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SPECIAL ISSUE ON JUUL

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Introduction to the Special Issue on JUUL Use

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This special issue addresses key topics relating to the public health impact of the use of electronic nicotine delivery devices (ENDS), particularly JUUL-brand ENDS. Smokers smoke for nicotine, but are harmed by the byproducts of combustion. ENDS can play a role in tobacco harm reduction offering a noncombustible alternative source of nicotine for adult smokers who would otherwise continue smoking. Papers presented here estimate the prevalence of ENDS and JUUL use among young and older adults, and document the 12-month smoking trajectories of adults who purchased a JUUL Starter Kit. Overall, smoking prevalence was halved, with most smokers switching completely as dual use declined. This held for subpopulations defined by demographics and psychiatric comorbidity. For those who did not switch, most significantly reduced (50%+) their cigarette consumption. Another study reports that dependence declines as smokers switch from smoking to using JUUL. The public health potential of ENDS is undermined by use of ENDS by nonsmokers, especially underage individuals. Some smoking was reported by adult former and never smokers, with little evidence of persistent smoking, and lower risk of smoking among those using JUUL more frequently. Regarding underage use, one paper reports that technology can ensure age-verification at point of sale. Population modeling integrating impacts on diverse populations indicates that availability of ENDS is expected to avert millions of premature deaths in the US. We believe these papers make a substantial contribution to the field of tobacco science and smoking controlnt.

Key words: smoking; ENDS; JUUL; smokers; exsmokers; nonsmokers; dependence
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Cigarette smoking continues to exact a serious toll on public health as the greatest preventable cause of premature mortality.[1] Tobacco control efforts have been successful in reducing that toll, both through social policies such as taxation of cigarettes and education about the harms of smoking, as well as through treatment to help individual smokers quit. Nevertheless, 34 million American adults[2] and 1.1 billion worldwide[3] continue to smoke cigarettes, leading to over 7 million premature deaths every year due to disease caused by smoking of conventional cigarettes,[4] which exposes smokers to the products of combustion.

We must continue and even accelerate current initiatives to reduce smoking of conventional cigarettes, but also change the current trajectory in a meaningful way, as well as explore expanded and novel approaches. Tobacco Harm Reduction is an important *complement* to current initiatives. The concept is simple and compelling – efforts to help smokers quit and to limit tobacco initiation among underage individuals should be continued and expanded. Moreover, we also must supplement these efforts by providing a less harmful source of nicotine to reduce the risk to those who continue to smoke.

The vast majority of harm associated with cigarette smoking comes from the toxicants in smoke created through combustion. Some 45 years ago, Michael Russell,[5] a pioneer in nicotine research, noted: "People smoke for the nicotine but die they die from the tar." The concept was reinforced in the 2014 Surgeon General's Report, which was emphatic: "The burden of death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other combusted tobacco

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products; rapid elimination of their use will dramatically reduce this burden."[1,6]

Tobacco harm reduction is not a new concept.[7] However, electronic nicotine delivery systems (ENDS) represent a significant opportunity to realize tobacco harm reduction at the population level around the world. ENDS deliver nicotine through an inhaled aerosol (typically along with propylene glycol and/or vegetable glycerin, and flavorants), without any tobacco leaf and with no combustion. The long-term effects of using ENDS cannot be known precisely, but there is considerable data to conclude that ENDS use would carry much less risk than cigarette smoking. The Royal College of Medicine (United Kingdom) concluded that ENDS are likely to be at least 95% less risky, and a study by the US National Academies of Science, Engineering and Mathematics also concluded that ENDS would be associated with less risk than smoking. Thus, smokers switching from smoking to ENDS would be expected to have significant benefit to those individuals as well as to public health of the overall population.[8,9] The use of ENDS has grown rapidly, making it important to have contemporary data on who uses ENDS, how their use affects cigarette smoking, and the net effect of such use on population health.

As part of the growth of the ENDS category, products have evolved and diversified. One of the most widely used ENDS in this US is the JUUL System (henceforth "JUUL"), a nicotine-salt, pod-based ENDS made by Juul Labs Inc (JLI). JUUL has been a subject of considerable scientific interest, both because of its widespread use among adults as well as concerns about use of JUUL among underage youth; over 150 papers have been published with "JUUL" in the title and/or abstract.

Here, we present a collection of papers reporting several behavioral studies, sponsored by JLI, of JUUL use among adults. The studies address an array of important research questions, such as: Who uses JUUL? What is the trajectory of JUUL use over time? and concomitantly, What happens to cigarette smoking among JUUL users? A final paper uses population modeling to integrate a diverse set of findings to project the impact on population health of the availability of ENDS such as JUUL.

Studies outside of this special issue have documented important features of JUUL, which bear on interpretation of the behavioral data presented here, and on their implication for public health. Two clinical studies showed that exposure to smoking-related toxicants drops steeply when smokers switch to JUUL, approaching the reductions seen for those abstaining from both smoking and JUUL use.[10,11] Two studies also have found that even the smokers who engage in dual use – continuing to smoke cigarettes while using JUUL – experience substantial reduction in exposures to smoking-related toxicants.[11,12] Pharmacokinetic studies find that the nicotine delivery profile of JUUL, as well as its reinforcement potential ("abuse liability")[13-15] have concluded that JUUL lies between cigarettes and nicotine gum on these measures.

Importantly, the harm reduction potential of ENDS for adult smokers cannot come at the cost of high levels of underage use, which is of substantial concern. Underage use of ENDS, including JUUL, continues to be unacceptably high. There are encouraging signs – data from the National Youth Tobacco Survey[16] document a significant decline in underage use of ENDS, including a ~70% decline in self-reported JUUL use as a primary brand, and Monitoring the Future data also show a steep decline in underage use of JUUL.[17] Nevertheless, more needs to be done to accelerate this trend. One of the papers in this special issue[18] describes an application of technologically-based solutions to restrict underage access to JUUL products and potentially, to all ENDS. Other forthcoming papers address issues in underage use of JUUL and other ENDS, and can form the basis for data-driven measures to reduce underage use.

The studies in this special issue focus on deepening our understanding of JUUL use by adults, with the aim of improving our knowledge of how use of JUUL impacts subsequent combustible cigarette smoking, considering both potentially favorable transitions – eg, when smokers switch away from smoking cigarettes – and potentially unfavorable ones – eg, when never-smokers use JUUL and subsequently smoke.

The papers in the special issue cover a range of questions. For example, Prakash et al[19] document the prevalence of ENDS use – and JUUL use specifically – among adults, with some focus on young adults, as this is an important population particularly likely to use ENDS.

Seven papers, the core of this collection, draw upon JLI's behavioral research program using data from the Adult JUUL System Users Switching & Smoking Trajectories (ADJUSST) study, which was carried out by the Centre for Substance Use Research (CSUR) with JLI sponsorship. A large sample (~55,000) of adults who had recently purchased a JUUL Starter Kit were enrolled in a study that aimed to assess their behavior over a 12-month period. (Data from a separate study of similar design have been published by Russell et al.)[20] The sample included individuals who were current, former, and never smokers at baseline. The primary outcome was past 30-day smoking, and JUUL use also was assessed. The study methods are described in the paper by Shiffman et al,[21] which also presents analyses relevant to evaluating survey non-response, finding minimal suggestion of bias in the outcomes.

Six other papers analyze ADJUSST data to document the trajectories of smoking and JUUL use in diverse populations, by smoking status and other variables. Goldenson et al[22] document high levels of "switching" – defined as no smoking at all in the previous 30 days – among those who entered the study as established smokers. Analyses in this paper also establish a link between subjective reinforcement from initial use of JUUL and later switching away from smoking, empirically validating the concept that a certain degree of reinforcement ("abuse liability") is necessary to facilitate switching.[23,24] Kim et al[25] consider how switching varies among smokers across populations of special interest, particularly by ethnicity and income, but also by mental health comorbidity, finding similar patterns across these diverse cohorts. Selya et al[26] examine the trajectory of dual use (continuing to smoke cigarettes while using JUUL) over time, and also document substantial reductions in cigarette consumption among dual users.

Le et al[27] examine smoking trajectories among former smokers, and Shiffman et al[28] examine these trajectories among baseline never-smokers. Both papers find that a small minority of these participants reported cigarette-smoking during the subsequent year, but that more frequent JUUL use is associated with lower likelihood of smoking.

Finally, Prakash et al[29] provide an overall perspective on the smoking trajectories of participants in the ADJUSST study by considering the 12-month smoking status across the full range of participants' baseline smoking status. They find that the prevalence of cigarette smoking decreased by more than half between baseline and 12 months follow-up.

Further providing perspective is the paper by Wissmann et al,[30] which uses population modeling to integrate data from ADJUSST and other sources (eg, PATH, NYTS) on both adults and youth, to project the expected impact on population health of the availability of ENDS such as JUUL. The modeling projects that 2.5 million premature deaths could be averted by the year 2100.

An additional paper, from a different study, examines dependence on JUUL. Shiffman et al[31] analyze how dependence changes as smokers transition from cigarette smoking to JUUL use, finding that dependence significantly decreases, comparably for those using a higher-concentration nicotine e-liquid (5.0% by weight) and for those using a lower-concentration (3.0%).

These studies address core questions for understanding JUUL use, and its impact on population health. These are also the questions of core interest to the US Food and Drug Administration's (FDA) Center for Tobacco Products (CTP). Congress granted the FDA the authority to regulate tobacco products, enabling CTP to authorize new tobacco products if they are deemed to be "appropriate for the protection of the public health." Thus, the public health concerns and regulatory agenda are aligned to support the availability of reduced-risk products that have a net positive effect on the health of the population as a whole.

CTP determines whether a product is appropriate for the protection of public health upon review of the product's Premarket Tobacco Product Application (PMTA). The studies presented in this special issue, along with the results from many additional studies, have been submitted to CTP as part of JLI's PMTA for JUUL products, which requests authorization to continue marketing the JUUL device and JUULpods in 2 flavors (Virginia Tobacco and Menthol) at the 5.0% and 3.0% nicotine concentrations. As part of the transparency built into the PMTA process, all data and statistical code are provided to CTP. As of this writing, JLI's PMTA is under scientific review by CTP.

We believe the findings presented here provide

crucial information in addressing many issues which have been raised regarding the effect of ENDS use, JUUL in particular, on combustible cigarettes use. As such, we believe these papers make a substantial contribution to the field of tobacco science and tobacco control.

Conflict of Interest Statement

Through PinneyAssociates, Saul Shiffman provides consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc. In that role, he acted as internal editor and coordinator for the papers in this special issue. (Within the last 2 years, PinneyAssociates has also consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction.) Erik Augustson is a full-time employee of Juul Labs Inc. As Senior Director of Behavioral Affairs at JLI, he oversaw the conduct of the behavioral research reported in this special issue.

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Prevalence of ENDS and JUUL Use, by Smoking Status, in National Samples of Young Adults and Older Adults in the U.S.

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Objectives: In this paper, we estimate the prevalence of electronic nicotine delivery systems (ENDS) and JUUL brand ENDS use among adults in the US, overall and by smoking history. **Methods:** We obtained 2019 cross-sectional online surveys assessing smoking, use of any ENDS, and JUUL specifically, in a national probability sample of 11,833 US adults. Data were analyzed for young adults (YA; aged 18-24) and older adults (OA; aged 25+). **Results:** Past 30-day ENDS prevalence was 8.0% in YA and 4.7% in OA; equivalent JUUL figures were 3.1% and 1.2%. ENDS/JUUL use was more prevalent among current and former smokers than never smokers, where prevalence was ≤ 2% (YA: 2.0%/0.9%; OA: 0.9%/0.1%). JUUL use was higher among recent (< 1 year) quitters than among long-term (≥ 1 year) quitters. Among those who had ever used both ENDS and other tobacco, strong majorities reported using other tobacco first. Among JUUL users who also had used other tobacco ≥ 95% had used other tobacco first. **Conclusions:** Past-30-day ENDS use (including JUUL) was ≤ 8% among young adults and ≤ 5% in older adults. Most (> 98%) ENDS and JUUL users were current or former smokers, which is relevant to assessment of the population impact of these products.

Key words: electronic nicotine delivery system; smoking; prevalence; JUUL; tobacco
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Electronic nicotine delivery systems (ENDS), commonly referred to as 'electronic cigarettes' or e-cigarettes, have grown in popularity in the past decade among adults as an alternative to smoking combustible tobacco cigarettes (henceforth: 'cigarettes').[1-6] ENDS were the most frequent method reported by adult smokers for quitting smoking in the United States (US) in 2014-15, used in 34.7% of respondents' most recent quit attempts.[7] Although the long-term health risks of ENDS are not fully understood,[8] available clinical and toxicological evidence suggests that they pose significantly less risk to adult smokers than combustible cigarettes.[9,10] Complete switching from smoking to ENDS use by smokers who are otherwise unlikely to stop smoking can benefit population health.[9,11-14]

The availability of newer ENDS products in the US also has been accompanied by increases in use of these products in more recent years by individuals underage for purchase of tobacco products.[15] Annual and biannual US government sponsored surveys report the prevalence of ENDS use among the underages,[15-17] sometimes broken down by product or brand.[18-21] There has been a particular interest in documenting the use of JUUL-brand ENDS,[20,21] in part, because JUUL was among the most-commonly reported ENDS brand in 2017;[22] over 150 published papers have focused on JUUL-brand ENDS (search conducted in PubMed for

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"JUUL" in title/abstract in January, 2021). Adult prevalence is less frequently reported with such granularity but is also of interest, especially when distinguishing users based on users' smoking and tobacco-use history. To assess the net population health impact of ENDS it is necessary to understand both the potential beneficial uses of ENDS products (ie, by adult current smokers who would have otherwise continued smoking, and adult former smokers who may use ENDS as a means to prevent resumption of smoking) as well as potentially harmful use (ie, by non-smokers or non-users of tobacco products who would not otherwise have used tobacco products).

Shifts in available ENDS products are likely to have implications for current adult prevalence of tobacco and nicotine product use. According to the National Health Interview Survey (NHIS), US adult ENDS use decreased from 3.7% to 2.8% in the 2014-2017 period,[23,24] prior to increase in use of newer ENDS products/brands such as JUUL. The most recent data, from 2019,[25] indicate that adult prevalence had increased to 4.5% overall, with notably higher prevalence of 9.3% among young adults 18-24. The proportion of users who are young adults was higher for ENDS than for any other tobacco product class.[26,27] Young adulthood is now the prime period for smoking initiation and progression.[28] This period is also the time when many individuals are newly making decisions absent parental supervision, and is associated with high levels of risk-taking.[26] All of this suggests the importance of studying ENDS use in this age cohort.

The prevalence of ENDS use is most common among current and former smokers. For example, the Truth Longitudinal Cohort study examined use of JUUL, reporting that in 2018-19, the majority of JUUL users aged 18+ had prior smoking history: the prevalence of past-30-day JUUL use was 10 times higher among current smokers than never smokers.[29] Other nationally-representative adult prevalence surveys also have consistently reported that most adult ENDS users (60%-80% across surveys) are current and former smokers, the majority of whom report using these products to stop smoking.[2,23,29-32] A Cochrane Review of randomized clinical trials of ENDS concluded that ENDS were effective for quitting smoking, in a smoking-cessation setting. Three naturalistic follow-ups of adults who purchased JUUL reported substantial rates of complete switching away from cigarettes, with rates of past-30-day non-smoking ranging from 28% to 41% 3 months after the purchase, and rising further at later time-points, suggesting the potential for ENDs such as JUUL to facilitate switching.[33-35]

To address prevalence of adult ENDS use, and its distribution by smoking status, this paper reports data from a 2019 survey assessing adult use of ENDS, including data specifically on the use of JUUL, and combustible cigarettes in national probability samples, analyzing the data specifically for young adults (18-24) and older adults (25+).

METHODS

Survey Procedure

This prevalence study consisted of 2 cross-sectional survey waves collected approximately 4 months apart: Wave 1 was fielded in April-May 2019, and Wave 2 in August-September 2019. A random sample of subjects was drawn for each wave from KnowledgePanel (Ipsos-Insight, LLC), the largest probability-based online research panel in the US, which is designed to be representative of the non-institutionalized US population aged 18 years and older,[36] and has been used in several recent studies assessing use of ENDS.[37-39] Adults are recruited to KnowledgePanel via residential address-based sampling or random digit dialing. The KnowledgePanel sampling frame covers 97% of US residential addresses; the panel currently has over 55,000 adult members. KnowledgePanel members average of 1-2 surveys per month,[36,40] although tobacco surveys are rare (eg, one in 2020). The sample included both young adults ("YA" 18-24) and older adults ("OA" 25+), and these were weighted and analyzed separately (International Tobacco Control Project, 2018).[41] Participants were invited to complete a 25-minute online survey after giving consent and confirming eligibility and were reimbursed USD20 for completion (standard for KnowledgePanel).

Members of the KnowledgePanel were eligible for this study if they were aged 18 years or older, lived in the US, and provided informed consent. The Advarra® Institutional Review Board (https://www.advarra.com/about-advarra/accreditation-and-compliance) approved the study.

In Wave 1 of the survey, 9766 invitations were

sent, 6155 panel members responded to the invitation and of those, 5660 completed the study, yielding a 63.0% completion rate. In Wave 2, 12,001 invitations were sent, 6414 panel members responded to the invitation and of those, 6223 completed the study, yielding a 53.4% completion rate. These completion rates are in line with the KnowledgePanel's typical completion rate of 60%. Wave 1 of the survey included 558 YA (aged 18-24 years) and 5102 OA (aged 25 years or older). Wave 2 included 584 YA and 5639 OA. Close to 1200 respondents in KnowledgePanel participated in both survey waves, as panel members were sampled with replacement (ie, a Wave 1 participant could be sampled again in Wave 2). As the present analyses pooled data from the 2 waves, to maximize sample size and maintain the independence of observations in the pooled sample, in cases where a participant answered both waves, only the Wave 1 responses were used. Additionally, across the total dataset, 16 cases (5 YA, 11 OA) were dropped because of a skip pattern anomaly that allowed these respondents to enter discordant responses indicating that they were unaware of ENDS or JUUL but then reporting current use of those products.

Survey Measures

Smoking and ENDS use. The primary measures of this study were self-reported ever and current cigarette smoking, use of ENDS of any brand, and use of JUUL. Status definitions followed those in other prevalence studies.[2] Ever smoking was assessed by the question: "Have you ever tried cigarette smoking, even one or 2 puffs?" (Yes/No). Participants who responded "Yes" were asked the number of days on which they had smoked in the past 30 days; those who had smoked in the past 30 days categorized as current smokers. Former smokers reported ever but not current (past 30-day) smoking, and never smokers were those who responded that they had never tried smoking. Former smokers were stratified by how long they had been abstinent, less than a year ("Recent Quitters") or one year or more ("Long-term Quitters"), consistent with other studies.[42,43] History and current use of other tobacco products were not assessed in Wave 1 but were assessed in Wave 2; Supplemental Tables S1-S4 summarizes data related to other tobacco use.

Questions about ENDS and JUUL use were asked only of those who indicated they were aware of ENDS or JUUL, respectively, to avoid exposing unaware individuals to these products. Those who were not aware were classified as never-users. The 2 waves differed in the details of how ENDS and JUUL use were assessed. In the first survey wave, ever use of a JUUL was assessed with the question: "Have you ever used a JUUL e-cigarette, even once or twice?" (Yes/No), among those indicating that they were aware of JUUL. Participants who responded "Yes" were asked the number of days on which they had used a JUUL in the past 30 days, with those responding that they had vaped one or more days in the past 30 categorized as current JUUL users. Former JUUL users were classified as those who reported ever but not current (past 30-day) JUUL use, and never users were those who responded that they had never used a JUUL or were unaware of JUUL. Other ENDS use was assessed similarly, but asking about "any type of e-cigarette other than JUUL e-cigarettes." Overall ENDS use prevalence was calculated by combining use of JUUL and use of ENDS other than JUUL.

In the second survey wave, ENDS and JUUL use groups were similarly defined, but the format of questions assessing ever and current ENDS and JUUL use changed slightly, such that respondents identified the brand of ENDS they had used (ever or past 30 days) by selecting them from a list that included JUUL (see methodological note in Supplement 2). This was not unlike the change in questionnaires between the 2013 and 2014 NYTS surveys.[44,45]

Following CDC's approach to analyzing the sequence of product initiation from a cross-sectional survey,[46] participants who indicated having used any of the assessed products (cigarettes, ENDS, JUUL) were asked the age at which they first used that product.[46,47] The order of first product use was determined from comparison of the reported ages of first use. Participants who reported the same age of first use for 2 products were asked to indicate which product they used first, and this was used to resolve the order, except in cases where participants indicated they could not recall or skipped this follow-up question; those are tabulated as "used at the same age." In the second wave only, participants were also asked these order-of-first-use questions

Table 1
Sociodemographic Characteristics of Young and Older Adults

Sociodemographic Characteristics	Young Adults (18-24) (N = 858)	Older Adults (25+) (N = 9422)
Age in years, Mean (SD)	21.10 (2.05)	51.05 (15.87)
Female Sex (vs Male)	49.9 (564)	51.8 (4926)
Race/Ethnicity		
Non-Hispanic White	53.9 (507)	64.8 (6807)
Non-Hispanic Black	13.8 (68)	11.6 (856)
Non-Hispanic Other Race	6.7 (43)	7.1 (392)
Hispanic Ethnicity	23.2 (213)	15.4 (1075)
Non-Hispanic Multiracial	2.4 (27)	1.2 (292)
Marital Status		
Married	6.3 (84)	62.0 (5965)
Divorced, Separated or Widowed	0.5 (6)	16.7 (1721)
Never Married	93.1 (768)	21.3 (1736)
Highest Level of Education Completed		
High School Graduate or Less Education	44.4 (275)	38.7 (2907)
Some College or Associate Degree	43.5 (375)	26.3 (2712)
Bachelor's Degree or More Education	12.2 (208)	35.0 (3803)
Annual Household Income		
Less than USD50,000	34.9 (450)	33.5 (2990)
USD50,000 - USD100,00	30.8 (271)	30.7 (3020)
Greater than USD100,000	34.4 (137)	35.8 (3412)
Census Region		
Northeast	16.7 (141)	17.9 (1687)
Midwest	21.4 (194)	20.7 (2143)
South	38.2 (307)	37.6 (3405)
West	23.7 (216)	23.8 (2187)

Note.
Values represent % (N) unless noted otherwise.
Pooled prevalence data across waves.
Percentages are population-weighted; Ns are unweighted.

for other tobacco products as well.

Demographics and weighting. Data on self-reported age, sex, race, and state of residence (grouped into 4 Census regions).[48] were used for post-survey weighting. To adjust for survey non-response and selection bias, a post-stratification weighting adjusted the final survey sample to match the US adult population based on sex, age and census region, per the US Census Bureau's Current Population Survey.[49]

Data Analysis

All analyses were conducted in parallel for YA (aged 18-24) and OA (aged 25+). Percentages of ever and current (past 30-day) prevalence of smoking, ENDS use and JUUL use were calculated from the survey responses. Descriptive analyses examined the proportion of current, former and never smokers who were current users of any ENDS and of JUUL, respectively, with former smokers stratified by recent versus long-term quitters; and con-

Table 2
Prevalence of Ever and Past-30-day Cigarette Smoking, Any Type of ENDS Use, and JUUL ENDS Use among Young (18-24) and Older (25+) Adults, US, 2019

	Young Adults (18-24) (N = 858)		Older Adults (25+) (N = 9422)	
Measure	**Weighted % (95% CI)**	**Unweighted N**	**Weighted % (95% CI)**	**Unweighted N**
Cigarette Smoking				
Ever smoked a cigarette	31.6 (27.6, 36.0)	309	71.1 (70.1, 72.1)	6813
Smoked a cigarette in past 30 days	8.4 (6.3, 11.2)	80	14.5 (13.7, 15.3)	1248
Any ENDS Use (JUUL or Other)				
Ever used any ENDS	28.7 (24.8, 32.9)	276	19.5 (18.6, 20.4)	1689
Used any ENDS (JUUL or other) in the past 30 days	8.0 (5.9, 10.7)	78	4.7 (4.3, 5.3)	394
JUUL Use				
Ever used JUUL	11.4 (8.9, 14.5)	115	4.1 (3.6, 4.6)	327
Used JUUL in past 30 days	3.1 (2.0, 4.7)	34	1.2 (1.0, 1.5)	99

Note.
CI = confidence interval
Pooled prevalence data across waves.
Percentages are population-weighted; Ns are unweighted.

versely, the proportion of current ENDS/JUUL users who were current, former or never smokers. Finally, among those who had indicated ever use of 2 products (cigarettes and JUUL, cigarettes and other ENDS, JUUL and other ENDS), we report percentages within subgroups by which product they used first. A parallel analysis for all non-ENDS tobacco products (ie, not just cigarettes), in Wave 2 only, is reported in supplemental material.

All sample sizes presented in tables are unweighted, and all percentages are survey weighted. Two-sided 95% confidence intervals were based on the binomial or multinomial distributions, as appropriate.[50] All analyses were conducted in R v. 4.0.2.

RESULTS

Table 1 shows the demographic profile of the samples. The samples were predominantly white, but with substantial representation of Black and Hispanic participants. As would be expected, the YA sample was younger, and also more likely to never have been married and to have achieved less educational attainment. A greater proportion of the YA sample was classified as Hispanic, reflecting the fact that the average age of Hispanic adults is lower.[49]

As shown in Table 2, current past-30-day prevalence of any ENDS use was 8.0% in YA and 4.7% in OA. Young adults also had higher ever use (28.7%) than OA did (19.5%). A similar pattern was observed for use of JUUL specifically, which was also higher among YA (11.4% ever use, 3.1% current use) than among OA (4.1% ever use, 1.2% current use). The highest prevalence in both age cohorts was for cigarette smoking, both ever smoking (YA: 31.6%, OA: 71.1%) and current smoking (YA: 8.4%, OA: 14.5%). As shown in Supplemental Table S1, the prevalence of all tobacco use was higher among OA than YA.

Table 3 presents prevalence of current ENDS use among current, former and never smokers in YA and OA. Prevalence of ENDS use was high-

Table 3
Prevalence of Current (Past-30-day) Use of Any ENDS (JUUL or other) and JUUL Products among Adults by Age Cohort and Smoking Status, US, 2019

	Young Adults (18-24) (N = 858)				Older Adults (25+) (N = 9422)			
Smoking Group	% Reporting Past 30-day Any ENDS Use (JUUL or Other) (95% CI)	n/N	% Reporting Past 30-day JUUL Use (95% CI)	n/N	% Reporting Past 30-day Any ENDS Use (JUUL or Other) (95% CI)	n/N	% Reporting Past 30-day JUUL Use (95% CI)	n/N
Current Smokers[a]	30.1 (21.0, 40.8)	29/80	18.6 (10.5, 28.6)	16/80	16.3 (13.4, 19.2)	190/1248	5.2 (3.4, 7.0)	58/1248
Former Smokers[b]	17.2 (11.0, 23.7)	37/228	3.9 (0.0, 9.4)	12/228	4.0 (3.0, 5.1)	195/5549	0.8 (0.4, 1.3)	39/5549
Recent Quitters (< 1 year)	19.0 (7.4, 33.8)	10/54	5.2 (0.0, 18.9)	3/54	18.5 (12.0, 25.1)	45/245	7.0 (2.4, 11.8)	16/245
Long-Term Quitters (1+ year)	16.7 (9.6, 24.1)	27/174	3.5 (0.0, 9.2)	9/174	3.3 (2.3, 4.3)	150/5304	0.5 (0.1, 0.9)	23/5304
Never Smokers[c]	2.0 (0.03, 4.2)	11/549	0.9 (0.0, 2.2)	6/549	0.4 (0.0, 0.9)	8/2593	0.1 (0.0, 0.3)	2/2593

Note.
CI = confidence interval
Pooled prevalence data across waves.
Percentages are population-weighted; Ns are unweighted.
[a] Reported smoking at all in the past 30 days.
[b] Reported having smoked at all in the past, but not in the past 30 days; Recent versus Long-term Quitters designated by whether quitting occurred within the past year or over one year ago.
[c] Reported never having smoked at all; history of other tobacco use is not known

est among current smokers (30.1% of YA smokers; 16.3% of OA smokers), and lowest among never smokers (2.0% of YA never smokers; 0.4% of OA never smokers). Supplemental Table S2 shows parallel figures when all tobacco use is considered; the prevalence of ENDS use was ≤ 1% among never-users of tobacco (other than ENDS). Among former smokers, those who had been quit for a year or more had lower ENDS prevalence, with especially large age-cohort differences among those who had been quit for a year or more (YA 16.7%; OA 3.3%).

Table 3 also presents parallel figures for current JUUL use among current, former and never smokers in YA and OA. Prevalence of JUUL use was highest among current smokers (18.6% of YA; 5.2% of OA), and lowest among never smokers (0.9% of YA; 0.1% of OA). The prevalence of JUUL use was < 0.5% among never-users of tobacco (Supplemental Table S3). The figures for former smokers, by time since quitting, also parallel the figures for the overall ENDS category, although the sample sizes were smaller, leading to wider confidence intervals.

Table 4 presents the reported order of first use among those indicating ever use of 2 products (cigarettes and any ENDS, cigarettes and JUUL, other ENDS and JUUL). The vast majority of adults who had ever smoked a cigarette and also used ENDS indicate smoking cigarettes first (88.1% of YA, and 99.0% of OA). A minority of respondents in both age cohorts reported using ENDS first (11.3% of YA and 0.9% of OA). Figures were similar for use of JUUL: 92.5% of YA and 98.3% of OA who used JUUL and smoked had smoked first. As shown in Supplemental Table S4, which considers all tobacco products, among the YA, 13.9% of those who smoked and used ENDS used ENDS

Table 4
First Product Tried among Younger and Older Adults Who Had Ever Used Combustible Cigarettes and Any ENDS or JUUL ENDS, US, 2019

Measure	Younger Adults (18-24)				Older Adults (25+)			
Product Used First	**% (95% CI)**	**n/N**	**Non-missing % (95% CI)**	**Valid n/N**	**% (95% CI)**	**n/N**	**Non-missing % (95% CI)**	**Valid n/N**
Ever Smoked Cigarettes and Used Any ENDS (JUUL or Other)	**(N = 208)**				**(N = 1640)**			
Smoked Cigarette First	87.1 (83.4, 91.4)	175/208	88.1 (84.4, 92.2)	175/206	98.0 (97.4, 98.6)	1613/1640	99.0 (98.6, 99.5)	1613/1627
Used Any ENDS (JUUL or other) First	11.1 (7.5, 15.5)	29/208	11.3 (7.6, 15.4)	29/206	0.9 (0.3, 1.5)	12/1640	0.9 (0.5, 1.3)	12/1627
Used at the Same Age	0.6 (0.0, 5.0)	2/208	0.7 (0.0, 4.8)	2/206	0.1 (0.0, 0.7)	2/1640	0.1 (0.0, 0.6)	2/1627
Undetermined/Missing[a]	1.2 (0.0, 5.5)	2/208	—	—	1.0 (0.4, 1.6)	13/1640	—	—
Ever Smoked Cigarettes and Used JUUL	**(N = 93)**				**(N = 319)**			
Product Used First:	% (95% CI)	n/N	Valid % (95% CI)	Valid n/N	% (95% CI)	n/N	Valid % (95% CI)	Valid n/N
Smoked Cigarette First	88.2 (83.2, 94.6)	84/93	92.4 (88.2, 97.7)	84/91	95.0 (93.1, 97.2)	307/319	98.3 (97.2, 99.6)	307/311
Used JUUL First	7.3 (2.3, 13.7)	7/93	7.6 (3.5, 13.0)	4/91	1.2 (0.0, 3.3)	3/319	1.2 (0.1, 2.5)	3/311
Used at the Same Age	0.0 (0.0, 0.0)	0/93	0.0 (0.0, 0.0)	0/91	0.5 (0.0, 2.6)	1/319	0.5 (0.0, 1.8)	1/311
Undetermined/Missing[a]	4.5 (0.0, 10.9)	2/93	—	—	3.3 (1.4, 5.5)	8/319	—	—
Ever Used JUUL and Ever Used Other (non-JUUL) ENDS	**(N = 115)**				**(N = 327)**			
Product First Used:	% (95% CI)	n/N	Valid % (95% CI)	Valid n/N	% (95% CI)	n/N	Valid % (95% CI)	Valid n/N
Used JUUL First	32.4 (24.2, 42.0)	32/115	35.1 (26.2, 44.9)	32/107	22.0 (17.2, 27.1)	74/327	23.9 (18.9, 28.9)	74/304
Used Other (non-JUUL) ENDS First	45.4 (37.2, 55.0)	59/115	49.2 (40.3, 59.0)	59/107	61.9 (57.0, 66.9)	205/327	67.1 (62.1, 72.1)	205/304
Used at the Same Age	14.5 (6.2, 24.1)	16/115	15.7 (6.8, 25.4)	16/107	8.3 (3.4, 13.4)	25/327	9.0 (4.0, 14.0)	25/304
Undetermined/Missing[a]	7.7 (0.0, 17.3)	8/115	—	—	7.8 (2.9, 12.8)	23/327	—	—

Note.
CI = confidence interval.
Pooled prevalence data across waves.
Percentages are population-weighted; Ns are unweighted.
Percentages may not sum to 100 due to rounding.
[a] Undetermined/Missing indicates that age of first use of one or both products, or response on whether ENDS/JUUL or cigarettes were used first, was not provided.

Table 5
Prevalence of Adult ENDS Use by Data Source among Nationally Representative Samples, 2018-19

	Ages	Survey Administration	Time Period	Current ENDS Use	
				Young Adult	Older Adult
National Health Interview Survey (NHIS) – 2018[30]	18+	In-person interview	Jan–Dec 2018	18–24: 7.6%[a]	25–44: 4.3%[a] 45–64: 2.1%[a] 65+: 0.8%[a]
– 2019[30]			Jan–Dec 2019	18–24: 9.3%[a]	25–44: 6.4%[a] 45–64: 3.0%[a] 65+: 0.8%[a]
Behavioral Risk Factor Surveillance System (BRFSS) – 2018[51]	18+	Phone-based survey	Jan–Dec 2018	18–24: 7.5%[a]	25+: 2.3%[a]
US Census Population Survey Tobacco Use Supplement (TUS-CPS) 2018-19[2]	18+	Phone and In-person	Jul 2018 Jan 2019 May 2019	18–24: 4.7%[b]	25+: 2.3%[b]
Truth Longitudinal Cohort (TLC) 2019[29]	18–34	Online	Feb - May 2019	18–20: 21.8%[b] 21–24: 16.7%[b]	25–34: 8.6%[b]
This Study – 2019	18+	Online	Apr 2019 Sept 2019	18–24: 8.0%[b]	25+: 4.7%[b]

Note.
[a] **Current ENDS use defined as "currently using e-cigarettes every day or some days."**
[b] **Current ENDS use defined as any use in the past 30 days.**

first; for JUUL use this was 5.0%. Among OA, less than 2% had used ENDS or JUUL first. Finally, among those who had ever used both JUUL and other ENDS, Table 4 shows that in both age cohorts the majority of those in whom order could be determined (58.4% of YA, 73.8% of OA) reported having started using ENDS with other non-JUUL ENDS.

DISCUSSION

To measure the prevalence of smoking, ENDS use, and JUUL use in the adult population, 2 waves of a survey in representative samples of US adults were conducted in 2019, with analyses addressing the behavior of both young adults (aged 18-24) and older adults (aged 25 and over). Prevalence of current, past-30-day ENDS use was higher among young adults (8.0%) than among older adults (4.7%). Likewise, prevalence of current JUUL use was higher among young adults (3.1%) as compared to older adults (1.2%).

The prevalence estimates from this survey are in line with those from other nationally representative US surveys, and particularly consistent with those from NHIS, as Table 5 shows. Estimates of ENDS use in the 2018-19 period among adults over 18 vary between 2.3% and 9.3% across age groups. Estimates vary across surveys such as NHIS,[30] BRFSS,[51] the TLC[29] and CPS-TUS;[2] this may be related to survey methodologies (eg, phone vs online surveys) and the definitions of current use of ENDS (some surveys measure current use by past-30-day use, others by use every day or some days).

Most surveys of adults also have demonstrated modest (and often non-significant) increases in overall adult ENDS-use prevalence in the past few years, but relatively larger and significant increases among adults below age 30.[52,53] The younger adults are also the group for whom smoking prevalence has declined most significantly in the same time period.[54] Time-series trend analyses of the CPS-TUS also demonstrate that the increase in reported ENDS use among adult smokers was associated with a statistically significant increase in the smok-

ing cessation rate at the population level over time.[55] Overall, these patterns suggest that adults may be using ENDS products as an alternative to cigarette smoking.

ENDS use, including JUUL use, was concentrated in those with a smoking and tobacco-use history. Use of ENDS was most prevalent among current smokers and former smokers. In both age cohorts, prevalence of current JUUL product use was highest among those who were current smokers, and between 15-50 times lower (among young adults and older adults, respectively) in those who have never smoked.

The finding that ENDS and JUUL use is most prevalent among current smokers is consistent with other prevalence surveys of ENDS use in the US adult population. NHIS[30] and BRFSS[1,31,51,56] also report that the vast majority of ENDS use was in current and former smokers. In NHIS, the adult prevalence of current ENDS use was more than 8 times higher among current smokers than among never-smokers.[30] Similar results were reported for both ENDS use and JUUL use in the TLC, a longitudinal survey of respondents aged 15-34.[29]

Use of ENDS by former smokers was intermediate, at about one-fifth the prevalence seen in current smokers. Use of ENDS and JUUL among former smokers may be driven, in part, by their vulnerability to smoking relapse. Recent former smokers often struggle to refrain from smoking, with relapse rates being high in the first year after quitting, and continuing risk thereafter.[57,58] Consistent with this, use of ENDS in general, and JUUL specifically, was much more prevalent among past-year quitters than among longer-term quitters. Similar findings were reported in NHIS.[30,59] Le et al[60] report that some former smokers (up to 20% of past-year quitters, up to 10% of longer-duration quitters) report some past-30-day smoking at particular follow-ups over the year after purchasing a JUUL Start Kit, but the likelihood of smoking was reduced when JUUL was used more frequently.

ENDS or JUUL use by adult never smokers was uncommon; overall, our findings suggest that < 1% of the adult never smokers are currently using JUUL or other ENDS. The prevalence was also low among the Wave 2 respondents who reported never having used any tobacco product. This survey does not address why never-smoking or never-tobacco-using adults were using ENDS or JUUL. As Shiffman et al[34] describe, many never smokers who purchase JUUL have previous history with ENDS use; this also aligns with the present findings on order of initiation, as the majority of adults who had ever used JUUL and other ENDS reported use of other ENDS first. In any case, use by never-smoking or never-tobacco-using individuals can lead to addiction and health risks. However, some evidence suggests that use of ENDS may divert individuals who would otherwise have smoked from taking up smoking,[61] in which case, their health risks would be lower than if they had gone on to smoke.

