

E-Cigarettes and Future Cigarette Use

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abstract

BACKGROUND: There has been little research examining whether e-cigarette use increases the risk of cigarette initiation among adolescents in the transition to adulthood when the sale of cigarettes becomes legal.

METHODS: The Children's Health Study is a prospectively followed cohort in Southern California. Data on e-cigarette use were collected in 11th and 12th grade (mean age = 17.4); follow-up data on tobacco product use were collected an average of 16 months later from never-smoking e-cigarette users at initial evaluation ($n = 146$) and from a sample of never-smoking, never e-cigarette users ($n = 152$) frequency matched to e-cigarette users on gender, ethnicity, and grade.

RESULTS: Cigarette initiation during follow-up was reported by 40.4% of e-cigarette users ($n = 59$) and 10.5% of never users ($n = 16$). E-cigarette users had 6.17 times (95% confidence interval: 3.30–11.6) the odds of initiating cigarettes as never e-cigarette users. Results were robust to adjustment for potential confounders and in analyses restricted to never users of any combustible tobacco product. Associations were stronger in adolescents with no intention of smoking at initial evaluation. E-cigarette users were also more likely to initiate use of any combustible product (odds ratio = 4.98; 95% confidence interval: 2.37–10.4), including hookah, cigars, or pipes.

CONCLUSIONS: E-cigarette use in never-smoking youth may increase risk of subsequent initiation of cigarettes and other combustible products during the transition to adulthood when the purchase of tobacco products becomes legal. Stronger associations in participants with no intention of smoking suggests that e-cigarette use was not simply a marker for individuals who would have gone on to smoke regardless of e-cigarette use.



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WHAT'S KNOWN ON THIS SUBJECT: Three studies have found associations between e-cigarette use and subsequent cigarette use in adolescents. However, the risk of initiation of cigarettes as adolescents reach an age at which the purchase of tobacco products becomes legal is unknown.

WHAT THIS STUDY ADDS: Adolescents who reported e-cigarette use had more than six times the odds of initiating cigarette use as never e-cigarette users. These findings suggest e-cigarette use may increase the risk of smoking during the transition to adulthood.

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Adolescent use of e-cigarettes has increased rapidly in recent years,¹ with several studies reporting higher rates of e-cigarette use than combustible cigarette use among high school students in 2014.¹⁻⁶ Among high school students in the National Youth Tobacco Survey, 13.4% of adolescents reported past 30-day use of e-cigarettes in 2014, compared with 9.2% of adolescents who reported past 30-day use of cigarettes.¹ Among high school students participating in the Southern California Children's Health Study (CHS), we found that 24.0% had ever tried e-cigarettes (including 9.6% who reported use in the past 30 days), compared with 18.7% who had tried cigarettes (5.7% in the past 30 days); >40% of e-cigarette users had never smoked a combustible cigarette.⁶ A critical question is whether e-cigarette use in adolescents who have never smoked cigarettes will lead to subsequent initiation of cigarette or other combustible product use.

The initial data addressing this question came from several cross-sectional studies that examined the association between e-cigarette use and self-reported intention to use cigarettes among adolescents with no previous history of cigarette use, using validated survey measures.⁷⁻¹³ E-cigarette users, representing several age groups and geographic locations, had 2 to 4 times the odds of indicating an intention to use cigarettes as never users,^{7,8} results consistent with those we reported in the CHS.⁹ To date there have been 3 reports from prospective cohort studies examining the relationship between e-cigarette use and subsequent initiation of combustible cigarette use in adolescence, including a study of 9th-grade students (mean age 14.1),¹⁴ a second study of 9th and 10th-grade students (mean age 14.7),¹⁵ and another small study of 16- to 26-year-olds, with few never-smoking e-cigarette

users at baseline that was not able to examine associations within specific developmental periods in this age range.¹⁶ All studies found that e-cigarette use was associated with elevated risk of initiation of combustible cigarettes. However, the risk of initiation of combustible cigarettes is likely to vary by age¹⁷; the developmental context of the end of high school is unique, because those turning 18 face particular challenges associated with the transition to adulthood, including postsecondary education or employment seeking, which co-occur at the age (18 years) at which the purchase of tobacco products becomes legal.

