] youth-targeted marketing,[27] availability of e-cigarettes in flavors attractive to youths,[16,27] and ease of accessing e-cigarettes due to either an absence or inconsistent enforcement of restrictions against sales to minors.[28]

We attempted to analytically address the possible influence of shared risk factors by adjusting for sociodemographic, environmental, and intrapersonal characteristics that presumably could affect use of both types of products. Adjusting for these factors reduced the OR estimates associated with e-cigarette use, but the associations remained statistically significant. In the adjusted models, baseline e-cigarette use was associated with a significant increase in odds of smoking initiation that ranged from 1.75 to 2.96, depending on the outcome.

Although it remains possible that factors not accounted for in this study may explain the association between e-cigarette use and initiation of combustible tobacco use, it is also plausible that exposure to e-cigarettes, which have evolved to become effective nicotine delivery devices, may play a role in risk of smoking initiation. Newer-generation e-cigarette devices with higher-voltage batteries and efficient machinery have been shown to heat e-cigarette solutions to high temperatures, which results in nicotine-rich aerosols that effectively and quickly deliver nicotine to the user, generating desirable psychoactive effects that may carry abuse liability.[29,30]

The neurodevelopmental and social backdrop of early adolescence may promote risk-taking behavior,[25] and neural plasticity may sensitize the adolescent brain to the effects of nicotine.[31] Hence, adolescent never smokers exposed to nicotine-rich e-cigarette aerosols and the pleasant sensations associated with vaping could be more liable to experiment with other nicotine-containing products, including combustible tobacco. Because this is an observational study, and one of the first to address this issue, inferences regarding whether this association is or is not causal cannot yet be made.

The study has several strengths, including a demographically diverse sample, repeated measures of tobacco use, exclusion of ever smokers at baseline, a high follow-up rate, comprehensive assessment of multiple combustible tobacco products, and statistical control for important covariates. A

limitation of the study is that e-cigarette use was measured only as any use and product characteristics (eg, nicotine strength and flavor) were not assessed. Thus, whether a specific frequency or type of e-cigarette use is associated with the initiation of combustible tobacco could not be determined.

This study focuses solely on initiation outcomes; however, future research should evaluate whether e-cigarette use is associated with an increased risk of escalating to regular, frequent use of combustible tobacco. The current sample was drawn from a specific location, which may restrict generalizability.

The age period focused on in this study captured an important, but brief window of susceptibility. In this and other samples,[2,3] youths commonly initiated use of combustible tobacco prior to 9th grade and e-cigarette use after 9th grade, suggesting that investigating other ages is warranted. Some important covariates (eg, advertising exposure, sensation seeking, and academic performance) were not assessed and should be included in future work.

Conclusions

Among high school students in Los Angeles, those who had ever used e-cigarettes at baseline compared with nonusers were more likely to report initiation of combustible tobacco use over the next year. Further research is needed to understand whether this association may be causal.

ARTICLE INFORMATION

Author Contributions: Dr Leventhal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Leventhal, Strong, Unger, Sussman, Audrain-McGovern.
Acquisition, analysis, or interpretation of data: Leventhal, Strong, Kirkpatrick, Unger, Riggs, Stone, Khoddam, Samet, Audrain-McGovern.
Drafting of the manuscript: Leventhal, Sussman, Stone, Khoddam, Samet, Audrain-McGovern.
Critical revision of the manuscript for important intellectual content: Strong, Kirkpatrick, Unger, Riggs, Samet, Audrain-McGovern.
Statistical analysis: Leventhal, Unger, Stone, Khoddam, Audrain-McGovern.
Obtained funding: Leventhal, Strong, Riggs, Audrain-McGovern.
Administrative, technical, or material support: Kirkpatrick, Sussman, Stone, Khoddam, Samet.
Study supervision: Leventhal, Kirkpatrick, Unger, Samet, Audrain-McGovern.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This research was supported by grants R01-DA033296 and P50-CA180905 from the National Institutes of Health.

Role of Funder/Sponsor: The National Institutes of Health 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.

REFERENCES

1. Benowitz NL. Pharmacology of nicotine. *Annu Rev Pharmacol Toxicol*. 2009;49:57-71.

2. Arrazola RA, Singh T, Corey CG, et al. Tobacco use among middle and high school students—United States, 2011-2014 [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2015;64(15);426]. *MMWR Morb Mortal Wkly Rep*. 2015;64(14):381-385.

3. Johnston LD, Miech RA, O'Malley PM, et al. Use of alcohol, cigarettes, and number of illicit drugs declines among US teens. http://www.monitoringthefuture.org/data/14data.html. Accessed April 3, 2015.