For those who have both used JUUL (or ENDS) and smoked cigarettes (or used other tobacco), the sequence in which the 2 products were first used is relevant to considering whether there is any possible causal relationship between the 2, as the cause must come before the effect. Like Kowitt, et al[62] we examined the sequence of product initiation, and found that the overwhelming majority of young adults who used ENDS (in general, and JUUL specifically) and who also smoked cigarettes or used other tobacco products, reported having initiated smoking/tobacco use before using JUUL or any ENDS. Not inconsistent with this, longitudinal studies have found that some individuals who initiate ENDS use subsequently smoke and are more likely to do so than non-ENDS-users. The challenge of such data has been establishing whether that linkage is causal, or reflects non-causal dynamics, such as shared predispositions to use ENDs and to smoke.[63-68] The findings on the sequence in older adults are less informative, as many would have initiated tobacco use at a time when ENDS did not yet exist.

A major strength of this cross-sectional survey is that it was nationally representative, with random selection from the largest probability-based online panel in the US, which also has been used in other surveys aiming for representativeness.[37-39] It also provided data on the use of JUUL, a commonly used brand of ENDS, which has received considerable attention in the literature on youth,[20,21] but for which limited data on adult prevalence have been available. The survey also provided data on the sequence of initiation of ENDS and JUUL in relation to cigarettes and other tobacco products, which is relevant to hypotheses about whether

ENDS use may cause individuals to smoke (ie, "gateway").[69]

Several limitations of this study should be acknowledged. First, these 2 cross-sectional surveys, conducted close in time to each other, provide a point estimate of prevalence, and do not address trends over time. As with any observational study, causal relationships cannot be inferred from these data. Second, the potential for misclassification of JUUL exists; authors have pointed out that users may have difficulty identifying the ENDS they are using,[70] and some surveys use photos of devices[71] to help respondents accurately identify the one they use. Finally, limited sample sizes in the survey limit the precision of our estimates, particularly among the young adults, and particularly in subsets with low prevalence, such as young adult former smokers. We combined 2 waves of data collection to maximize the sample size, and thus, the precision of estimates. This required pooling estimates based on slightly different methods of wording questions about product use. The combined estimates may balance whatever biases are inherent in each method of asking these questions. The first wave of the survey did not assess respondents' history of using tobacco products other than cigarettes and ENDS, reducing the sample on which these parameters could be assessed.

Conclusion

In this nationally representative cross-sectional survey of US adults, we found that past-30-day use of ENDS was higher among young adults than among adults 25 and older. This was also true for JUUL. ENDS and JUUL use was highest among current smokers. Among former smokers, it was higher among those who had stopped smoking within the past year, and thus, were particularly vulnerable to smoking relapse. Among those who had ever used JUUL or any ENDS and had also smoked, most (> 85%) participants had smoked prior to using ENDS or JUUL. Assessing prevalence of use of specific ENDS products among adults can help lay a foundation for understanding the public health impact of these products.

Human Subjects Approval Statement

This study was approved by the Advarra® Institutional Review Board.

Conflict of Interest Disclosure Statement

SP and CH were full-time employees of Juul Labs Inc during the time that this work was conducted. Through PinneyAssociates Inc, SS provides consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc. Within the last 2 years, PinneyAssociates Inc has consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction.

Author CH performed the statistical analyses in consultation with the other authors. All of the authors contributed to the conceptualization and to writing and review of the paper, and all had access to the data. Juul Labs Inc approved the research plan and provided comment on a near-final draft of the paper.

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SUPPLEMENT 1

Table S1
Prevalence of Ever and Past 30-day Use of Any Tobacco Product[a] among Young (18-24) and Older (25+) Adults (Wave 2), US, 2019

	Young Adults (18-24) Wave 2 (N = 584)		Older Adults (25+) Wave 2 (N = 5639)	
Measure	**Weighted % (95% CI)**	**Unweighted N**	**Weighted % (95% CI)**	**Unweighted N**
Ever Use of Any Tobacco Products[a]	37.8% (33.0, 42.8)	251	74.6% (73.3, 75.8)	4271
Used Any Tobacco Product[a] in the Past 30 Days	13.0% (10.2, 16.4)	86	19.4% (18.2, 20.5)	1012

Note.
CI = confidence interval. Percentages are population-weighted; Ns are unweighted
[a] Tobacco product use includes: cigarettes, cigars, chewing tobacco/snuff/dip, hookah, roll-your-own cigarettes, pipes filled with tobacco (not waterpipe), snus, dissolvable tobacco products, and bidis (small brown cigarettes wrapped in a leaf).

Table S2
Prevalence of Current (Past 30-day) Use of Any ENDS among Adults by Tobacco Product History, by Age Cohort (Wave 2), US, 2019

	Young Adults (18-24) Wave 2 (N = 584)		Older Adults (25+) Wave 2 (N = 5639)	
Tobacco Use Group	**% Reporting Past 30-Day ENDS Use (95% CI)**	**n/N**	**% Reporting Past 30-Day ENDS Use (95% CI)**	**n/N**
Currently Use Tobacco Products[a]	29.6% (17.1, 42.0)	27/86	13.3% (11.1, 15.6)	124/1012
Formerly Used Tobacco Products[b]	17.5% (10.0, 25.0)	24/165	3.5% (2.8, 4.2)	99/3253
Never Used Tobacco Products[c]	1.0% (0.0, 2.4)	4/327	0.2% (0.0, 0.5)	2/1351

Note.
CI = confidence interval. Percentages are population-weighted; Ns are unweighted.
[a] Reported smoking or used other tobacco products (except for JUUL and any ENDS) at all in the past 30 days.
[b] Reported having smoked or used other tobacco products (except for JUUL and any ENDS) at all in the past, but not in the past 30 days.
[c] Reported never having smoked or used other tobacco products (except for JUUL and any ENDS) at all.

Table S3
Prevalence of Current (Past 30-day) Use of JUUL Products among Adults by Tobacco Product History, by Age Cohort (Wave 2), US, 2019

	Young Adults (18-24) Wave 2 (N = 584)		Older Adults (25+) Wave 2 (N = 5639)	
Tobacco Use Group	**% Reporting Past 30-day JUUL Use (95% CI)**	**n/N**	**% Reporting Past 30-day JUUL Use (95% CI)**	**n/N**
Currently Use Tobacco Products[a]	19.2% (8.4, 29.0)	16/86	4.9% (3.4, 6.3)	45/1012
Formerly Used Tobacco Products[b]	7.4% (2.2, 12.5)	9/165	0.8% (0.4, 1.1)	21/3253
Never Used Tobacco Products[c]	0.4% (0.0, 1.2)	2/327	0.0% (0.0, 0.0)	0/1351

Note.
CI = confidence interval. Percentages are population-weighted; Ns are unweighted.
[a] Reported smoking or using other tobacco products (except for JUUL and any ENDS) at all in the past 30 days.
[b] Reported having smoked or used other tobacco products (except for JUUL and any ENDS) at all in the past, but not in the past 30 days.
[c] Reported never having smoked or used other tobacco products (except for JUUL and any ENDS) at all.

Table S4
First Product Tried among Younger and Older Adults Who Had Ever Used Any Tobacco Product and Any ENDS or JUUL ENDS (Wave 2), US, 2019

Measure	Younger Adults (18-24)				Older Adults (25+)			
Product Used First	**% (95% CI)**	**n/N**	**Valid % (95% CI)**	**Valid n/N**	**% (95% CI)**	**n/N**	**Valid % (95% CI)**	**Valid n/N**
Ever Used Any Tobacco Product and Used Any ENDS	**(N = 151)**				**(N = 980)**			
Used Other Tobacco Product First	43.9% (35.3, 53.5)	65/151	74.1% (64.9, 83.5)	65/90	98.8% (98.4, 99.5)	970/980	99.2% (98.8, 99.7)	970/977
Used Any ENDS	8.2% (0.0, 17.8)	17/151	13.9% (4.7, 23.3)	17/90	0.5% (0.1, 1.2)	5/980	0.5% (0.1, 1.1)	5/977
Used at the Same Age	7.1% (0.0, 16.6)	8/151	12.0% (2.8, 21.4)	8/90	0.3% (0.0, 0.9)	2/980	0.3% (0.0, 0.9)	2/977
Undetermined/ Missing[a]	56.1% (47.5, 65.0)	61/151	—	—	0.4% (0.0, 1.0)	3/980	—	—
Ever Used Any Tobacco Product and Used JUUL	**(N = 74)**				**(N = 250)**			
Used Other Tobacco Product First	64.5% (53.6, 76.9)	51/74	95.0% (90.4, 100.0)	51/53	96.3% (94.6, 98.5)	242/250	98.9% (98.1, 100.0)	242/244
Used JUUL First	3.4% (0.0, 15.7)	2/74	5.0% (0.3, 10.8)	2/53	1.1% (0.0, 3.3)	2/250	1.1% (0.4, 2.6)	2/244
Used at the Same Age	0.0% (0.0, 0.0)	0/74	0.0% (0.0, 0.0)	0/53	0.0% (0.0, 0.0)	0/250	0.0% (0.0, 0.0)	0/244
Undetermined/ Missing[a]	32.1% (21.1, 44.4)	21/74	—	—	2.6 (0.8, 4.7)	6/250	—	—

Note.
CI = confidence interval.
Percentages are population-weighted; Ns are unweighted.
Valid percentages exclude missing from the denominator; percentages may not sum to 100 due to rounding.
[a] Undetermined/Missing indicates that age of first use of one or both products, or response on whether ENDS/JUUL or tobacco products were used first, was not provided. A large number of younger adult participants did not respond to the following survey item used to calculate the order in which a given tobacco product was used: "How old were you when you first tried using [particular product], even once or twice?" To account for known status the valid % shows the responses of individuals whose order of first use could be ascertained.

SUPPLEMENT 2

Survey Measures Assessing ENDS and Juul Use across Survey Waves

We note that in the first survey wave, JUUL use was assessed based on a binary (Yes/No) response to the question: "Have you ever used a JUUL e-cigarette, even once or twice?" Similarly, ENDS use was assessed with a Yes/No response to the question: "Have you ever used any type of e-cigarette other than JUUL e-cigarettes, even once or twice?" Current (past 30-day) use was then assessed among those indicating ever use of JUUL or non-JUUL ENDS.

In the second survey wave, the format of questions was modified such that Ever Use of JUUL and non-JUUL ENDS was assessed based on the question: "Have you ever used any of the brands of e-cigarettes listed below, even once?" with a set of response options encompassing available US brands, including JUUL. Current JUUL and ENDS use was assessed based on the question: "Have you used any of these brands of e-cigarettes at all in the past 30 days?" with a similar set of response options encompassing available US brands including JUUL. The order of response options was randomized for respondents in the survey.

Previous analyses of the impact of format method effects for questions assessing tobacco product use by Delnevo et al[1] found that endorsement of ENDS use is almost doubled when the question is asked as a single Y/N response, compared to selecting an item from a list. Our analyses of prevalence separately by survey wave do not show a difference of this magnitude, and in fact, for one measure (current JUUL use), we see a movement in the opposite direction when the multiple response option question was used as compared to the binary response (see Supplement Table S5). There are likely potential issues of response bias or misclassification associated with use of either question format; however, the impact across waves in our survey does not seem to be drastic. As such, we report ever and current JUUL and ENDS use measures from the pooled data set in the main findings, along with confidence intervals. The true prevalence estimate likely lies somewhere within this range.

Supplementary Reference

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Table S5
Prevalence of Adult ENDS Use among Young (18-24) and Older (25+) Adults by Survey Wave, US, 2019

Measure	Younger Adults (18-24)				Older Adults (25+)			
	Wave 1 (N = 553)		Wave 2 (N = 305)		Wave 1 (N = 5094)		Wave 2 (N = 4328)	
	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N
Ever ENDS Use	29.8% (24.7, 35.5)	175	26.7% (21.2, 33.1)	101	21.1% (19.8, 22.3)	989	17.7% (16.4, 19.0)	700
Current ENDS Use	7.3% (4.7, 11.1)	41	9.2% (6.3, 13.3)	37	5.4% (4.8, 6.2)	247	3.9% (3.3, 4.7)	147
Ever JUUL Use	10.4% (7.3, 14.6)	66	13.1% (9.2, 18.3)	49	3.6% (3.0, 4.3)	152	4.6% (3.9, 5.4)	175
Current JUUL Use	2.5% (1.4, 4.5)	19	4.1% (2.2, 7.6)	15	1.2% (0.9, 1.7)	52	1.3% (0.9, 1.7)	47

Note.
Pooled prevalence data across waves.
Percentages are population-weighted; Ns are unweighted.
Wave 2 data excludes repeat surveys from Wave 1 participants.

The Adult JUUL Switching and Smoking Trajectories (ADJUSST) Study: Methods and Analysis of Loss-to-Follow-up

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Objectives: The Adult JUUL System User Switching and Smoking Trajectories (ADJUSST) study assessed the smoking and JUUL use trajectories of adults who purchased JUUL. In this paper, we describe study methods, characterize the sample, and assesses potential for bias due to loss to follow-up. **Methods:** We entered 55,414 US adults (≥ age 21) who purchased a JUUL Starter Kit for the first time (online or at retail) in 2018 into a naturalistic, longitudinal observational study, irrespective of baseline smoking status. Participants were invited for follow-ups 1, 2, 3, 6, 9, and 12 months later, focused on assessing past-30-day smoking and JUUL use. Analyses assessed potential bias due to non-response. **Results:** Over 90% of participants had a history of smoking; 62.8% were past-30-day smokers; 23.3% were former smokers. Participants' average age was 30; 75% were white. Most participants (77.6%) completed some follow-ups; 25% completed all follow-ups. Baseline differences among complete responders (N = 13,729), partial responders (N = 29,252), and complete non-responders (N = 12,433) were small. When recontacted, few 12-month non-responders said their non-response was due to smoking; many reported no past-30-day smoking. **Conclusions:** The study may elucidate smoking trajectories of adult JUUL users. The potential for bias due to loss to follow-up in ADJUSST was limited.

Key words: electronic nicotine delivery systems; JUUL; smoking; longitudinal study; loss-to-follow-up
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Cigarette smoking is the greatest cause of preventable death and disease in the Western world,[1] making stopping smoking an urgent public health priority. Russell[2] observed that people smoke for the nicotine but die from the tar, ie, nicotine helps maintain the behavior, but the harms associated with smoking are due largely to the products of combustion that smokers inhale. This insight has been noted by regulatory bodies and health experts,[1,3,4] leading to the idea that helping smokers to switch away from smoking to a product that delivers nicotine without smoke would reduce harm, even if it maintained nicotine use, which itself carries risk.[5]

The use of nicotine for tobacco harm reduction was advocated decades ago,[2,6] but the development

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of e-cigarettes, or electronic nicotine delivery systems (ENDS), has been thought to embody this potential.[3,7,8] Several randomized clinical smoking-cessation trials[9,10] and an observational follow-up of adult smokers initiating use of JUUL, a widely-used ENDS brand,[11] have concluded that using ENDS can help smokers switch away from smoking. However, ENDS also have attracted concern, particularly due to use by youth[12,13] and non-smokers.[14,15] Although smokers reduce their exposure to smoking-related toxicants when they switch from smoking to ENDS,[8] non-smokers or former smokers who take up ENDS take on new or renewed exposure to nicotine; it has been speculated that this also may increase the chances of progressing to smoking.[14,16,17] Accordingly, it is important to understand the trajectory of smoking behavior following adoption of ENDS, not only by smokers, but also by former and never-smokers.

A variety of methods have contributed to our understanding of ENDS use, including qualitative studies,[18] case studies,[19] cross-sectional surveys,[20,21] and randomized controlled clinical trials.[9,22] Longitudinal observational studies following ENDS users over time to examine changes in tobacco-use behavior over time can provide a unique perspective. Several such studies have been published,[23-25] typically assessing ENDS users' tobacco-use status a year after baseline assessment.

The Adult JUUL System Users Switching and Smoking Trajectories (ADJUSST) study described in this paper was a longitudinal observational in-market surveillance study, designed and carried out by researchers at the Centre for Substance Use Research (Glasgow, Scotland) to examine the trajectory of tobacco use over several timepoints in the year following the purchase of a JUUL Starter Kit (JSK) among adults with varying smoking histories. JUUL products are a pod-based ENDS brand using nicotine-salt e-liquids. JUUL is the single most commonly used brand of ENDS in the United States (US),[26] making it of particular interest. ADJUSST was not an interventional study but a naturalistic observational study; participants were not selected to have any particular behavioral goal (such as stopping smoking) nor told to aim for any particular outcomes. Participants were not provided with any product or instruction, or behavioral support, but just observed over time through survey responses.

This paper has 3 objectives: (1) to describe the overall methods of ADJUSST, and subsequent papers in this issue analyze the smoking trajectories of established smokers,[27,28] former established smokers,[29] and never-smokers;[30] (2) to describe the characteristics of JSK purchasers, including their smoking status and history; and (3) to address the issue of potential bias due to loss to follow-up in ADJUSST. Loss to follow-up is a challenge in all longitudinal studies.[31-33] It is not inherently problematic; the concern is that if non-responders differ from responders, it could bias the estimates of outcomes. An extreme example of this is the assumption in smoking-cessation treatment trials that all non-respondents are smoking,[34,35] an assumption supported by a study that re-contacted cessation-trial non-responders, and found that 100% had resumed smoking.[36] Analyses of non-respondents in ADJUSST address the potential for bias in 2 ways: (1) by comparing demographic and smoking characteristics of those with varying rates of responding; and (2) by analyzing reports from initial non-responders who were subsequently recontacted.

METHODS

Participants

We invited individuals who purchased a JUUL Starter Kit (JSK), which sold for USD40-USD50 and contained a JUUL device, a USB charging dock, and 4 JUULpods (Virginia Tobacco, Mint, Mango and Creme flavors, all 5.0% nicotine concentration), either in a retail store or through the manufacturer's website, between June and October 2018, to participate in "a survey about vaping, smoking, and JUUL products" for USD30 compensation. Online purchasers were emailed invitations within 1-2 days after the scheduled delivery of the JSK. Retail purchasers were invited to participate via cards in the package of approximately 500,000 JSKs distributed to retailers throughout the US. (These were used to recruit for other studies besides ADJUSST). The invitation cards contained a Web address and a unique code that was valid for one entry.

Eligibility criteria were: (1) age ≥ 21 years (the minimum purchase age at the ecommerce website and in many jurisdictions); (2) US permanent resident; (3) purchased a JSK for the first time within

the past 7 days, and (4) neither they nor family were employed by Juul Labs Inc or PAX Labs Inc. Participants whose survey entries had a duplicate IP address, duplicate contact email addresses, or a non-US IP address were excluded.

Procedure

Participants completed an informed consent form for "an online survey of your views and experiences of smoking cigarettes and using JUUL vapor products" whose purpose was "to better understand the types of people who buy the JUUL Starter Kit, their reasons for using a JUUL, and what impact, if any, using a JUUL has on cigarette smoking." All surveys were completed online in English. The surveys included branching logic programmed by investigators that routed participants to relevant questions based on their prior responses. Participants answered survey questions at their own pace. Participants who completed the baseline survey received email invitations for follow-up surveys approximately 1, 2, 3, 6, 9, and 12 months after completing the baseline assessment. The invitations noted: "You are eligible to take this survey whether or not you still use a JUUL, and whether or not you still smoke cigarettes," and reminded participants of the USD30 compensation and the confidentiality of their information. Participants received 2 reminders to complete each survey, and access to the survey expired 10 days after the initial invitation. Participants were eligible for the next survey even if they did not complete the previous one. The median time to complete was 18 minutes (IQR = 11) for the baseline survey and 10 minutes (IQR = 8) for follow-ups. Participants were compensated with a USD30 virtual Visa Reward Card for each survey (baseline or follow-up).

There were no constraints on participants' subsequent purchases or use of JUUL; they could purchase or not, and use or not, at their own discretion, and could move freely between purchase channels (ie, online enrollees could purchase at retail and vice versa).

Measures

The survey items were primarily adapted from the Waves 1 and 2 of the Adult Population Assessment of Tobacco and Health (PATH) Study.[37] The surveys covered a broad array of topics. Here, we focus on the assessments of smoking and JUUL use, and particularly on the variables that are used in analyses in the other papers in this issue.[27-30,38,39] The relevant survey items can be obtained at https://www.juullabs.com/wp-content/uploads/2021/03/ADJUSST-Baseline-and-Follow-Up.pdf.

Sociodemographic characteristics. At baseline, items assessed age in years, sex, race/ethnicity, marital status, highest level of educational attainment, annual household income and household size.

Past 30-day cigarette smoking (status, frequency and quantity). At baseline and at each follow-up, participants were asked: "In the past 30 days, have you smoked a cigarette, even one or 2 puffs?" Report of past-30-day smoking was used both at baseline, to classify participants by smoking status (see below, and Tables 1 and 2), and as an outcome at each follow-up, following the example of other similar studies.[37,40]

Participants who reported smoking in the past 30 days also were asked: "Do you now smoke cigarettes," with response options of "Every day," "Some days," or "Not at all." Those who said they smoked some days or every day were asked how many days of the last 30 they had smoked, and how many cigarettes (on average) they had smoked on the days they smoked. Average cigarettes per day variable was computed as ([days per month × cigarettes per smoking day]/30). Past-30-day smokers said they now smoked "not at all," who were considered non-smokers in some studies[23] were counted as smokers, but were not asked about the frequency/quantity of smoking.

Baseline smoking and ENDS history and smoking status. At baseline, we queried participants about their smoking. They were asked: "Have you ever smoked a cigarette, even one or 2 puffs?" Those who responded "Yes" were then asked: "How many cigarettes have you smoked in your entire life?" (dichotomized at 100 or more cigarettes). Based on these 2 questions, plus the questions about past-30-day smoking and now smoking every day, some days or not at all (above), participants were classified into one of 7 mutually exclusive cigarette smoking status groups (Table 1).

Neither history nor current use of non-cigarette, non-ENDS tobacco products (eg, cigars, hookah, smokeless tobacco) was assessed at baseline or at follow-up.

Table 1
Smoking Status of Participants (N = 55,414) at the Time of First Purchase of a JSK (Baseline Assessment)

Ever Smoked[a]	Smoked 100 Cigarettes in Lifetime[b]	Past 30-day Smoking[c]	Now Smoke Every Day or Some Days[d]	Smoking Status	Proportion of Sample % (N)
Yes	Yes	Yes	Yes	Current established smoker	41.3 (22,905)
Yes	Yes	Yes	No	Past-30-day established smoker now not smoking at all	9.1 (5024)
Yes	Yes	No	—	Former established smoker	11.0 (6086)
Yes	No	Yes	—	Current experimental smoker	11.1 (6166)
Yes	No	No	—	Former experimental smoker	12.2 (6786)
No	—	—	—	Never smoker	9.4 (5234)
—	—	—	—	Undetermined[e]	5.8 (3213)

Note.
[a] **"Have you ever smoked a cigarette, even one or 2 puffs?"**
[b] **"How many cigarettes have you smoked in your entire life? A pack usually has 20 cigarettes in it."**
[c] **"In the past 30 days, have you smoked a cigarette, even one or 2 puffs?"**
[d] **"Do you now smoke cigarettes every day, some days, or not at all?"**
[e] **Missing one or more variables necessary for classification: 77.9% missing current (past-30-day) smoking, 19.0% missing everyday/some days, 1.0% missing lifetime smoking, 2.0% missing ever-smoking. Missing data on some variables resulted in multiple missing values due to skip patterns.**

Duration of smoking and of abstinence from smoking. Participants who reported smoking regularly also were asked the age at which they first started smoking cigarettes regularly. Participants who reported smoking "Every day" or "Some days" were also asked about their duration of regular smoking. Participants who reported ever smoking, but not in the past 30 days or "Not at all" in the past 30 days were asked the duration of their past regular smoking and also asked when they had completely quit smoking ("Within past 12 months" vs "More than 12 months ago").

Readiness to quit smoking. Participants who reported past-30-day smoking at baseline were asked whether they planned to quit smoking in the next 30 days, an indicator of readiness to quit.

Cigarette dependence. At the baseline assessment, combustible cigarette dependence was assessed with the Adult Tobacco Dependence Index (TDI), a composite measure of 16 items drawn from the Wisconsin Inventory of Smoking Dependence Motives,[41] the Nicotine Dependence Syndrome Scale,[42] and the Diagnostic and Statistical Manual of Mental Disorders,[43] that was validated in the PATH Adult survey for assessing cigarette dependence.[44,45] Participants answered 15 items on scales from 1 ("Not true of me at all") to 5 ("Extremely true of me"); the single dichotomous DSM item was recoded to this scale, and a composite average score was computed.

Assessment of JUUL use and dependence at follow-ups. At each follow-up assessment, past-30-day use of JUUL was assessed in a manner parallel to assessment of smoking. Participants were asked whether they had used JUUL in the past 30 days ("even one or 2 puffs"). Those who had were asked whether they "now use a JUUL…'Every day', 'Some days', or 'Not at all'." Those using "Every day" or "Some days" were then asked about the number of days they used JUUL in the past 30 days and the number of times they used JUUL each day: ("On average, on those days you used a JUUL, how many times did you usually use a JUUL each day? Assume that one 'time' consists of around 15 puffs, or 10 minutes." [continuous]).[46] Those who reported they were now using JUUL "Not at all" were not

Table 2
Smoking History and Current Status of the Sample

Cohort	N	Percent	Percent of higher-order category
Total baseline sample	55,414		100.0%
Ever-smoking status unknown	66		
Ever status known	55,348		
Never smoked	5234	9.5%	
Ever smoked	50,114	90.5%	100.0%
Current smoker (past 30 days)	34,732	62.8%	72.9%
Former smoker	12,880	23.3%	27.1%
Current smoking status unknown	2502	4.5%	

asked frequency or quantity.

At each follow-up assessment level of JUUL dependence was assessed with the 16-item PATH TDI, adapted for JUUL. The PATH TDI has been explicitly validated for assessing dependence on ENDS, and for comparison of dependence on cigarettes compared to ENDS.[44,45]

Methods of the Re-engagement Survey

To gain insight into non-respondents to the follow-ups, enrollees who missed the 12-month survey (N = 26,561, 48% of the enrolled) were invited to a re-engagement survey. Invitations were sent 4-16 weeks after the 12-month survey period had ended (ie, 14 to 16 months after participants' enrollment). A reminder email was sent within 10 days of the initial email invitation, and availability of the survey ended 30 days after the first email invitation. The survey took approximately 15 minutes to complete, and completers were compensated USD30.

Altogether, 4692 (18%) of eligible enrollees completed the re-engagement survey. The profile of missed follow-ups in this sample mirrored that seen in the overall ADJUSST sample.

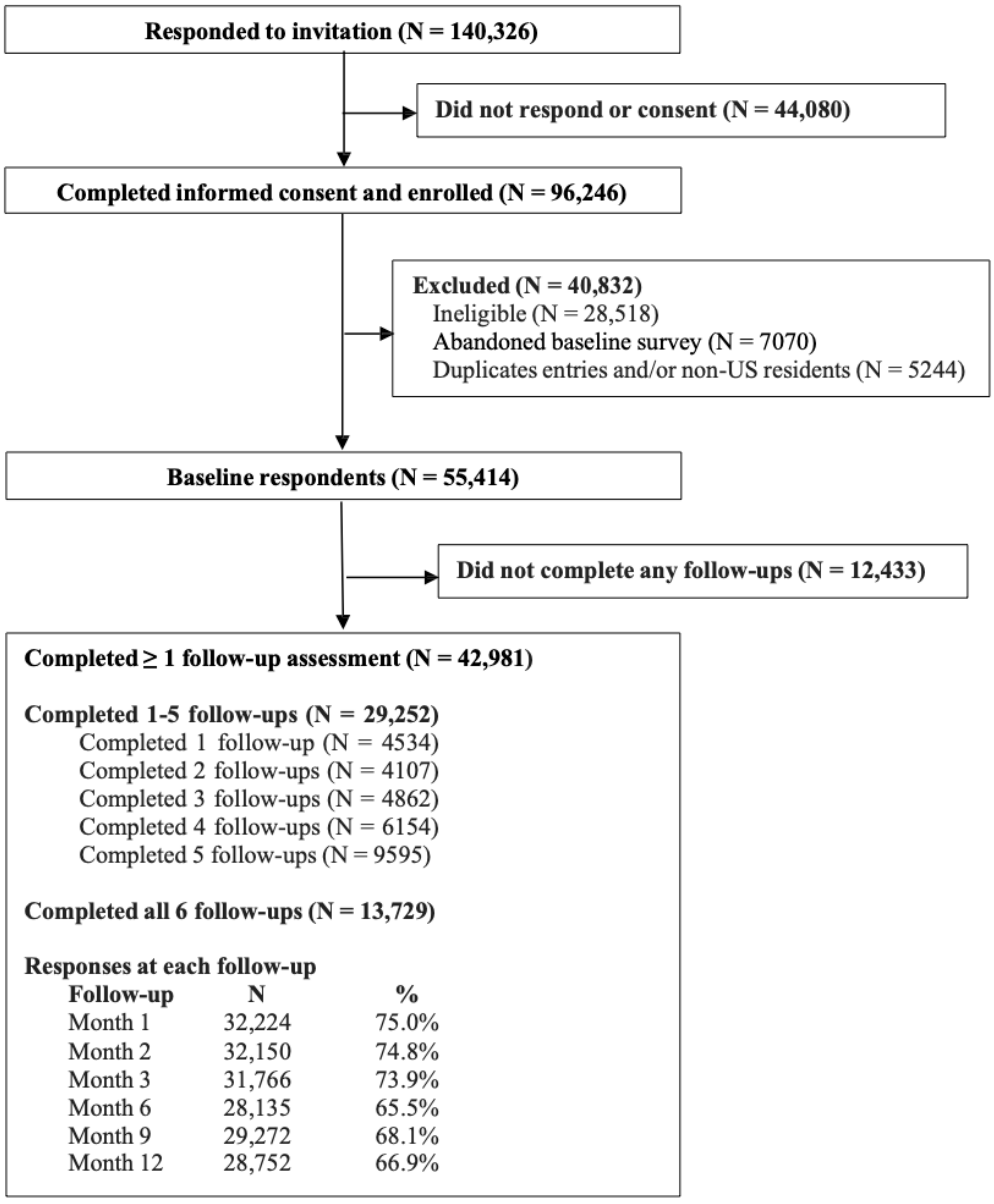
Measures

The survey included questions about respondents' current smoking and JUUL use at the time of the re-engagement survey (participants reported on their current behavior, not retrospectively on their behavior at the time of the missed 12-month survey). Paralleling the questions used in the follow-up surveys, participants were asked whether they had smoked at all, even a puff, in the preceding 30 days. The survey similarly asked about past-30-day use of JUUL.

Additionally, respondents were asked why they had failed to respond to scheduled surveys, checking as many listed reasons as applied. To summarize the multiple responses, respondents were assigned to a category in order of priority, ie, they were assigned to the highest-priority category, even if they also endorsed a lower-priority one. The categories, in order of priority, were: because they returned to smoking, stopped using JUUL, experienced survey issues (eg, survey unavailable, payment not enough for bother, etc., aggregated into a single category), or other reasons (eg, stopped smoking cigarettes). These responses were tallied by participants' baseline smoking status, paralleling the stratification used for analyses of baseline differences (Table 1).

Analysis of baseline characteristics by response to follow-up. Response to follow-ups was analyzed by grouping enrollees 3 ways based on their pattern of survey response: (1) those who provided smoking-status data at all follow-ups through 12 months; (2) those who provided data at some but not all follow-ups; and (3) those who provided data at none of the follow-ups. This allowed for various contrasts, informing analyses that use complete cases and those that use all available data, including partial data.

Figure 1
Participant Flow Diagram



Contrasts among these groups were performed for the demographic variables of age, sex, marital status, ethnicity, education, and income. Because the sample sizes are so large, making even small differences statistically significant, we focused on effect sizes – R^2 for continuous variables and the uncertainty coefficient (a measure of how much the predictor reduces uncertainty or variability in the follow-up status)[47] for categorical variables. These analyses were conducted on the entire enrolled co-

hort, and also separately within strata defined by smoking status and history (Table 1). Because the trends were similar across these strata, we focus on the whole-cohort analysis, but include the by-stratum analyses in supplemental material (Supplementary Tables S1-S7).

For participants with data on smoking behavior at baseline (established smokers and experimenters), additional analyses assessed differences among the 3 missing-data groups in baseline smoking characteristics (ie, daily vs non-daily smoking, number of days smoked in the past 30 days, cigarettes per day, at age initiation of regular smoking, duration of regular smoking, cigarette dependence, and plans to quit within 30 days).

Analysis of Re-engagement Data

Participants' reports of current smoking and current JUUL use, and their endorsed reasons for non-response, reported descriptively by baseline smoking status (Table 1).

RESULTS

A total of 55,414 individuals consented and completed the baseline survey (Figure 1). Over three-fourths of the enrollees (42,981, 77.6%) provided at least some follow-up data; the others (12,433; 22.4%) did not complete any follow-ups; one-fourth (N = 13,729; 24.8%) completed all 6 follow-ups.

Most enrollees (29,252; 52.8%) provided partial data; of these, 70.5% completed at least 3 of the 6 follow-ups. Their pattern of missed follow-ups was not characterized by discontinuation, ie, completing follow-ups, but then dropping from the study and completing no subsequent follow-ups. Rather, 83.5% of those with partial data showed a pattern of intermittent responding, ie, they missed one or more follow-ups, but then returned at subsequent follow-ups (respondents who missed only the 12-month follow-up [6.3% of those with partial data] could not be counted as returning, as this was the last observation in these analyses). In the partial-data cohort, 80.9% completed at least one of the follow-ups in the second half of the year, at or after 6 months.

Table 2 shows the reported smoking history at baseline of the baseline participants. Over 90% of enrollees reported a history of smoking. Most of these (72.9%) were smoking (past-30-days) at the time of enrollment. Among those with a history of smoking, 71.3% of those had smoked at least 100 cigarettes in their lifetime (the criterion for established smoking). Among participants who had ever smoked, 72.9% reported currently smoking (ie, in the past-30-days) at baseline.

Table 1 shows the more differentiated smoking status definitions that were used for analyses. The largest group of participants was current established smokers, who had smoked at least 100 cigarettes, lifetime, had smoked in the previous 30 days, and said they now smoked every day or some days. Goldenson et al[27] report their smoking trajectories, and Kim et al[28] report on subgroups of special interest. There was a substantial fraction of established smokers who said they had smoked in the past 30 days, but reported they were now smoking "not at all." Analyses of data from PATH (Supplement 2) suggest that these may be individuals who considered themselves to have stopped smoking more recently than 30 days ago. Selya et al[39] report on smoking trajectories of all the baseline smokers. Former established smokers, who had smoked at least 100 cigarettes but had not smoked in the past 30 days, were another group. Le et al[29] report their smoking trajectories. Experimental smokers were those who had smoked, but fewer than 100 cigarettes lifetime, and they were subdivided according to their current smoking at baseline. Finally, the smallest group was comprised of individuals who said they had never smoked cigarettes (although they could have used other tobacco products, which was not asked about in this survey). Shiffman and Holt[30] report their smoking trajectories. Prakash et al[38] report the smoking status of all groups at 12 months.

Comparisons of Responders and Non-responders on Baseline Demographic and Smoking Variables

Table 3 shows the distribution of baseline demographics for participants who completed all 6 follow-up assessments, 1-5 follow-ups, and no follow-ups. The table also shows statistical tests of differences, and indicators of effect size. All differences were statistically significant, given the large sample sizes, but the effect sizes were all small, with R^2 and UC ≤ 0.001 (ie, smaller than a 'small' effect size of 0.1).[48] The differences were also small in an

Table 3
Sociodemographic Characteristics by Survey Response Status

Sociodemographic Characteristics	No Smoking Data at Any Follow-ups (N = 12,433)	Smoking Data at 1-5 Follow-up(s) (N = 29,252)	Smoking Data at All 6 Follow-ups (N = 13,729)	Total (N = 55,414)	Test of Difference (p)	UC or R^2
Age (years), Mean (SD)	30.22 (11.48)	29.83 (10.63)	30.39 (10.37)	30.06 (10.77)	< .001	0.0005
Sex N (%)					< .001	0.0011
Male	7820 (63.6)	17,232 (59.4)	7776 (57.1)	32,828 (59.7)		
Female	4394 (35.7)	11,630 (40.1)	5766 (42.3)	21,790 (39.7)		
Transgender	81 (0.7)	168 (0.6)	77 (0.6)	326 (0.6)		
Race/Ethnicity N (%)					< .001	0.0006
Non-Hispanic White	8776 (77.8)	20,320 (75.0)	9501 (74.7)	38,597 (75.5)		
Non-Hispanic Black	342 (3.0)	968 (3.6)	539 (4.2)	1849 (3.6)		
Non-Hispanic Asian	527 (4.7)	1535 (5.7)	723 (5.7)	2785 (5.5)		
Non-Hispanic Other Race	536 (4.8)	1347 (5.0)	589 (4.6)	2472 (4.8)		
Hispanic Ethnicity	1100 (9.8)	2932 (10.8)	1362 (10.7)	5394 (10.6)		
Marital Status N (%)					< .001	0.0006
Married	2630 (22.1)	6281 (22.0)	3424 (25.3)	12,335 (22.8)		
Divorced, Separated or Widowed	1391 (11.7)	3134 (11.0)	1512 (11.2)	6037 (11.2)		
Never Married	7906 (66.3)	19,124 (67.0)	8599 (63.5)	35629 (66.0)		
Highest Level of Education N (%)					< .001	0.0007
High school graduate or less	3723 (34.0)	8053 (30.3)	3740 (29.7)	15,516 (31.0)		
Some college or associate degree	4366 (39.9)	11,125 (41.9)	5443 (43.2)	20,934 (41.8)		
Bachelor's degree or more	2849 (26.0)	7398 (27.8)	3426 (27.2)	13,673 (27.3)		
Annual Income N (%)					< .001	0.0003
< $50k	5321 (54.0)	13,090 (53.7)	6430 (55.3)	24,841 (54.2)		
$50k-$100k	2610 (26.5)	6687 (27.4)	3221 (27.7)	12,518 (27.3)		
> $100k	1920 (19.5)	4587 (18.8)	1971 (17.0)	8478 (18.5)		

Note.
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as N (%) unless otherwise noted. Denominators may be less than column heads due to missing data.
Participants were invited to complete 6 total follow-up assessments post-baseline to the 12-month follow-up.
Tests of differences in sociodemographic characteristics between: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥ 1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all 6 follow-up assessments post-baseline with conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict smoking data status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

absolute sense; eg, age varied by less than one year and membership in income strata by less than 3%.