We examined whether e-cigarette use among older adolescents in the transition to adulthood leads to greater likelihood of initiation of cigarettes as they reach the legal age to purchase cigarettes. We used prospective data from the CHS, a population-based cohort of adolescents from whom data on e-cigarette use were first collected in grades 11 or 12 (mean age 17.4) in spring of 2014, to examine risk of initiation of combustible tobacco products at follow-up (median 15.6 months later). We hypothesized that never-smoking e-cigarette users in this critical age range would be more likely than never-smoking never e-cigarette users to begin using combustible cigarettes during the subsequent year.

METHODS

Study Design and Sample

Participants enrolled in the CHS completed the initial evaluation questionnaire in school classrooms when they were in 11th or 12th grade. Questionnaires were completed with study staff supervision between January 2014 and June 2014, when use of e-cigarettes was first assessed in the cohort.^{6,18} To maximize efficiency

in the design of the prospective follow-up study to evaluate the risk of cigarette and other combustible tobacco product initiation associated with e-cigarette use, we used an exposure frequency-matched cohort study design in which we contacted never-smoking e-cigarette users and a sample of never-smoking never e-cigarette users to complete a follow-up questionnaire (Fig 1). We attempted to contact all never-smoking e-cigarette users ($n = 213$) and a randomly selected frequency matched sample of never-smoking, never e-cigarette users ($n = 213$) from among all never-smoking never e-cigarette users in the cohort at initial evaluation; never-users were frequency matched to e-cigarette users by gender, ethnicity, and grade (11 or 12). Participants completed an online follow-up questionnaire between February 2015 and March 2016. Follow-up questionnaires were completed by 149 (70.0%) e-cigarette users and 154 (72.3%) never e-cigarette users; 146 e-cigarette users and 152 never users provided complete data on their use of cigarettes between initial evaluation and follow-up and were included in analyses. All participants were 18 years of age or older at follow-up. Participants turning 18 were sent a link to the follow-up online survey by e-mail (using e-mail address provided at the 11th- and 12th-grade data collection); additional attempts to contact participants were made by text message and telephone calls. Those not responding or who had not provided other contact information were sent letters soliciting participation to the last known residential address or were contacted through parents or other contacts previously provided by participants.

Ethics Statement

The study was approved by the University of Southern California Institutional Review Board.

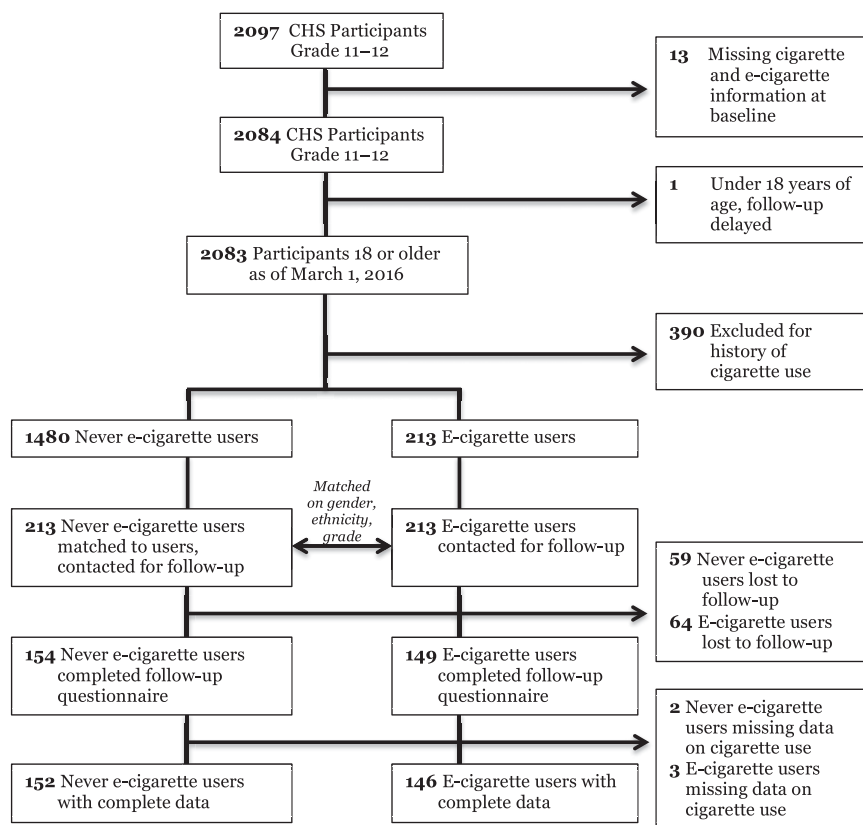


FIGURE 1 Selection of participants for assessment of the association between e-cigarette use and subsequent initiation of combustible cigarettes.