4. Benner AD. The transition to high school. *Educ Psychol Rev*. 2011;23(3):299-328.

5. Eaton DK, Kann L, Kinchen S, et al. Youth risk behavior surveillance—United States, 2009. *MMWR Surveill Summ*. 2010;59(5):1-142.

6. Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg JE. *Monitoring the Future: National Survey Results on Drug Use 1975-2014: Overview: Key Findings on Adolescent Drug Use*. Ann Arbor: Institute for Social Research at the University of Michigan; 2015.

7. Audrain-McGovern J, Rodriguez D, Tercyak KP, et al. Identifying and characterizing adolescent smoking trajectories. *Cancer Epidemiol Biomarkers Prev*. 2004;13(12):2023-2034.

8. Radloff LS. The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. *J Youth Adolesc*. 1991;20(2):149-166.

9. Strong DR, Hartman SJ, Nodora J, et al. Predictive validity of the expanded susceptibility to smoke index. *Nicotine Tob Res*. 2015;17(7):862-869.

10. Camenga DR, Kong G, Cavallo DA, et al. Alternate tobacco product and drug use among adolescents who use electronic cigarettes, cigarettes only, and never smokers. *J Adolesc Health*. 2014;55(4):588-591.

11. Cooper ZD, Haney M. Comparison of subjective, pharmacokinetic, and physiological effects of marijuana smoked as joints and blunts. *Drug Alcohol Depend*. 2009;103(3):107-113.

12. Covey LS, Tam D. Depressive mood, the single-parent home, and adolescent cigarette smoking. *Am J Public Health*. 1990;80(11):1330-1333.

13. Tyas SL, Pederson LL. Psychosocial factors related to adolescent smoking. *Tob Control*. 1998;7(4):409-420.

14. Cardenas VM, Breen PJ, Compadre CM, et al. The smoking habits of the family influence the uptake of e-cigarettes in US children. *Ann Epidemiol*. 2015;25(1):60-62.

15. Wills TA, Knight R, Williams RJ, et al. Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents. *Pediatrics*. 2015;135(1):e43-e51.

16. Kong G, Morean ME, Cavallo DA, et al. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. *Nicotine Tob Res*. 2015;17(7):847-854.

17. US Centers for Disease Control and Prevention. *National Youth Tobacco Survey Methodology Report*. Atlanta, GA: CDC; 2011.

18. Cloninger C, Przybeck T, Syrakic D, Wetzel R. *The Temperament and Character Inventory (TCI): A Guide to Its Development and Use*. St Louis, MO: Center for Psychobiology of Personality; 1994.

19. Thompson MP, Ho CH, Kingree JB. Prospective associations between delinquency and suicidal behaviors in a nationally representative sample. *J Adolesc Health*. 2007;40(3):232-237.

20. Katz EC, Fromme K, D'Amico EJ. Effects of outcome expectancies and personality on young adults' illicit drug use, heavy drinking, and risky sexual behavior. *Cognit Ther Res*. 2000;24(1):1-22.

21. McCulloch C, Searle S. *Generalized, Linear, and Mixed Models*. New York, NY: John Wiley & Sons; 2001.

22. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley & Sons; 1987.

23. SAS Institute Inc. *SAS 9.3 System Options: Reference*. 2nd ed. Cary, NC: SAS Institute Inc; 2011.

24. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979;6(2):65-70.

25. Steinberg L. A social neuroscience perspective on adolescent risk-taking. *Dev Rev*. 2008;28(1):78-106.

26. Peters RJ Jr, Meshack A, Lin MT, et al. The social norms and beliefs of teenage male electronic cigarette use. *J Ethn Subst Abuse*. 2013;12(4):300-307.

27. Gostin LO, Glasner AY. E-cigarettes, vaping, and youth. *JAMA*. 2014;312(6):595-596.

28. Collaco JM, Drummond MB, McGrath-Morrow SA. Electronic cigarette use and exposure in the pediatric population. *JAMA Pediatr*. 2015;169(2):177-182.

29. Vansickel AR, Eissenberg T. Electronic cigarettes. *Nicotine Tob Res*. 2013;15(1):267-270.

30. Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability. *Nicotine Tob Res*. 2015;17(2):158-162.

31. Counotte DS, Smit AB, Pattij T, Spijker S. Development of the motivational system during adolescence, and its sensitivity to disruption by nicotine. *Dev Cogn Neurosci*. 2011;1(4):430-443.