Table 4 shows the baseline smoking characteristics of baseline current established smokers, by follow-up response status. Again, some differences were statistically significant, but effect size indices

Table 4
Smoking Characteristics by Survey Response Status, Among Current Established Smokers at Baseline

Smoking Characteristics	No Smoking Data at Any Follow-up (N = 4919)	Smoking Data at 1-5 Follow-up(s) (N = 12,309)	Smoking Data at All 6 Follow-ups (N = 5677)	Total (N = 22,905)	Test of Difference (p)	UC or R^2
"Now smoking…" N (%)					< .001	0.0004
Some days	2237 (45.5)	5732 (46.6)	2448 (43.1)	10,417 (45.5)		
Every day	2682 (54.5)	6577 (53.4)	3229 (56.9)	12,488 (54.5)		
Age started smoking regularly (years)	18.26 (4.07)	18.18 (3.71)	18.10 (3.76)	18.18 (3.80)	.111	0.0002
Years regular smoker	13.30 (11.81)	12.21 (10.77)	12.83 (10.42)	12.60 (10.93)	< .001	0.0017
Cigarette smoking dependence at baseline[a]	2.98 (1.08)	3.00 (1.07)	3.07 (1.08)	3.01 (1.08)	< .001	0.0008
No. days smoked cigarettes in past 30 days at baseline	23.30 (9.44)	23.19 (9.50)	23.58 (9.40)	23.31 (9.46)	.044	0.0003
No. cigarettes smoked per day at baseline	11.94 (9.08)	10.98 (8.08)	11.37 (8.31)	11.28 (8.37)	< .001	0.0021
Planning to quit within 30 days N (%)	1998 (43.6)	4997 (43.0)	2359 (44.0)	9354 (43.4)	.421	0.00005

Note.
[a] Combustible cigarette dependence, 16-item measure validated in PATH Study Adult Survey (Range: 1-5).[44]
Data presented as Mean (SD) unless otherwise noted. Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Denominators may be less than column heads due to missing data. Age started smoking regularly was only assessed among those who affirmed smoking fairly regularly at some point in their lifetime. Dependence, number of days smoked cigarettes in the past 30 days, number of cigarettes smoked per day, and years smoked regularly were only assessed among those who were currently smoking some days and every day at baseline.
Tests of differences in smoking characteristics were conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict smoking data status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

never exceeded 0.002; for example, those with no follow-up data had the lowest cigarette dependence score, but only by 0.09 points, and their baseline cigarette consumption exceeded those of the other groups by less than one cigarette per day. They did not differ in readiness to quit smoking. For smoking experimenters at baseline (Table 5), the only statically significant difference by follow-up response was that those with complete data were less likely to be ready to quit smoking at baseline – by about 5%.

Re-engagement Study

Table 6 shows the percent of respondents in the re-engagement survey who reported they had not smoked at all in the preceding 30 days, grouped by participants' baseline smoking status. As expected, and consistent with data on the participants who did complete the original 12-month assessment,[38] the prevalence of no smoking in the past 30 days was highest among those who had not been smoking at baseline. For example, 87% of never smokers and around 80% of former smokers reported no past-30-day smoking. The prevalence of reported past-30-day abstinence from smoking was 46% among baseline current established smokers and 67% among baseline past-30-day established smokers who had said they were smoking "not

Table 5
Smoking Characteristics by Survey Response Status, among Current Smoking Experimenters at Baseline

Smoking Characteristics	No Smoking Data across Follow-up (N = 1435)	Smoking Data at 1-5 Follow-up(s) (N = 3228)	Smoking Data at all 6 Follow-ups (N = 1503)	Total (N = 6166)	Test of Difference (p)	UC or R^2
No. of Cigarettes Smoked in Lifetime N (%)					.145	0.0009
1 or more puffs but never a whole cigarette	107 (7.5)	256 (7.9)	151 (10.1)	514 (8.3)		
1 to 10 cigarettes	316 (22.0)	710 (22.0)	328 (21.8)	1354 (22.0)		
11 to 20 cigarettes	376 (26.2)	838 (26.0)	373 (24.8)	1587 (25.7)		
21 to 50 cigarettes	347 (24.2)	808 (25.0)	339 (22.6)	1494 (24.2)		
51 to 99 cigarettes	289 (20.1)	616 (19.1)	312 (20.8)	1217 (19.7)		
"Now smoking…" N (%)					.690	0.0002
Not at all	514 (37.5)	1228 (39.7)	579 (39.9)	2321 (39.2)		
Some days	622 (45.4)	1361 (44.0)	632 (43.5)	2615 (44.2)		
Every day	234 (17.1)	507 (16.4)	242 (16.7)	983 (16.6)		
Age started smoking regularly (years)	19.01 (4.22)	18.82 (3.59)	18.89 (3.53)	18.88 (3.73)	.581	0.0004
Years regular smoker	8.05 (10.94)	7.13 (9.93)	7.63 (10.28)	7.47 (10.27)	.092	0.0014
Cigarette smoking dependence at baseline[a]	2.39 (1.12)	2.40 (1.18)	2.38 (1.11)	2.39 (1.15)	.853	0.0001
No. days smoked cigarettes in past 30 days at baseline	14.77 (11.53)	14.36 (11.36)	14.14 (11.48)	14.40 (11.43)	.513	0.0004
No. cigarettes smoked per day at baseline	7.97 (9.25)	7.18 (8.61)	7.36 (8.45)	7.41 (8.73)	.103	0.0013
Planning to quit within 30 days N (%)	354 (45.6)	776 (44.8)	321 (39.9)	1451 (43.8)	.038	0.0010

Note.
[a] Combustible cigarette dependence, 16-item measure validated in PATH Study Adult Survey (Range: 1-5).[44]
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as Mean (SD) unless otherwise noted. Denominators may be less than column heads due to missing data.
Age started smoking regularly was only assessed among those who affirmed smoking fairly regularly at some point in their lifetime. Dependence, number of days smoked cigarettes in the past 30 days, number of cigarettes smoked per day, and years smoked regularly were only assessed among those who were currently smoking some days and every Participants were invited to complete 6 total follow-up assessments post-baseline to the 12-month follow-up.
Tests of differences in smoking characteristics among: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥ 1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all 6 follow-up assessments post-baseline were conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict smoking data status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

at all." In all but the baseline current established smokers group, the majority were abstinent at the time of re-engagement. As Supplementary Table S8 shows, among baseline smokers (established

Table 6
Reported Smoking Status, and Reasons for Non-response, among Participants in the Re-engagement Survey, Stratified by Baseline Smoking Status

	Participants[a] Baseline Smoking Status					
	Current Established Smokers (N = 1900)	Other Past 30-day Established Smokers (N = 430)	Former Established Smokers (N = 532)	Current Experimenters (N = 531)	Former Experimenters (N = 585)	Never Smokers (N = 449)
Smoking status at Re-engagement						
% not smoking past 30 days	46.0%	66.7%	80.7%	64.9%	79.3%	86.9%
Reasons for non-response[†]						
Started smoking	4.5%	4.1%	1.9%	5.9%	2.8%	3.1%
Stopped using JUUL	3.6%	4.8%	4.1%	4.8%	6.0%	7.2%
Survey process reasons	80.9%	79.9%	83.0%	79.1%	81.9%	80.7%
Other reasons	11.0%	11.1%	10.9%	10.2%	9.3%	9.1%
Stopped smoking cigarettes[‡]	2.0%	4.1%	1.9%	2.9%	2.0%	1.9%

Note.
[a] Coded to be exhaustive and mutually exclusive by prioritizing assignment to reasons in the order shown. That is, for example, respondents who endorsed "Started smoking" were tallied under that category even if they also endorsed "Survey process reasons"
[b] This was coded as part of the "Other reasons" category, but is also reported separately here.

and experimenters), both those who reported being ready to quit at baseline and those who did not reported past-30-day abstinence exceeding 40% at re-engagement.

Table 6 also shows respondents' stated reasons for their prior non-response, by baseline smoking status. In each group, less than 6% indicated it was because they had started or restarted smoking cigarettes. Similarly, the percent reporting that they stopped responding because they had stopped using JUUL was under 5% for almost all groups, and below 8% for all. Across all groups, having stopped smoking cigarettes was cited by less than 5% as a reason for non-response. By far, the most common reasons given by all smoking status groups (approximately 80% of respondents in all groups) were reasons related to survey issues, such as not being paid enough, surveys being too long, or having responded too late, after the survey window had closed. As Supplementary Table S8 shows, among baseline smokers (established and experimenters) both those who reported being ready to quit at baseline and those who did not largely attributed their non-response to survey issues, and few cited smoking or stopping JUUL use as a reason.

DISCUSSION

We collected data from a large cohort of adults who newly purchased a JUUL Starter Kit, and followed up on them multiple times over the succeeding year. As such, the study is expected to provide relevant insights into the trajectory of smoking and JUUL use in a sample with varied smoking history. The majority of JUUL purchasers were past-30-day smokers at the time of the purchase. Therefore, understanding whether they continue to smoke or switch away from smoking when using JUUL can elucidate the potential for public health benefit from use of JUUL.

Conversely, some JSK purchasers were former- or never-smokers, whose use of JUUL or any other ENDS carries risk, particularly if it were to lead to smoking in individuals who would not otherwise have smoked. The prevalence of JUUL use

in these non-smoking groups is much lower than that among smokers; Prakash et al[49] report that the prevalence of JUUL use is 3.9% among young adult former smokers, and 0.8% among former-smoking adults 25 and older; for never-smokers, the prevalence figures were 0.9% for young adults and 0.1% in the older cohorts. Nevertheless, the use of JUUL in these groups is of concern. Thus, this study may provide important information about both the beneficial and harmful trajectories of ENDS use and smoking after adoption of JUUL. More in-depth analyses by Le et al[29] and Shiffman and Holt[30] provide data on subsequent smoking in former- and never-smokers, respectively.

The study provides detail about JUUL purchasers' trajectories, with multiple observations over 12 months (comprising over 180,000 follow-up observations), but many participants did not respond to every (or, in some cases, any) follow-up. Loss to follow-up occurs in all longitudinal surveys. For example, the International Tobacco Control Survey reported 37% attrition at the first follow-up of US participants, dropping to a cumulative loss of 63% at the second follow-up.[50] The present survey had shorter follow-up intervals, but correspondingly more numerous follow-ups and narrower windows for responding to survey invitations.

In any case, one has to be sensitive to the potential that such non-response could bias the data that are available for analysis. Accordingly, analyses were undertaken to evaluate the potential for bias due to differential drop-out by participants differing in characteristics. Comparisons of demographic and smoking history variables among enrollees who provided no, some, or all follow-up data found only small differences. Even when they were found to be statistically significant, due to the large sample sizes, the observed differences were small both in absolute terms, and in terms of statistical effect-sizes, which showed them to be consistently smaller than even 'small' effects.[48] Importantly, the observed differences did not consistently suggest that non-respondents were more predisposed to later smoking. For example, among baseline current established smokers, enrollees who provided partial or no follow-up data had *lower* cigarette dependence scores, which were associated with *lower* likelihood of later smoking.[27] On baseline readiness to quit, a robust predictor of later switching,[27] there were no differences by follow-up response, and among experimental smokers, those who completed all follow-ups were least likely to have been ready to quit smoking. Some demographic characteristics that have been shown to favor later smoking in established smokers using JUUL (eg, being older, female, or Hispanic)[11] were also lower in non-responders. In short, these analyses do not support any suggestion that non-respondents at follow-up were more predisposed to smoking.

A similar conclusion derives from a second set of analyses to assess potential bias due to non-response, by examination of reports from enrollees who had missed at least the 12-month follow-up in the study. One concern was that participants might have failed to respond because they had resumed smoking, which could bias the smoking status reported by the remaining responders. However, resumption of smoking was rarely a reason for discontinuation, reported by only 4.5% of baseline established smokers and 5.9% of experimenters. The predominant reasons for discontinuation, endorsed by approximately 80% in all groups, were those typically associated with surveys, and unrelated to outcomes of interest, such as finding it inconvenient to respond or missing the survey time window. The pattern of missed assessments, which showed that respondents with some missing follow-ups typically returned to do subsequent follow-ups, was consistent with the cited temporal reasons for missing follow-ups. Results were similar for smokers who had and had not been ready to quit at baseline, again providing no evidence of bias related to the likelihood of later switching.

In smoking cessation trials, where smokers are being treated to achieve abstinence, it is typically assumed that non-respondents to follow-up are smoking, and that they avoid responding to avoid reporting failure. Indeed, in a re-engagement study that recontacted a group of non-respondents, Foulds et al[36] report that 100% reported they had resumed smoking, supporting the strong imputation in smoking cessation treatment trials that all non-respondents are smoking. The data collected at re-engagement with non-respondents in this study were different; among baseline established smokers, almost half reported past-30-day abstinence. Even among those who had not been ready

to quit at baseline, 40% reported abstinence (lower than the 54% reported by those who were ready to quit, consistent with the observation that readiness to quit smoking foretells a higher switch rate).[27] Other groups that had not been smoking at baseline reported still higher rates of abstinence.

A key distinction between the cessation treatment setting and this naturalistic observational study is that treatment trials are centered on abstinence goals that define success and failure for participants. That was not the case in ADJUSST; participants purchased JUUL on their own, without needing to subscribe to any particular goal, and they were not given any particular directions or goals, so there was no prospect of 'failure.' Moreover, the respondents had not been provided with any 'treatment,' so there was no prospect of embarrassing or disappointing clinicians who had been trying to help them. This likely removes the social incentive to avoid contact in order to avoid reporting 'failure.' Indeed, non-interventional survey studies following ENDS users have not imputed failure to those lost to follow-up, nor required biochemical verification of non-smoking status.[51-56]

Limitations and Strengths

As with any study, ADJUSST has limitations. Like other surveys of similar design,[24,37,50] it relied on participants' self-reports and did not use biochemical verification of smoking status. The sample is not necessarily representative of the population of JSK purchasers; it is not known how purchasers who volunteered for the study might differ from those who did not, either online or at retail. As the study used online surveys in English, participation required knowledge of English and access to the Internet, which are not universal. Furthermore, the sample is not representative of all JUUL users; enrollees had purchased a JSK, which suggests a greater level of interest and commitment than might be evident, for example, in someone who borrows others' ENDS to sample them. In this sense, the study represents more engaged JUUL users, which is a population of interest in itself. The ADJUSST study was based on an adult sample; the results do not speak to the behavior of adolescent JUUL users.

The study documented the behavior of JSK purchasers/users; it did not have a comparison group of non-users, so the observed trajectories of smoking cannot be compared to what might occur absent JUUL use. Past-30-day smokers who then indicated they were smoking "not at all" were not asked details of their past-30-day smoking, which makes it difficult to characterize this group's smoking behavior, both at baseline and in follow-ups. Finally, an important limitation is that participants were not assessed for history or current use of non-cigarette, non-ENDS tobacco products such as cigars or smokeless tobacco, so these important antecedent or concurrent behaviors are not known. Of course, as in any research, it is possible that participation and answering questions about behavior could have affected the behavior, but smoking is highly resistant to change, even with deliberate intervention.

Among the study's strengths was a large sample of real-world JUUL users across a diverse range of baseline smoking status.

The analyses of loss to follow-up have additional limitations. Whereas the analyses included a wide range of often-used baseline demographic and smoking variables for prediction, it is possible that some trait not assessed here might have more strongly differentiated the groups and indicated likely bias in later outcomes. The re-contact analysis was based on a subset of enrollees who had not completed the 12-month follow-up, but did complete the re-engagement survey. The status of those who did not respond to the re-engagement survey may have been different. However, even if this were so, the predominance of abstinence among the re-engagement responders clearly indicates that imputing smoking to all individuals who did not complete follow-ups would be incorrect. Nevertheless, the potential for some bias due to non-response must be considered when interpreting outcomes.

In summary, 2 different analyses suggested that the effects of non-response to follow-ups in the ADJUSST study are modest and unlikely to bias subsequent reports of smoking. The ADJUSST study has potential to shed light on trajectories of smoking and ENDS use over time following initiation of ENDS use by adults with varying smoking status and smoking history.

Human Subjects Approval Statement

This study was approved by the Advarra® Institutional Review Board.

Conflict of Interest Disclosure Statement

Through PinneyAssociates Inc, SS and MAS provide consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc. Within the last 2 years, PinneyAssociates Inc has consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction. EMA and NIG are full-time employees of Juul Labs Inc. FH, NM, and CR are full-time employees of the Centre for Substance Use Research (CSUR), an independent research consultancy which designed the study and assessments described in this paper and oversaw collection of data through Dacima Inc under contract to Juul Labs Inc.

CSUR managed, cleaned, and summarized the data. MAS performed the statistical analyses under the direction of SS. All of the authors contributed to writing and review of the paper, and had access to the data. The sponsor approved the research plan and provided comment on a near-final draft of the paper.

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Supplement 1

Table S1
Sociodemographic Characteristics by Survey Response Status, among Current Established Smokers at Baseline

Sociodemographic Characteristics	No Smoking Data at Any Follow-ups (N = 4919)	Smoking Data at 1-5 Follow-up(s) (N = 12,309)	Smoking Data at All 6 Follow-ups (N = 5677)	Total (N = 22,905)	Test of Difference (p)	UC or R^2
Age (years), Mean (SD)	33.71 (12.09)	32.50 (10.96)	32.96 (10.47)	32.88 (11.11)	< .001	0.0018
Sex N (%)					< .001	0.0014
Male	2946 (60.6)	6825 (55.8)	2995 (53.1)	12,766 (56.2)		
Female	1894 (39.0)	5328 (43.6)	2615 (46.4)	9837 (43.3)		
Transgender	20 (0.4)	69 (0.6)	26 (0.5)	115 (0.5)		
Race/Ethnicity N (%)					< .001	0.0007
Non-Hispanic White	3666 (81.2)	9021 (78.3)	4162 (78.5)	16,849 (78.9)		
Non-Hispanic Black	101 (2.2)	321 (2.8)	175 (3.3)	597 (2.8)		
Non-Hispanic Asian	224 (5.0)	666 (5.8)	284 (5.4)	1174 (5.5)		
Non-Hispanic Other Race	213 (4.7)	524 (4.5)	242 (4.6)	979 (4.6)		
Hispanic Ethnicity	313 (6.9)	994 (8.6)	441 (8.3)	1748 (8.2)		
Marital Status N (%)					< .001	0.0008
Married	1374 (28.7)	3245 (26.8)	1711 (30.5)	6330 (28.1)		
Divorced, Separated or Widowed	748 (15.6)	1755 (14.5)	837 (14.9)	3340 (14.8)		
Never Married	2667 (55.7)	7102 (58.7)	3061 (54.6)	12,830 (57.0)		
Highest Level of Education N (%)					< .001	0.0005
High school graduate or less	1382 (30.8)	3155 (27.4)	1534 (28.7)	6071 (28.4)		
Some college or associate degree	1898 (42.3)	4960 (43.1)	2314 (43.3)	9172 (43.0)		
Bachelor's degree or more	1212 (27.0)	3390 (29.5)	1499 (28.0)	6101 (28.6)		
Annual Income N (%)					< .001	0.0008
< $50k	2041 (50.4)	5584 (52.5)	2720 (54.6)	10,345 (52.6)		
$50k-$100k	1232 (30.4)	3122 (29.3)	1496 (30.0)	5850 (29.7)		
> $100k	778 (19.2)	1933 (18.2)	769 (15.4)	3480 (17.7)		

Note.
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as N (%) unless otherwise noted. Denominators may be less than column heads due to missing data.
Participants were invited to complete 6 total follow-up assessments post-baseline to the 12-month follow-up.
Tests of differences in sociodemographic characteristics between: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥ 1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all 6 follow-up assessments post-baseline with conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict Survey Response Status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

Table S2
Sociodemographic Characteristics by Survey Response Status, among Past-30-day Established Smokers Now Not Smoking at All at Baseline

Sociodemographic Characteristics	No Smoking Data at Any Follow-ups (N = 1074)	Smoking Data at 1-5 Follow-up(s) (N = 2707)	Smoking Data at All 6 Follow-ups (N = 1243)	Total (N = 5024)	Test of Difference (p)	UC or R^2
Age (years), Mean (SD)	29.67 (10.13)	30.00 (10.03)	30.69 (9.76)	30.10 (9.99)	.037	0.0013
Sex N (%)					.002	0.0017
Male	720 (67.3)	1643 (61.2)	745 (60.4)	3108 (62.3)		
Female	341 (31.9)	1026 (38.2)	482 (39.1)	1849 (37.1)		
Transgender	9 (0.8)	16 (0.6)	7 (0.6)	32 (0.6)		
Race/Ethnicity N (%)					.109	0.0014
Non-Hispanic White	812 (81.2)	1996 (78.8)	907 (79.2)	3715 (79.4)		
Non-Hispanic Black	27 (2.7)	86 (3.4)	45 (3.9)	158 (3.4)		
Non-Hispanic Asian	27 (2.7)	109 (4.3)	42 (3.7)	178 (3.8)		
Non-Hispanic Other Race	44 (4.4)	136 (5.4)	45 (3.9)	225 (4.8)		
Hispanic Ethnicity	90 (9.0)	206 (8.1)	106 (9.3)	402 (8.6)		
Marital Status N (%)					.010	0.0013
Married	229 (21.8)	622 (23.3)	335 (27.1)	1186 (24.0)		
Divorced, Separated or Widowed	118 (11.3)	307 (11.5)	156 (12.6)	581 (11.7)		
Never Married	701 (66.9)	1740 (65.2)	744 (60.2)	3185 (64.3)		
Highest Level of Education N (%)					.283	0.0005
High school graduate or less	323 (32.7)	766 (30.3)	343 (29.6)	1432 (30.6)		
Some college or associate degree	406 (41.0)	1136 (44.9)	520 (44.9)	2062 (44.1)		
Bachelor's degree or more	260 (26.3)	629 (24.8)	296 (25.5)	1185 (25.3)		
Annual Income N (%)					.040	0.0012
< $50k	496 (54.9)	1262 (53.9)	589 (55.5)	2347 (54.5)		
$50k-$100k	253 (28.0)	666 (28.4)	329 (31.0)	1248 (29.0)		
> $100k	154 (17.1)	414 (17.7)	144 (13.6)	712 (16.5)		

Note.
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as N (%) unless otherwise noted. Denominators may be less than column heads due to missing data.
Participants were invited to complete 6 total follow-up assessments post-baseline to the 12-month follow-up.
Tests of differences in sociodemographic characteristics between: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥ 1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all 6 follow-up assessments post-baseline with conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict Survey Response Status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

Table S3
Sociodemographic Characteristics by Survey Response Status, among Former Established Smokers at Baseline

Sociodemographic Characteristics	No Smoking Data at Any Follow-ups (N = 1268)	Smoking Data at 1-5 Follow-up(s) (N = 3219)	Smoking Data at All 6 Follow-ups (N = 1599)	Total (N = 6086)	Test of Difference (p)	UC o r R^2
Age (years), Mean (SD)	31.46 (11.46)	32.06 (11.48)	32.87 (10.99)	32.15 (11.35)	.004	0.0018
Sex N (%)					< .001	0.0019
Male	896 (71.2)	2047 (64.1)	1,016 (64.1)	3959 (65.6)		
Female	356 (28.3)	1132 (35.4)	559 (35.3)	2047 (33.9)		
Transgender	6 (0.5)	15 (0.5)	9 (0.6)	30 (0.5)		
Race/Ethnicity N (%)					.907	0.0003
Non-Hispanic White	942 (80.2)	2381 (79.8)	1173 (79.3)	4496 (79.8)		
Non-Hispanic Black	32 (2.7)	68 (2.3)	41 (2.8)	141 (2.5)		
Non-Hispanic Asian	52 (4.4)	139 (4.7)	65 (4.4)	256 (4.5)		
Non-Hispanic Other Race	51 (4.3)	126 (4.2)	74 (5.0)	251 (4.5)		
Hispanic Ethnicity	98 (8.3)	268 (9.0)	126 (8.5)	492 (8.7)		
Marital Status N (%)					.002	0.0014
Married	353 (29.1)	994 (31.6)	564 (35.7)	1911 (32.2)		
Divorced, Separated or Widowed	128 (10.6)	344 (10.9)	178 (11.2)	650 (10.9)		
Never Married	730 (60.3)	1805 (57.4)	840 (53.1)	3375 (56.9)		
Highest Level of Education N (%)					.009	0.0012
High school graduate or less	332 (29.1)	769 (26.0)	340 (22.9)	1441 (25.8)		
Some college or associate degree	468 (41.0)	1243 (42.0)	663 (44.7)	2374 (42.5)		
Bachelor's degree or more	342 (29.9)	948 (32.0)	480 (32.4)	1770 (31.7)		
Annual Income N (%)					.289	0.0005
< $50k	508 (49.0)	1246 (46.5)	606 (45.0)	2360 (46.6)		
$50k-$100k	289 (27.9)	823 (30.7)	425 (31.6)	1537 (30.4)		
> $100k	239 (23.1)	613 (22.9)	315 (23.4)	1167 (23.0)		

Note.
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as N (%) unless otherwise noted. Denominators may be less than column heads due to missing data.
Participants were invited to complete 6 total follow-up assessments post-baseline to the 12-month follow-up.
Tests of differences in sociodemographic characteristics between: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥ 1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all 6 follow-up assessments post-baseline with conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict Survey Response Status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

Table S4
Sociodemographic Characteristics by Survey Response Status, among Current Experimental Smokers at Baseline

Sociodemographic Characteristics	No Smoking Data at Any Follow-ups (N = 1435)	Smoking Data at 1-5 Follow-up(s) (N = 3228)	Smoking Data at All 6 Follow-ups (N = 1503)	Total (N = 6166)	Test of Difference (p)	UC or R^2
Age (years), Mean (SD)	27.80 (10.67)	27.16 (9.74)	27.32 (9.21)	27.35 (9.85)	.123	0.0007
Sex N (%)					.024	0.0009
Male	892 (62.8)	1964 (31.3)	860 (57.6)	3716 (60.7)		
Female	520 (36.6)	1224 (38.2)	620 (41.5)	2364 (38.7)		
Transgender	9 (0.6)	15 (0.5)	13 (0.9)	37 (0.6)		
Race/Ethnicity N (%)					.002	0.0022
Non-Hispanic White	942 (73.3)	2022 (68.4)	937 (67.1)	3901 (69.2)		
Non-Hispanic Black	37 (2.9)	125 (4.2)	69 (4.9)	231 (4.1)		
Non-Hispanic Asian	85 (6.6)	216 (7.3)	106 (7.6)	407 (7.2)		
Non-Hispanic Other Race	69 (5.4)	164 (5.6)	59 (4.2)	292 (5.2)		
Hispanic Ethnicity	152 (11.8)	429 (14.5)	225 (16.1)	806 (14.3)		
Marital Status N (%)					.162	0.0005
Married	226 (16.6)	489 (15.6)	248 (16.8)	963 (16.1)		
Divorced, Separated or Widowed	138 (10.1)	260 (8.3)	119 (8.1)	517 (8.7)		
Never Married	999 (73.3)	2383 (76.1)	1110 (75.1)	4492 (75.2)		
Highest Level of Education N (%)					.097	0.0007
High school graduate or less	453 (36.7)	938 (32.9)	475 (34.9)	1866 (34.3)		
Some college or associate degree	464 (37.6)	1133 (39.7)	548 (40.3)	2145 (39.4)		
Bachelor's degree or more	318 (25.7)	781 (27.4)	337 (24.8)	1436 (26.4)		
Annual Income N (%)					.024	0.0011
< $50k	676 (59.7)	1535 (58.5)	785 (62.0)	2996 (59.6)		
$50k-$100k	279 (24.6)	619 (23.6)	306 (24.2)	1204 (24.0)		
> $100k	178 (15.7)	470 (17.9)	175 (13.8)	823 (16.4)		

Note.
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as N (%) unless otherwise noted. Denominators may be less than column heads due to missing data.
Participants were invited to complete 6 total follow-up assessments post-baseline to the 12-month follow-up.
Tests of differences in sociodemographic characteristics between: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥ 1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all 6 follow-up assessments post-baseline with conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict Survey Response Status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

Table S5
Sociodemographic Characteristics by Survey Response Status, among Former Experimental Smokers at Baseline

Sociodemographic Characteristics	No Smoking Data at Any Follow-ups (N = 1585)	Smoking Data at 1-5 Follow-up(s) (N = 3543)	Smoking Data at All 6 Follow-ups (N = 1658)	Total (N = 6786)	Test of Difference (p)	UC or R^2
Age (years), Mean (SD)	25.14 (8.40)	25.05 (7.79)	25.61 (7.84)	25.21 (7.95)	.059	0.0008
Sex N (%)					.001	0.0014
Male	1055 (66.9)	2180 (61.9)	1002 (60.8)	4237 (62.8)		
Female	511 (32.4)	1312 (37.3)	640 (38.8)	2463 (36.5)		
Transgender	10 (0.6)	29 (0.8)	7 (0.4)	46 (0.7)		
Race/Ethnicity N (%)					< .001	0.0023
Non-Hispanic White	1058 (72.9)	2314 (69.7)	1043 (66.6)	4415 (69.7)		
Non-Hispanic Black	57 (3.9)	148 (4.5)	93 (5.9)	298 (4.7)		
Non-Hispanic Asian	63 (4.3)	163 (4.9)	109 (7.0)	335 (5.3)		
Non-Hispanic Other Race	65 (4.5)	204 (6.1)	78 (5.0)	347 (5.5)		
Hispanic Ethnicity	208 (14.3)	491 (14.8)	243 (15.5)	942 (14.9)		
Marital Status N (%)					.001	0.0013
Married	176 (11.7)	383 (11.1)	244 (15.0)	803 (12.2)		
Divorced, Separated or Widowed	79 (5.2)	171 (5.0)	66 (4.1)	316 (4.8)		
Never Married	1253 (83.1)	2894 (83.9)	1317 (80.9)	5464 (83.0)		
Highest Level of Education N (%)					.005	0.0012
High school graduate or less	477 (35.2)	994 (31.6)	431 (29.1)	1902 (31.8)		
Some college or associate degree	530 (39.1)	1266 (40.2)	649 (43.8)	2445 (40.8)		
Bachelor's degree or more	349 (25.7)	889 (28.2)	402 (27.1)	1640 (27.4)		
Annual Income N (%)					.074	0.0008
< $50k	701 (58.2)	1613 (55.9)	756 (55.8)	3070 (56.4)		
$50k-$100k	246 (20.4)	697 (24.2)	335 (24.7)	1278 (23.5)		
> $100k	258 (21.4)	573 (19.9)	264 (19.5)	1095 (20.1)		

Note.
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as N (%) unless otherwise noted. Denominators may be less than column heads due to missing data.
Participants were invited to complete 6 total follow-up assessments post-baseline to the 12-month follow-up.
Tests of differences in sociodemographic characteristics between: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥ 1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all 6 follow-up assessments post-baseline with conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict Survey Response Status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

Table S6
Sociodemographic Characteristics by Survey Response Status, among Never Smokers at Baseline

Sociodemographic Characteristics	No Smoking Data at Any Follow-ups (N = 1341)	Smoking Data at 1-5 Follow-up(s) (N = 2628)	Smoking Data at All 6 Follow-ups (N = 1265)	Total (N = 5234)	Test of Difference (p)	UC or R2
Age (years), Mean (SD)	24.30 (7.07)	24.02 (6.49)	24.42 (6.80)	24.19 (6.72)	.175	0.0007
Sex N (%)					.002	0.0015
Male	874 (65.8)	1723 (66.0)	783 (62.5)	3380 (65.1)		
Female	431 (32.4)	871 (33.4)	458 (36.6)	1760 (33.9)		
Transgender	24 (1.8)	17 (0.6)	11 (0.9)	52 (1.0)		
Race/Ethnicity N (%)					.009	0.0021
Non-Hispanic White	853 (70.4)	1575 (65.4)	787 (67.4)	3215 (67.2)		
Non-Hispanic Black	68 (5.6)	156 (6.5)	88 (7.5)	312 (6.5)		
Non-Hispanic Asian	55 (4.5)	169 (7.0)	80 (6.9)	304 (6.4)		
Non-Hispanic Other Race	69 (5.7)	128 (5.3)	62 (5.3)	259 (5.4)		
Hispanic Ethnicity	166 (13.7)	379 (15.8)	150 (12.9)	695 (14.5)		
Marital Status N (%)					.115	0.0007
Married	101 (8.0)	209 (8.4)	129 (10.5)	439 (8.8)		
Divorced, Separated or Widowed	65 (5.2)	120 (4.8)	49 (4.0)	234 (4.7)		
Never Married	1092 (86.8)	2166 (86.8)	1055 (85.6)	4313 (86.5)		
Highest Level of Education N (%)					< .001	0.0034
High school graduate or less	523 (48.2)	969 (43.5)	406 (37.2)	1898 (43.1)		
Some college or associate degree	363 (33.4)	870 (39.0)	465 (42.6)	1698 (38.5)		
Bachelor's degree or more	200 (18.4)	389 (17.5)	221 (20.2)	810 (18.4)		
Annual Income N (%)					.646	0.0003
< $50k	576 (59.3)	1191 (58.9)	601 (59.9)	2368 (59.3)		
$50k-$100k	192 (19.8)	433 (21.4)	194 (19.3)	819 (20.5)		
> $100k	203 (20.9)	398 (19.7)	208 (20.7)	809 (20.2)		

Note.
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as N (%) unless otherwise noted. Denominators may be less than column heads due to missing data.
Participants were invited to complete 6 total follow-up assessments post-baseline to the 12-month follow-up.
Tests of differences in sociodemographic characteristics between: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥ 1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all 6 follow-up assessments post-baseline with conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict Survey Response Status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

Table S7
Sociodemographic Characteristics by Survey Response Status, among Those with Undetermined Smoking Status at Baseline

Sociodemographic Characteristics	No Smoking Data at Any Follow-ups (N = 811)	Smoking Data at 1-5 Follow-up(s) (N = 1618)	Smoking Data at All 6 Follow-ups (N = 784)	Total (N = 3213)	Test of Difference (p)	UC or R^2
Age (years), Mean (SD)	31.85 (13.17)	29.96 (11.19)	31.93 (11.81)	30.92 (11.90)	< .001	0.0066
Sex N (%)					.069	0.0013
Male	437 (56.0)	850 (53.3)	375 (48.6)	1662 (52.8)		
Female	341 (43.7)	737 (46.2)	392 (50.8)	1470 (46.7)		
Transgender	3 (0.4)	7 (0.4)	4 (0.5)	14 (0.5)		
Race/Ethnicity N (%)					.281	0.0019
Non-Hispanic White	503 (78.3)	1011 (73.4)	492 (74.9)	2006 (74.9)		
Non-Hispanic Black	20 (3.1)	64 (4.6)	28 (4.3)	112 (4.2)		
Non-Hispanic Asian	21 (3.3)	73 (5.3)	37 (5.6)	131 (4.9)		
Non-Hispanic Other Race	25 (3.9)	65 (4.7)	29 (4.4)	119 (4.5)		
Hispanic Ethnicity	73 (11.4)	165 (12.0)	71 (10.8)	309 (11.5)		
Marital Status N (%)					.017	0.0019
Married	171 (22.8)	339 (21.9)	193 (25.0)	703 (22.9)		
Divorced, Separated or Widowed	115 (15.3)	177 (11.4)	107 (13.9)	399 (13.0)		
Never Married	464 (61.9)	1034 (66.7)	472 (61.1)	1970 (64.1)		
Highest Level of Education N (%)					.250	0.0010
High school graduate or less	233 (36.5)	462 (34.2)	211 (30.8)	906 (33.9)		
Some college or associate degree	237 (37.2)	517 (38.3)	284 (41.4)	1038 (38.8)		
Bachelor's degree or more	168 (26.3)	372 (27.5)	191 (27.8)	731 (27.3)		
Annual Income N (%)					.007	0.0029
<$50k	323 (58.5)	659 (56.2)	373 (61.6)	1355 (58.2)		
$50k-$100k	119 (21.6)	327 (27.9)	136 (22.5)	582 (25.0)		
>$100k	110 (19.9)	186 (15.9)	96 (15.9)	392 (16.8)		

Note.
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as N (%) unless otherwise noted. Denominators may be less than column heads due to missing data.
Participants were invited to complete 6 total follow-up assessments post-baseline to the 12-month follow-up.
Tests of differences in sociodemographic characteristics between: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥ 1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all 6 follow-up assessments post-baseline with conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict Survey Response Status. R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups. For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

Table S8
Reasons for Non-Response, among Participants in the Re-engagement Survey, among Current Established Smokers and Current Experimenters at Baseline, Stratified by Readiness to Quit Smoking at Baseline

	Participants' Baseline Smoking Status			
	Current Established Smokers		Current Experimenters	
	Plan to Quit, Next 30 Days (N = 757)	No Plans to Quit, Next 30 Days (N = 1051)	Plan to Quit, Next 30 Days (N = 117)	No Plans to Quit, Next 30 Days (N = 148)
Smoking Status at Re-engagement				
% not smoking past 30 days	54.3%	40.6%	58.6%	52.4%
Reasons for Non-Response[a]				
Started smoking	3.9%	4.9%	5.2%	6.2%
Stopped using JUUL	4.1%	3.1%	6.0%	6.8%
Survey process reasons	80.9%	80.8%	75.0%	77.4%
Other reasons	11.1%	11.2%	13.8%	9.6%
Stopped smoking cigarettes[b]	2.3%	1.8%	5.2%	1.4%
	p = .548 UC = 0.0009		p = .747 UC = 0.0034	

Note.
[a] Coded to be exhaustive and mutually exclusive by prioritizing assignment to reasons in the order shown. That is, for example, respondents who endorsed "Started smoking" were tallied under that category even if they also endorsed "Survey process reasons"
[b] This was coded as part of the "Other reasons" category, but is also reported separately here
Uncertainty coefficient (UC) is an effect-size estimate representing the proportional reduction in error when values of participant characteristics are used to predict Survey Response Status. Lower values represent a weaker relationship, with 0 representing no relationship and 1.0 a perfect relationship.

Supplement 2

Insights from PATH on Smoking Patterns in Respondents Who Say They Smoked in the Preceding 30 Days, but Say They Now Smoke "Not At All"

Some studies define current smokers as those who report they now smoke "every day" or "some days," considering those who say they now smoke "not at all" as non-smokers.[1,2] The ADJUSST study defined current smoking more inclusively, as reporting any smoking, even a puff, in the past 30 days, even if they then said that they now smoke "not at all."

However, skip patterns in the survey were such that those who reported past-30-day smoking but then said they now smoked "not at all" were not asked how many days they had smoked or how many cigarettes per day, and thus, did not contribute to the calculations of the sample's cigarette consumption, either at baseline or in follow-up assessments. To gain insight into the smoking behavior of respondents who showed this response pattern, we turned to the Population Assessment of Tobacco and Health (PATH) study,[2] which also asked both smoking-status questions (past-30-day smoking and now smoking every day, some days, or not at all), but did have a skip defined for further questions about frequency and quantity of smoking. Specifically, all respondents who were asked how many days in the past 30 days they smoked and how many cigarettes they smoked. Additionally, they were asked how long ago they had last smoked.