Participants aged 18 or older provided written informed consent. Written parental informed consent and student assent were obtained for all CHS participants before data collection in 2014.

Measures

Tobacco and Alternative Tobacco Product Use

At each survey, participants were asked whether they had ever tried e-cigarettes, cigarettes, cigars, pipes, or hookah and the number of days each product was used in the past 30 days.⁶ Participants who had “never tried” a product (not “even 1 or 2 puffs”) were classified as “never users.” Those reporting an age at first use of each tobacco product were classified as “ever users” of that product. All analyses were restricted to never cigarette smokers at initial evaluation.

Sociodemographic Characteristics

Self-administered questionnaires completed by parents of participants¹⁸ were used to assess gender, ethnicity (Hispanic, non-Hispanic white, other), and parental education (highest level of education of either parent; <12th grade, high school diploma or general equivalency diploma, some college, college degree, some graduate school or higher).

Susceptibility to Cigarette Use

Susceptibility to tobacco product use has been defined as the absence of a firm commitment not to smoke.^{10,11,13} In the current study, susceptibility to future cigarette use was assessed using validated measures (see Supplemental Material). Adolescents were classified as having no susceptibility if they responded “definitely not” to questions about

intention to initiate use of cigarettes in the future.¹⁰

Social Environment

The cigarette social environment was evaluated based on the following questions: (1) “How many of your 4 closest friends use [cigarettes]?” (0–4 friends); (2) “How would your best friends act toward you if you used [cigarettes]?” (very unfriendly, unfriendly, friendly, or very friendly); and (3) “Does anyone who lives with you now use [cigarettes]?” (yes/no). These factors have been strongly associated with cigarette use¹⁷ and more recently have been associated with e-cigarette use in the CHS.⁶

Statistical Analysis

On the basis of prospectively collected data, we used unconditional logistic regression models to evaluate the association between e-cigarette use at initial evaluation and subsequent cigarette use at follow-up. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the odds of smoking initiation. All models were adjusted for gender, ethnicity, grade and highest parental education, factors that have been associated both with e-cigarette use and cigarette use in previous studies.^{17,19} Potential confounding by history of combustible tobacco use other than cigarettes at initial evaluation, social environment characteristics, age at initial evaluation, age at follow-up, and time from initial evaluation to follow-up (in months) was evaluated on the basis of a change in effect estimate of >10% with inclusion of any of these variables. A missing indicator category was included where appropriate. Formal tests of interaction were used to evaluate whether effect estimates differed by gender, ethnicity (Hispanic white, non-Hispanic white, other), grade (11 or 12), ever use of hookah (a combustible product that has been previously associated with

TABLE 1 Demographic Characteristics of Participants by E-Cigarette Use at Initial Assessment and by Cigarette Use at Follow-up, *N* = 298