Thus, PATH provides data on the smoking behavior of these past-30-day but not-at-all responders. To examine the smoking profile of ADJUSST respondents who at baseline reported smoking in the past 30 days, but then said they now smoke "not at all," we identified 1005 PATH Wave 4 respondents who gave that pattern of responses. Their responses indicated that they had smoked on an average of 3.4 (SD = 6.5) days in the past month (N = 996 for this parameter), consuming an average of 1.2 (SD = 3.3) cigarettes per day (N = 702). The majority (69%) reported that they had not smoked in the preceding 7 days (N = 681).

In sum, the PATH data indicate that there is a group of adults who report they smoked in the past 30 days, but now smoke not at all, and that respondents who give such responses are smoking little, smoking infrequently, and a modest number of cigarettes. The majority report 7-day abstinence, suggesting they may consider themselves to have recently stopped smoking, which may explain their 'not at all' response when asked to characterize what their smoking status is "now." In any case, these data from PATH, though on a different sample and not addressing ENDS use, shed some light on how to interpret this response pattern.

Supplementary References

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Switching away from Cigarettes across 12 Months among Adult Smokers Purchasing the JUUL System

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Objectives: In this study, we assessed complete switching away from cigarette smoking among adult smokers who purchased a JUUL Starter Kit (JSK). **Methods:** Adult (age ≥ 21) established smokers (smoked ≥ 100 lifetime cigarettes) who purchased a JSK in 2018 were invited to complete online surveys 1, 2, 3, 6, 9 and 12 months after initial JSK purchase. Point prevalence of switching (no past 30-day smoking) was assessed at each follow-up. Repeated measures logistic regression models evaluated associations of sociodemographic factors, baseline smoking characteristics and time-varying JUUL System ("JUUL") use characteristics and switching across the 12-month period. **Results:** Respondents (N = 17,986) were 55.0% male, 78.3% white, mean age = 32.65 years (SD = 10.81), mean baseline cigarettes/day = 11.10 (SD = 8.16). The proportion self-reporting switching increased over time: one-month (27.2%[3718/13,650]), 2-month (36.4%[4926/13,533]), 3-month (41.0%[5434/13,257]), 6-month (46.6%[5411/11,621]), 9-month (49.4%[6017/12,186]), and 12-month (51.2%[6106/11,919]); 33.1% reported switching at both 9-month and 12-month follow-ups. In prospective analyses, smokers with lower cigarette dependence, shorter smoking history, lower cigarette consumption, more frequent JUUL use, greater satisfaction from initial JUUL use, and higher JUUL dependence were significantly more likely to switch. **Conclusions:** Rates of switching with JUUL increased over time. Over 50% of respondents reported complete switching away from cigarettes 12 months following purchase. Greater use of and dependence on JUUL predicted switching.

Key words: smoking; electronic nicotine delivery system; cigarette; switching; JUUL
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The adverse health effects of smoking are primarily caused by exposure to the byproducts of tobacco combustion.[1] Electronic nicotine delivery systems (ENDS) expose users to lower levels of carcinogens and toxicants than cigarette smoking;[2] thus, may benefit public health if smokers who are unwilling or unable to quit cigarette smoking switch completely to using ENDS.[2-4]

The extant evidence suggests use of ENDS may increase smoking cessation rates;[5] observational studies indicate that use of ENDS is associated with abstinence from smoking,[6-17] and randomized trials demonstrate that ENDS may be equally or more effective for smoking cessation than transdermal nicotine patches.[18-20] Two analyses of a cohort of smokers who purchased the JUUL System ("JUUL;" Juul Labs Inc), a widely-used closed-system ENDS with a nicotine-salt formulation,

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found that 47% and 54% of respondents reported switching (ie, no smoking in the past 30 days) 3 and 6 months later, respectively.[21,22] However, there is a lack of longitudinal data assessing trajectories of switching among smokers who use ENDS such as JUUL over longer periods of time.

Analyses of the nationally-representative Population Assessment of Tobacco and Health (PATH) Study have identified characteristics associated with switching away from cigarettes among adult smokers who use ENDS. Longitudinal analyses have found that smokers who were daily (vs non-daily) ENDS users were more likely to make a subsequent report of past 30-day switching away from smoking,[12-16] and smokers with greater levels of baseline nicotine dependence were less likely to switch.[23] Additionally, data suggest greater dependence on ENDS may be associated with transition to exclusive ENDS use, possibly via transfer of dependence from cigarettes to ENDS.[24,25] However, given the year-long interval between assessments and timing of the PATH study (Wave 1 started data collection in 2013), there is a lack of more recent data on switching trajectories at more granular timepoints (ie, several times over the course of a year).

Some authorities hypothesize that ENDS must provide sufficient levels of reinforcement and satisfying effects to support complete substitution for cigarettes.[3,4] Recent trials in which smokers were provided with ENDS suggest that greater initial satisfaction and subjective reward are prospectively associated with increased likelihood of continued ENDS use and decreased cigarette consumption after several weeks of use.[26-28] Yet, it is unknown if positive initial responses to use of ENDS are prospectively associated with complete switching among ENDS users over longer periods of time.

The current longitudinal prospective cohort study followed a sample of adult smokers in the United States (US) who purchased a JUUL Starter Kit (JSK) over a one-year period. The primary aims of this naturalistic observational in-market surveillance study were to assess: (1) rates of complete past 30-day switching away from smoking, over time; and (2) associations of relevant sociodemographic, smoking, and JUUL use characteristics and subsequent switching at 6 timepoints (1-, 2-, 3-, 6-, 9-, and 12-month follow-up) across the 12-month period. Secondary aims included evaluation of sustained switching at the 9- and 12-month follow-up times, and patterns of JUUL use over time.

METHODS

Participants

A sample of adults (age ≥ 21 years) in the US were invited to participate in the Adult JUUL Switching and Smoking Trajectories (ADJUSST) Study upon purchasing a JSK in a retail store or online via the manufacturer's e-commerce platform, between June and October 2018.[29] Study inclusion criteria were: (1) age ≥ 21 years; (2) purchased a JSK for the first time within the past 7 days; (3) permanent residency in the US. Employees of Juul Labs Inc or PAX Labs Inc were excluded. The analytic sample was restricted to baseline Current Established Smokers (smoked ≥ 100 cigarettes in lifetime, smoked in the past 30 days, currently smoked some days or every day)[30,31] with data on past 30-day switching (past 30-day abstinence from smoking) at ≥ 1 follow-up assessment. Other analyses of JSK purchasers in ADJUSST are reported in companion papers in this issue – continuing smokers (ie, dual users),[32] former smokers,[33] and non-smokers,[34] and switching among special populations.[35]

Procedure

Individuals who purchased a JSK in a retail store were invited via recruitment cards embedded in the JSK package; online purchasers were invited via a post-purchase recruitment email. All surveys were administered online. All participants provided written informed consent and were compensated $30 for each survey they completed (baseline and follow-ups); compensation was not tied in any way to individual survey responses.

After participants completed the initial baseline assessment they were subsequently invited by email to complete 1-, 2-, 3-, 6-, 9- and 12-month follow-up assessments. Additional details regarding the overall study methods are described in 2 publications using data from a parallel study of adult smokers who purchased a JSK,[21,22] and in this issue.[29]

Measures

Past 30-day "switching" away from cigarette smoking. At each follow-up, participants were

asked: "In the past 30 days, have you smoked a cigarette, even one or 2 puffs?" (yes/no). A "No" response (ie, no smoking in the past 30 days) was defined as "switching," the primary outcome measure for the study, as in previous research.[12-14] Sustained switching was calculated among participants who provided sufficient data at the 9-month and 12-month follow-ups; a report of no past 30-day smoking at both the 9-month and 12-month follow-up was defined as sustained switching, and smoking at either follow-up was operationalized as failure to demonstrate sustained switching.

Past 30-day JUUL use. At each follow-up, participants reported whether they had used JUUL in the past 30 days ("Have you used a JUUL in the past 30 days, even one or 2 puffs?" [yes/no]).

Factors assessed for association with switching. Factors known to be associated with smoking abstinence were included in multivariable models as *a priori* regressors.[23,36-40] Participants reported their age, sex, race/ethnicity, highest level of education completed, total household income in the past 12-months, and marital status (Table 1).

At baseline, items assessed duration of regular smoking (years; continuous), number of days smoked cigarettes in past 30 days (open-ended; 1-30), and number of cigarettes smoked per smoking day (open-ended; continuous). Participants also reported if/when they planned to quit smoking (coded as planning to quit smoking in the next 30 days vs not planning to quit). Baseline combustible cigarette dependence was assessed with the Adult Tobacco Dependence (TD) Index, a composite measure of 16 items that was previously validated in the PATH Adult survey for assessing both cigarette and ENDS dependence (Range: 1-5; higher scores indicate greater dependence).[41,42] Participants who reported having started using their JUUL at baseline completed a version of the modified Cigarette Evaluation Questionnaire (mCEQ), a psychometrically validated[43,44] measure of subjective effects for cigarettes that has been previously used with ENDS,[45] adapted for JUUL. The mCEQ contained a composite "Satisfaction" subscale comprised of 3 items that were answered on 7-point response scales (from 1 ["Not at all] to 7 ["Extremely"]).

JUUL use characteristics assessed at each follow-up assessment were included as time-varying regressors; items were asked only of participants who reported past 30-day JUUL use. Level of JUUL dependence was assessed with the 16-item PATH TD Index adapted for JUUL, participants also reported the single (primary) JUULpod flavor they used most often in the past 30 days (one of 8 commercially available flavors in 2018; Table 1), as evidence suggests that use of ENDS (including JUUL) in non-tobacco (vs tobacco) flavors may be associated with switching.[16,21,22,46-48] Past 30-day frequency and daily quantity of JUUL use were only asked of 'every day' or 'some day' users and assessed with 2 items: (1) number of days used JUUL in the past 30 days (1-30 days); and (2) number of times used JUUL each day ("On average, on those days you used a JUUL, how many times did you usually use a JUUL each day? Assume that one 'time' consists of around 15 puffs, or 10 minutes").

Smoking Subgroups

Based on a prior classification and regression tree (CART) analysis[49] (ie, a forward stepwise statistical technique that identifies predictive characteristics to empirically partition a sample into mutually exclusive subgroups), smokers were divided into 6 subgroups based on 2 variables: (1) the number of days they reported smoking in the past 30 days at baseline (1-19, 20-29, or 30 days); and (2) their duration of regular smoking (≤ 5 years vs > 5 years): Infrequent – short-term smokers (smoked 1-19 days and regular smoking ≤ 5 years); Infrequent – long-term smokers (smoked 1-19 days and regular smoking > 5 years); Frequent – short-term smokers (smoked 20-29 days and regular smoking ≤ 5 years); Frequent – long-term smokers (smoked 20-29 days and regular smoking > 5 years); Daily – short-term smokers (smoked all 30 days and regular smoking ≤ 5 years), and Daily – long-term smokers (smoked all 30 days and regular smoking > 5 years).

Data Analysis

Sample characteristics and switch rates were assessed descriptively at baseline and across follow-up. Repeated-measure logistic regression models assessed associations of time-invariant and time-varying regressors and past 30-day switching averaged across the 6 follow-up assessments. Switching (yes or no) was modeled with binary logit link dis-

Table 1
Sociodemographic, Smoking, and JUUL Use Characteristics of Sample

Sociodemographic Characteristics	N (%) or Mean (SD)	Number Available[a]
Age in Years – Mean (SD)	32.65 (10.81)	17,986
Sex		17,858
Male	9820 (55.0)	
Female	7943 (44.5)	
Transgender	95 (0.5)	
Race/Ethnicity		16,830
Non-Hispanic White	13,183 (78.3)	
Non-Hispanic African-American	496 (3.0)	
Non-Hispanic Asian	950 (5.6)	
Non-Hispanic Other Race	766 (4.6)	
Hispanic Ethnicity	1435 (8.5)	
Marital Status		17,711
Married	4956 (28.0)	
Divorced, Separated or Widowed	2592 (14.6)	
Never Married	10,163 (57.4)	
Highest Level of Education Completed		16,852
High school graduate or less education	4689 (27.8)	
Some college or associate degree	7274 (43.2)	
Bachelor's degree or more education	4889 (29.0)	
Annual Household Income		15,624
Less than $50,000	8304 (53.2)	
$50,000-$100,000	4618 (29.6)	
Greater than $100,000	2702 (17.3)	
Smoking Characteristics at Baseline		
No. Days Smoked in Past 30, Mean (SD)	23.31 (9.47)	17,777
No. Cigarettes Smoked per Day, Mean (SD)	11.10 (8.16)	17,518
No. of Years Regular Smoking, Mean (SD)	12.41 (10.66)	17,890
Cigarette Dependence,[b] Mean (SD)	3.04 (1.08)	17,944
Plan to Quit Smoking in Next 30 Days	7356 (43.3)	16,983

(continued on next page)

Table 1 (*continued*)
Sociodemographic, Smoking, and JUUL Use Characteristics of Sample

Sociodemographic Characteristics	N (%) or Mean (SD)	Number Available[a]
JUUL Use Characteristics		
Satisfaction – First JUUL Use,[c] Mean (SD)	5.46 (1.09)	12,722
No. Days JUUL Use in Past 30,[d] Mean (SD)	24.52 (8.40)	70,086[e]
No. Times JUUL Use per Day,[d] Mean (SD)	11.09 (12.00)	69,846[e]
JUUL Dependence,[b,d] Mean (SD)	2.44 (0.94)	70,731[e]
Primary JUULpod Flavor Used in Past 30 Days[d]		70,155[e]
Virginia Tobacco	10,100 (14.4)	
Classic Tobacco	2298 (3.3)	
Menthol	4470 (6.4)	
Mint	20,671 (29.5)	
Mango	20,450 (29.1)	
Fruit	3215 (4.6)	
Creme	5671 (8.1)	
Cucumber	3280 (4.7)	

Note.
N = 17,986
[a] Number of participants or observations with valid (non-missing) data available for the respective variable and denominators for percentages for categorical variables.
[b] Adapted from Tobacco Dependence Index in PATH adult survey (Range: 1-5).
[c] Adapted from modified Cigarette Evaluation Questionnaire (Range: 1-7), assessed at baseline, only among those using JUUL or having used JUUL in the past.
[d] Time-varying variable (assessed at all follow-up assessments, variables aggregated [categorical] or averaged [continuous] across all follow-ups).
[e] 76,166 possible observations across 1-, 2-, 3-, 6-, 9- and 12-month follow-up assessments.

tributions. First, separate univariate models were conducted for each regressor (ie, including only the respective variable and time as regressors). Then, a series of 3 adjusted models including subsets of the independent variables were tested: (1) adjusting for baseline sociodemographic and smoking characteristics; (2) additionally adjusting for JUUL use characteristics, except initial satisfaction (because initial "Satisfaction" was assessed only among those already using JUUL); and (3) adjusting for all variables, including "Satisfaction."

To assess prospective associations of time-varying JUUL characteristics and switching explicitly, separate repeated-measure models were tested in which JUUL use characteristics (ie, frequency and daily quantity of use, JUUL dependence, primary JUULpod flavor) were tested as predictors of switching at the subsequent time-point up to 12 months (ie, JUUL use characteristics at the 1-, 2-, 3-, 6-, 9-month follow-ups were modeled as time-lagged regressors of switching at the 2-, 3-, 6-, 9- and 12-month follow-ups).

Time was coded as a continuous variable corresponding to month of follow-up assessment and included as a linear covariate; a quadratic time trend also was tested in a separate model. Regression models utilized all available data (listwise deletion). Analyses were conducted in SPSS version 25 (Armonk,

NY); regression coefficients were exponentiated to obtain odds ratios (ORs) with 95% confidence intervals (CIs) with alpha = .05 (2-tailed).

RESULTS

Participant Accrual and Follow-up

A total of 22,905 current established smokers completed the baseline assessment; the final analytic sample consisted of smokers who provided data for past 30-day switching at least one follow-up assessment (N = 17,986; 78.5% of baseline [68.7% retail purchasers]). Across the 6 follow-up assessments, response rates ranged from 75.9% to 66.3% (Table S1), and the largest proportion of participants (31.6% [N = 5677]) completed all 6 follow-ups (Table S2).

Within the cohort that provided partial data (ie, completed 1-5 follow-ups), 70.3% completed 3 or more follow-ups and 80.1% completed at least one of the follow-ups in the second half of the year (ie, 6-, 9- or 12-months). Additionally, 82.7% demonstrated intermittent responding – they missed one or more follow-ups, but then returned at subsequent follow-ups, rather than discontinuation (ie, completing a follow-up, but then dropping-out and completing no subsequent follow-ups).

Analyses comparing the baseline characteristics of participants who provided: (1) complete follow-up data; (2) partial follow-up data; and (3) no follow-up data indicate that there were minimal differences in sociodemographic and smoking characteristics ($R^2s \leq .002$), and some differences (eg, lower baseline cigarette dependence) were not suggestive of lower switch rates in non-responders (Table S3). Additionally, in a subsequent survey of participants who did not respond at 12 months 46% reported switching at time of re-contact (Table S4), suggesting that the potential for bias due to non-response was limited.[29]

Sample Characteristics

The sample had a mean age of 32.65 years (SD = 10.81); the majority self-reported as male (55.0%) and non-Hispanic white (78.3%), with smaller proportions of other racial/ethnic groups – Hispanic ethnicity (8.5%), non-Hispanic Asian (5.6%), and non-Hispanic African-American (3.0%; Table 1). Over half were never married (57.4%), and 72.2% reported completing at least some college. At baseline, on average, participants smoked 23.31 days (SD = 9.47) in the past 30 days and 11.10 cigarettes (SD = 8.16) per smoking day. The mean duration of regular smoking was 12.41 years (SD = 10.66) and 43.3% planned to quit smoking in the next 30 days. Mean cigarette dependence score was 3.04 (SD = 1.08); scores on the "Satisfaction" composite subscale of the mCEQ were intermediate between ratings of "A lot" and "Quite a lot" (mean [SD] = 5.46 [1.09]).

Across all 6 follow-up assessments, on average, participants reported using their JUUL 24.52 days (SD = 8.40) out of the past 30 days and 11.09 times per day (SD = 12.00; Table 1); mean levels of JUUL dependence were slightly lower than the midpoint of the 5-point scale (mean [SD] = 2.44 [0.94]). Patterns of JUUL use at each follow-up are displayed in Table S5. Aggregated across all 6 follow-ups, the largest proportion of participants reported primarily using Mint (29.5%) and Mango (29.1%) JUULpods, followed by Virginia Tobacco (14.4%), Creme (8.1%), and Menthol (6.4%).

Point Prevalence of Past 30-day Switching across Follow-up Period and Trend over Time

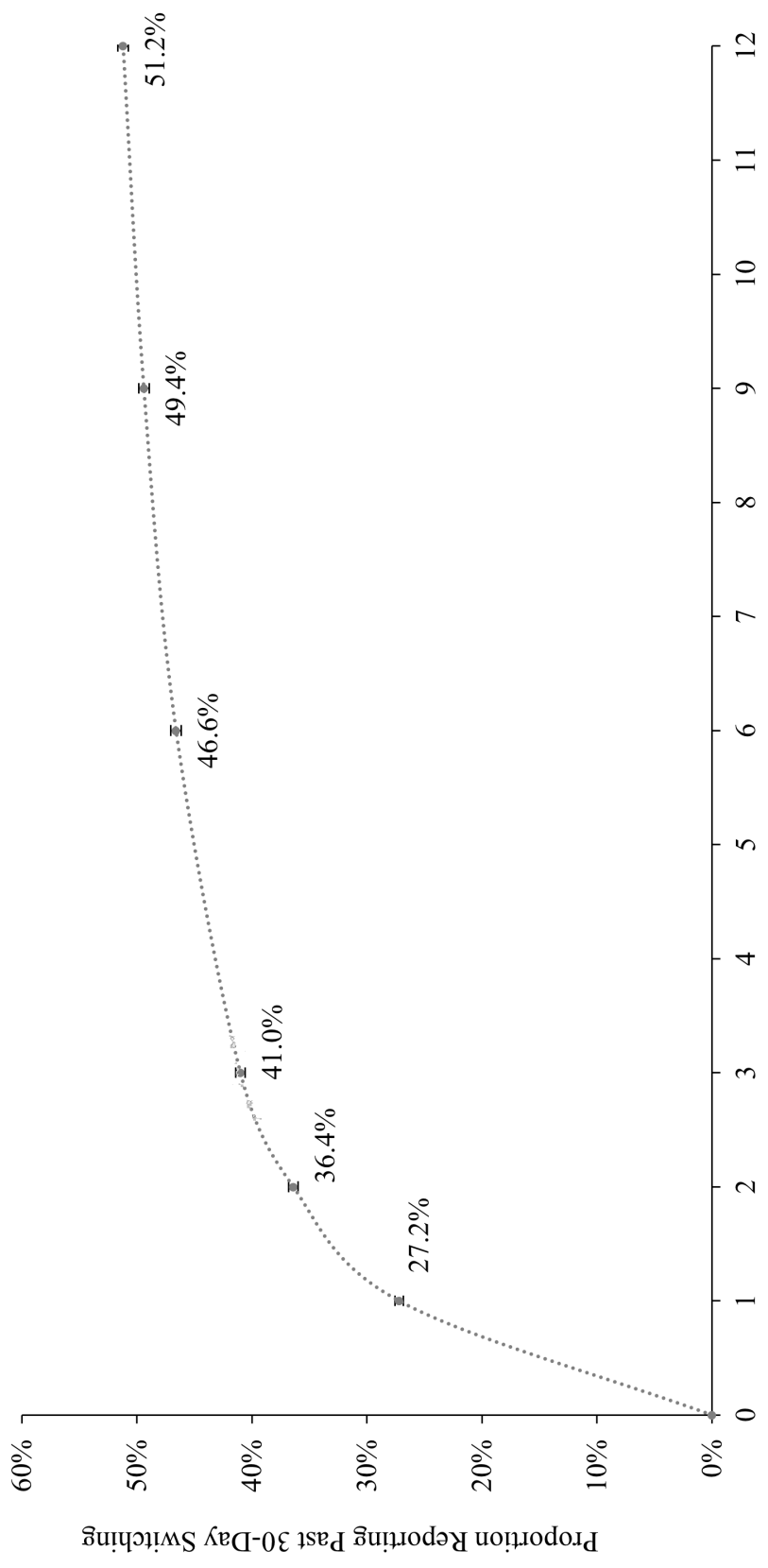
The proportion of respondents self-reporting past 30-day switching increased at each follow-up assessment:

- one-month (27.2%[3718/13,650]),
- 2-month (36.4%[4926/13,533]),
- 3-month (41.0%[5434/13,257]),
- 6-month (46.6%[5411/11,621]),
- 9-month (49.4%[6017/12,186]), and
- 12-month (51.2%[6106/11,919]; Figure 1).

Additionally, 33.1% (4047/12,218) reported switching at both the 9-month and 12-month follow-ups. Among respondents at the 12-month follow-up (N = 11,919), 46.5% were exclusively using JUUL, 4.8% were neither smoking nor using JUUL, 43.2% were dual users, and 5.6% were exclusively smoking.

Switching increased with time, such that the odds of switching in the univariate model increased by 8% of the past-month rate with each month after JSK purchase (Time effect: OR [95% CI] = 1.08 [1.08, 1.09]; Table 2). The time effect remained consistent in the 3 adjusted models (ORs Range: 1.09-1.10). Additionally, there was a statistically

Figure 1
Proportion of Current Established Smokers Reporting Switching across 12-Month Follow-up Period (± SE)



Note.
Current Established Smokers, N = 11,621-13,650.
Switching: "No" response to the question: "In the past 30 days, have you smoked a cigarette, even one or 2 puffs?"

Table 2
Association of Sociodemographic, Smoking, and JUUL Characteristics and Switching

Regressors / Sociodemographic Characteristics	Univariate Models OR (95% CI)	Adjusted Model 1[a] OR (95% CI)	Adjusted Model 2[b] OR (95% CI)	Adjusted Model 3[c] OR (95% CI)
Age in Years, Mean (SD)	0.98 (0.97, 0.98)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.86 (0.81, 0.90)	0.94 (0.89, 1.00)	0.93 (0.88, 0.99)	0.91 (0.85, 0.98)
Transgender	0.92 (0.67, 1.27)	0.82 (0.56, 1.21)	0.79 (0.54, 1.16)	0.79 (0.50, 1.24)
Race/Ethnicity				
Non-Hispanic White	Ref	Ref	Ref	Ref
Non-Hispanic African-American	1.12 (0.97, 1.29)	1.11 (0.93, 1.31)	1.13 (0.95, 1.35)	1.16 (0.94, 1.43)
Non-Hispanic Asian	1.00 (0.90, 1.11)	0.93 (0.82, 1.05)	0.88 (0.77, 1.00)	0.95 (0.80, 1.12)
Non-Hispanic Other Race	1.04 (0.92, 1.17)	0.99 (0.87, 1.13)	1.01 (0.89, 1.16)	0.97 (0.82, 1.15)
Hispanic Ethnicity	1.18 (1.08, 1.29)	1.02 (0.93, 1.13)	1.04 (0.94, 1.15)	1.02 (0.90, 1.15)
Marital Status				
Married	Ref	Ref	Ref	Ref
Divorced, Separated or Widowed	0.77 (0.71, 0.84)	0.86 (0.78, 0.95)	0.86 (0.78, 0.96)	0.85 (0.75, 0.96)
Never Married	1.07 (1.01, 1.13)	0.76 (0.71, 0.82)	0.75 (0.69, 0.81)	0.72 (0.65, 0.79)
Highest Level of Education Completed				
High school graduate or less education	Ref	Ref	Ref	Ref
Some college or associate degree	0.91 (0.86, 0.97)	0.89 (0.83, 0.95)	0.90 (0.83, 0.96)	0.90 (0.83, 0.98)
Bachelor's degree or more education	0.97 (0.91, 1.04)	0.85 (0.78, 0.92)	0.87 (0.80, 0.94)	0.91 (0.82, 1.01)
Annual Household Income				
Less than $50,000	Ref	Ref	Ref	Ref
$50,000-$100,000	0.98 (0.92, 1.04)	1.02 (0.95, 1.09)	1.01 (0.94, 1.08)	1.02 (0.94, 1.11)
Greater than $100,000	1.07 (1.00, 1.15)	1.08 (0.99, 1.18)	1.07 (0.98, 1.17)	1.11 (0.99, 1.24)
Smoking Characteristics at Baseline				
No. Days Smoked in Past 30 Days	0.96 (0.96, 0.96)	0.97 (0.97, 0.98)	0.97 (0.97, 0.98)	0.97 (0.97, 0.98)
No. Cigarettes Smoked per Day	0.96 (0.96, 0.97)	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1.00)
Duration of Regular Smoking (Years)	0.97 (0.97, 0.97)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)
Cigarette Dependence (Range: 1-5)	0.77 (0.75, 0.78)	0.95 (0.92, 0.99)	0.91 (0.87, 0.94)	0.88 (0.85, 0.92)
Plan to Quit Smoking in Next 30 Days	1.65 (1.57, 1.73)	1.70 (1.60, 1.79)	1.68 (1.59, 1.78)	1.65 (1.54, 1.76)

(continued on next page)

Table 2 (*continued*)
Association of Sociodemographic, Smoking, and JUUL Characteristics and Switching

Regressors Sociodemographic Characteristics	Univariate Models OR (95% CI)	Adjusted Model 1[a] OR (95% CI)	Adjusted Model 2[b] OR (95% CI)	Adjusted Model 3[c] OR (95% CI)
JUUL System Use Characteristics during Use				
Satisfaction from Initial JUUL Use (Range: 1-7)	1.27 (1.24, 1.31)	—	—	1.17 (1.13, 1.21)
Time-Varying Effects				
Time effect, months (linear)[e]	1.08 (1.08, 1.09)	1.09 (1.09, 1.10)	1.10 (1.10, 1.11)	1.10 (1.09, 1.11)
No. Days Used JUUL in Past 30 Days[d]	1.03 (1.03, 1.03)	—	1.03 (1.03, 1.03)	1.03 (1.02, 1.03)
No. Times Used JUUL per Day[d]	1.01 (1.01, 1.01)	—	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
JUUL Dependence[d]	1.17 (1.14, 1.19)	—	1.10 (1.07, 1.13)	1.08 (1.04, 1.11)
Primary JUULpod Flavor Used in Past 30 Days[d]				
Virginia Tobacco	Ref	—	Ref	Ref
Classic Tobacco	0.82 (0.75, 0.90)	—	0.81 (0.72, 0.91)	0.81 (0.70, 0.93)
Menthol	1.06 (0.98, 1.15)	—	1.06 (0.95, 1.17)	1.03 (0.91, 1.17)
Mint	1.15 (1.08, 1.22)	—	1.04 (0.97, 1.12)	1.01 (0.93, 1.10)
Mango	1.14 (1.07, 1.20)	—	1.06 (0.99, 1.14)	1.05 (0.96, 1.14)
Fruit	1.06 (0.98, 1.16)	—	1.06 (0.95, 1.18)	1.04 (0.91, 1.18)
Creme	0.90 (0.84, 0.98)	—	0.87 (0.79, 0.96)	0.84 (0.75, 0.94)
Cucumber	1.06 (0.97, 1.16)	—	0.97 (0.87, 1.07)	0.96 (0.85, 1.09)

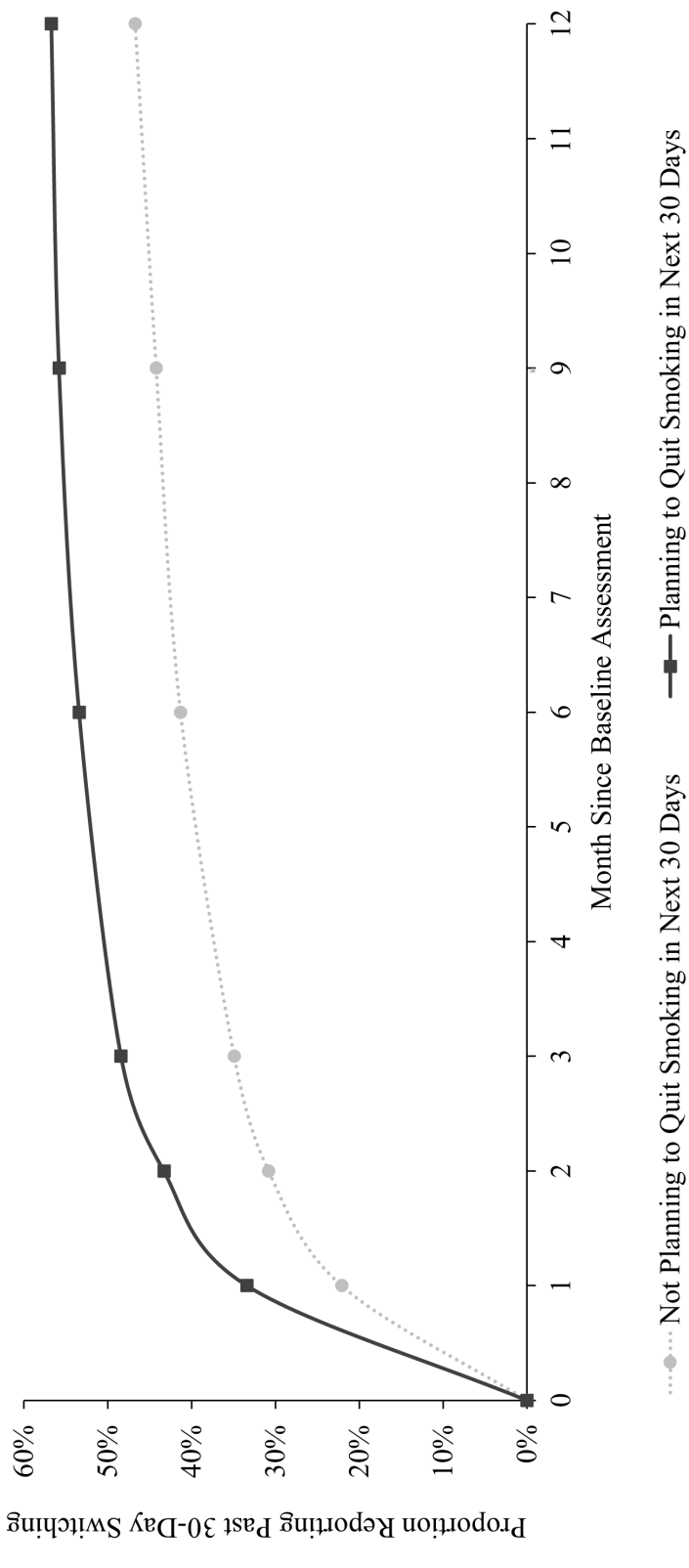
Note.
Model 1: N = 13,534 participants, 57,401 observations; Model 2: N = 13,182 participants, 51,383 observations; Model 3: N = 9323 participants, 36,161 observations.
[a] Adjusted for all baseline sociodemographic and smoking characteristics.
[b] Adjusted for all baseline sociodemographic, smoking and JUUL System use characteristics except initial satisfaction.
[c] Adjusted for all sociodemographic, smoking and JUUL System use characteristics.
[d] Time-varying covariate.
[e] Time was coded as continuous variable, in months.
A quadratic time term was significant (p < .001) when tested in a separate model.

significant negative quadratic effect of time (quadratic time term, p < .001), indicating that incremental increases in switching slowed over time (ie, the largest increases in switch rates were in the first 3 months, and the rate of switching increased more gradually thereafter).

Association of Sociodemographic, Smoking, and JUUL Use Characteristics and Switching across Follow-up

In the univariate models, age, sex, race/ethnicity, marital status, and education level were significantly associated with switching (Table 2). Increased past 30-day frequency (OR [95% CI] = 0.96 [0.96, 0.96]) and daily quantity (OR [95% CI] = 0.96 [0.96, 0.97]) of cigarette smoking, longer duration of regular smoking (OR [95% CI] = 0.97 [0.97, 0.97]) and higher levels of cigarette dependence (OR [95% CI] = 0.77 [0.75, 0.78]) were associated with significantly lower odds of switching (Table 2). Greater satisfaction from initial JUUL use (OR [95% CI] = 1.27 [1.24, 1.31]) and planning to

Figure 2
Proportion of Participants Reporting Switching by Planning to Quit Smoking across 12-Month Follow-up Period



Note.
Participants Not Planning to Quit Smoking in Next 30 Days: 1-Month, N = 7260; 2-Month, N = 7230; 3-Month, N = 7072; 6-Month, N = 6224; 9-Month, N = 6541; 12-Month, N = 6370.
Participants Planning to Quit Smoking in Next 30 Days: 1-Month, N = 5633; 2-Month, N = 5548; 3-Month, N = 5439; 6-Month, N = 4768; 9-Month, N = 4970; 12-Month, N = 4881.

quit smoking in the next 30 days (OR [95% CI] = 1.65 [1.57, 1.73]; Figure 2) were associated with significantly greater odds of switching.

Across the follow-up period, time-varying JUUL use characteristics including increased past 30-day frequency of JUUL use (OR [95% CI] = 1.03 [1.03, 1.03]), greater daily quantity of JUUL use (OR [95% CI] = 1.01 [1.01, 1.01]) and higher levels of JUUL dependence (OR [95% CI] = 1.17 [1.14, 1.19]) were positively associated with switching (Table 2). Each one-day increase in past 30-day JUUL use was associated with a 3% increase in odds of switching; similarly, each one-episode increase in JUUL use per day was associated with a 1% increase in odds of switching. A one-point increase in JUUL dependence was associated with a 17% increase in the odds of switching. Compared to participants who primarily reported using Virginia Tobacco JUULpods, primary users of Mint (OR [95% CI] = 1.15 [1.08, 1.22]) and Mango (OR [95% CI] = 1.14 [1.07, 1.20]) had increased unadjusted odds of switching, and primary users of Classic Tobacco (OR [95% CI] = 0.82 [0.75, 0.90]) and Creme (OR [95% CI] = 0.90 [0.84, 0.98]) had lower odds of switching.

Point Prevalence of Past 30-day Switching across Follow-up Period by Smoking Subgroup

Given univariate analyses that found smoking history and smoking frequency were strongly associated with switching, we summarized switching in subgroups previously empirically defined by duration of regular smoking and baseline past 30-day smoking frequency.[49] The sample was primarily comprised of daily long-term smokers (43.2% [N = 7663]) followed by infrequent short-term smokers (14.5% [N = 2574]), frequent long-term smokers (13.3% [N = 2356]), daily short-term smokers (10.3% [N = 1822]), infrequent long-term smokers (10.2% [N = 1810]) and frequent short-term smokers (8.4% [N = 1495]). Across all follow-up assessments, rates of switching varied by smoking subgroup, with higher switch rates observed among less frequent and shorter-term smokers (Figure 3). At the 12-month assessment, switch rates were highest among infrequent short-term smokers (63.6%), followed by infrequent long-term smokers (59.9%), frequent short-term smokers (55.8%), frequent long-term smokers (54.1%), daily short-term smokers (53.6%), and daily long-term smokers (43.1%). The steepest increase in switching over time was seen in the daily long-term smokers, who more than doubled their switching rates from month 1 to month 12.

Adjusted Models Assessing Associations of Sociodemographic, Smoking, and JUUL Use Characteristics with Switching across Follow-up

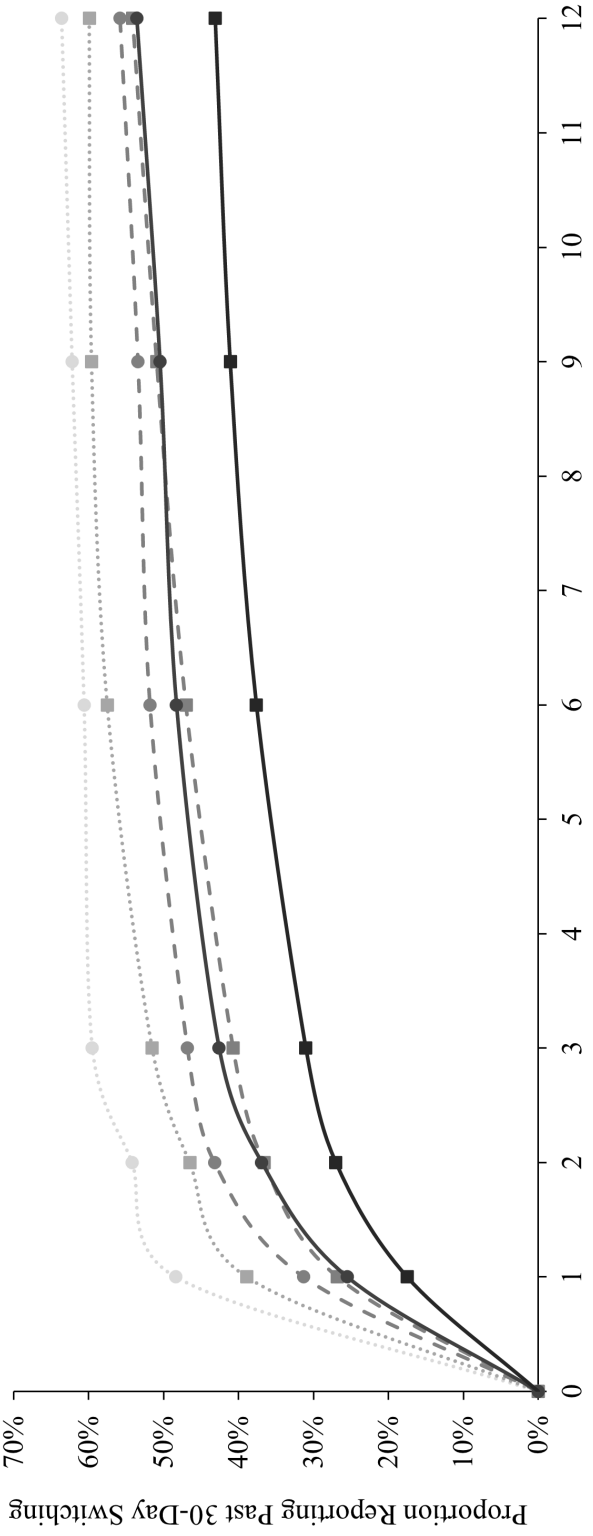
In the first adjusted model that included all baseline sociodemographic and smoking variables (Model 1), age, sex and race/ethnicity were not significantly associated with switching; however, marital status and education level were both significantly associated with switching across the entire follow-up period (Table 2).

Participants who planned to quit smoking in the next 30 days had greater odds of switching averaged across the follow-up period (OR [95% CI] = 1.70 [1.60, 1.79]; Table 2 and Figure 2). Past 30-day frequency (OR [95% CI] = 0.97 [0.97, 0.98]) and quantity of smoking (OR [95% CI] = 0.99 [0.98, 0.99] as well as duration of regular smoking (OR [95% CI] = 0.98 [0.97, 0.99]) and greater cigarette dependence (OR [95% CI] = 0.95 [0.92, 0.99]) remained significantly associated with reduced odds of switching.

In the second adjusted model (Model 2) that included time-varying JUUL use characteristics in addition to all sociodemographic and smoking variables, race/ethnicity, marital status, and education level were associated with switching (Table 2). Heavier and longer smoking history was associated with lower odds of switching, and participants who reported planning to quit smoking in the next 30 days had greater odds of switching (OR [95% CI] = 1.68 [1.59, 1.78]). More frequent and greater daily quantity of JUUL use and greater JUUL dependence were also significantly associated with increased odds of switching. After covariate adjustment, primary use of Mint or Mango (vs Virginia Tobacco) JUULpods was not significantly associated with increased odds of switching.

In the third adjusted model (Model 3), there was a statistically significant association between baseline subjective "Satisfaction" from JUUL use and switching across follow-up period; each one-point increase in "Satisfaction" was associated with a 17% increase in the odds of switching (OR [95% CI] = 1.17 [1.13, 1.21]; Table 2). Similar to Model

Figure 3
Proportion of Smoker Subgroups Reporting Switching across 12-Month Follow-up Period



Note.
Infrequent Short-Term Smokers, N = 1674-1857; Infrequent Long-Term Smokers, N = 1199-1382; Frequent Short-Term Smokers, N = 924-1074; Frequent Long-Term Smokers, N = 1505-1820; Daily Short-Term Smokers, N = 1153-1357; Daily Long-Term Smokers, N = 4971-5950.
Switching: "No" response to the question: "In the past 30 days, have you smoked a cigarette, even one or 2 puffs?"
Infrequent, Short-Term Smokers, smoked 1-19 days in the past 30 days and regular smoking ≤ 5 years.
Infrequent, Long-Term Smokers, smoked 1-19 days in the past 30 days and regular smoking > 5 years.
Frequent, Short-Term Smokers, smoked 20-29 days in the past 30 days and regular smoking ≤ 5 years.
Frequent, Long-Term Smokers, smoked 20-29 days in the past 30 days and regular smoking > 5 years.
Daily, Short-Term Smokers, smoked 30 days in the past 30 days and regular smoking ≤ 5 years.
Daily, Long-Term Smokers, smoked 30 days in the past 30 days and regular smoking > 5 years.

Table 3
Time-Lagged Associations of Time-Varying JUUL Use Characteristics and Switching

	Univariate Models OR (95% CI)	Adjusted Model[a] OR (95% CI)
Time-Varying JUUL Use Characteristics		
No. Days Used JUUL in Past 30 Days	1.02 (1.02, 1.03)	1.02 (1.02, 1.03)
No. Times Used JUUL per Day	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)
JUUL Dependence	1.20 (1.17, 1.23)	1.14 (1.11, 1.18)
Primary JUULpod Flavor Used in Past 30 Days		
Virginia Tobacco	Ref	Ref
Classic Tobacco	0.78 (0.71, 0.86)	0.75 (0.66, 0.86)
Menthol	1.05 (0.96, 1.15)	1.04 (0.93, 1.16)
Mint	1.16 (1.09, 1.24)	1.07 (0.98, 1.16)
Mango	1.13 (1.06, 1.21)	1.06 (0.98, 1.15)
Fruit	1.07 (0.97, 1.17)	1.02 (0.91, 1.15)
Creme	0.92 (0.84, 0.99)	0.87 (0.79, 0.96)
Cucumber	1.00 (0.91, 1.10)	0.90 (0.80, 1.01)

Note.
Adjusted model: N = 11,016 participants, N = 35,178 observations.
[a] Adjusted for all sociodemographic, smoking and JUUL System use characteristics.

2, marital status and education were significantly associated with switching as were smoking and JUUL use characteristics. There were no statistically significant associations between primary use of non-tobacco (vs Virginia Tobacco) JUULpods, and increased switching.

Time-Lagged Associations of Time-Varying JUUL Use Characteristics and Switching

In the time-lagged models, after adjustment for covariates, the prospective associations of JUUL use characteristics were similar in magnitude to effects seen in the cross-sectional model (Table 3). Specifically, respondents who used JUUL more frequently (both days per month and times used per day) and who demonstrated greater dependence on JUUL had greater odds of switching at the subsequent follow-up. No JUULpod flavors, compared to Virginia Tobacco, were associated with increased rates of switching.

Patterns of Past 30-day JUUL Use across Follow-up Period

The proportion of participants reporting past 30-day JUUL use remained high across the 12-month follow-up period (≥ 89.7% at each follow-up), ranging from 99.2% at the one-month follow-up to 89.7% at the 12-month follow-up (Table S5), while showing some decline over time – odds of past 30-day JUUL use decreased by 14% of the prior month's rate with each subsequent month post-baseline (Time effect: OR [95% CI] = 0.86 [0.85, 0.86]). There was little variability in frequency of past 30-day JUUL use (Range: 23.44-25.30 days) and daily quantity of JUUL use (Range: 10.83-11.31 times/day) across the 6 follow-up assessments (Table S5).

DISCUSSION

In this sample of adult smokers who purchased a JSK, rates of switching increased across the one-

year follow-up period, with over 50% of respondents reporting complete past 30-day switching 12 months after purchase; 33.1% reported sustained switching at both the 9-month and 12-month follow-ups. Consistent with observations in smoking cessation studies, rates of switching varied as a function of smoking frequency and duration[50,51] – switching decreased with increasing frequency and duration of smoking. However, switch rates were high among all subgroups of smokers – over 40% at the 12-month follow-up, even among long-term daily smokers. Consistent with previous research, more frequent use of JUUL and greater JUUL dependence were associated with increased likelihood of switching away from combustible cigarettes,[12-16] and greater satisfaction from JUUL use at baseline also was positively associated with switching.

The progressive increase in switching rates across the one-year period stands in contrast to cessation trials in which rates of abstinence from cigarettes drop steeply over time.[52] A key difference between this study and cessation trials is that participants did not necessarily start using JUUL with an immediate intent to quit smoking (ie, there was no explicit expectation of a change in smoking, and no quit date was set), allowing participants to transition away from cigarettes at their own pace. As observed in previous research,[13,53] initial dual use, rather than signaling failure and relapse, seemed to function as a transition to complete switching.[32] In fact, the majority of smokers who purchased a JSK were not ready to quit (ie, not planning on quitting smoking in the next 30 days), and would not typically have qualified for smoking-cessation treatment; yet, over 45% of these respondents reported complete switching 12 months later.

Conceptual models of drug use posit that initial positive subjective responses predict subsequent uptake;[54-56] some qualitative evidence suggests satisfaction with ENDS is central to successful switching,[57] and trials have found that smokers who rated ENDS as more rewarding were more likely to report decreased cigarette consumption.[26,27] These findings support the paradigm that "abuse liability" (ie, pharmacological reward and reinforcement) may be a key attribute of ENDS for facilitating smokers' switching away from cigarettes.[4] This concept has been articulated by the US Food and Drug Administration (FDA) Center for Tobacco Products, which considered the abuse liability of IQOS, and it deemed to be similar to that of cigarettes, noting that IQOS, "[C]an provide an adequate nicotine source for dependent populations, including current [smokers]."[58] Consistent with this, greater subjective satisfaction during initial JUUL use (ie, at the baseline assessment) was prospectively associated with significantly higher rates of complete past 30-day switching across the one-year follow-up period. Furthermore, greater frequency and daily quantity of JUUL use and greater dependence on JUUL also predicted increased switching. Although this observational study cannot establish causality, these findings suggest that JUUL use may facilitate switching.

Greater frequency and quantity of smoking and higher levels of combustible cigarette dependence were associated with a lower likelihood of switching. These findings are consistent with the smoking cessation literature that demonstrates longer-term, heavier, and more dependent smokers are less likely to achieve smoking abstinence.[50,51] Additionally, one study of smokers who used ENDS found that those who were more cigarette-dependent at baseline were less likely to switch away from cigarettes at a subsequent time.[23] The comparatively high switch rates among all smoker subgroups (over 40% at 12-month follow-up) suggest that JUUL use may facilitate switching, even among heavier and more dependent smokers.

The current study was a naturalistic observational surveillance study; there was no intervention – participants purchased JUUL on their own as they wished, received no instructions or advice, and no behavioral objective was defined. The switch rates observed in this study were higher than for other epidemiological studies of US smokers and ENDS users,[6-17] including the PATH study. Comparing switch rates across studies is difficult due to differences in the study designs and samples. The current study was based on use of JUUL, a nicotine-salt ENDS with greater nicotine delivery than early-generation ENDS products,[59] and differences in switching could be attributable to the characteristics of JUUL (vs other ENDS devices).

All smokers in the current sample had newly purchased a JSK, which implies a degree of commitment and motivation to use the product. This represents a sample of real-world motivated users,

likely a different population than that defined by past-30-day use in other studies. At the same time, the sample included smokers who would be expected to have limited switch rates – established smokers who had smoked at least 100 cigarettes lifetime, including those who were not ready to stop smoking, and excluded 'experimenters' and established smokers who reported smoking in the past 30 days at baseline but currently smoking "not at all" – who demonstrated higher switching rates.[60]

There has been considerable interest in the role of flavors in facilitating switching among smokers. In an unadjusted (univariate) model, primary users of Mint and Mango (vs Virginia Tobacco) JUULpods were more likely to switch; however, in the adjusted models these associations were attenuated and no longer statistically significant. These results should be interpreted with respect to changes in the availability of flavors in the US marketplace; at the start of the study in 2018, all 8 JUULpod flavors were commercially available in the US. Juul Labs Inc voluntarily removed non-tobacco and non-menthol JUULpods (Mango, Fruit, Cucumber, Creme) from retail stores in November 2018 and entirely from the US marketplace in October 2019.[61] Mint was removed in November 2019.[62] The FDA issued final guidance prioritizing enforcement against cartridge-based ENDS with flavors other than tobacco or menthol in January 2020.[63] Although there were no statistically significant differences in switch rates by primary JUULpod flavor, approximately 75% of participants primarily used flavors other than tobacco or menthol. Thus, overall, a greater number of smokers switched using non-tobacco flavors, suggesting that such flavors may have had the greatest population impact (ie, greater utilization of non-tobacco flavors may have resulted in more switching). Future research is needed to assess the effect of the removal of flavors from the marketplace on smokers' use of JUUL or other ENDS and switching.

The current study has several key strengths, including its large sample of JUUL purchasers, longitudinal design, contemporaneously collected data, multiple follow-up assessments, and JUUL-specific measures. In contrast to surveys that assess participants annually, the assessment schedule in this study (6 assessments over one year) provides finer temporal detail to assess the trajectories of switching over time and elucidate potential mechanisms underlying the process of switching away from cigarettes.

The recruitment and inclusion of only recent JUUL purchasers may limit generalization to all JUUL users, but provides an ecologically-valid assessment of switching trajectories upon true adoption of JUUL. In contrast to other surveys, participants in this study were not classified as "users" based merely on any use in the preceding 30 days, but rather, on the specific purchase of JUUL. Smokers who are motivated to purchase ENDS (including JUUL) are highly relevant to real-world adoption of ENDS products, and thus, a population of significant public health interest. However, study volunteers may differ from the larger population of users.

Compared to the US population of smokers,[52] the sample of JUUL purchasers in this study was younger, less racially diverse, and more affluent; however, the sample did include substantial numbers of older and non-white smokers. The younger age of the sample is characteristic of ENDS users, who are typically younger than cigarette smokers,[64-67] and has implications for public health, as switching away from cigarettes at younger ages is associated with improved health outcomes.[68] The study did not include a contrast group of smokers who were not using JUUL, nor was it randomized. Additional clinical and epidemiological research is needed to infer causality.

Interpretation of the primary switching outcome may be limited by participant attrition – participants who were less successful in switching could conceivably have been more likely to drop out, suggesting actual switch rates lower than those reported. However, analyses of loss to follow-up revealed little evidence of selective drop-out by baseline characteristics, including smoking behavior.[29] Demographic and smoking history differences between responders and non-responders were consistently small in magnitude, and some characteristics of non-responders, such as lower cigarette dependence, did not indicate that non-responders would have lower switching rates. Additionally, following completion of the study, participants who did not respond at 12 months were recontacted and reported comparable switching rates, further suggesting minimal bias due to non-response.[29]

These findings suggest that assuming participants who dropped out subsequently returned to smoking (ie, an "intent-to-treat" analysis) would underestimate true switching rates, and similar to other large longitudinal observational studies (eg, PATH and International Tobacco Control survey) treating these participants as missing is likely to provide a more accurate estimate of switching. Thus, although it is possible that the analysis based on responders yields higher switching rates, such an effect is likely to be modest.

Like other large-scale observational studies, the current study was also limited by reliance on self-report data and lack of biochemical verification of smoking abstinence. Use of non-cigarette tobacco products (eg, cigars) was not assessed at baseline or follow-up, limiting the study's ability to characterize participants' tobacco use and relate it to switching. Use of non-JUUL ENDS products was not included in the current analysis; another manuscript in this issue found that greater proportions of smokers who reported regular past 30-day use of non-JUUL ENDS at baseline (vs non-users) reported switching at 12 months.[60] The follow-up period was limited to one year for this analysis, and future research should assess switching beyond this period.

Conclusions

Among adult smokers who purchased JUUL, rates of switching increased over the one-year follow-up period, with over 50% of respondents reporting switching away from smoking 12 months after their initial JUUL purchase. Greater satisfaction and engagement with JUUL were associated with switching away from combustible cigarettes, supporting the importance of sufficient satisfying effects in facilitating switching, and suggesting that JUUL use did play a role in switching. Although the observational design of this study precludes causal inferences, it provides prospective evidence that a substantial proportion of smokers who purchased JUUL completely switched away from cigarette smoking one year later. These data suggest that adoption of JUUL may help smokers switch completely away from cigarette smoking, reducing their exposure to smoking-related toxicants, thereby improving individual, and ultimately, population health.

Human Subjects Approval Statement

This study was approved by Advarra Institutional Review Board (Approval no. 00027699, May 31, 2018).

Conflict of Interest Disclosure Statement

NIG, GML, and EMA are full-time employees of Juul Labs Inc. CH, DL, AG, and SP were full-time employees of Juul Labs Inc during the time that this work was conducted. Through PinneyAssociates Inc., SS provides consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc. Within the last 2 years, PinneyAssociates Inc has consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction. Under contract to Juul Labs Inc, the Centre for Substance Use Research, an independent research consultancy, designed the study and assessments and oversaw the work of Dacima Inc, who hosted the survey and collected the data. CSUR managed, cleaned, and summarized the data.

Author NIG performed the statistical analyses in consultation with the other authors. All of the authors contributed to the conceptualization and to writing and review of the paper, and all had access to the data. Juul Labs Inc approved the research plan and provided comment on a near-final draft of the paper.

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Table S1
Proportion of Analytic Sample that Completed Each Follow-up Assessment

Completed 1-Month Follow-up N (%)	Completed 2-Month Follow-up N (%)	Completed 3-Month Follow-up N (%)	Completed 6-Month Follow-up N (%)	Completed 9-Month Follow-up N (%)	Completed 12-Month Follow-up N (%)
13,650 (75.9)	13,533 (75.2)	13,257 (73.7)	11,621 (64.6)	12,186 (67.8)	11,919 (66.3)

Note.
N = 17,986
A total of 4919 smokers did not complete a follow-up assessment post-baseline and were excluded from the analytic sample.

Table S2
Number of Follow-Ups Completed among Analytic Sample

Number of Follow-Ups Completed	N (%)
1 Follow-Up	1907 (10.6)
2 Follow-Ups	1745 (9.7)
3 Follow-Ups	2020 (11.2)
4 Follow-Ups	2538 (14.1)
5 Follow-Ups	4099 (22.8)
6 Follow-Ups	5677 (31.6)

Note.
N = 17,986

Table S3
Differences in Baseline Smoking Characteristics by Survey Response Status, Among Current Established Smokers

Baseline Smoking Characteristics	No Smoking Data at Any Follow-Up (N = 4919)	Smoking Data at 1-5 Follow-Up(s) (N = 12,309)	Smoking Data at All 6 Follow-Ups (N = 5677)	Total (N = 22,905)	Test of Difference (p)	R^2
Age started smoking regularly (years), Mean (SD)	18.26 (4.07)	18.18 (3.71)	18.10 (3.76)	18.18 (3.80)	.11	0.0002
Years regular smoker, Mean (SD)	13.30 (11.81)	12.21 (10.77)	12.83 (10.42)	12.60 (10.93)	< .001	0.0017
Cigarette smoking dependence at baseline,[a] Mean (SD)	2.98 (1.08)	3.00 (1.07)	3.07 (1.08)	3.01 (1.08)	< .001	0.0008
No. days smoked cigarettes in past 30 days, Mean (SD)	23.30 (9.44)	23.19 (9.50)	23.58 (9.40)	23.31 (9.46)	.04	0.0003
No. cigarettes smoked per day at baseline, Mean (SD)	11.94 (9.08)	10.98 (8.08)	11.37 (8.31)	11.28 (8.37)	< .001	0.0021

Note.
[a] Combustible cigarette dependence, 16-item measure validated in PATH Study Adult Survey (Range: 1-5).
Adapted from manuscript, "The Adult JUUL Switching and Smoking Trajectories (ADJUSST) Study: methods and analysis of loss-to-follow-up" included in this issue.
Abbreviations: UC, uncertainty coefficient (effect size indicator for contingency tables with categorical or ordinal variables).
Data presented as N (%) unless otherwise noted.
Denominators may be less than column heads due to missing data.
Tests of differences in smoking characteristics between: (1) participants who did not provide valid smoking data at any follow-up assessment post-baseline; (2) participants who provided valid smoking data at ≥1 but not all follow-up assessments; and (3) participants who provided valid smoking data at all six follow-up assessments post-baseline were conducted with either χ^2 (categorical variables) or one-way analysis of variance (continuous variables).
Uncertainty coefficient represents the proportional reduction in error when values of participant characteristics are used to predict smoking data status.
R^2 is an effect size indicator continuous variables, expressing the percentage of variance in the continuous variable that is accounted for by the differences between respondent groups.
For both effect-size estimates, lower values represent weaker relationships, with 0 representing no relationship and 1.0 a perfect relationship.

Table S4
Smoking Status and Reasons for Non-Response among Current Established Smokers

Smoking Status or Reason for Non-Response	N (%)
Proportion not smoking in past 30 days	865 (46.0)
Reasons for non-response[a]	
Started smoking	84 (4.5)
Stopped using JUUL	67 (3.6)
Survey-related reasons	1504 (80.9)
Other reasons	205 (11.0)
Stopped smoking cigarettes[b]	38 (2.0)

Note.
N = 1900
Adapted from manuscript, "The Adult JUUL Switching and Smoking Trajectories (ADJUSST) Study: Methods and Analysis of Loss-to-Follow-Up" included in this issue.
Individual denominators may be less than total sample size due to missing data.
[a] Coded to be exhaustive and mutually exclusive by prioritizing assignment to reasons in the order shown. Respondents who endorsed "Started smoking" were tallied under that category even if they also endorsed "Survey process reasons."
[b] Coded as part of "Other reasons" category, also reported separately.

Table S5
JUUL Use Characteristics at Each Follow-Up Assessment

JUUL Use Characteristics	1-Month Follow-Up (N = 13,757)	2-Month Follow-Up (N = 13,664)	3-Month Follow-Up (N = 13,387)	6-Month Follow-Up (N = 11,741)	9-Month Follow-Up (N = 12,333)	12-Month Follow-Up (N = 12,083)
Prevalence of Past 30-Day JUUL Use	13,650 (99.2)	13,313 (97.4)	12,813 (95.7)	10,983 (93.5)	11,278 (91.4)	10,844 (89.7)
No. Days Used JUUL in Past 30 Days, Mean (SD)	25.30 (7.27)	25.13 (7.92)	24.73 (8.32)	24.28 (8.69)	23.86 (9.01)	23.44 (9.26)
No. Times Used JUUL per Day, Mean (SD)	10.83 (12.03)	11.03 (12.00)	11.04 (11.95)	11.17 (11.95)	11.31 (12.03)	11.22 (12.02)

Note.
Values represent N (%) unless noted otherwise.
Sample sizes may be less than column heads due to missing data.

Supplementary Results
Participant Accrual and Attrition

A total of 22,905 current established smokers completed the baseline assessment (68.7% retail purchasers [N = 12,356]; 33.7% online purchasers [N = 6067]), over three-quarters (78.5%; N = 17,986) provided at least some follow-up data; the remaining 21.5% (N = 4919) completed the baseline survey but did not complete any follow-up assessments. Across the follow-up period, the response rates ranged from 75.9% to 66.3%: 1-month, 75.9% (N = 13,650); 2-month, 75.2% (N = 13,533); 3-month, 73.7% (N = 13,257); 6-month, 64.6% (N = 11,621); 9-month, 67.8%. (N = 12,186); 12-month: 66.3% (N = 11,919; Table S1). Among current established smokers who completed ≥1 follow-up (N = 17,986), 31.6% (N = 5677) completed all six follow-ups, 22.8% (N = 4099) completed five, 14.1% (N = 2538) completed four, 11.2% (N = 2020) completed three, 9.7% (N = 1745) completed two and 10.6% (N = 1907) completed one follow-up (Table S2).

Dual Use of Cigarettes and JUUL: Trajectory and Cigarette Consumption

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Objectives: Many smokers who start using ENDS engage in dual use of cigarettes and ENDS. This paper examines time trends in dual use after a JUUL Starter Kit purchase, and changes in cigarette consumption among those remaining dual users. **Methods:** In the ADJUSST study, a cohort of adult smokers who purchased a JUUL Starter Kit were followed naturalistically 6 times over 12 months. Trends in dual use and reported complete switching away from cigarettes (ie, no past 30-day smoking), and changes in daily average cigarettes per day from baseline at 6 and 12 months were examined. **Results:** Dual use declined over time as complete switching increased. By 12 months, 43.2% reported dual using, and 51.2% reported switching away from cigarettes. Among dual users, approximately 60% reduced their cigarette consumption substantially (by ≥ 50%); average reductions in cigarette consumption were > 80%. Only a small minority (3%-10%) substantially increased cigarette consumption. **Conclusions:** Dual use of smoking and JUUL declines over time as switching away from smoking increases. This suggests that, for most smokers, dual use is a transitional state leading to switching completely away from cigarettes. Furthermore, dual use is often marked by substantial reductions in cigarette consumption.

Key words: cigarette consumption; dual use; e-cigarettes; smoking
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Although the rates of cigarette smoking in the United States (US) have declined in recent years, cigarette smoking continues to be the single greatest preventable cause of death and disability,[1] with cigarette smoking leading to 480,000 deaths annually in the US.[2]

Since approximately 2007, when electronic nicotine delivery systems (ENDS) entered the US market,[3] smokers have had the option of using ENDS in place of cigarettes as a source of nicotine. Indeed, ENDS use among US adults has increased as smoking has declined.[4,5] ENDS are estimated to be much less harmful to adult smokers' health than continued smoking of conventional cigarettes,[6] and as such, can represent a harm reduction method for adult smokers who would not otherwise quit.[7] The harm reduction potential of ENDS is strongest for adult smokers who switch completely away from cigarettes.[7] However, surveys suggest that many smokers who use ENDS engage in dual use — continuing to smoke while using ENDS.[8,9] The implications of dual use are not well-understood with respect to subsequent smoking and, ultimately, effects on dual users' health.

Some studies have concluded that dual users are less likely to quit or switch away from cigarettes,[10,11] and are reported to have high risk of subsequently returning to exclusive smoking.[12,13] Others have suggested that dual users smoke as many cigarettes as exclusive smokers do, implying that they may increase their exposure to toxicants.[14,15] These findings raise concerns that ENDS use augments and extends, rather than offsets and shortens, dual users' cigarette consumption and duration. Thus, ex-

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amining tobacco use behavior among dual users is relevant for understanding what long-term health implications of dual use are likely to be.

Existing studies of dual users that employ cross-sectional comparisons with exclusive smokers are problematic because they fail to account for dual users' cigarette consumption *prior* to starting ENDS. For example, an analysis of switching among adult smokers using JUUL found that the smokers who engaged in dual use (vs switching completely) had higher cigarette consumption at baseline,[16] making cross-sectional comparisons between dual users and smokers invalid. Thus, longitudinal studies are needed to track changes in smoking behavior over time among smokers after initiating with ENDS.

Other research suggests that dual use is a transition phase towards reduced cigarette use[17,18] or completely switching away from cigarettes.[5,19,20] Adult dual users report higher intentions to quit[21] and more frequent quit attempts than exclusive smokers.[21] Some report that adult dual users smoke fewer cigarettes per day (CPD) than exclusive smokers,[17,18,22] especially if they use ENDS daily.[18] Furthermore, some studies suggest that reduced cigarette consumption promotes rather than inhibits subsequent cessation of smoking.[23,24]

Thus, it remains unclear whether dual use of ENDS and cigarettes results in a reduction in cigarette consumption (and a corresponding reduction in exposure to smoking-related toxicants) and a transition to switching completely away from cigarettes, or a harmful behavior that leads to continued smoking and potentially increases net toxicant exposure. This question can best be answered in longitudinal data tracking adult smokers' behavior upon adoption of ENDS: the current study utilizes a longitudinal cohort of adult smokers who purchased a JUUL Starter Kit, which contained the JUUL System device (henceforth, 'JUUL') and 4 different flavored e-liquid JUUL pods in 2018 and were followed over the course of a year in a non-interventional naturalistic setting. These aims address the research questions of how the prevalence of dual use relative to other tobacco-use categories (eg, switching completely away from cigarettes) changes over time in an ENDS-using cohort of smokers, and whether smokers change their cigarette consumption after initiating ENDS use.

METHODS

Procedures

The sample was drawn from the Adult JUUL Switching and Smoking Trajectories (ADJUSST) study, a nationwide study of US adults (age 21+) who recently purchased a JUUL Starter Kit. The ADJUSST study followed this cohort in a longitudinal, non-interventional, naturalistic observational in-market surveillance study. Baseline assessments focused on sociodemographic characteristics, baseline smoking and ENDS use status and history. Follow-up assessments at 1, 2, 3, 6, 9, and 12 months focused on past 30-day JUUL use and smoking. All assessments were conducted online. Other tobacco use (non-cigarette and non-ENDS) was not assessed. The ADJUSST Study is not weighted, as the profile of the reference population of JUUL Starter Kit purchasers is not known. Further details of ADJUSST, including details on recruitment and participation, are available in a sister paper.[25]

Those who completed all follow-ups were similar to those who missed some or all follow-ups (see below for details of response patterns) in terms of sociodemographic characteristics (age, sex, race/ethnicity, marital status, education, and income; R^2 or UC ≤ .001, indicating a small effect size) and baseline smoking characteristics (smoking status, age of first regular smoking, duration of regular smoking, cigarette dependence, number of smoking days in past 30 days, CPD in past 30 days, and readiness to quit smoking; R^2 or UC ≤ .002).[25] Additionally, a re-engagement survey of ADJUSST participants who missed the 12-month assessment showed high rates of non-smoking (with the lowest among baseline established smokers at 46% not smoking in the past 30 days), and most in the re-engagement survey (approximately 80%) cited survey process issues as opposed to smoking (< 6%) as the reason for non-response.[25] Thus, we do not anticipate substantial bias due to missed follow-ups.

The current study's analyses focused on current smokers or subsets of current smokers at baseline, defined as follows:[25] (1) smoked in the past 30 days ("even a puff"), and (2) report they now smoke "some days" or "every day" (vs "not at all"). The 2 different aims of this study utilize different analytic samples of smokers, as described in each section below.

Objective 1: Trends in Dual Use, Smoking and JUUL Use

Sample. Analysis of dual use trends focused on baseline established smokers (N = 22,905), ie, past 30-day smokers smoking every day or some days, and having smoked 100 cigarettes/lifetime.[26] Established smokers were used for this analysis, as experimental smokers (ie, those who smoked < 100 cigarettes/lifetime) exhibit unstable use behavior, and as such may introduce instability into the trajectory analysis. Among baseline established smokers, 21.5% (N = 4919) did not complete any follow-ups, 24.8% (N = 5677) completed all 6 follow-ups (complete-case sample; Table S1), and the remaining 53.7% (12,309) provided at least partial data at some, but not all, follow-ups. Of those who provided at least some follow-up data, 75.9% provided data on smoking and JUUL one month, 75.2% at 2 months, 73.7% at 3 months, 64.6% at 6 months, 67.8% at 9 months, and 66.3% at 12 months; 80.1% provided data for at least one follow-up in the last half of the year (6 months or later). Shiffman et al[25] present analyses of nonresponse.

Measures. The current study focused on past 30-day dual use (both using JUUL and smoking) and switching completely away from cigarettes (no smoking, "not even a puff" in the past 30 days). To describe characteristic patterns over time, 4 tobacco-use categories were derived from the combination of past 30-day smoking and past 30-day use of JUUL ("even a puff"). Specifically, they were: (1) dual use – any past 30-day use of both JUUL and cigarettes; (2) JUUL only – JUUL use without smoking; (3) Smoking only – smoking without JUUL use; and (4) No JUUL/no smoking – use of neither JUUL nor cigarettes. A higher order category captured switching completely away from cigarettes: no smoking, regardless of JUUL use (the sum of JUUL-only and No JUUL/no smoking).

Analyses. Generalized estimating equation (GEE) analyses examined trends over time in the percentage of baseline established smokers who engaged in dual use, considering both linear trends and deviations from linearity (quadratic trend), while accounting for clustering of observations within participants over time. GEEs account for multiple, and variable observations per participant. Detailed analysis of demographic and tobacco use predictors of switching (largely vs dual use) is presented in a sister paper.[16] As a sensitivity analysis, to mitigate the effect of participants exiting the sample at particular time-points, we also analyzed trends in the "complete-case sample," ie, those who completed all follow-up assessments (Table S1).

Objective 2: Changes in Cigarette Consumption

Sample. The second set of analyses examined changes in dual users' cigarette consumption after initiating JUUL ENDS use. These analyses were conducted on 2 samples: (1) *all* smokers at baseline (smoked in the past 30 days, and smoked "some days" or "every day")[25] who reported being dual users at the relevant follow-up; and (2) the subset of baseline smokers who reported smoking at least 10 CPD on smoking days (to allow material room for reduction). These analyses focused on all baseline smokers (whether 'established' or not) because any amount of smoking presents risk, and the interest was in assessing changes in cigarette consumption, including among experimental smokers, whose consumption might even be expected to increase over time. Whereas smoking (and by extension dual use) was defined by past 30-day smoking, only participants who also reported smoking "some days" or "every day" (vs "not at all") at each follow-up were asked detailed cigarette consumption questions. Of N = 26,522 baseline smokers, 50.6% (N = 13,431) completed the 6-month follow-up and provided data on past 30-day smoking, and 52.0% (N = 13,795) did at the 12-month follow-up. Of the N = 13,742 smokers who smoked 10+ CPD on smoking days at baseline, 47.0% (N = 6821) provided data on past 30-day smoking at the 6-month follow-up and, and 48.8% (N = 7088) did so at 12 months.

Measures. Daily average cigarette consumption in the past 30 days was derived as CPD on smoking days × number of smoking days in the past 30 days /30 days, thus taking into account days smoked as well as daily cigarette consumption. Changes in cigarette consumption were analyzed at 6 and 12 months, and expressed as percent reduction from baseline cigarette consumption. *A priori*, a threshold of 50% or more reduction was set to indicate "substantial" reduction, based on previous literature.[27] Similarly, *increases* of 50% or more were also

Table 1
Characteristics of Current Established Smokers, for Objective 1: Trends in Tobacco-use Categories

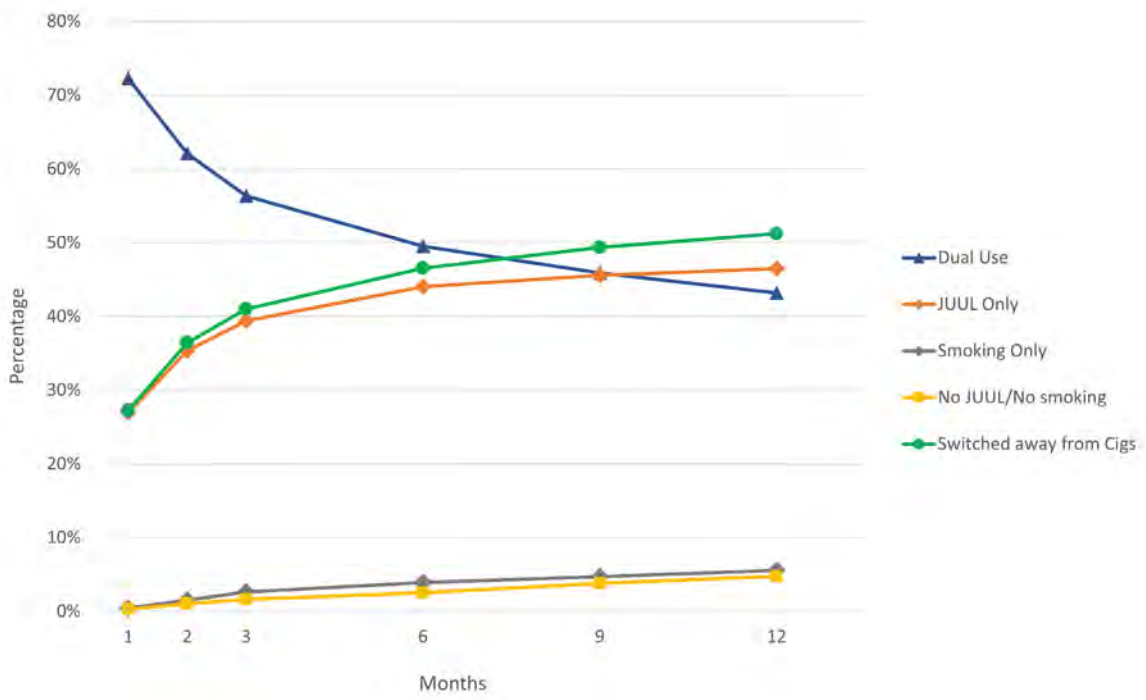
		Baseline Established Smokers[a] (N = 22,905)
Sex	Male	56.2% (12,766)
	Female	43.3% (9837)
	Transgender	0.5% (115)
Age [Median, IQR]		30 (24-39)
Education	High school or lower	28.4% (6071)
	Associate degree or some college	43.0% (9172)
	College degree or higher	28.6% (6101)
Race/ Ethnicity	Non-Hispanic white	78.9% (16,849)
	Non-Hispanic black	2.8% (597)
	Non-Hispanic Asian	5.5% (1174)
	Non-Hispanic other	4.6% (979)
	Hispanic	8.2% (1748)
Marital Status	Married	28.1% (6330)
	Divorced, separated, or widowed	14.8% (3340)
	Never married	57.0% (12,830)
CPD on days smoked --[Median, IQR]		10.0 (5.0-17.0)
Daily smoking in past 30 days		53.5% (12,104)
Number of smoking days in past 30 days -- [Median, IQR]		30.0 (20.0-30.0)
Daily average cigarette consumption --[Median, IQR]		8.7 (2.5-15.0)
Years of regular smoking -- [Median, IQR]		10.0 (4.0-19.0)
Age of first regular smoking -- [Median, IQR]		18.0 (16.0-19.0)
Cigarette dependence[b] (1-5 scale) -- [Median, IQR]		3.1 (2.2-3.9)

Note.
IQR: Interquartile range. Categorical variables are presented as percentage (N) and continuous variables are presented as median (interquartile range).
[a] Established smokers were defined as those who ever smoked, smoked at all in the past 30 days, smoked "some days" or "every day," and smoked ≥ 100 cigarettes in their life at baseline.
[b] Cigarette dependence was assessed with the Adult Tobacco Dependence (TD) Index with a range of 1-5, with higher scores indicating greater dependence; see Goldenson et al for details.[16]

regarded as substantial.

Due to the questionnaire skip pattern described above, participants who reported now smoking "not at all" (vs "some days" or "all days") at follow-up despite reporting some smoking ("even a puff") in the past 30 days were not queried on detailed smoking behavior. This means that cigarette consumption data, and thus, change in cigarette consumption data, are not available for this "not at all" group. Although other studies consider those reporting "not at all" smoking now as abstinent,[12,28] we conservatively include this group as

Figure 1
Percentage of Established Smokers at Baseline Who are in Each of the Tobacco-use Categories at Follow-up



Note.
"Switched away from cigarettes" is defined as not smoking, so includes both JUUL-only and No JUUL/no smoking.

smokers. The fact that detailed cigarette consumption is missing for this group has potential to bias the cigarette-consumption data, as analyses on an analogous cohort on PATH data showed that they are likely to be light smokers (Table S2).