	E-Cigarette Use (2014)				Cigarette Use (2015)		
	Overall <i>n</i> (%) ^a	No <i>n</i> (%)	Yes <i>n</i> (%)	OR (95% CI) ^b	No <i>n</i> (%)	Yes <i>n</i> (%)	OR (95% CI) ^b
Gender							
Female	124 (41.6)	63 (50.8)	61 (49.2)	Ref	100 (80.6)	24 (19.4)	Ref
Male	174 (58.4)	89 (51.1)	85 (48.9)	0.96 (0.60–1.55)	123 (70.7)	51 (29.3)	1.84 (1.04–3.26)
Race/ethnicity							
Hispanic white	146 (49.0)	74 (50.7)	72 (49.3)	Ref	107 (73.3)	39 (26.7)	Ref
Non-Hispanic white	126 (42.3)	66 (52.4)	60 (47.6)	0.98 (0.57–1.71)	95 (75.4)	31 (24.6)	0.94 (0.50–1.79)
Other	26 (8.7)	12 (46.2)	14 (53.8)	1.23 (0.49–3.13)	21 (80.8)	5 (19.2)	0.85 (0.27–2.67)
Education (highest parental)							
≤12th grade	86 (30.4)	44 (51.2)	42 (48.8)	1.16 (0.60–2.24)	62 (72.1)	24 (27.9)	1.14 (0.54–2.43)
Some college	100 (35.3)	48 (48.0)	52 (52.0)	1.31 (0.74–2.32)	75 (75.0)	25 (25.0)	1.04 (0.54–2.01)
College degree or higher	97 (34.3)	53 (54.6)	44 (45.4)	Ref	73 (75.3)	24 (24.7)	Ref
Grade							
11	160 (53.7)	79 (49.4)	81 (50.6)	Ref	121 (75.6)	39 (24.4)	Ref
12	138 (46.3)	73 (52.9)	65 (47.1)	0.88 (0.55–1.42)	102 (73.9)	36 (26.1)	1.22 (0.70–2.13)
Susceptibility to cigarette use							
Not susceptible	216 (73.2)	122 (56.5)	94 (43.5)	Ref	175 (81.0)	41 (19.0)	Ref
Susceptible	79 (26.8)	28 (35.4)	51 (64.6)	2.48 (1.44–4.27)	46 (58.2)	33 (41.8)	3.03 (1.71–5.39)
Others at home use cigarettes							
No	242 (81.8)	125 (51.7)	117 (48.3)	Ref	181 (74.8)	61 (25.2)	Ref
Yes	54 (18.2)	25 (46.3)	29 (53.7)	1.24 (0.68–2.24)	40 (74.1)	14 (25.9)	1.04 (0.52–2.06)
Friends use cigarettes							
No	231 (82.5)	128 (55.4)	103 (44.6)	Ref	180 (77.9)	51 (22.1)	Ref
Yes	49 (17.5)	16 (32.7)	33 (67.3)	2.61 (1.35–5.06)	30(61.2)	19 (38.8)	2.58 (1.30–5.09)
Friends are friendly to cigarette use							
No	217 (73.8)	121 (55.8)	96 (44.2)	Ref	164 (75.6)	53 (24.4)	Ref
Yes	77 (26.2)	29 (37.7)	48 (62.3)	2.13 (1.24–3.65)	56 (72.7)	21 (27.3)	1.15 (0.63–2.10)

^a Total varies due to missing values.

^b Adjusted for gender, ethnicity, grade, and highest parental education.

e-cigarette use,²⁰ yes versus no), or susceptibility to smoking at initial evaluation (yes vs no). Additional analyses evaluated the risk of initiation of any combustible tobacco product (cigarettes, cigars, hookah, or pipes) associated with e-cigarette use at initial evaluation. Polytomous regression models were used to evaluate the risk of initiation of cigarette use (but no use in the past 30 days) and the risk of past 30-day cigarette use, relative to participants not initiating use of cigarettes. In sensitivity analyses, models evaluating the risk of initiation of cigarettes were restricted to nonusers of any combustible tobacco product at initial evaluation (cigarettes, cigars, hookah, pipes). All statistical analyses were based on 2-sided hypotheses tested at a .05 level of significance. Analyses were performed using SAS 9.4.

Role of the Funding Source

The funder had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

RESULTS

E-cigarette users and never users were similar on matching factors (gender, ethnicity, grade) and parental education. In adjusted models males were more likely to initiate cigarette use (OR = 1.84; 95% CI: 1.04–3.26; Table 1). Adolescents who were classified as susceptible to cigarette use were more likely to report e-cigarette use at initial evaluation (OR = 2.48; 95% CI: 1.44–4.27) and to report cigarette use at follow-up (OR = 3.03; 95% CI: 1.71–5.39). Having one or more friends who smoked combustible

tobacco products also increased the likelihood of e-cigarette use at initial evaluation (OR = 2.61; 95% CI: 1.35–5.06) and cigarette use at follow-up (OR = 2.58; 95% CI: 1.30–5.09); having friends who were friendly to cigarette use was associated with e-cigarette use at initial evaluation (OR = 2.13; 95% CI: 1.24–3.65) but not with cigarette use at follow-up. The median age of participants at initial evaluation was 17.4 years (interquartile range [IQR]: 16.8–17.9); median age at follow-up was 18.6 years (IQR: 18.3–19.0 years); median time from initial evaluation to follow-up was 15.6 months (IQR: 12.6–18.2 months).