Supplemental analyses (see cigarette consumption analysis, Tables S4 and S5) report an alternate measure of reduction in cigarette consumption: CPD on smoking days only, which isolates daily quantity from frequency (days per month).

RESULTS

Objective 1: Trends in Tobacco Use Categories

Table 1 shows the characteristics of the established smokers at baseline who comprised the analytic sample for trend analyses on tobacco-use categories. The sample was 56.2% male, 78.9% non-Hispanic white, had a median age of 30 years, and 71.6% had at least some college. These participants smoked a median of 10 CPD at baseline and just over half smoked daily. Mean cigarette dependence was 3.0 on a 1-5 scale, which is higher than estimates for the adult smokers population.[25] A sister paper shows that higher dependence is associated with lower likelihood of switching.[16]

Figure 1 shows the trends in tobacco-use categories over the 12-month study period. One month after initial JUUL purchase, 72.3% of established smokers were dual using, and this declined monotonically throughout the study to 43.2% at the 12-month follow-up. Complete switching accounted for the majority of the decline in dual use: among dual users at month one, 42.5% had switched completely away from cigarettes at the 12-month follow-up, while 6.4% had returned

Table 2
Characteristics of All Baseline Smokers (1st Column), and the Subset Smoking 10+ CPD on Smoking Days at Baseline (2nd Column), for Objective 2: Changes in Cigarette Consumption

		Cigarette Consumption Analysis	
		All Baseline Smokers[a] (N = 26,522)	Baseline Smokers[a] s moking 10+ CPD on Smoking Days (N = 13,742)
Sex	Male	56.4% (14,842)	56.6% (7714)
	Female	43.0% (11,317)	43.1% (5877)
	Transgender	0.5% (139)	0.3% (42)
Age [Median, IQR]		29 (23-38)	33 (26-43)
Education	High school or lower	29.2% (7173)	32.7% (4180)
	Associate degree or some college	42.5% (10,429)	44.0% (5,11)
	College degree or higher	28.3% (6949)	23.3% (2977)
Race/ Ethnicity	Non-Hispanic white	77.3% (19,044)	83.9% (10,715)
	Non-Hispanic black	3.0% (747)	2.0% (261)
	Non-Hispanic Asian	5.9% (1454)	4.2% (537)
	Non-Hispanic other	4.6% (1140)	3.8% (488)
	Hispanic	9.1% (2240)	6.0% (766)
Marital Status	Married	27.1% (7045)	33.5% (4527)
	Divorced, separated, or widowed	14.3% (3730)	18.5% (2509)
	Never married	58.6% (15,240)	48.0% (6498)
CPD on days smoked[b] -- [Median, IQR]		10.0 (4.0-15.0)	15.0 (10.0-20.0)
Daily smoking in past 30 days		49.8% (13,023)	74.2% (10,139)
Number of smoking days in past 30 days -- [Median, IQR]		29.0 (15.0-30.0)	30.0 (29.0-30.0)
Daily average cigarette consumption[a] -- [Median, IQR]		7.5 (1.7-15.0)	15.0 (10.0-20.0)
Years of regular smoking -- [Median, IQR]		9.0 (3.0-18.0)	13.0 (7.0-22.0)
Age of first regular smoking -- [Median, IQR]		18.0 (16.0-20.0)	18.0 (16.0-19.0)
Cigarette dependence[b] -- [Median, IQR]		2.9 (2.1-3.8)	3.5 (2.9-4.2)

Note.
CPD: Cigarettes per day. IQR: Interquartile range. Categorical variables are presented as percentage (N) and continuous variables are presented as median (interquartile range).
[a] Baseline smokers were defined as those who ever smoked, smoked at all in the past 30 days, and who smoked "some days" or "every day" at baseline.
[b] Cigarette dependence was assessed with the Adult Tobacco Dependence (TD) Index with a range of 1-5, with higher scores indicating greater dependence; see Goldenson et al for details.[16]

to exclusive smoking. Sensitivity testing using the complete-case sample showed extremely similar trends, with slightly lower (approximately 1-3 percentage point) rates of dual use, and equivalently higher rates of complete switching (Figure S1, Table S3).

Consistent with the trend evident in Figure 1, GEE analyses showed that the likelihood that participants were dual using declined linearly over time (OR = 0.91 [0.91-0.92], p < .001), indicating a 9%-per-month reduction in the odds of dual use. There was also a positive quadratic effect of time

Table 3
Tobacco Use Status (Switching away from Cigarettes and Dual Use) and Change in Cigarette Consumption Status (Substantial Reduction, No Substantial Change, or Substantial Increase) among All Baseline Smokers (Top Sub-rows) and Those Smoking 10+ CPD on Smoking Days at Baseline (Bottom Sub-rows) at 6-month (Top Row) and 12-month (Bottom Row) Follow-ups

					Dual Users, Stratified by Consumption Change			
		Switched away from cigarettes[a,c]	Smoking only[c]	All Dual Use[c]	Past 30-day smoking but "not at all" now[b,d]	Now smoking every day or some days (% of those with evaluable cigarette consumption)		
						Substantial reduction[e]	No substantial change[e]	Sub-stantial increase[e]
6-month follow-up	All Baseline Smokers	48.8% (6548)	3.7% (499)	47.5% (6384)	16.2% (1004)	60.5% (3018)	31.7% (1583)	7.8% (390)
	10+ CPD on Smoking Days at Baseline	41.0% (2796)	4.5% (307)	54.5% (3718)	11.0% (398)	62.4% (1972)	35.0% (1108)	2.6% (82)
12-month follow-up	All Baseline Smokers	53.1% (7330)	5.2% (722)	41.6% (5743)	15.4% (867)	59.1% (2693)	31.3% (1428)	9.6% (438)
	10+ CPD on Smoking Days at Baseline	46.6% (3305)	6.1% (434)	47.2% (3349)	10.6% (348)	63.2% (1827)	33.6% (973)	3.2% (93)

Note.
CPD: cigarettes per day. Percentages (N) are shown with respect to the corresponding sample in the column heading/sub-heading.
[a] Parallel figures for those who were 'established' smokers at baseline (smoked > 100 cigarettes lifetime) are reported by Goldenson et al as 46.6% at 6 months and 51.2% at 12 months.[16]
[b] Respondents who reported smoking "not at all" were not asked how often or how much they were smoking, and thus cannot be assessed for change in cigarette consumption.
[c] Denominator size changes as follows across rows: row 1: N = 13,341; row 2: N = 6821; row 3: N = 13,795; row 4: N = 7088.
[d] Denominator size changes as follows across rows: row 1: N = 6384; row 2: N = 3718; row 3:N = 5743; row 4: N = 3349.
[e] Denominator size changes as follows across rows: row 1: N = 4991; row 2: N = 3162; row 3: N = 4559; row 4: N = 2893.

(OR = 1.01 [1.01-1.01], p < .001), indicating that the decline in dual use slightly decelerated (ie, became less steep) over time. Results were essentially identical for the complete-case sample (see supplemental trends in tobacco use analyses, Table S3 and Figure S1).

Objective 2: Changes in Cigarette Consumption

Table 2 shows the characteristics of all baseline smokers, and the subset who smoked 10+ CPD on smoking days, the 2 analytic samples for analyses on cigarette consumption. Both samples had approximately 56% males, were majority non-Hispanic white (> 75%), with approximately 70% of participants having attended college. Both groups smoked every day or nearly every day in the past month. The subset who smoked 10+ CPD on smoking days at baseline were comprised of more non-Hispanic white participants (approximately 83% vs 77%) and had higher cigarette dependence scores.

Changes in cigarette consumption among all baseline smokers. Table 3 shows the percentages of dual users who substantially reduced their cigarette consumption, substantially increased consumption, or neither (no substantial change) 6 and 12 months after baseline. For context, as progressively

Table 4
Changes in Cigarette Consumption and Follow-up Cigarette Consumption Values among All Baseline Smokers (1st Column) and Those Smoking 10+ CPD on Smoking Days (2nd Column), Who Dual Use at 6-month (1st Row) and 12-month (2nd Row) Follow-ups

		All Smokers at Baseline			10+ CPD on Smoking Days at Baseline		
		Substantial reduction[a]	No substantial reduction[b]	Smoked in p30d, "not at all" now	Substantial reduction[a]	No substantial reduction[b]	Smoked in p30d, "not at all" now
6-month follow-up		N = 6384 (47.5% of all smokers at baseline)			N = 3718 (54.5% of those smoking 10+ CPD on smoking days at baseline)		
	Percentage decrease in cigarette consumption [median, IQR]	86.7% (70.0% - 95.0%)	0.0% (-28.6% - 25.0%)	NA[d]	86.7% (70.0% - 96.0%)	1.7% (0.0% - 29.6%)	NA[d]
	Average[c] daily cigarette consumption [median, IQR]	1.0 (0.3 – 2.7)	10.0 (3.3 – 15.0)	NA[d]	1.7 (0.5 – 4.2)	15.0 (10.0 – 20.0)	NA[d]
12-month follow-up		N = 5743 (41.6% of all smokers at baseline)			N = 3349 (47.2% of those smoking 10+ CPD on smoking days at baseline)		
	Percentage decrease in cigarette consumption [median, IQR]	86.7% (68.0% - 95.5%)	0.0% (-38.9% - 25.3%)	NA[d]	87.2% (66.7% –96.0%)	6.8% (0.0% - 30.0%)	NA[d]
	Average[c] daily cigarette consumption [median, IQR]	1.0 (0.3 – 3.0)	10.0 (2.7 – 15.0)	NA[d]	1.7 (0.5 – 4.7)	15.0 (10.0 – 20.0)	NA[d]

Note.
CPD: cigarettes per day. IQR: Interquartile range.
[a] Substantial reduction is defined as a reduction of ≥ 50% in CPD on days smoked at follow-up versus baseline.
[b] Includes no substantial change (< 50% change in either direction), or a substantial increase (≥ 50%) in CPD at ollow-up versus baseline.
[c] Average daily consumption is derived as CPD on days smoked × number of days smoked in past 30 days/30 days.
[d] Respondents who reported now smoking "not at all" were not asked how often or how much they were smoking, and thus, cannot be assessed for change in cigarette consumption.

fewer participants remain dual users (ie, on whom changes in consumption are assessed) at successive follow-ups (Figure 1), the proportions of dual use and complete switching are also presented. Because changes in cigarette consumption cannot be computed among those who said they were smoking "not at all," the percent of respondents in that category are also presented.

At 6 months, roughly equal proportions of baseline smokers were dual using (47.5%), as had switched completely away from cigarettes (48.8%). Of these dual users at 6 months, 16.2% reported smoking "not at all," and thus did not record cigarette consumption data. Among those who said they were smoking some days or every day, 60.5% had substantially reduced their cigarette consumption (ie, by 50% or more) from baseline. This group decreased their cigarette consumption to a median of one cigarette per day, representing an 86.7% decrease in cigarette consumption from baseline (Table 4).

By 12 months, more participants had switched away from cigarettes (53.1%) and correspondingly fewer remaining dual users (41.6%). Consump-

tion data among these remaining dual users at 12 months closely resembled that of dual users at 6 months, with a similar percentage (15.4%) smoking "not at all," and having substantially reduced their consumption (59.1%). Reducers smoked a median of one CPD, representing an 86.7% decrease.

Conversely, a minority (7.8%) of dual users substantially *increased* their cigarette consumption at 6 months, while the remaining 31.7% had not substantially changed their smoking in either direction. These non-reducers had no net change from baseline. To understand changes in cigarette consumption among those who substantially increased their smoking, we examined actual increases in CPD. Baseline cigarette consumption was modest, at a median of 1.3 CPD, and 41.3% showed an increase of only 2 CPD or less, with a median increase of 3.2 CPD.

These patterns were similar at 12 months as at 6 months, with approximately the same proportion who maintained similar levels of cigarette consumption (31.3%), but a slightly higher proportion who substantially increased (9.6%). As at 6 months, increasers at 12 months had modest baseline consumption (median of one CPD) and small increases (median of 3 CPD) at follow-up.

Changes in cigarette consumption among baseline smokers of 10+ cigarettes/day. Among the subset of smokers who smoked 10+ CPD on smoking days at baseline, 54.5% were dual users at 6 months and 41.0% had switched completely away from cigarettes. Of the dual users, 11.0% reported smoking "not at all," and 62.4% of those smoking every day or some days had substantially reduced their cigarette consumption, averaging reductions of 86.7%, to a median of 1.7 CPD.

More of the smokers had switched away from cigarettes at 12 months (46.6%) and fewer remained dual users (47.2%). Cigarette consumption among the dual users also closely resembled that of dual users at 6 months, with a similar percentage (10.6%) smoking "not at all" and a similar percentage having substantially reduced their consumption (63.2%). Reducers smoked a median of 1.7 CPD, representing an 87.2% decrease.

Conversely, only 2.6% of the 10+ CPD smokers substantially *increased* their cigarette consumption at 6 months, and the remaining 35.0% did not substantially change their consumption. These non-reducers averaged 15 CPD, representing a negligible (1.7%) reduction in cigarette consumption. Among those who substantially increased, baseline consumption was 10 CPD, with the median increase being 7.0 CPD.

Patterns among non-reducers at 12 months were similar to those at 6 months, with approximately the same proportion who maintained similar levels of cigarette consumption (33.6%) and who substantially increased (3.2%). As at 6 months, those who increased at 12 months had a baseline consumption of 10 CPD, with a median increase of 8.

All results were highly similar for an alternate metric of cigarette consumption (CPD on smoking days, without taking into account number of days smoked; Tables S4, S5), although reductions were consistently smaller when measured using CPD on smoking days.

DISCUSSION

In this study, we examined dual use of cigarettes and JUUL ENDS, and evaluated time trends of dual use, as well as changes in cigarette smoking consumption following smokers' initial purchase and use of a JUUL Starter Kit. Most established smokers reported dual use initially (one month after JUUL purchase), but dual use rates declined significantly over the following year, with by far the most common transition being to complete switching away from cigarettes (42.5% of initial dual users) as opposed to returning to exclusive smoking (6.4%). Additionally, most smokers who were dual-using at 6 or 12 months substantially reduced their cigarette consumption (ie, by 50%) following JUUL purchase and use. Although detailed consumption data were not available from dual users reporting smoking "not at all" at follow-up – who would be considered abstinent in other studies[12] – supplemental analyses of an analogous cohort in the PATH study suggest that consumption is low among this group (Table S2). Those who did not reduce their consumption by half most often sustained their baseline cigarette consumption. Only a small minority (< 1% of baseline smokers) substantially increased their cigarette consumption, and increases were usually small.

Thus, we observed 2 phenomena associated with dual use: reductions in cigarette consumption dur-

ing dual use, and transition to complete switching from smoking. The 2 may be related. For example, randomized trials show that use of nicotine replacement therapy products to reduce cigarette consumption also leads to complete cessation, even among smokers who were not initially ready to quit smoking.[23] Moreover, those who substantially reduced their smoking were more likely to transition to complete abstinence from smoking.[29,30] Thus, reductions in cigarette consumption during dual use may be part of the process of transitioning to complete switching over time.

The decline in dual use over time shows a trend complementary to that of switching rates, as shown in the sister paper on switching,[16] indicating that most of those who transitioned away from dual use eventually switch completely away from cigarettes (as opposed to returning to exclusive smoking). Indeed, of those engaged in dual use one month after purchase, over 40% had switched away from smoking at 12 months. In other words, dual use appears to be a transitional state in a process of switching away from cigarettes. This is consistent with some previous research showing an inverse association between ENDS use and cigarettes per day among smokers.[22]

Additionally, the time trend modeling suggests that dual use may continue to decline beyond the follow-up duration presented here, though at a slower rate than that observed early in smokers' adoption of JUUL ENDS. Thus, continued research can further evaluate longer-term trends in dual use among this population of smokers who purchase and use JUUL System.

Although this study only analyzed smoking behavior, and not toxicant exposures or health impacts, the observed reductions in cigarette consumption are relevant to toxicant exposures, and thus, likely relevant to subsequent health impacts. Toxicological research has examined the effect of complete switching and of dual use on exposure to harmful and potentially harmful constituents (HPHCs) that have been identified by the US Food and Drug Administration as relevant to smoking-related harm.[14] Because dual use involves the addition of HPHCs from ENDS, on top of those from continuing smoking, there has been concern that dual users may have higher aggregate HPHC exposure than exclusive smokers.[15] However, the reduction in cigarette consumption we report demonstrates that many dual users do *not* maintain their baseline cigarette consumption, but rather, substantially reduce it. This was also seen in a randomized study that instructed smokers to switch completely to JUUL for 6 weeks, in which those who engaged in dual use had reduced their cigarette consumption by 77%.[31] That study also showed that the dual users reduced their exposure to NNAL, an important HPHC, by half, while maintaining nicotine levels. This pattern also was seen in a different study, in which smokers were randomized to switch completely to JUUL, dual use with up to 50% of their baseline cigarette consumption, or abstain completely from all tobacco and nicotine for 6 days, in supervised confinement.[32] A similar study with another ENDS product produced similar results.[33] Dual use resulted in reductions in 12 different HPHCs that were approximately half of those seen among the complete abstainers, while complete switching resulted in reductions equivalent to complete abstinence.

In the current study, counting both those who switch completely away from smoking and those dual users who substantially reduced their cigarette consumption, over 70% of smokers who start using JUUL demonstrate a substantial reduction in cigarette consumption at follow-up, and likely experience a corresponding reduction in primary HPHC exposure. However, the impact of other sources of HPHCs (eg, residual thirdhand smoke residues in smokers' environments, or exposure to others' secondhand smoke) is unclear. Although any level of cigarette smoking poses health risks,[34] the dose-response effect of smoking on several health outcomes[35-37] suggests that substantial reductions in cigarette consumption and HPHC exposures could plausibly result in improved health outcomes among dual users. More research is needed to evaluate the ultimate clinical impact of this level of reduction.

While reducing their exposure to smoking-related HPHCs, both the dual user and most switchers continued to be exposed to nicotine from JUUL, which also carries risk. Although JUUL uses a nicotine-salt formulation, which has been speculated to deliver more nicotine, pharmacokinetic studies show that peak nicotine levels and total nicotine exposure is lower after a single use of JUUL than

after smoking a usual-brand cigarette.[38] Delivery from JUUL was within the range of seen for other ENDS, though higher than some.[39-42] Another experimental study showed that smokers who were randomized to switch to JUUL (in the 5.0% nicotine concentration used in the present study) for 6 days approximately maintained their baseline nicotine intake while drastically reducing their exposure to smoke-related HPHCs. Those randomized to reduce their cigarette consumption by half while using JUUL showed slightly, non-significantly reduced nicotine exposure.[32] Thus, although we did not assess nicotine exposure among dual users in this study, this suggests that the majority, who materially reduced their cigarette consumption, were unlikely to have increased their nicotine exposure.

Our findings on dual use differ from some previous work concluding that dual use is associated with maintaining cigarette consumption after starting ENDS,[15] high rates of returning to exclusive smoking,[12,13] and lower likelihood of quitting or switching.[10,11] It is possible that the differences are due to differences among ENDS products. This study was unique in focusing on users of JUUL, a nicotine-salt based ENDS that delivers more nicotine than some (but not all) other ENDS.[39-42] However, our data were limited to users of JUUL, and do not allow for any comparative inferences about other products.

The discrepancy between current and previous findings also may be due to differences in study sample and design, with the key difference being the timing of dual use initiation relative to study enrollment. The current study followed smokers longitudinally after they had just purchased JUUL, and thus, was able to capture the large percentage who switch away from cigarettes in the first few months afterwards (Figure 1). In contrast, most previous studies examining smoking outcomes among dual users fail to account for former dual users who had already switched completely away from cigarettes prior to ascertainment, thus likely restricting analyses to those who were so far unable to switch, consequently overestimating smoking and dual use rates. Moreover, cross-sectionally comparing the smoking behavior between separate groups of ongoing dual users and exclusive smokers is less valid than measuring *changes* in cigarette consumption in the same individuals, as we have done here. Therefore, the current findings mitigate concerns about dual use resulting in more greater cigarette consumption by demonstrating that, in a real-world population of adult smokers who purchased JUUL, dual use of both products was most often a temporary, transitional state marked by substantial reductions in cigarette consumption as smokers switch completely away from cigarettes.

In interpreting these data on dual use, it is important to keep in mind that most smokers who purchased and used a JUUL switched completely away from smoking by 12 months, and many had done so by 6 months.[16] Thus, the analyses presented here do not represent the cigarette consumption of the overall population of those smokers, but rather, focus on the subset who continued to smoke while also using JUUL. Our metric of reduction in cigarette consumption among dual users excluded the increasing proportion of JUUL users who reduced cigarette consumption by 100% – that is, those who switched completely – who constituted a majority of the smokers by 12 months. Also excluded, due to skip patterns in the ADJUSST study, were individuals who reported smoking in the past 30 days, but then also said they were now smoking "not at all," a pattern of responding associated with low cigarette consumption (Table S2). Thus, our data, although informative on the prevalence and nature of dual use, understate the reductions in cigarette consumption and exposures associated with adoption and use of JUUL.

It is important to emphasize that this was not a smoking-cessation or intervention study. ADJUSST participants were given no explicit expectation or goal to quit smoking upon JUUL purchase; in fact, many smokers were *not* ready to quit smoking at baseline, as indicated by not planning to quit within 30 days,[43] which would have disqualified them from traditional smoking cessation treatment. Nevertheless, many smokers who purchased JUUL reduced their cigarette consumption and switched away from smoking over time.

Limitations and Strengths

Limitations of this study should be taken into account in understanding its implications. First, given the observational nature of this study and the lack of a non-ENDS user group, causal conclusions about the role of JUUL use in subsequent duration

and heaviness of cigarette smoking cannot be made. Second, the completion rate at any given follow-up wave was limited, and it is possible that those engaged in dual use or continued smoking at baseline were more likely to miss follow-ups; however, analyses of differences between those with complete versus limited data, as well as analyses of data collected from follow-up of those who missed assessments, showed little indication of bias.[25] Third, our analyses relied on self-report, consistent with practices in similar surveys.[11,28,44-47] Fourth, the reductions in cigarette consumption may not indicate proportionate reductions in exposure to HPHCs, as smokers may compensate by increasing the intensity of smoking and thus their exposures. However, these reductions in cigarette consumption occurred in the context of using another nicotine product, which should obviate compensation. Indeed, experimental studies show that dual use with a 50%+ reduction in cigarette consumption substantially reduces HPHC exposure at follow-up.[31-33] Another limitation is that other types of tobacco use were not assessed in the ADJUSST study; thus, it is unclear how these may impact trajectories of dual use or reductions in cigarette consumption. A related question is the potential impact of other ENDS use; Prakash[48] reports that those already using other ENDS at baseline were less likely to be smoking 12 months later.

The sample is not representative of the larger population of dual users, as it is comprised of smokers who purchased JUUL. This likely represents a set of users with a greater demonstrated interest in using ENDS, as it excludes individuals who might be characterized as "users" on the basis of having merely tried JUUL in the preceding month.[11,28,44-47] Thus, the study represents the trajectory of smokers who more significantly adopted JUUL, making it informative about the potential for such adoption. Additionally, characteristics of this sample (eg, majority white, young, high levels of education, and low-to-moderate baseline cigarette consumption) did not match those of smokers in general,[9] although they are closer to the profile of ENDS users with respect to age, race, and socioeconomic status.[49-52] Nevertheless, caution should be taken when generalizing these findings to other populations.

Strengths of this study include a large sample followed repeatedly over the course of 12 months with data on cigarette consumption.

Conclusions

Smokers who purchase and use JUUL show high prevalence of dual use after one month, but this is progressively displaced by complete switching away from smoking. Moreover, when dual using, most of the JUUL users show substantial reductions (50%+) in cigarette consumption, which is likely to result in commensurate reductions in exposure to HPHCs.[32,33] Importantly, this dual-use state with reduced cigarette consumption is usually transitional, and most often gives way to complete switching away from cigarettes,[7] which drastically reduces the health risks relative to cigarette smoking.[7,53,54]

Human Subjects Approval Statement

This study was approved by Advarra Institutional Review Board (Approval no. 00027699, May 31, 2018).

Conflict of Interest Disclosure Statement

Through PinneyAssociates, AS and SS provide consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc. Within the last 2 years, PinneyAssociates has consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction. MG was a full-time employee of Juul Labs Inc during the time that this work was conducted, and EMA is full-time employees of Juul Labs Inc.

Under contract to JUUL Labs Inc, the Centre for Substance Use Research, an independent research consultancy, designed the study and assessments and oversaw collection of data through Dacima Inc. CSUR managed, cleaned, and summarized the data.

SS and EMA conceptualized the study. AS performed statistical analyses and all authors interpreted results. AS wrote the first draft of the manuscript with assistance from MG. All authors critically revised the manuscript and approved the final version.

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SUPPLEMENTARY MATERIALS

Dual Use of Cigarettes and JUUL: Trajectory and Cigarette Consumption Complete-Case Sensitivity Sample

RATIONALE

The main analyses of trends in tobacco-use categories (Figure 1) use all available data, including partial data from participants who did not complete all assessments. Here we use the subset of participants with complete follow-up data ("complete-case sample") as a sensitivity sample (see Trends in Tobacco-Use Categories Supplement below; Figure S1, Table S3).

METHODS

The sub-sample of ADJUSST participants with complete data at all time points ("complete-case sample," described in Shiffman et al (in this issue))[1] was used as a sensitivity sample (N = 5677).

RESULTS

Table S1 shows the characteristics of the complete-case sample used in the supplementary analysis on trends in tobacco-use categories (Figure S1; Table S3). The complete-case sample is extremely similar to the full sample presented in the main manuscript with respect to demographic characteristics, smoking history, and cigarette and JUUL use at follow-up.

Analysis of Past 30-day but "Not at All" Now Smoking in PATH Rationale

RATIONALE

This supplement examines the minority of participants with uncertain smoking status at each wave, as determined by reporting having smoked in the past 30 days but then reporting "not at all" smoking now (vs "some days" or "every day." In the ADJUSST study, respondents who said they smoked in the past 30 days, but then said they now smoke "not at all" were not asked how many days they had smoked nor how many cigarettes per day, and thus did not contribute to the calculations of the sample's cigarette consumption. This is consistent with other studies' use of defining those who report smoking "not at all" now as abstinent (eg, Coleman et al;[2]); however, here we conservatively consider them smokers and include them in all analyses to the extent possible.

To gain insight into the smoking behavior of respondents who showed this response pattern, we turned to the PATH study,[3] which also asked both smoking-status questions (past-30-day smoking and now smoking every day, some days, or not at all), but did not use them to skip over further questions about frequency and quantity of smoking. Specifically, all respondents who reported smoking at least one day in the past 30 days were asked how many days in the past 30 days they smoked (this was set to 30 for those who now smoke "every day," as per PATH logic) as well as how many cigarettes they smoked. Additionally, they were asked how long ago they had last smoked. Thus, PATH provides data on the smoking behavior of these past-30-day but not-at-all (P30D-NAA) smokers.

METHODS

We identified a sample of smokers with P30D-NAA response patterns in PATH Wave 4, and who had also provided adult Wave 3 data. To parallel the analyses in the ADJUSST study, we stratified individuals by their smoking status at Wave 3 (the equivalent of ADJUSST baseline) and tallied their reported smoking behavior at Wave 4.

RESULTS

Table S2 below shows the results. Wave-4 P30D-NAA smokers who were current smokers at baseline

Table S1
Characteristics of Complete-case Sample of Established Smokers

		Established Smokers,[a] Complete-Case Sample (N = 5677)
Sex	Male	53.1% (2995)
	Female	46.4% (2615)
	Transgender	0.5% (26)
Age [Median, IQR]		30.0 (25.0-38.0)
Education	High school or lower	28.7% (1534)
	Associate degree or some college	43.3% (2314)
	College degree or higher	28.0% (1499)
Race/ Ethnicity	Non-Hispanic white	78.5% (4162)
	Non-Hispanic black	3.3% (175)
	Non-Hispanic Asian	5.4% (284)
	Non-Hispanic other	8.3% (441)
	Hispanic	4.6% (242)
Marital Status	Married	30.5% (1711)
	Divorced, separated, or widowed	14.9% (837)
	Never married	54.6% (3061)
CPD on days smoked -- [Median, IQR]		10 (5-17)
Daily smoking in past 30 days		55.5% (3101)
Number of smoking days in past 30 days -- [Median, IQR]		30.0 (20.0-30.0)
Daily average cigarette consumption -- [Median, IQR]		9.3 (2.7-15.0)
Years of regular smoking -- [Median, IQR]		10.0 (5.0-19.0)
Age of first regular smoking -- [Median, IQR]		18.0 (16.0-19.0)
Cigarette dependence[b] (1-5 scale) -- [Median, IQR]		3.1 (2.3-3.9)

Note.
Smoking status defined at baseline. Categorical variables are presented as percentage (N) and continuous variables are presented as median (interquartile range).
[a] Established smokers were defined as those who ever smoked, smoked at all in the past 30 days, smoked "some days" or "every day," and smoked ≥ 100 cigarettes in their life at baseline.
[b] Cigarette dependence was assessed with the Adult Tobacco Dependence (TD) Index with a range of 1-5, with higher scores indicating greater dependence; see Goldenson et al. for details.[4]

(had smoked at all in the past 30 days, and were smoking "every day" or "some days") reported smoking 7.6 days in the past month, and averaging 2.9 cigarettes per day. Only 19% smoked frequently, defined as 20 or more days per month. A minority (37.7%) reported having smoked in the 7 days preceding the assessment.

SUMMARY AND CONCLUSIONS

In sum, the PATH data strongly suggest that respondents with the P30D-NAA response pattern (ie, reporting they smoked in the past 30 days, but reporting they now smoke not at all) are smoking very little, smoking in frequently and a modest number of cigarettes. The majority report 7-day abstinence, suggesting they may consider themselves to have stopped smoking, which may help explain their 'not at

Table S2
Smoking Patterns Reported by Wave 4 Respondents in PATH Who Indicated They Had Smoked in the Past 30 Days, but Also Indicated They Now Smoked "Not at All"

	Current Smoker[a] at Wave 3 N = 213		
	N	Mean/%	SD
Overall CPD (mean, SD), baseline (Wave 3)	206	5.8	7.6
Overall CPD (mean, SD), 1 year later (Wave 4)	178	2.9	5.0
Days smoked past 30 days† (mean, SD) 1 year later (Wave 4)	210	7.6	9.8
% smoking 20+ days in past 30[b] (%), 1 year later (Wave 4)	40	19.0%	--
% smoked in past week (%), 1 year later (Wave 4)	80	37.7%	--

Note.
[a] **Defined as a reported any smoking (even a puff) in the past 30 days and that they now smoke every day or some days.**
[b] **Per PATH logic, respondents who indicated they smoked every day were assigned smoking 30 days out of 30.**

all' response when asked to characterize their current smoking. This is consistent with other studies which consider the 'not at all' group as abstinent; however, we conservatively continue to consider these participants as smokers. In any case, these data from PATH, though on a different sample, and not addressing ENDS use, shed some light on how to interpret the P30D-NAA response pattern.

Trends in Tobacco Use Categories Supplement

RATIONALE

The main analysis uses all available data to examine trends in tobacco-use categories. This has the advantage of using all available data, including that from participants who were not fully compliant. However, when evaluating trends over time, it is possible that progressive differential non-response at follow-up can yield patterns that mimic change over time. For example, if dual users were more likely to drop out, the rate of dual use might artifactually appear to be declining. For this reason, it is useful to also examine the trends in complete cases, where trends are evaluated on a constant consistent sample (see Complete-Case Sensitivity Sample above).

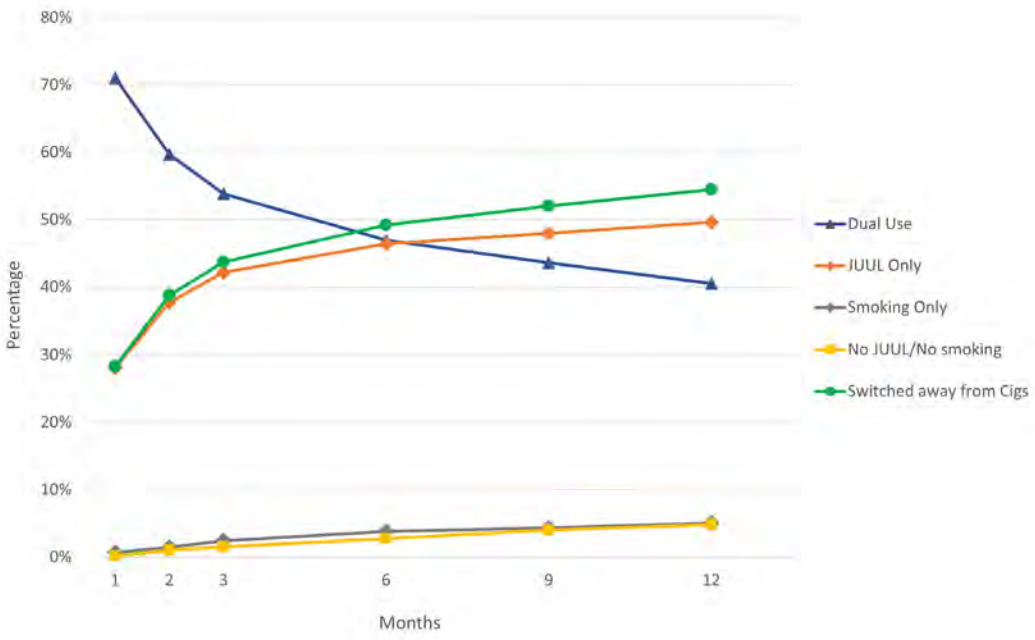
RESULTS

Figure S1 shows the trends in the 4 tobacco-use categories among the complete-case sample (Table S1) over the 12-month study period. One month after initial JUUL System purchase, 71.0% were dual using, and this declined monotonically to 40.5% at the 12-month follow-up. Complete switching accounted for the majority of the decline in dual use: among dual users at month one, 44.0% had switched completely away from cigarettes at the 12-month follow-up. Few smokers returned to exclusive smoking during the study (no more than approximately 6% of the baseline sample).

These results are highly similar to those reported in the main manuscript, with slightly fewer dual users (by 1-3 percentage points) among the complete-case sample than the full ADJUSST sample (Table S3).

Consistent with the trend evident in Figure S1, GEE analyses showed that the likelihood that participants were dual using declined over time (OR = 0.91 [0.91-0.92], $p < .001$), such that their odds of dual use were 9% lower every month after baseline. There was also a small quadratic increase in this trend (OR = 1.01 [1.01-1.01], $p < .001$), indicating that the decline in dual use decelerated over time.

Figure S1
Percentage of Established Smokers at Baseline Who are in Each of the Tobacco Use Categories at Follow-up. "Switched away from Cigarettes" is Defined as Not Smoking, so Includes JUUL-only and No JUUL/No Smoking



Note.
"Switched away from cigarettes" is defined as not smoking so includes both the JUUL-only and No JUUL/no smoking.

SUMMARY AND CONCLUSIONS

A complete-case analysis showed a progressive decline in the prevalence of dual use, along with a progressive increase in complete switching. The patterns seen in this analysis closely mirror those seen in the all-available-data analyses; thus, establishing their robustness, and indicating that the observed trends truly reflect changes over time, even within a stable cohort of JUUL System users.

Cigarette Consumption Analysis Supplement

RATIONALE

The main analyses use a definition of cigarette consumption that represents daily average cigarette consumption, taking into account both cigarettes per day on smoking days, as well as number of days smoked out of the past 30 days. However, this frequency-quantity measure leaves it unclear whether any changes in cigarette consumption reflect changes in both cigarettes per day and number of days smoked. Thus, it is of interest to specifically examine changes in quantity of daily cigarette consumption, when evaluating changes in cigarette consumption after smokers initiate JUUL System ENDS.

MEASURES

These supplemental analyses defined daily cigarette consumption as cigarettes per day (CPD) on days smoked (ie, without taking into account number of days smoked in the past 30 days).

Table S3
Comparison of Tobacco Use Trajectories between the Full Sample (Main Manuscript) and Complete-Case Sample (Supplement)

		1 month	2 months	3 months	6 months	9 months	12 months
Dual Use	Full sample	72.3%	62.1%	56.4%	49.5%	45.9%	43.2%
	Complete-case sample	71.0%	59.7%	53.8%	47.0%	43.6%	40.5%
JUUL only	Full sample	26.9%	35.4%	39.4%	44.0%	45.6%	46.5%
	Complete-case sample	28.1%	37.8%	42.2%	46.4%	48.0%	49.6%
Smoking only	Full sample	0.5%	1.5%	2.7%	3.9%	4.7%	5.6%
	Complete-case sample	0.7%	1.5%	2.4%	3.8%	4.3%	5.0%
No JUUL, no smoking	Full sample	0.3%	1.0%	1.6%	2.5%	3.8%	4.8%
	Complete-case sample	0.2%	1.0%	1.5%	2.8%	4.1%	4.8%
Switched away from cigarettes	Full sample	27.2%	36.4%	41.0%	46.6%	49.4%	51.2%
	Complete-case sample	28.3%	38.8%	43.7%	49.2%	52.1%	54.5%

RESULTS

Table S4 shows the percentages of dual users who substantially reduced their cigarette consumption, substantially increased consumption, or did not substantially change 6 and 12 months after baseline. For context, as progressively fewer participants remain dual users (ie, are in the sample for assessing changes in consumption) at successive follow-ups (Figure S1), the proportions of dual user and complete switching are also presented. Because changes in cigarette consumption cannot be computed among those who said they were smoking "not at all," the percent of respondents in that category are also presented.

At 6 months, 47.5% of baseline smokers were dual users, while 48.8% had switched completely away from cigarettes. Of these dual users at 6 months, 16.2% reported smoking "not at all," and thus, did not record cigarette consumption data. Among those who said they were smoking some days or every day, 51.4% had substantially reduced their cigarette consumption (ie, by 50% or more) relative to baseline. This group of substantial reducers decreased their cigarette consumption to a median of 3 CPD, representing a 72.7% decrease in cigarette consumption from baseline (Table S5). Tobacco-use categories at 12 months were similar to those at 6 months, with more participants who had switched away from cigarettes (53.1%) and correspondingly fewer remaining dual users (41.6%). Consumption data among these remaining dual users at 12 months also closely resembled that of dual users at 6 months, with a similar percentage (15.4%) smoking "not at all" (thus, not reporting on cigarette consumption), and a similar percentage having substantially reduced their consumption (50.1%).

Conversely, a minority (7.8%) of dual users substantially *increased* their cigarette consumption at 6 months, and the remaining 40.8% had not substantially changed their smoking in either direction. These 2 groups of non-reducers on average smoked 10 CPD at 6 months, representing no net change from baseline. To understand changes in cigarette consumption among those who substantially increased their smoking, we examined the actual increases in CPD. In this group, baseline cigarette consumption was modest, at a median of 3 CPD, and 41.5% showed an increase of another 3 CPD or less, with a median increase of 5 CPD. Changes in cigarette consumption status among remaining dual users at 12 months was similar to those at 6 months, with approximately the same proportion who maintained similar levels of cigarette consumption (40.2%), but a slightly higher proportion who substantially increased (9.7%). Cigarette consumption among those who increased at 12 months was similar to consumption among those who increased at 6 months, with modest baseline consumption (median of 3 CPD) and moderately small increases (median of 4 CPD) at follow-up.

Table S4
Tobacco Use Status (Switching away from Cigarettes and Dual Use) and Change in Cigarette Consumption Status (Substantial Reduction, No Substantial Change, or Substantial Increase) among All Baseline Smokers (Top Sub-rows) and Those Smoking 10+ CPD on Smoking Days at Baseline (Bottom Sub-rows) at 6-month (Top Row) and 12-month (Bottom Row) Follow-ups

					Dual Use, Stratified by Consumption Change			
		Switched away from cigarettes[a,c]	Smoking only[c]	All Dual Use[c]	Past 30-day smoking but "not at all" now[b, d]	Now smoking every day or some days(% of those with evaluable cigarette consumption)		
						Substantial reduction[e]	No substantial change[e]	Substantial increase[e]
6-month follow-up	All Baseline Smokers	48.8% (6548)	3.7% (499)	47.5% (6384)	16.2% (1004)	51.4% (2580)	40.8% (2049)	7.8% (393)
	10+ CPD on Smoking Days at Baseline	41.0% (2796)	4.5% (307)	54.5% (3718)	11.0% (398)	58.3% (1860)	39.6% (1264)	2.1% (67)
12-month follow-up	All Baseline Smokers	53.1% (7330)	5.2% (722)	41.6% (5743)	15.4% (867)	50.1% (2299)	40.2% (1846)	9.7% (446)
	10+ CPD on Smoking Days at Baseline	46.6% (3305)	6.1% (434)	47.2% (3349)	10.6% (348)	58.2% (1697)	39.0% (1138)	2.8% (81)

Note.
CPD: cigarettes per day. Percentages (N) are shown with respect to the corresponding sample in the column heading/ subheading.
[a] Parallel figures for those who were 'established' smokers at baseline (smoked > 100 cigarettes lifetime) are reported by Goldenson et al as 46.6% at 6 months and 51.2% at 12 months.[2]
[b] Respondents who reported smoking "not at all" were not asked how often or how much they were smoking, and thus, cannot be assessed for change in cigarette consumption.
[c] Denominator size changes as follows across rows: row 1: N = 13,341; row 2: N = 6821; row 3: N = 13,795; row 4: N = 7088.
[d] Denominator size changes as follows across rows: row 1: N = 6384; row 2: N = 3718: row 3: N = 5743; row 4: N = 3349.
[e] Denominator size changes as follows across rows: row 1: N = 5022; row 2: N = 3191: row 3: N = 4591; row 4: N = 2916.

Among the subset of smokers who smoked 10+ CPD on smoking days at baseline, 54.5% were dual users at 6 months and 41.0% had switched completely away from cigarettes. Of these dual users at 6 months, 11.0% reported smoking "not at all," and thus, did not provide cigarette consumption data. Among those who reported smoking some days or every day, 58.3% had substantially reduced their cigarette consumption. These substantial reducers decreased their consumption to a median of 4.0 CPD, representing a 75.0% decrease in cigarette consumption from baseline. Tobacco-use categories at 12 months were similar to those at 6 months, with more participants having switched away from cigarettes (46.6%) and fewer remaining dual users (47.2%). Consumption data among these remaining dual users at 12 months also closely resembled that of dual users at 6 months, with a similar percentage (10.6%) smoking "not at all" (thus, not reporting on cigarette consumption), and a similar percentage having substantially reduced their consumption (58.2%).

Conversely, only 2.1% of the 10+CPD smokers who were dual using at 6 months had substantially *in-*

Table S5
Changes in Cigarette Consumption and Follow-up Cigarette Consumption Values among All Baseline Smokers (1st Column) and Those Smoking 10+CPD on Smoking Days (2nd Column), Who Dual Use at 6-month (1st Row) and 12-month (2nd Row) Follow-ups

		All Smokers at Baseline			10+ CPD on Smoking Days at Baseline		
		Substantial reduction[a]	No substantial reduction[b]	Smoked in p30d, "not at all" now [a]	Substantial reduction	No substantial reduction[b]	Smoked in p30d, "not at all" now
6-month follow-up		N = 6384 (47.5% of all smokers at baseline)			N = 3718 (54.5% of those smoking 10+ CPD on smoking days at baseline)		
	Percentage decrease in cigarette consumption [median, IQR]	72.7% (60.0% - 83.3%)	0.0% (0.0% - 25.0%)	NA[c]	75.0% (60.0% - 87.7%)	6.3% (0.0% - 30.0%)	NA[c]
	CPD [median, IQR]	3.0 (1.0 – 5.0)	10.0 (4.0 – 15.0)	NA[c]	4.0 (2.0 – 5.0)	15.0 (10.0 – 20.0)	NA[c]
12-month follow-up		N = 5743 (41.6% of all smokers at baseline)			N = 3349 (47.2% of those smoking 10+ CPD on smoking days at baseline)		
	Percentage decrease in cigarette consumption [median, IQR]	71.4% (58.3% - 84.1%)	0.0% (-25.0% -25.0%)	NA[c]	75.0% (60.0% - 86.7%)	6.3% (0.0% - 27.3%)	NA[c]
	CPD [median, IQR]	3.0 (2.0-5.0)	10.0 (4.0-15.0)	NA[c]	4.0 (2.0-5.0)	15.0 (10.0-20.0)	NA[c]

Note.
CPD: cigarettes per day. IQR: Interquartile range.
[a] Substantial reduction is defined as a reduction of ≥ 50% in CPD on days smoked at follow-up versus baseline.
[b] Includes no substantial change (< 50% change in either direction), or a substantial increase (≥ 50%) in CPD at follow-up versus baseline.
[c] Respondents who reported now smoking "not at all" were not asked how often or how much they were smoking, and thus cannot be assessed for change in cigarette consumption.

creased their cigarette consumption, and the remaining 39.6% did not substantially change their baseline consumption. Together, these 2 groups of non-reducers on average smoked 15 CPD, on average, representing a negligible (6.3%) reduction in baseline cigarette consumption. Among those who substantially increased, baseline consumption was 10 CPD, and 85.1% increased by another 10 CPD, with the median increase being 8.0 CPD. Changes in cigarette consumption among non-reducing dual users at 12 months were similar to those at 6 months, with approximately the same proportion who maintained similar levels of cigarette consumption (39.0%) and who substantially increased (2.8%). Changes in cigarette consumption among those who increased at 12 months were similar to consumption of those who increased at 6 months, with baseline consumption of 10 CPD and most having increased by another 10 CPD or less.

These results are highly similar to those in the main analyses that examine cigarette consumption using a definition that takes into account CPD on days smoked as well as number of days smoked. These supplemental results consistently show slightly lower rates of substantial reduction (by no more than 10 percentage points for all baseline smokers; and by no more than 5 percentage points for the subset who smoked 10+ CPD on smoking days at baseline), which was mirrored by corresponding increases in rates of those who did not substantial change in cigarette consumption. Those who did reduce had slightly smaller

reductions (by approximately 10 percentage points) using this measure of consumption compared to that in the main text. Notably, the percentage who substantially *increased* is nearly identical as presented in the main text.

SUMMARY AND CONCLUSIONS

An analysis using a different measure of cigarette consumption (CPD on days smoked) showed among smokers who dual use at follow-up, more than half had substantially reduced their smoking consumption. Actual reductions were over 70% among those who had substantially reduced. Conversely, less than 10% had substantially *increased* their cigarette consumption at follow-up. These findings are very similar to those using the frequency-quantity measure of cigarette consumption presented in the main text; however, the reductions were slightly lower when only measuring quantity, with fewer dual users having substantially reduced smoking (by approximately 10 percentage points) and a slightly lower magnitude of actual reduction in CPD (by approximately 10-15 percentage points). Together, the two sets of results suggest that quantity alone does not fully account for the reduction observed using a quantity-frequency measure. In other words, that smokers who dual use reduce both the number of cigarettes they smoke on smoking days, as well as the number of days they smoke.

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Switching away from Cigarette Smoking with JUUL: Populations of Special Interest

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Objectives: In this study, we examined complete switching away from cigarettes across various medico-socio-demographic subpopulations of adult smokers who purchased a JUUL Starter Kit (JSK) electronic nicotine delivery system. **Methods:** We analyzed trajectories of smoking over 12 months in 17,986 adult smokers who purchased a JSK. Populations of special interest were characterized by race/ethnicity, income, diagnoses of potentially smoking-related illness (SRI), depression, and anxiety. **Results:** Across all 16 subgroups examined, a consistent pattern of trends was observed where complete switching increased, and dual-use decreased over time. Non-Hispanic Asian race/ethnicity, low income, diagnoses of potential SRI, depression, and anxiety were associated with significantly lower switching rates; however, complete switching rates at month 12 were near 50% for all groups, and surpassed the dual-use rates in all subgroups except for those with potential SRI. **Conclusions:** Substantial rates of complete switching were consistently achieved across all medico-socio-demographic subgroups 12 months following the purchase of the JSK. The potential benefits of switching with JUUL on smokers are likely to be experienced by a wide range of adult smokers.

Key words: switching; electronic nicotine delivery system; smoking; cigarettes; special populations
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Despite efforts made in tobacco control, smoking continues to be the most important preventable cause of morbidity and mortality in the United States (US).[1] The detrimental health effects of cigarettes, although universal, are disproportionately burdensome to select subpopulations, such as racial/ethnic minorities, those in a low socioeconomic status (SES), and those with mental health comorbidities. Smokers who already have developed illnesses potentially related to smoking are also an important subpopulation, as their need to stop smoking is even more urgent, and they may be particularly resistant to quitting. These subpopulations have a higher prevalence of smoking[2] and are less likely to succeed in quitting smoking.[3] Therefore, it is important to assess how interventions and harm-reduction products such as electronic nicotine delivery systems (ENDS) affect these subpopulations.

The disparity in smoking prevalence and quit rates across medico-socio-demographic subgroups has been documented. For example, the smoking prevalence is as high as 24% among American Indian/Alaskan Native adults compared to 15.2% in non-Hispanic Whites.[2] The quit rate in non-Hispanic black Americans has been consistently ~ 15% lower than that of white Americans.[4] A similar trend has been observed in low-income smokers, where those in a lower income category are 3 times more likely to be current smokers[2] and half as likely to achieve cigarette abstinence[5] compared to those in a higher income category. Those with potential smoking-related illnesses (SRI) have a longer and heavier history of smoking and a higher level of nicotine dependence,[6,7] which are likely to have contributed to their comorbidities and low cessation rate.[8,9] A high prevalence of smoking and low quit rates also are observed in those with mental

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health diagnoses.[10-12] Research on these subpopulations' responsiveness to existing smoking cessation interventions is scarce, but limited evidence suggests that cessation rates are lower than those in the general population.[13-15] The disadvantages these subgroups face contribute to limiting these groups' participation in the decline of smoking prevalence that is occurring at the larger population-level. This slower decline ultimately has resulted in a paradoxical worsening in smoking disparity,[16,17] even as we see the all-time lowest prevalence of adult smoking in the overall US population since the beginning of monitoring in the 1960s.

ENDS have been proposed as a less harmful substitute for smoking for adult smokers who are unable or unwilling to quit smoking.[18] Switching to ENDS has advantages over smoking by delivering nicotine with substantially lower levels of exposure to toxicants present in tobacco cigarette smoke.[19] A growing body of literature has explored the potential of ENDS as a smoking cessation aid[20-24] and demonstrated promising prospects in a traditional smoking cessation context. However, many smokers are unable to or unwilling to quit smoking. In such cases, switching completely away from cigarettes with ENDS can be a favorable alternative,[25-29] as it can reduce smokers' exposure to smoking-related toxicants, in some studies to roughly the same degree as abstaining from both smoking and ENDS.[30,31]

The literature on switching has yielded mixed results, likely made heterogeneous by variations in samples, methods and time-frames.[25-29,32-34] Weaver et al,[32] while reporting negative results for ENDS use, also note that the nature of the ENDS devices used has varied over studies and over time, with newer devices thought to be more effective in delivering nicotine to facilitate switching. Two studies examining adult smokers using the JUUL System (henceforth "JUUL") ENDS have suggested that many smokers can switch away from smoking. Russell et al[35] indicated that 54% of smokers who purchased a JUUL Starter Kit (JSK) reported switching away from smoking (no smoking in the past 30 days) at 6 months. In The Adult JUUL Switching and Smoking Trajectories (ADJUSST) Study, Goldenson et al[36] similarly found that most smokers (51%) completely switched away from combustible cigarettes 12 months after purchasing a JSK. Goldenson et al[36] also showed that switch rates increase over time, and Selya et al[37] showed that rates of dual use (use of JUUL while also smoking) concomitantly decrease over time.

However, it remains unknown if these favorable trends with JUUL also are seen in the aforementioned subpopulations with a history of smoking disparities. The evidence on such differences in switching among ENDS users is limited. For example, Harlow et al[38] and Park et al[39] demonstrated decreased odds of switching among non-Hispanic black and non-Hispanic other race smokers, respectively; however, these associations were not replicated in other papers.[40-42] Similarly, Kurti et al[41] and Kalkhoran et al[42] showed that low income was associated with decreased odds of switching, but others found no such relationship.[38,39] However, complete switching has been reported even among smokers with lower rates of smoking cessation, such as those with a history of recurrent relapse and physical/mental health issues.[43-45]

This study extends the findings on complete switching reported by Goldenson for the overall smoker population[36] by examining 16 subgroups across 5 domains of medico-socio-demographic factors under special consideration: race/ethnicity, income, diagnosis of potential SRI, and mental health issues (depression and anxiety, in particular). To document trajectories of smoking after adult smokers' adoption of JUUL products in these subpopulations, this study analyzes data of the ADJUSST study, where established smokers who purchased and used JUUL on their own in the open marketplace reported their smoking behavior over 12 months.

METHODS

Procedures

The data were from the ADJUSST study, a longitudinal observational study of US adults who purchased a JSK (a JUUL device, a charging dock, and 4 e-liquid pods) between 2018 and 2019.[46] Those who purchased a JSK were invited to participate, either through a card inserted in the package (retail purchaser) or an email (online purchaser) in a longitudinal study that followed their cigarette smoking and JUUL use. Those who were (1) 21 years or older, (2) permanent residents of the US, (3) purchased the JSK for the first time within the

past 5 days, and (4) not employees or family of employees of Juul Labs Inc, or PAX Labs Inc were eligible to participate. Participants who complete the baseline survey received email invitations for all follow-up surveys, even if they did not respond to the prior surveys. Participants were neither encouraged to stop smoking nor given a direction or support for any specific behavior or behavior change. Each survey invitation noted that participants were eligible to participate whether or not they were using JUUL and whether or not they were smoking. More details of the ADJUSST study have been described by Shiffman et al.[46]

The present study analyzed a cohort of baseline smokers to assess the association between their medico-socio-demographic characteristics and complete switching away from combustible cigarettes. For these analyses, smokers were defined as those who at baseline smoked in the past 30 days, report smoking 'every day' or 'some days', and had smoked 100 or more cigarettes in their lifetime; these are sometimes referred to as "established smokers." Participants who met the other 2 criteria, but who reported now smoking "not at all" at baseline were not included.

Participant Disposition and Missing Data

The study sample included 17,986 adult (21+) baseline smokers who completed at least one of 6 follow-up assessments post-baseline (months 1, 2, 3, 6, 9, and 12). The number of respondents who participated each follow-up was as follows: 13,650, 13,533, 13,257, 11,621, 12,186, and 11,919 at months 1, 2, 3, 6, 9, and 12, respectively. Descriptive analyses on smoking status over time used all of these 76,166 data-points (an average of 4.23 follow-ups per participant).

Among those who responded to some but not all follow-up surveys (ie, 1-5 surveys), 70.3% provided 3 or more follow-ups. A strong majority (82.7%) of this partial-response cohort showed a pattern of intermittent responding (eg, missing one or more follow-ups, but then returning at subsequent follow-ups) rather than discontinuation (eg, initially responding, then dropping out and completing no subsequent follow-ups). A strong majority (80.1%) completed at least one of the follow-ups in the second half of the year (ie, at or after 6 months).

Survey nonresponse has the potential to cause biases if responders differ from non-responders. However, analyses by Shiffman et al[46] showed that (1) those with no follow-up data, (2) those with partial data, and (3) those who completed all 6 follow-ups did not show meaningful differences in their sociodemographic characteristics and baseline smoking history (R^2 or uncertainty coefficients ≤ 0.002). Also, the observed differences were small and did not consistently suggest that non-responders would have had lower switching rates (eg, they had lower cigarette dependence, which was associated with *higher* rates of switching).[36] Furthermore, when nonrespondents to the month 12-survey were re-contacted, 46% reported complete switching.[46] Collectively, these results indicate that biases from participation rates are likely to be limited. As it also can be useful to examine data from complete cases for trends over time, so as to follow the same cohort of individuals without a changing sample over timepoints, data based on complete cases (N = 5677) are shown in the Supplementary Material 1.

The generalized estimating equation (GEE) modeling was necessarily based on those participants with non-missing data on all 11 covariates (described below), resulting in a dataset of 57,314 observations from 13,461 participants. In this analysis, the number of participants at each follow-up was 10,328, 10,187, 9957, 8770, 9149, and 8923 at months 1, 2, 3, 6, 9, and 12, respectively.

Measures

Defining special populations. Five special subpopulations were defined based on baseline medico-socio-demographic characteristics. Race/ethnicity was coded into 5 levels based on participants' racial, ethnic, and national origin. Three strata of income were defined, based on the federally-defined poverty level (FPL),[47] which takes into account household income and household size. The strata corresponded approximately to ≤ 150% of the FPL, 150%-400% of FPL, and ≥ 400% FPL, and were referred to as low, medium, and high income. See the Supplemental Material 2 for details.

Medical history was self-reported by questions on whether the participant had ever been told by a health professional of a diagnosis of particular diseases. A composite stratum of potential SRI was defined by diagnosis of chronic obstructive pulmonary disease (COPD), emphysema, congestive

Table 1
Baseline Characteristics and JUUL Use of the Sample, Stratified by Sociodemographic Groups

Characteristics		Race					Income			Total
		White	Black	Asian	Hispanic	Other/ multi	< 150% FPL	150 – 400% FPL	> 400% FPL	
N		13,183	496	950	1435	766	6279	4839	4506	17,986
Race/ ethnicity*	White						4560 (77.13%)	3672 (80.39%)	3324 (78.27%)	13183 (78.33%)
	Black						210 (3.55%)	119 (2.61%)	88 (2.07%)	496 (2.95%)
	Asian						232 (3.92%)	205 (4.49%)	371 (8.74%)	950 (5.64%)
	Hispanic						589 (9.96%)	362 (7.92%)	316 (7.44%)	1435 (8.53%)
	Other/multi						321 (5.43%)	210 (4.60%)	148 (3.48%)	766 (4.55%)
Income*	< 150% FPL	4560 (39.46%)	210 (50.36%)	232 (28.71%)	589 (46.49%)	321 (47.28%)				6279 (40.19%)
	150 – 400% FPL	3672 (31.78%)	119 (28.54%)	205 (25.37%)	362 (28.57%)	210 (30.93%)				4839 (30.97%)
	> 400% FPL	3324 (28.76%)	88 (21.10%)	371 (45.92%)	316 (24.94%)	148 (21.80%)				4506 (28.84%)
Smoking-related illness - Yes*;**		471 (3.57%)	10 (2.02%)	10 (1.05%)	25 (1.74%)	15 (1.96%)	226 (3.60%)	134 (2.77%)	112 (2.49%)	581 (3.23%)
Depression - Yes*;**		4276 (32.44%)	116 (23.39%)	118 (12.42%)	399 (27.80%)	273 (35.64%)	2463 (39.23%)	1457 (30.11%)	1033 (22.92%)	5495 (30.55%)
Anxiety - Yes*;**		4124 (31.28%)	99 (19.96%)	90 (9.47%)	385 (26.83%)	272 (35.51%)	2300 (36.63%)	1364 (28.19%)	1052 (23.35%)	5272 (29.31%)
Age*;**		30 (24-39)	30 (24-40)	30 (25-36)	27 (23-34)	27 (23-35)	26 (22-34)	30 (25-38)	33 (27-42)	30 (24-38)
Gender*;**	Male	6967 (52.85%)	293 (59.07%)	723 (76.11%)	881 (61.39%)	389 (50.78%)	3172 (50.83%)	2639 (54.82%)	2887 (64.43%)	9820 (54.99%)
	Female	6154 (46.68%)	198 (39.92%)	225 (23.68%)	539 (37.56%)	370 (48.30%)	3014 (48.30%)	2153 (44.72%)	1581 (35.28%)	7943 (44.48%)
	Transgender	62 (0.47%)	5 (1.01%)	2 (0.21%)	15 (1.05%)	7 (0.91%)	54 (0.87%)	22 (0.46%)	13 (0.29%)	95 (0.53%)
Education*;**	HS or lower	3509 (28.26%)	129 (28.35%)	94 (10.66%)	432 (32.07%)	210 (29.17%)	2538 (40.48%)	1222 (25.28%)	597 (13.27%)	4689 (27.82%)
	Associate	5436 (43.77%)	231 (50.77%)	245 (27.78%)	584 (43.36%)	345 (47.92%)	2842 (45.33%)	2232 (46.18%)	1640 (36.45%)	7274 (43.16%)
	Bachelor or more	3474 (27.97%)	95 (20.88%)	543 (61.56%)	331 (24.57%)	165 (22.92%)	889 (14.18%)	1379 (28.53%)	2262 (50.28%)	4889 (29.01%)

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heart failure, a stroke, or a heart attack or a need for bypass surgery. Two mental health conditions were included: a self-reported diagnosis of depression and anxiety by a health professional.

Outcome: complete switching away from cigarettes. Participants' complete switching status was evaluated independently at each follow-up wave, where participants were asked: "In the past 30 days, have you smoked a cigarette, even one or 2 puffs?" As in similar longitudinal surveys of smoking trajectories of ENDS users (such as the Population Assessment of Tobacco and Health,[25,38,42,48] the International Tobacco Control Project,[49] and the Tobacco Use Supplement to the Current Population Survey[50]), those who indicated that they have not smoked in the past 30 days were considered to have completely switched away from cigarettes at that time. Also as in these other similar surveys, determination of smoking status relied on self-reports, with no biochemical verification. The use of noncigarette tobacco products (eg, cigars, hookah), either historical or concurrent, was not assessed.

Table 1 (*continued*)
Baseline Characteristics and JUUL Use of the Sample, Stratified by Sociodemographic Groups

Characteristics		Race					Income			Total
		White	Black	Asian	Hispanic	Other/ multi	< 150% FPL	150 – 400% FPL	> 400% FPL	
N		13,183	496	950	1435	766	6279	4839	4506	17,986
Marital status*;**	Married	3745 (28.79%)	103 (21.28%)	296 (32.14%)	315 (22.32%)	159 (21.06%)	1122 (17.91%)	1306 (27.06%)	1791 (39.94%)	4956 (27.98%)
	W/D/S	2052 (15.78%)	66 (13.64%)	56 (6.08%)	127 (9.00%)	99 (13.11%)	923 (14.74%)	728 (15.08%)	551 (12.29%)	2592 (14.63%)
	Never married	7210 (55.43%)	315 (65.08%)	569 (61.78%)	969 (68.67%)	497 (65.83%)	4218 (67.35%)	2792 (57.85%)	2142 (47.77%)	10163 (57.38%)
Planning to quit smoking in next 30 days*		5527 (44.37%)	228 (49.03%)	266 (29.26%)	546 (39.91%)	316 (43.95%)	2575 (43.76%)	2048 (44.44%)	1806 (41.67%)	7356 (43.31%)
Smoking frequency*;**		30 (20-30)	29 (16–30)	28 (15-30)	25 (12-30)	30 (20-30)	30 (19-30)	30 (20-30)	30 (15-30)	30 (20-30)
Smoking quantity*;**		10 (5-20)	7 (4-11)	6 (3-10)	6 (3-10)	8 (4-15)	10 (5-15)	10 (5-17)	10 (4-15)	10 (5-15)
Years smoked regularly*;**		10 (5-20)	8 (3-18)	8 (4-15)	6 (3-13)	7 (3-15)	7 (3-15)	10 (5-19)	11 (5-20)	10 (4-18)
Cigarette dependence*;**		3.12 (2.25-3.94)	2.81 (2.07-3.56)	2.84 (2.00-3.62)	2.75 (1.88-3.56)	3.00 (2.12-3.81)	3.12 (2.31-4.00)	3.06 (2.25-3.88)	2.88 (2.00-3.69)	3.06 (2.19-3.88)
Average JUUL use frequency**		26.5 (18.33-30)	24 (16.17-29.83)	27.5 (20-30)	25.75 (18-30)	25 (17.5-30)	25.83 (18.33-30)	26.67 (18.75-30)	27 (18.17-30)	26.25 (18.33-30)
Average JUUL sessions per day*		8 (4.4-13.67)	7.6 (4.17-14.20)	7.33 (4.04-13)	8.17 (4.4-14.5)	7.6 (4.4-13.33)	8.67 (4.83-15)	7.75 (4.33-13.5)	7 (4-11.67)	8 (4.4-13.75)

*** significant difference between 5 racial/ethnic groups (p < .01)**
**** significant difference between 3 income levels (p < .01)**
FPL: Federal poverty line, HS: High school, W/D/S: widowed/divorced/separated

Note.
Statistics represent valid frequency (percentage) for categorical variables and median (interquartile range) for continuous variables. p-values are computed from chi-square tests for categorical variables or ANOVA for continuous variables.

Covariates. Multivariable models predicting switching were adjusted for 11 covariates. Baseline characteristics included age, gender, educational attainment, marital status, smoking frequency, smoking quantity, duration of regular smoking, cigarette dependence, and baseline readiness to quit smoking (planning to quit in the next 30 days). See Tables 1 and 2 for categories used. Baseline data were collected on the number of days smoked in the past 30 days and the number of cigarettes smoked on days smoked. The duration of regular smoking was collected, accounting for the time he/she stayed off cigarettes. Cigarette dependence was calculated from a 16-item scale (scored 1-5), measuring the level of experiences such as craving and withdrawal symptoms (comprised of items from the Brief Wisconsin Inventory of Smoking Dependence Motives[51] and Nicotine Dependence Syndrome Scale[52]). This scale has been validated through the Population Assessment of Tobacco and Health data for assessment of dependence on both cigarettes and on ENDS, and shown to predict smoking cessation.[53]

JUUL product use frequency and quantity were collected at each follow-up assessment, based on the self-reported number of days the participant used JUUL in the past 30 days and the number of JUUL use sessions (use of around 15 puffs, or 10 minutes[54]) on days he/she used JUUL product. Averaged frequency and quantity of JUUL use were calculated for each participant using all available responses.

Data Analysis

Longitudinal trajectories of participants' cigarette and JUUL use, including complete switching away from cigarettes, dual use of both JUUL and cigarettes, cigarette-only use, and use of neither cigarettes nor JUUL were plotted. "Switching" was defined as no smoking in the past 30 days, whether

Table 2
Baseline Characteristics and JUUL Use of the Sample, Stratified by Physical and Psychological Comorbidities

Characteristics		Smoking-related illness		Depression		Anxiety		Total
		Yes	No	Yes	No	Yes	No	
N		581	17,405	5495	12,491	5272	12,714	17,986
Race/ Ethnicity*;**;***	White	471 (88.70%)	12,712 (77.99%)	4276 (82.52%)	8907 (76.47%)	4124 (82.98%)	9059 (76.38%)	13,183 (78.33%)
	Black	10 (1.88%)	486 (2.98%)	116 (2.24%)	380 (3.26%)	99 (1.99%)	397 (3.35%)	496 (2.95%)
	Asian	10 (1.88%)	940 (5.77%)	118 (2.28%)	832 (7.14%)	90 (1.81%)	860 (7.25%)	950 (5.64%)
	Hispanic	25 (4.71%)	1410 (8.65%)	399 (7.70%)	1036 (8.89%)	385 (7.75%)	1050 (8.85%)	1435 (8.53%)
	Other/multi	15 (2.82%)	751 (4.61%)	273 (5.27%)	493 (4.23%)	272 (5.47%)	494 (4.17%)	766 (4.55%)
Income*;**;***	< 150% FPL	226 (47.88%)	6053 (39.95%)	2463 (49.73%)	3816 (35.76%)	2300 (48.77%)	3979 (36.48%)	6279 (40.19%)
	150–400% FPL	134 (28.39%)	4705 (31.05%)	1457 (29.42%)	3382 (31.69%)	1364 (28.92%)	3475 (31.86%)	4839 (30.97%)
	> 400% FPL	112 (23.73%)	4394 (29.00%)	1033 (20.86%)	3473 (32.55%)	1052 (22.31%)	3454 (31.66%)	4506 (28.84%)
Smoking-related illness – Yes**;***				255 (4.64%)	326 (2.61%)	236 (4.48%)	345 (2.71%)	581 (3.23%)
Depression - Yes*;***		255 (43.89%)	5240 (30.11%)			4001 (75.89%)	1494 (11.75%)	5495 (30.55%)
Anxiety - Yes*;**		236 (40.62%)	5036 (28.93%)	4001 (72.81%)	1271 (10.18%)			5272 (29.31%)
Age*;**;***		47 (36-57)	29 (24-38)	28 (23-38)	30 (24-39)	28 (23-37)	30 (24-39)	30 (24-38)
Gender*;**;***	Male	270 (47.12%)	9550 (55.25%)	2092 (38.33%)	7728 (62.32%)	1914 (36.54%)	7906 (62.65%)	9820 (54.99%)
	Female	298 (52.01%)	7645 (44.23%)	3303 (60.52%)	4640 (37.42%)	3267 (62.37%)	4676 (37.05%)	7943 (44.48%)
	Transgender	5 (0.87%)	90 (0.52%)	63 (1.15%)	32 (0.26%)	57 (1.09%)	38 (0.30%)	95 (0.53%)
Education*;**;***	HS or lower	178 (33.65%)	4511 (27.64%)	1562 (29.80%)	3127 (26.93%)	1481 (29.60%)	3208 (27.07%)	4689 (27.82%)
	Associate	252 (47.64%)	7022 (43.02%)	2466 (47.05%)	4808 (41.41%)	2335 (46.67%)	4939 (41.68%)	7274 (43.16%)
	Bachelor or more	99 (18.71%)	4790 (29.35%)	1213 (23.14%)	3676 (31.66%)	1187 (23.73%)	3702 (31.24%)	4889 (29.01%)

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JUUL was also used in that particular month or not. Overall, 99% of respondents used JUUL during the study, and prevalence of JUUL use remained at 90% or higher for the duration of the follow-up.[36]

To assess the relationship between medico-socio-demographic characteristics and complete switching, generalized estimating equation (GEE) modeling was used with the "geepack" package[55] of R software.[56] As expected,[57] depression and anxiety diagnoses were highly co-linear (r = 0.63), and therefore, were examined in separate models, as were diagnosis of potential SRIs. Specifically, one model tested the effects of race/ethnicity and income (fully adjusted for each other) on complete switching. Subsequent models respectively assessed potential SRI, depression, and anxiety and their relationships with switching while accounting for race/ethnicity and income. All models were adjusted for time (in continuous months) and the aforementioned 11 covariates.

RESULTS

Most participants identified themselves as non-

Table 2 (*continued*)
Baseline Characteristics and JUUL Use of the Sample, Stratified by Physical and Psychological Comorbidities

Characteristics		Smoking-related illness		Depression		Anxiety		Total
		Yes	No	Yes	No	Yes	No	
N		581	17,405	5495	12,491	5272	12,714	17,986
Marital status*;**;***	Married	207 (36.13%)	4749 (27.71%)	1240 (22.65%)	3716 (30.37%)	1259 (24.01%)	3697 (29.65%)	4956 (27.98%)
	W/D/S	229 (39.97%)	2363 (13.79%)	955 (17.45%)	1637 (13.38%)	855 (16.31%)	1737 (13.93%)	2592 (14.63%)
	Never married	137 (23.91%)	10026 (58.50%)	3279 (59.90%)	6884 (56.26%)	3129 (59.68%)	7034 (56.42%)	10163 (57.38%)
Planning to quit smoking in next 30 days		231 (43.10%)	7125 (43.32%)	2255 (43.55%)	5101 (43.21%)	2209 (44.49%)	5147 (42.83%)	7356 (43.31%)
Smoking frequency*;**;***		30 (30-30)	30 (18-30)	30 (20-30)	30 (15-30)	30 (20-30)	30 (16-30)	30 (20-30)
Smoking quantity*;**;***		18 (10-20)	10 (5-15)	10 (5-17)	10 (5-15)	10 (5-16)	10 (5-15)	10 (5-15)
Years smoked regularly*;***		28 (15-39)	9.5 (4-18)	9 (4-18)	10 (4-19)	9 (4-17)	10 (4-19)	10 (4-18)
Cigarette dependence*;**;***		3.69 (3.00-4.38)	3.00 (2.19-3.87)	3.31 (2.44-4.06)	2.94 (2.06-3.75)	3.31 (2.44-4.12)	2.94 (2.06-3.75)	3.06 (2.19-3.88)
Average JUUL use frequency		25 (17.5-30)	26.25 (18.33-30)	26.25 (18.33-30)	26.25 (18.17-30)	26.67 (18.8-30)	26.17 (18-30)	26.25 (18.33-30)
Average JUUL sessions per day*;**;***		8.45 (4.75-15)	8 (4.4-13.75)	8.17 (4.5-14)	7.83 (4.4-13.6)	8.25 (4.6-14.67)	7.8 (4.33-13.4)	8 (4.4-13.75)

*** significant difference between those with and without severe physical illness (p < .01)**
**** significant difference between those with and without depression (p < .01)**
***** significant difference between those with and without anxiety (p < .01)**
FPL: Federal poverty line, HS: High school, W/D/S: widowed/divorced/separated

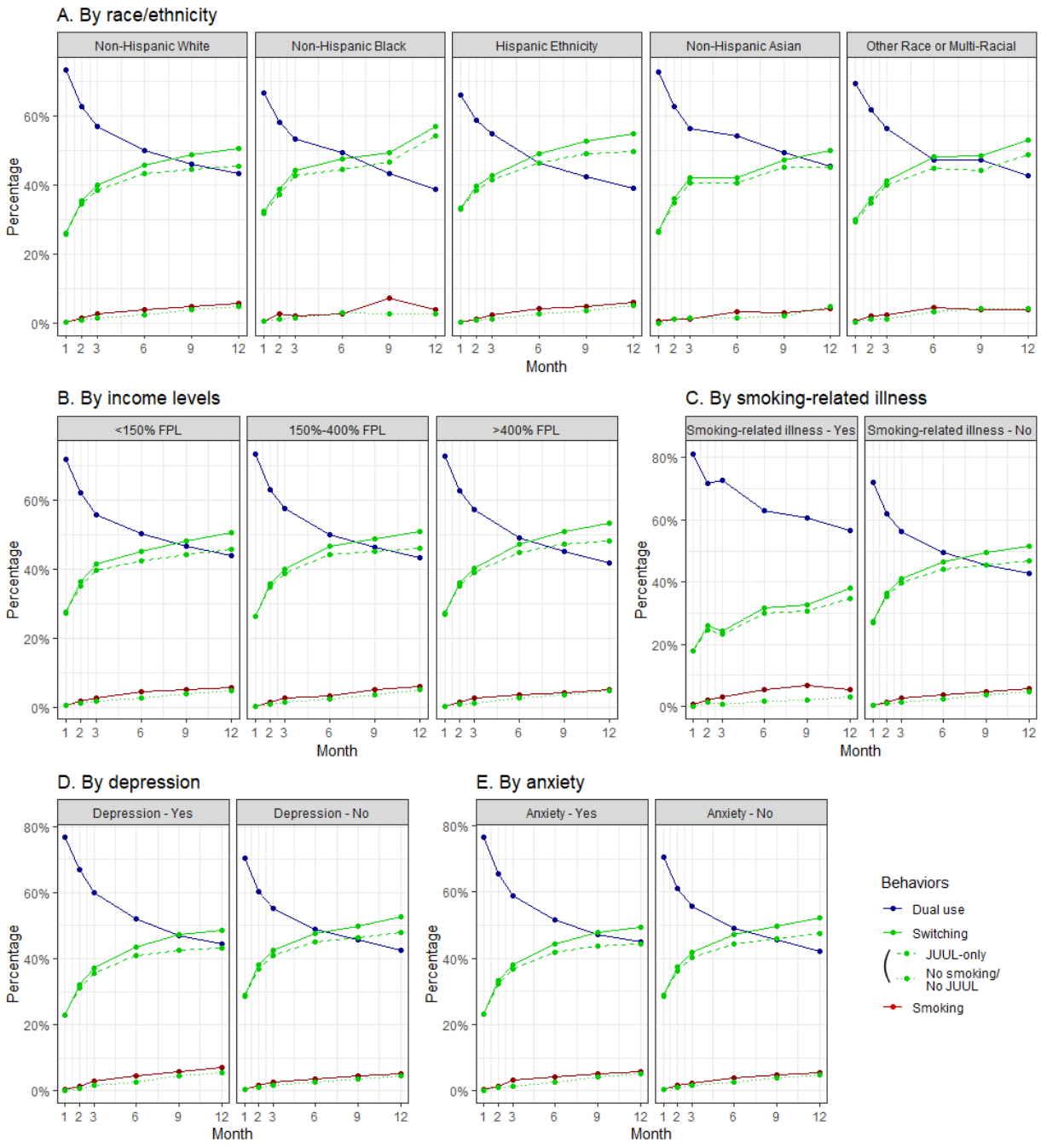
Note.
Statistics represent valid frequency (percentage) for categorical variables and median (interquartile range) for continuous variables. p-values are computed from chi-square tests for categorical variables or ANOVA for continuous variables.

Hispanic white (N = 13,183, 78.33%). The majority had never been diagnosed with potential SRI (N = 17,405, 96.77%), depression (N = 12,491, 69.45%), or anxiety (N = 12,714, 70.69%); the income strata were relatively evenly distributed (Low: N = 6279, 40.19%; Middle: N = 4839, 30.97%; High: N = 4506, 28.84%). Baseline characteristics and average JUUL product use behaviors of participants are described in Table 1 (stratified by race/ethnicity and income levels) and Table 2 (stratified by the diagnosis of potential SRI, depression, and anxiety).