To assess the potential for selection bias, we compared sociodemographic characteristics of study participants for whom follow-up data were obtained with those lost to follow-up. Participants from whom follow-up data were collected were more

TABLE 2 Association Between E-Cigarette Use at Initial Assessment in 2014 and Subsequent Cigarette Use at Follow-up in 2015

	Cigarette Use at Follow-up (2015)			
	No		Yes	
	<i>n</i> (%)	<i>n</i> (%)	OR (95% CI) ^a	OR (95% CI) ^b
E-cigarette use at initial assessment (2014)				
No	136 (89.5)	16 (10.5)	Ref	
Yes	87 (59.6)	59 (40.4)	6.17 (3.30–11.6)*	5.48 (2.69–11.2)*

^a Adjusted for gender, ethnicity, grade and highest parental education.

^b Additionally adjusted for use of hookah, cigar, or pipe at initial evaluation.

* $P < .005$.

likely to have a parent with at least a college education (Supplemental Table 5). No notable differences in gender, ethnicity, grade, or susceptibility to cigarette use were observed between retained participants and those lost to follow up.

Among never e-cigarette users at initial evaluation, 16 (10.5%) reported use of cigarettes at follow-up; among ever e-cigarette users at the initial evaluation, 59 (40.4%) reported use of cigarettes at follow-up (Table 2). The adjusted OR for the association of e-cigarette use with subsequent smoking of combustible cigarettes was 6.17 (95% CI: 3.30–11.6). After further adjustment for cigar, pipe, or hookah use at initial evaluation, the association of e-cigarette use with subsequent smoking was slightly attenuated but still statistically significant (OR = 5.48; 95% CI: 2.69–11.2). Results did not

differ appreciably after additional adjustment for social environment characteristics at initial evaluation (whether others in the home smoked, number of friends who smoked, friends' attitudes toward smoking), age at initial evaluation, age at follow-up, or time in months from initial evaluation to follow-up (results not shown). E-cigarette users had 5.49 times (95% CI: 2.68–11.2) the odds of initiating cigarette smoking but not having smoked in the past 30 days, and 7.50 times (95% CI: 2.41–23.4) the odds of reporting use of cigarettes in the past 30 days at follow-up compared with never e-cigarette users. Estimates were based on 39 (27.1%) initiators and 18 (12.5%) past 30-day cigarette users among e-cigarette users at baseline, compared with 12 (7.9%) initiators and 4 (2.6%) past 30-day cigarette users among never e-cigarette users at baseline; 2 participants reported initiation of smoking but did not report the number of days smoked

in the past 30 days (results not tabulated).

Among adolescents who were not classified as susceptible to cigarette use at initial evaluation, 36.2% ($n = 34$) of e-cigarette users and 5.7% ($n = 7$) of never e-cigarette users reported initiation of cigarettes at follow up (OR_{not susceptible} = 9.69; 95% CI: 4.02–23.4; Table 3). In contrast, among those who were classified as susceptible to smoking at initial evaluation, e-cigarette users were only slightly more likely to initiate cigarette use at follow-up (47.1% v. 32.1%; OR_{susceptible} = 2.12; 95% CI: 0.79, 5.74; interaction $P = .03$). We also examined interactions of e-cigarette use at initial evaluation with gender, ethnicity, grade level, time from initial contact to completion of follow-up questionnaire, and use of hookah at initial evaluation. The risk of initiation of cigarette use associated with e-cigarettes did not differ by these characteristics.

In an analysis restricted to those who reported no use of any combustible tobacco product at initial evaluation, e-cigarette users were also more likely to initiate use of any combustible tobacco product at follow-up (OR = 4.98; 95% CI: 2.37–10.4; Table 4) and to initiate use of cigarettes (OR = 4.29; 95% CI: 1.84–10.0), hookah (OR = 2.86; 95% CI: 1.21–6.78), cigars (OR = 4.39; 95% CI: 1.72–11.2), and pipes (OR = 8.21; 95% CI: 1.20–56.2).

TABLE 3 Association Between E-Cigarette Use at Initial Assessment in 2014 and Subsequent Cigarette Use at Follow-up in 2015 by Indication of Susceptibility to Smoking at Initial Evaluation

	Not Susceptible			Susceptible		
	Cigarette Use at Follow-up (2015)			Cigarette Use at Follow-up (2015)		
	No <i>n</i> (%)	Yes <i>n</i> (%)	OR (95% CI) ^a	No <i>n</i> (%)	Yes <i>n</i> (%)	OR (95% CI) ^a
E-cigarette use at initial assessment (2014)						
No	115 (94.3)	7 (5.7)	Ref	19 (67.9)	9 (32.1)	Ref
Yes	60 (63.8)	34 (36.2)	9.69 (4.02–23.4)	27 (52.9)	24 (47.1)	2.12 (0.79–5.74)

P interaction = .025. Ref, referent.

^a Adjusted for gender, ethnicity, grade, and highest parental education.

DISCUSSION

We prospectively evaluated the risk of smoking initiation associated with e-cigarette use in the transition to adulthood when it becomes legal to purchase cigarettes. In this sample of never cigarette users at initial evaluation, >40% of e-cigarette users initiated cigarette use during the 16-month (average) follow-up. Those who reported e-cigarette use had >6 times the odds of initiating cigarette use as never e-cigarette users. The associations remained statistically significant after adjustment for use of other combustible tobacco products at study entry and for social environmental factors. The increased risk of smoking initiation associated with previous e-cigarette use was also observed in sensitivity analyses restricted to never-users of any combustible tobacco product at initial evaluation; moreover, risk of subsequent initiation of any combustible tobacco product was also increased. Notably, the association of e-cigarettes with initiation of cigarette use was much stronger among those classified as not susceptible to becoming smokers. These findings suggest that e-cigarette use may promote smoking during the transition to adulthood, even in those considered to be at lower risk because of personal or environmental factors.

Three studies on the longitudinal association between e-cigarette use and subsequent cigarette use among adolescents have been published.^{14–16} In the first, among ninth-grade students (mean age 14.1 years) with no history of combustible tobacco product use at initial evaluation, those who reported ever use of e-cigarettes had 1.75 (95% CI: 1.10–2.77) times the odds as never users of reporting subsequent use of cigarettes 12 months later, and 2.73 (95% CI: 2.00–3.73) times the odds of reporting use of any combustible tobacco product after adjustment for ever use of nonnicotine or tobacco

TABLE 4 Association Between E-Cigarette Use at Initial Assessment in 2014 and Subsequent Cigarette Use at Follow-up in 2015, Restricted to Never Users of Any Combustible Tobacco Product

Tobacco Product Use (2015)	E-Cigarette Use at Initial Assessment (2014)		OR (95% CI) ^a
	No	Yes	
	n (%)	n (%)	
Any combustible product			
No	109 (87.9)	26 (49.1)	Ref
Yes	23 (17.4)	27 (50.9)	4.98 (2.37–10.4)**
Cigarette			
No	118 (89.4)	37 (67.3)	Ref
Yes	14 (10.6)	18 (32.7)	4.29 (1.84–10.0)**
Hookah			
No	116 (87.9)	40 (74.1)	Ref
Yes	16 (12.1)	14 (25.9)	2.86 (1.21–6.78)*
Cigars			
No	122 (92.4)	39 (72.2)	Ref
Yes	10 (7.6)	15 (27.8)	4.39 (1.72, 11.2)**
Pipes			
No	129 (98.5)	49 (89.1)	Ref
Yes	2 (1.5)	6 (10.9)	8.21 (1.20–56.2)*

Total varies due to missing values. Ref, referent.

^a Adjusted for gender, ethnicity, grade, and highest parental education.

** $P < .005$.

* $P < .05$.

substances, smoking expectancies (whether adolescents think they will enjoy smoking, or feel bad from smoking), and other potentially confounding characteristics at study entry.¹⁴ The second study was also among younger youth in grades 9 and 10 at baseline (mean age 14.7 years) and found similar results: e-cigarette users had 2.87 (95% CI: 2.03–4.05) times the odds of initiating combustible cigarette use between baseline and follow-up 1 year later as never users, after adjustment for age, gender, ethnicity, parental education, parental support, and rebelliousness.¹⁵ The third study found similar prospective associations in adolescents and young adults 16 to 26 years of age who reported being nonsusceptible to smoking at baseline, but the estimates were based on only 16 never-smoking e-cigarette users at initial evaluation.¹⁶ The current results extend the literature by showing that these associations generalize to the period at the end of high school. Our findings, together with those from the other prospective studies of youth and young adult populations, suggest

that e-cigarette use is a clear and consistent indicator of likelihood of subsequent initiation of cigarette and other combustible tobacco product use at ages spanning from early adolescence through emerging adulthood.

It is possible in principle that e-cigarette use among never smoking adolescents is a marker for those who would have begun to smoke even if e-cigarettes were not available. In these adolescents, the availability of e-cigarettes use may have delayed the initiation of smoking among those who would have gone on to smoke anyway. However, the risk of smoking associated with e-cigarette use was even higher among participants who reported no intention to smoke at initial assessment than among the group of adolescents who indicated they were likely to begin smoking. Among nonsusceptible individuals, 36% of e-cigarette users initiated cigarette use, compared with only 6% of nonusers (Table 3). Another recent study found that e-cigarette users had different psychological profiles than cigarette users.^{21,22} Together, these findings suggest

that e-cigarettes are not merely a marker for individuals who would have gone on to smoke combustible cigarettes, regardless of the availability of e-cigarettes, but that e-cigarette use is likely introducing new youth to tobacco products and is increasing the likelihood of future smoking among the low-risk group who expressed confidence that they would not do so.

It is also possible that e-cigarette users who initiated smoking were more likely to be experimenting with cigarettes and less likely than other initiators to progress to regular cigarette use and nicotine dependence. The duration of follow-up and small sample size (particularly among never e-cigarette users who began smoking) was insufficient to fully address this question. However, the prospective association of e-cigarette use with cigarette use in the past 30 days was similar to that for initiation but no use in the past 30 days. These results provide no evidence that e-cigarette users who initiate smoking are any less likely to progress to regular use of cigarettes than youth who did not begin tobacco use with e-cigarettes.

There are some uncertainties to the conclusions from this study. Participants who were lost to follow-up were less likely to have a parent with at least a college education. However, in analyses examining whether the risk of initiation of smoking associated with e-cigarette use differed by education, no interaction was observed, nor were the estimates of effect of e-cigarette use on cigarette initiation confounded by education; thus, differential loss to follow-up in the cohort seems unlikely to be an explanation for the observed results.

We did not collect information on type of e-cigarette used or nicotine content of e-cigarette at initial evaluation, factors that may increase the likelihood of transition from e-cigarette to cigarette or other combustible tobacco use. Although the study addresses a potentially vulnerable age range, results may not be generalizable to older populations or to other geographic regions. Finally, because the rate of initiation of cigarette use in never e-cigarette users was low in our Southern California population (10.5% based on 16 new users), the odds ratio associated with e-cigarette use was not precisely estimated. However, the associations were large and highly statistically significant.

There are several plausible mechanisms through which e-cigarette use in adolescence may lead to subsequent initiation of cigarettes or other combustible tobacco products.^{17,23,24} E-cigarettes may lead to initiation of use of other combustible products because flavorings desensitize users' lungs to the harsh and aversive effects of nicotine inhalation, providing a more gradual transition from never smoking to use of combustible cigarettes or other combustible products. Flavorings, in combination with devices appealing to youth in this technological age (eg, "techie" e-devices with programmable settings) may act to promote smoking initiation among adolescents and may also play a role in product use maintenance or progression to greater levels of use. Regular use of nicotine, and the development of nicotine dependence, may also lead adolescents to seek other forms of nicotine. Adolescents first introduced to nicotine via e-cigarettes may

develop a dependence on nicotine and may then move on to other forms of nicotine, including cigarettes or other combustible products. Individuals genetically susceptible to the addictive properties of nicotine may be at particularly high risk. Finally, rapid increases in e-cigarette use in adolescent populations have already begun to contribute to the normalization of e-cigarette use, which indirectly functions to normalize "smoking-like" behaviors more generally (eg, clouds of smoke/vapor in public places become normative). The normalization of these social behaviors may facilitate initiation of cigarette smoking if society becomes more accepting of alternative tobacco product use.

Future work exploring these and other mechanisms through which e-cigarette use in adolescence may influence willingness to initiate cigarette smoking is warranted. Regardless of the mechanisms underlying the associations of e-cigarettes with cigarette use, this research adds much needed data to the emerging evidence that e-cigarettes are associated with increased risk of smoking among adolescents. Because e-cigarette use is common in adolescents and young adults, further prospective follow-up of this and other cohorts is needed to determine whether e-cigarette use will increase population rates of cigarette and other combustible tobacco products and their associated burden of disease.

ABBREVIATIONS

CHS: Children's Health Study
CI: confidence intervals
IQR: interquartile range
OR: odds ratio

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