Although most of the characteristics demonstrated statistically reliable differences between race/ethnicity, income, and comorbidity subgroups, these differences were small. Whereas smoking history and JUUL use did not show meaningful differences between most subgroups, the proportion of non-Hispanic Asian participants planning to quit smoking in the next 30 days (29.26%) was lower than that of other racial/ethnic subgroups (39.91% ~ 49.03%). The subgroup with potential SRI showed the most distinct profile, with statistically large differences in the longer duration of regular smoking (Cohen's d = 1.44), age (1.34), higher baseline smoking quantity (0.81) and greater dependence (0.58) than those without those conditions.

Longitudinal trajectories of smoking and JUUL use are depicted in Figure 1, stratified by medico-socio-demographic characteristics. Consistently across all subgroups, the proportion of complete switching grew throughout the follow-up period, while, conversely, the percentage of dual users decreased. In most subgroups, switching rates surpassed the dual use rates between months 6 and 9, and the majority had switched completely at 12 months; the rate of cigarette smoking only re-

Figure 1
Trajectories in Switching, Dual-use, and Cigarette-only Use, 12 Months after Purchasing the JUUL System



Note.
Dual use: use of both JUUL and cigarettes, Switching: no cigarette use (which subsumes 2 behavior patterns: exclusive JUUL use ("JUUL-only") and no use of either JUUL or cigarettes ("No smoking/No JUUL"), both groups shown separately and considered part of switching), Smoking: cigarette-only use without JUUL use.
Rates were calculated for each subgroup from the following number of participants at each wave: 13,650 (month 1), 13,533 (month 2), 13,257 (month 3), 11,621 (month 6), 12,186 (month 9), 11,919 (month 12).

Table 3
Association between Medico-socio-demographic Characteristics and Complete Switching

		Sociodemographics	Smoking-related illness	Depression	Anxiety
Race/ethnicity	White	Reference			
	Black	**1.13 (1.01–1.26)**	**1.13 (1.01–1.25)**	**1.12 (1.004–1.24)**	**1.11 (1.0005–1.24)**
	Asian	**0.89 (0.83–0.97)**	**0.89 (0.83–0.97)**	**0.87 (0.81–0.94)**	**0.87 (0.80–0.94)**
	Hispanic	1.02 (0.96–1.09)	1.02 (0.96–1.09)	1.02 (0.95–1.08)	1.02 (0.95–1.08)
	Other/multi	0.99 (0.91–1.08)	0.99 (0.91–1.08)	0.99 (0.91–1.08)	0.99 (0.91–1.08)
Income	< 150% FPL	Reference			
	150–400% FPL	1.03 (0.98–1.07)	1.02 (0.98–1.07)	1.02 (0.97–1.06)	1.02 (0.98–1.06)
	> 400% FPL	**1.07 (1.02–1.13)**	**1.07 (1.02–1.13)**	**1.06 (1.01–1.11)**	**1.07 (1.02–1.12)**
Smoking-related illness	No		Reference		
	Yes		**0.88 (0.78–0.998)**		
Depression	No			Reference	
	Yes			**0.84 (0.81–0.88)**	
Anxiety	No				Reference
	Yes				**0.86 (0.83–0.90)**

Note.
Sociodemographics model: Generalized estimating equation (GEE) model on race/ethnicity and income against complete switching across 12 months, adjusted for time and 10 covariates (age, gender, educational attainment, marital status, baseline smoking frequency/quantity, years smoked regularly, baseline cigarette dependence, intention to quit smoking in 30 days, averaged JUUL-use frequency, and quantity across assessments)
Smoking-related illness model: GEE model on smoking-related illness against complete switching across 12 months, adjusted for time, race/ethnicity, income, and 11 covariates
Depression model: GEE model on depression against complete switching across 12 months, adjusted for time, race/ethnicity, income, and 11 covariates
Anxiety model: GEE model on anxiety against complete switching across 12 months, adjusted for time, race/ethnicity, income, and 11 covariates
Statistics represent odds ratios (95% confidence intervals). Boldface indicates statistical significance. Analyses were conducted on 57,314observations from 13,461 participants who provided a non-missing set of covariates.

mained relatively consistent at around 5%. Those with potential SRI also demonstrated increased switching over time, although the proportion of switchers had not yet overtaken the proportion of dual users at 12 months.

The results from the GEE models analyzing group differences in switching are presented in Table 3. In the model addressing sociodemographic factors, non-Hispanic black smokers had 13% higher odds of completely switching away from cigarettes, compared to the reference group of non-Hispanic white smokers. Non-Hispanic Asians had 11% lower odds of switching. These effects remained statistically significant after all adjustments, including adjusting for the Asian participants' lower likelihood of being ready to quit at baseline. However, the likelihood of switching did not vary across other ethnic categories. Higher income was associated with 7% higher odds of switching compared to smokers in the lowest income level. That effect also remained consistent throughout all adjustments. The model addressing smoking-related illness demonstrated 12% decreased odds of complete switching in those with potential SRIs. Depression and anxiety also were associated with lower odds of switching (16% and 14%, respectively), even after adjusting for covariates.

The results based on complete data showed slightly higher (3% ~ 4%) rates of complete switching (Supplementary Material 1) than those based on all available data, but were overall consistent across subgroups. The complete-case data replicated the trends over time, based on data on the same people over the entire year, which are thus unaffected by variations in the sample over time.

DISCUSSION

In this study, we analyzed the trajectories in cigarette smoking in a cohort of adult smokers who newly purchased a JSK. Analyses of the total cohort of adult smokers in the ADJUSST study showed that rates of switching increased over time as dual-use decreased,[36,37] and more than half of the

baseline smokers had switched away from smoking at 12 months.[36] Here, we examined the extent to which those patterns and outcomes apply similarly to subpopulations of special interest. During the 12 months post-purchase, similar results were seen across subgroups of interest, some of which are associated with disadvantage. Whereas analyses found statistically significant changes in the likelihood of complete switching between certain subgroups (ie, increased among those in higher income levels than those in the lowest; decreased among those with depression, anxiety, or potential SRI than those without), those differences were small. Close to one-half of smokers had switched away from smoking, even among most of the groups with lower odds of switching. Additionally, all of the subgroups showed the pattern seen in the overall ADJUSST smoker cohort: switching increased and dual use declined over time.

The subpopulation of smokers with potential SRI showed a similar temporal trend as all the other groups – with dual use declining and switching increasing over time – but did not achieve the same levels of switching at 12 months. This group was notable for being older, heavier, longer-term, and more dependent smokers. This is not surprising, as they were suffering from medical conditions that emerge in advanced ages and later stages of smoking, which are likely smoking-related.[1] Thus, this group is comprised of smokers who not only had long, extensive smoking histories, but who also persisted in smoking or were unable to quit even after developing smoking-related diseases,[8,9] and likely being strongly or repeatedly advised to quit smoking.[58] The analysis adjusted for the basic differences in their smoking history, but may not have captured other characteristics that may have made it difficult for them to stop smoking. In any case, although their switching rates were lower than other groups, more than one-third of this group reported switching at 12 months, and the temporal trends suggested continued increases in switching and declining rates of dual use. This is consistent with findings of Goldenson et al,[36] that smokers with more extensive smoking histories take longer to achieve switching.

We observed a lower switch rate among non-Hispanic Asian Americans when all time points were considered, seemingly due to lower rates at 6 months (despite an initial steep rise in switching). Non-Hispanic Asian smokers are a highly heterogeneous group in national origin and acculturation, within which subgroups have varying degrees of motivation to quit.[59,60] In this sample, they showed particularly low readiness for smoking cessation. However, even with the lower readiness to quit at the time of the JSK purchase, switching among non-Hispanic Asian smokers, albeit delayed, ultimately reached the same level as non-Hispanic Whites at month 12. This temporal trend suggests that, in the long run, Asian Americans may experience similar switch rates as Whites and other ethnicities.

Similarly, the decreased odds of complete switching among those with depression and anxiety are not surprising, given the literature on difficulty quitting associated with such diagnoses;[10-12] however, their trajectories over the 12-month study period were parallel to those of participants without such diagnoses. Smoking is far more prevalent among adults with psychiatric conditions, and smoking cessation is especially challenging in these cohorts.[10-12] Many reasons have been proposed for this disadvantage;[12,61,62] however, both those with depression and those with anxiety ultimately achieved complete switching rates comparable to those without such mental comorbidities, suggesting the potential benefits of ENDS are likely to be realized in these subpopulations as well.

Limited past evidence suggested decreased likelihood of switching among non-Hispanic Black smokers.[38-41] In this study, non-Hispanic Black smokers achieved higher switching rates at 12 months than did non-Hispanic White smokers. There also have been indications that low-income individuals might have less success at switching.[38,41,42] In models controlling for other factors, the highest-income group had slightly higher switching rates, especially starting at 6 months; nevertheless, the majority of low-income smokers had switched at 12 months. Low-income individuals suffer many disadvantages, including social stressors unrelated to smoking, which may make behavior change difficult.[63] The findings of this study indicate most of these medico-socio-demographic subgroups consistently achieve switching at a level approaching that of the general population of JUUL purchasers.

Although approximately one-half of this cohort of smokers had switched at 12 months, others had

not, and most of these were engaged in dual use of both cigarettes and JUUL. This raises the question of how much these dual users were smoking, which would inform expectations of their exposure to toxicants. Selya et al[37] reported that, at month 12, nearly 60% of dual users had decreased their cigarette consumption by at least 50% from their baseline levels; their actual reductions in cigarette consumption were about 80%. A separate, randomized experimental study of such dual use found that, 50%+ reductions in cigarette consumption was associated with a reduction in harmful and potentially harmful chemicals by half of what is seen after complete abstinence.[64]

Our findings should be interpreted in the context of several limitations. This sample consisted of baseline smokers who purchased the JSK, which represents a group of 'committed' ENDS users. Therefore, the results of this study are likely not generalizable to the general population of smokers or even to ENDS users as conventionally defined by any past-30-day use. As this study did not have a control group of smokers who were not using JUUL, the results do not warrant causal inferences. The analyses focused on the established smokers who at baseline reported past-30-day smoking, and who also stated they were smoking every day or some days at baseline, excluding a substantial cohort of established smokers at baseline who also said they had smoked in the previous 30 days, but then said were now smoking "not at all." That group had higher switching rates,[65] indicating that the switching rates for all past-30-day established smokers are higher than those reported here.

The study is based on self-reports. Respondents' smoking status was also based on self-report without biochemical verification. This approach is consistent with that in prior studies assessing the trajectory of smoking among ENDS users, which have similarly used self-report without biochemical verification.[25,38,42,48-50] The distinction is that in naturalistic observational survey studies such as this, unlike smoking cessation studies, participants are not provided with treatment, and are not expected or directed to quit smoking, likely leaving less incentive for participants to lie about their smoking status.

This analysis also did not account for participants' use of non-JUUL brand ENDS. Prakash et al[65] reported those who were already using ENDS at baseline are more likely to report cigarette abstinence at month 12. The study also did not assess participants' use of noncigarette tobacco products (eg, cigars, smokeless tobacco), whether historically or during the study. Such uses could have affected participants' smoking or JUUL use.

A substantial number of baseline participants did not complete all follow-up assessments. If those missing follow-ups were materially different and had a lower likelihood of switching, this could have resulted in biasing the reported switch rates upwards. However, Shiffman et al[46] report that those missing who missed some assessments were similar to those who completed all of them, limiting the prospect of such bias. Nevertheless, the potential effects of non-response should be considered.

As these analyses were limited to 12 months of follow-up; further trajectories should be monitored to ensure the long-term continuation of complete switching. Lastly, the sociodemographic and medical disadvantages examined in this study are not independent of each other and there may be multiplicative effects of multiple combined disadvantages.[66] These warrant further research.

This study has multiple strengths as well. The ADJUSST study provided detailed data on ENDS users' smoking trajectories. As "purchasers," the participants in this study are distinct from "past-month ENDS users" who are the usual subjects of ENDS analyses. They represent self-motivated JUUL product users and real-world ENDS adopters, demonstrating switching rates much higher than other studies.[25-28] Furthermore, the ADJUSST study prospectively followed nearly 18,000 eligible baseline smokers across 12 months, addressing the limitations raised in the previous literature such as the small sample size and the use of cross-sectional data or limited number of follow-up assessments. By demonstrating consistent switching rates across different medico-socio-demographic subgroups, our results indicate that even individuals with sociodemographic and medical disadvantages are comparably likely to achieve complete switching away from cigarettes to JUUL.

Conclusion

Although ENDS offer a prospect to reduce smoking-related harms among current smokers, the potential benefit of ENDS ideally should be dis-

tributed broadly across subpopulations, especially those that have been disproportionately affected by cigarettes. In this study, we assessed complete switching away from combustible cigarettes among baseline smokers of various medico-socio-demographic characteristics, stratified by race/ethnicity, income, potential SRI, depression, and anxiety. The findings of these analyses confirm that the trajectories of switching observed in the overall JUUL users[36] remain consistent across the sociodemographically- and medically-disadvantaged subgroups studied here. As noncombustible nicotine products for smokers, ENDS may serve as a potentially reduced risk alternative to cigarettes and reduce the smoking-related harms in these historically challenging populations in smoking cessation.

Human Subjects Approval Statement

This study was approved by the Advarra® Institutional Review Board.

Conflict of Interest Disclosure Statement

SK and SS provide consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc through PinneyAssociates Inc. Within the last 2 years, PinneyAssociates Inc has consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction. GML is a full-time employee of Juul Labs Inc.

Under contract to JUUL Labs Inc, the Centre for Substance Use Research, an independent research consultancy, designed the study and assessments and oversaw collection of data through Dacima Inc. CSUR managed, cleaned, and summarized the data. SK performed the statistical analyses under the direction of SS and GML. All of the authors contributed to writing and review of the paper, and had access to the data. The sponsor approved the research plan and provided comment on a near-final draft of the paper.

Acknowledgements

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SUPPLEMENATARY MATERIALS 1

Rationale of Complete-case Analyses

This supplement reports analyses based on complete cases; that is, respondents who provided smoking relevant data at all 6 follow-up points. Whereas the main analyses with all-available data have the advantage of maximizing the utility of data and capturing the overall trend, conclusions generated from all-available data may be skewed if the loss to follow-up were systemically related to research-related factors.[1] For example, if persistent smokers consciously chose to drop out from the survey, the rates of switching in all-available data may seem higher than the true rate would have been. Although Shiffman et al's study (in this issue) on those who were lost to follow-up demonstrates that missing follow-ups was unrelated to individuals' demographics or smoking profile, and reasons for non-response were mostly unrelated to their cigarette or JUUL use, complete-case analyses with those who completed all 6 follow-up surveys were conducted to give a picture of the patterns over time with the same group of participants over time.[2]

Methods

Among 17,986 ADJUSST participants who were eligible for the main analyses, a subsample of 5677 baseline smokers who provided all 6 follow-up assessments was identified. Those with one or more missing baseline covariates were excluded for generalized estimating equation (GEE) modeling, yielding 4305 participants for the analyses. All other analytic details remained the same with the main analyses.

Results

Baseline characteristics and JUUL use of the complete-case subsample (N = 5677) are described in the Table S1. The complete-case subsample was extremely comparable to the all-available sample (N = 17,986) including their distribution in population-defining characteristics such as race/ethnicity, income, diagnosis of potential smoking-related illnesses (SRI), and mental health conditions (depression, anxiety).

The temporal trends of cigarette/JUUL use in the complete-case subsample are depicted in the Figure S1, stratified by the medico-socio-demographic characteristics of interest. Results were highly consistent with those seen in the main sample reported in the body of the paper. As in the main sample, the switching rates progressively increased while dual-use rates declined over the course of 12 months. In most subgroups, the crossover between switching and dual-use was observed between months 6 and 9, with more than half of the subgroup achieving complete switching at month 12. The proportion of those who reported exclusive cigarette smoking was low (~ 5%). Those with potential SRI were the only subgroup whose switching rates failed to surpass the dual-use rates and did not reach 50% at month 12. The overall temporal trends were highly consistent with those of the main analyses across all subgroups with the 12-month switching rates trending 3-4% higher in the complete-case subsample.

Between-group differences in switching from the generalized estimating equation (GEE) models are presented in Table S2. Race/ethnicity, income levels, and diagnosis of potential SRI did not predict a significant change in the odds of complete switching. Depression and anxiety were associated with lower odds of switching among those who have been diagnosed with such mental illness, even after adjusting for race/ethnicity, income and 11 covariates described in the main manuscript. Compared to results from main analyses, diagnoses of depression and anxiety remained consistent risk factors in achieving complete switching, while race/ethnicity, income and SRI were rendered non-significant in the analyses of complete-case subsample.

Conclusion

Analyses of the complete-case subset of respondents yielded results that were consistent with the main analyses using all available data. As in the main analysis, the complete-case subsample demonstrated longitudinal trajectories in which complete switching increases, dual-use decreases, and cigarette-only smoking

remains stable. Some effects that were significant in the larger all-available data analysis (lower switch rates among non-Hispanic Asians and individuals with potential SRI; higher switch rates among non-Hispanic Blacks and those in the highest income group) were not statistically significant in the complete-case analysis. Notwithstanding these minor differences that may have originated from a smaller sample size, these analyses in the complete-case subsample demonstrated highly parallel results observed in main analyses with the all-available sample. ADJUSST participants' varying loss to follow-up had minimal effects on the temporal trends across all medico-socio-demographic subgroups, suggesting the robustness of the analyses.

Table S1
Baseline Characteristics and JUUL Use of the Complete-case Subsample, Compared to All-available Sample

Characteristics		Complete-case subsample
N		5677
Race/Ethnicity	White	4162 (78.47%)
	Black	175 (3.30%)
	Asian	284 (5.35%)
	Hispanic	441 (8.31%)
	Other/multi	242 (4.56%)
Income	< 150% FPL	2073 (41.58%)
	150%-400% FPL	1580 (31.70%)
	> 400% FPL	1332 (26.72%)
Smoking-related illness - Yes		175 (3.08%)
Depression - Yes		1762 (31.04%)
Anxiety - Yes		1720 (30.30%)
Age		30 (25 – 38)
Gender	Male	2995 (53.14%)
	Female	2615 (46.40%)
	Transgender	26 (0.46%)
Education	HS or lower	1534 (28.69%)
	Associate	2314 (43.28%)
	Bachelor or more	1499 (28.03%)
Marital status	Married	1711 (30.50%)
	W/D/S	837 (14.92%)
	Never married	3061 (54.57%)
Planning to quit smoking in next 30 days		2359 (44.03%)
Smoking frequency		30 (20 – 30)
Smoking quantity		10 (5 – 17)
Years smoked regularly		10 (5 – 19)
Cigarette dependence		3.12 (2.25 – 3.94)
Average JUUL use frequency		26.33 (18.83 – 30)
Average JUUL sessions		8.33 (4.83 – 13.5)

Note.
FPL: Federal poverty line, HS: High school, W/D/S: widowed/divorced/separated
Statistics represent valid frequency (percentage) for categorical variables and median (interquartile range) for continuous variables.

Figure S1
Trajectories in Switching, Dual-use, and Cigarette-only Use, 12 Months after Purchasing the JUUL System, Complete-case Subsample (N = 5677)

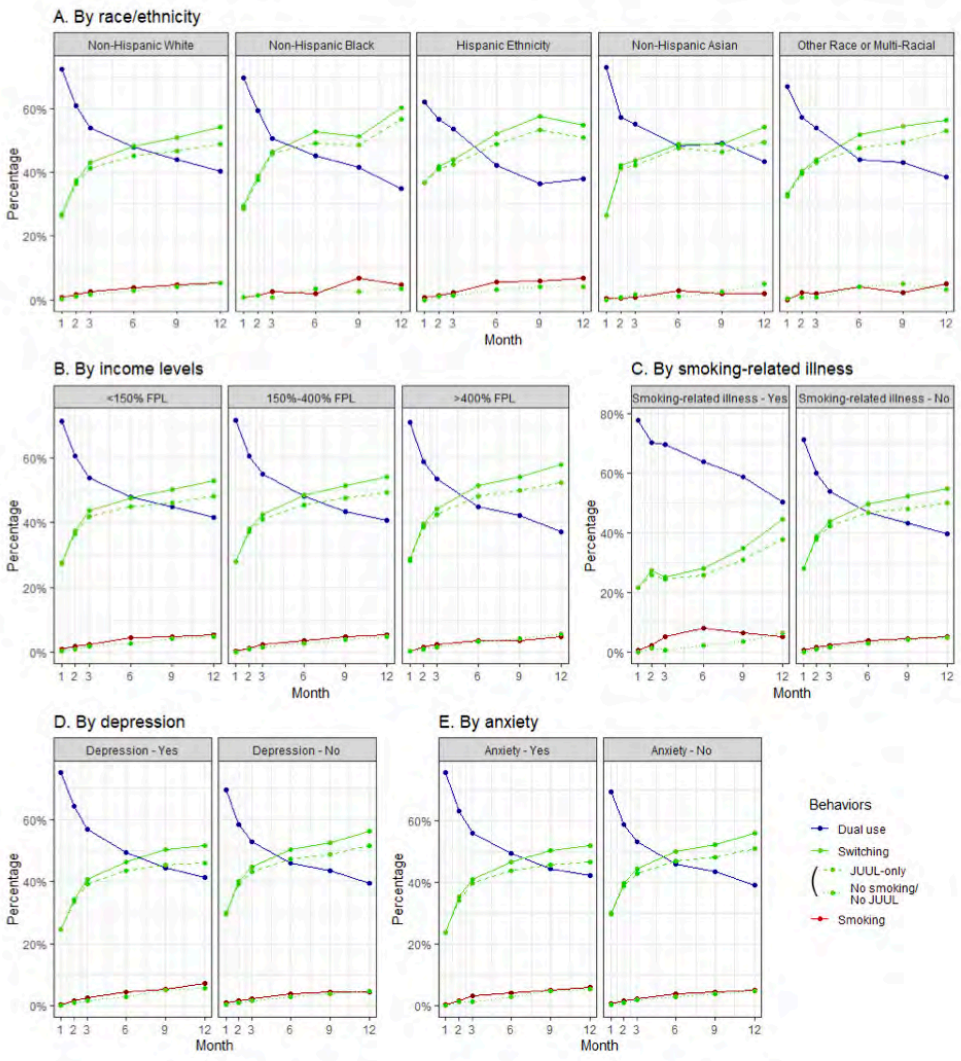

Table S2
Association between Medico-socio-demographic Characteristics and Complete Switching: Complete-case Analyses

		Sociodemographics	Smoking-related illness	Depression	Anxiety
Race/ethnicity	White		Reference		
	Black	1.06 (0.80 – 1.41)	1.06 (0.80 – 1.40)	1.05 (0.79 – 1.40)	1.04 (0.79 – 1.38)
	Asian	0.86 (0.70 – 1.07)	0.86 (0.70 – 1.07)	0.85 (0.68 – 1.06)	0.84 (0.67 – 1.04)
	Hispanic	1.06 (0.90 – 1.26)	1.06 (0.90 – 1.26)	1.06 (0.90 – 1.25)	1.06 (0.89 – 1.25)
	Other/multi	1.02 (0.82 – 1.27)	1.02 (0.81 – 1.27)	1.03 (0.82 – 1.28)	1.03 (0.82 – 1.28)
Income	< 150% FPL		Reference		
	150–400% FPL	1.01 (0.90 – 1.13)	1.01 (0.90 – 1.13)	1.00 (0.90 – 1.12)	1.00 (0.90 – 1.13)
	> 400% FPL	1.10 (0.97 – 1.25)	1.10 (0.97 – 1.25)	1.09 (0.96 – 1.24)	1.10 (0.96 – 1.25)
Smoking-related illness	No		Reference		
	Yes		0.82 (0.58 – 1.16)		
Depression	No			Reference	
	Yes			**0.89 (0.81 – 0.99)**	
Anxiety	No				Reference
	Yes				**0.84 (0.76 – 0.94)**

Note.
Sociodemographics model: Generalized estimating equation (GEE) model on race/ethnicity and income against complete switching across 12 months, adjusted for time and 11 covariates (age, gender, educational attainment, marital status, planning to quit smoking in next 30 days, baseline smoking frequency/quantity, years smoked regularly, baseline cigarette dependence, averaged JUUL-use frequency, and quantity across waves)
Smoking-related illness model: GEE model on smoking-related illness against complete switching across 12 months, adjusted for time, race/ethnicity, income, and 11 covariates
Depression model: GEE model on depression against complete switching across 12 months, adjusted for time, race/ethnicity, income, and 11 covariates
Anxiety model: GEE model on anxiety against complete switching across 12 months, adjusted for time, race/ethnicity, income, and 11 covariates
Statistics represent odds ratios (95% confidence intervals). Boldface indicates statistical significance. Analyses were conducted on 25,830 observations from 4305 participants who provided a non-missing set of covariates.

Supplementary References

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SUPPLEMENTARY MATERIALS 2

Definition of Income Strata

As is often done for economic analyses, income strata were defined based in their relation to the US federal poverty level (FPL),[1] which defines the poverty threshold based on household income and household size. Specifically, using the household size (reported in 7 levels, ranging from one-person to more than 6 people), household income (collected in 10 levels, ranging from less than < $10,000 to $200,000 or more) was recoded into 3 levels: an income of less than 150% of FPL (at their respective household size), between 150% and 400%, and greater than 400%. In cases where the household size was not reported, the number of people in the household was imputed based on the participant's age, following the Census Bureau's report on the average size of the household by age.[2] Because the household income was collected in categories that do not exactly correspond to the FPL or its derivatives, classification was undertaken using the closest bracket of the reported household income. Principles of assignment are summarized in the Table S3.

Table S3
Principles of Reassigning Household Income to Levels Stratified by Income-to-poverty Ratio

HH size	Federal Poverty Level	Rounded cutoff		Assignment		
		150%	400%	Less than 150%	150%-400%	More than 400%
1	$12,060	$18,000	$48,000	Less than $25,000	Between $25,000 and $49,999	More than $50,000
2	$16,240	$24,000	$65,000	Less than $25,000	Between $25,000 and $75,000	More than $75,000
3	$20,420	$31,000	$82,000	Less than $50,000	Between $50,000 and $75,000	More than $75,000
4	$24,600	$37,000	$98,000	Less than $50,000	Between $50,000 and $75,000	More than $75,000
5	$28,780	$43,000	$115,000	Less than $75,000	Between $75,000 and $100,000	More than $100,000
6+	$37,140	$56,000	$149,000	Less than $75,000	Between $75,000 and $150,000	More than $150,000

Note.
HH: Household

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Cigarette Smoking Trajectories in Adult Former Smokers Using the JUUL System

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Objective: In this study, we assessed cigarette smoking over 12 months among adult former smokers who newly purchased a JUUL Starter Kit (JSK). Methods: Prevalence of past 30-day smoking and factors associated with smoking were assessed among adult (age ≥ 21) former established smokers, stratified as recent (quitting ≤ 12 months) and long-term quitters (> 12 months), who purchased a JSK and completed ≥ 1 of 6 follow-up assessments (N = 4786). Results: Recent quitters had higher rates (16.6%-19.9%) of past 30-day smoking than long-term quitters (6.4%-9.2%) across the 12-month period; smoking prevalence did not significantly increase over time in either subgroup. Few participants (6.5% of recent quitters, 2.8% of long-term quitters) reported smoking at both 9 and 12 months, a pattern that might indicate persistent smoking. Past 30-day JUUL use remained high (≥ 87%) across the 12 months. Participants who used JUUL more frequently were less likely to smoke. Conclusions: Among former smokers who purchased JUUL, prevalence rates of smoking were low and stable across the 12-month period, suggesting there was not a growing cohort of former smokers resuming smoking. Smoking was more common in recent quitters than long-term quitters. Greater use of JUUL was associated with reduced odds of smoking resumption.

Key words: ENDS; JUUL; former smokers; smoking; relapse
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Substantial declines in the prevalence of cigarette smoking over the past 2 decades have resulted in a large and growing population of former smokers.[1] In the United States (US), former smokers now outnumber current smokers.[2] Maintaining abstinence from smoking in this population is critical for public health. The process of quitting and maintaining continuous smoking abstinence is challenging for many former smokers, and the risk of relapse to cigarette smoking is high.[3-5]

The greatest risk of smoking relapse is within the first 12 months of a quit attempt and declines over time;[6-8] over 90% of smokers relapse within the first year, while those who maintain abstinence have an approximately 10% risk of relapse thereafter.[6,9,10] Some former smokers continue to experience cravings for years after quitting.[11] Previous research in clinical and general populations of former smokers have identified multiple risk factors for relapse: (1) sociodemographic factors such as low socioeconomic status,[12] younger age, single marital status;[4,7,13] (2) physical and mental health

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factors including higher body mass index,[14] anxiety, depression;[15,16] and (3) smoking characteristics including higher nicotine dependence,[17-19] and shorter duration of abstinence.[7,10,13,20]

Nicotine is the primary psychoactive constituent that maintains addiction to tobacco products;[21] although nicotine is not benign,[22] the adverse health consequences of cigarettes are overwhelmingly attributable to exposure to the combustion of tobacco and its byproducts,[1] rather than nicotine itself.[21] Use of electronic nicotine delivery systems (ENDS) among adults has increased in recent years, including among former smokers,[23,24] and there is concern that ENDS may increase risk of relapse in former smokers. Conversely, recent quitters who are struggling to maintain abstinence may use ENDS to avoid resuming smoking. Among the few studies that have been conducted, findings have been mixed.

Several studies have found lower rates of resumption of smoking in former smokers who use ENDS, suggesting a potential benefit of ENDS use in mitigating smoking resumption.[25-30] Others show an increased resumption risk[31-33] or no association.[34] In an analysis of Waves 1 and 2 of the Population Assessment of Tobacco and Health (PATH) survey, which collected data from 2013-2015, daily ENDS users had higher odds of stopping smoking compared with never ENDS users; however, ENDS users also had higher risk of smoking resumption compared with never-users.[35] In another nationally representative survey in the US (National Health Interview Survey), daily ENDS users (vs ENDS never-users) also were more likely to stop smoking, and ENDS users who used ENDS more frequently were more likely to have stopped smoking.[30]

The JUUL System (henceforth, "JUUL"), a closed-system ENDS with nicotine-salt formulation, is a widely-used brand of ENDS in the US.[36] Prevalence data reported in this journal issue demonstrate that use of JUUL among former smokers is generally low, although far more prevalent among recent quitters (5%) than among longer-term quitters (0.7%).[37] Smokers who recently quit and who are at risk for smoking resumption may potentially benefit from using ENDS, if it helps divert them from smoking. Hence, assessing use of JUUL among former smokers can elucidate rates of subsequent smoking, recognizing that some smoking is expected in this population at risk for relapse, particularly among those who have stopped smoking more recently. The current analysis of the Adult JUUL Switching and Smoking Trajectories (ADJUSST) Study evaluated trajectories of cigarette smoking (ie, point prevalence of past 30-day smoking) at 6 follow-up assessments over a 12-month period (1, 2, 3, 6, 9, and 12 months) among former smokers (both recent and longer-term quitters) who purchased a JUUL Starter Kit (JSK).

This study extends the literature in several ways: it focuses on a single and widely-used ENDS product (ie, JUUL); as ENDS are a diverse range of products with large variations in design and nicotine delivery, this avoids the heterogeneity involved in analyses of ENDS as a category.[38] The cohort in this study was defined by an initial purchase of a JSK, which implies a substantial engagement with the product, in contrast to studies that have identified ENDS users on the basis of any use in the previous 30 days, which can include casual or isolated occasions of use. The study also includes recently-collected data, multiple data-points over a one-year period, and data to characterize the quantity and frequency of smoking reported among the former smokers, which provides greater detail and granularity than previous studies.[31-34] In addition to assessing and quantifying smoking at each individual follow-up, analyses assessed smoking at both the 9- and 12-month follow-ups, which was considered a potential indicator of sustained smoking at the end of the observation period. Additionally, analyses assessed associations of amount and frequency of JUUL use and other sample characteristics and resumption of cigarette smoking.

METHODS

Participants and Procedures

Data were from the ADJUSST Study, a longitudinal observational cohort study of US adults who newly purchased a JSK in 2018. Additional details describing the overall study methodology are provided in Shiffman et al.[39] Participants were adult (aged ≥ 21 years) US permanent residents who were recruited following their initial purchase of a JSK (within the past 7 days of baseline) either at a retail store (via recruitment card in packaging) or online from the manufacturer's ecommerce platform (via post-purchase recruitment email). Individuals were

excluded if they were employed by or related to an employee of Juul Labs Inc or PAX Labs Inc.

Former established smokers (FES) were defined as individuals who, at baseline, had smoked ≥ 100 cigarettes in their lifetime and had not smoked in the past 30 days, even one or 2 puffs. At baseline, there were 6086 FES, of whom 4818 (79.2% of baseline) completed at least one of 6 online follow-up assessments post-baseline; 1599 FES (26.3%) completed all 6 follow-ups. FES were stratified into 2 subgroups, Recent FES ("Recent Quitters") and Long-term FES ("Long-term Quitters") based on the question "When did you completely quit smoking cigarettes?" ("Within past 12 months" vs "More than 12 months ago"). Participants (N = 32) who were missing data on this item were excluded. Thus, the final analytic sample included 4786 FES, of whom 47.2% (N = 2260) were recent quitters and 52.8% (N = 2526) were long-term quitters. Supplemental Figure S1 displays the flow chart for defining the analytic sample.

Analyses focused on loss to follow-up reported in this journal issue showed that baseline differences between those with no follow-up data, complete follow-up data, and partial follow-up data were extremely small ($R^2s \leq .002$).[39] Among the 3219 (52.9%) who provided partial data, 71.7% completed the majority of the follow-ups. Only 22.0% showed patterns indicating discontinuation, ie, completing follow-ups, but then dropping from the study and completing no subsequent follow-ups; a strong majority (78.0%) missed follow-ups then returned at subsequent follow-ups, and 81.5% completed at least one of the follow-ups in the second half of the year, at or after 6 months. Patterns were similar for recent and long-term quitters.

Measures

Cigarettes smoking outcomes. Past 30-day Smoking Status: The primary outcome of this study, past 30-day smoking, was assessed at baseline and at each follow-up survey with the question: "In the past 30 days, have you smoked a cigarette, even one or 2 puffs?" (yes/no). Neither history nor current use of noncigarette tobacco products other than ENDS (eg, cigars, hookah, smokeless tobacco) was assessed in this study.

Participants who responded "yes" to past 30-day smoking at follow-up assessments were then asked about their current smoking status: "Do you now smoke cigarettes…" (not at all/some days/every day). FES who reported past 30-day smoking but currently smoking "not at all" were considered to have smoked (contrary to other published studies)[40] but evaluated separately, as they were not asked to report past 30-day frequency (days/month) or daily quantity (cigarettes/day) of smoking. Data from the PATH survey demonstrate that year-ago ex-smokers with this pattern of responses (ie, past 30-day smokers who now smoke "not at all") report light and intermittent smoking (Supplementary Results and Supplemental Table S1); thus, their exclusion from estimates of cigarette consumption likely increase these estimates.

Frequency of days smoked and daily quantity of cigarettes. At baseline, former smokers were asked to report the average number of cigarettes they used to smoke per day when they were smoking fairly regularly. At each follow-up assessment, participants who reported smoking in the past 30 days and smoking every day or some days were asked to report the number of days in the past 30 that they smoked, and the number of cigarettes smoked, on average, on those days. The average number of cigarettes per day (CPD) was computed as ([number of days smoked per month × number of cigarettes smoked on days smoked] / 30 days).

JUUL use measures. Past 30-day JUUL Use Status: In a manner parallel to assessment of smoking, at each follow-up assessment, participants were asked: "Have you used a JUUL in the past 30 days, even one or two puffs?" Those who reported past 30-day JUUL use, were then asked: "Do you now use a JUUL…" (every day/some days/not at all). Those who responded "not at all" were not asked about frequency or quantity of JUUL use. The others were asked to report the number of days on the past 30 they had used JUUL, and the number of uses per day on those days ("On average, on those days you used a JUUL, how many times did you usually use a JUUL each day? Assume that one 'time' consists of around 15 puffs, or 10 minutes."). Participants who reported no past 30-day use of JUUL were assigned values of zero for frequency and quantity of use.

Baseline sociodemographics and smoking history. Baseline variables included in this analysis were selected based on the literature as potential risk

Table 1
Baseline Sociodemographic and Smoking History Characteristics of Recent versus Long-term Quitters

	Recent Quitter[a] % or Mean (SD)	Long-Term Quitter[b] % or Mean (SD)	Total[c] % or Mean (SD)	Test of Difference[d]
	N = 2260	N = 2526	N = 4786	(p-value)
Sociodemographic Characteristics				
Age in Years	(N = 2260)	(N = 2526)	(N = 4786)	< .001
Mean (SD)	28.81 (9.67)	35.45 (11.72)	32.31 (11.29)	
Age Category (%)	(N = 2260)	(N = 2526)	(N = 4786)	
21 to 24	47.96	17.81	32.05	
25 to 29	20.22	19.64	19.91	< .001
30 to 39	18.14	32.34	25.64	
40 or older	13.67	30.21	22.40	
Sex (%)	(N = 2247)	(N = 2500)	(N = 4747)	
Male	63.95	64.40	64.19	.069
Female	35.29	35.32	35.31	
Transgender	0.76	0.28	0.51	
Race/Ethnicity (%)	(N = 2096)	(N = 2337)	(N = 4433)	
Non-Hispanic White	76.43	82.76	79.77	
Non-Hispanic Black	3.01	1.93	2.44	< .001
Non-Hispanic Asian[e]	4.77	4.32	4.53	
Non-Hispanic Other[f]	5.20	3.85	4.49	
Hispanic Ethnicity	10.59	7.15	8.78	
Marital Status (%)	(N = 2212)	(N = 2482)	(N = 4694)	
Married	21.88	42.99	33.04	< .001
Divorced, Separated or Widowed	9.45	12.45	11.04	
Never Married	68.67	44.56	55.92	
Education (%)	(N = 2057)	(N = 2359)	(N = 4416)	
High school graduate or less education	31.26	19.58	25.02	< .001
Some college or associate degree	43.32	42.39	42.82	
Bachelor's degree or more education	25.43	38.02	32.16	
Annual Household Income (%)	(N = 1881)	(N = 2123)	(N = 4004)	
Less than $50,000	55.50	37.64	46.03	< .001
$50,000-$100,000	27.75	33.68	30.89	
Greater than $100,000	16.75	28.69	23.08	

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factors or confounders in the relationship between ENDS use and smoking relapse in former smokers.[31,33] Smoking history characteristics assessed at baseline included smoking history before quitting (number of cigarettes per day before quitting, number of years smoked regularly before quitting), age first smoked regularly before quitting, time since quit smoking (recent vs long-term quitters), and smoking mentholated (vs nonmentholated) cigarettes as a regular brand before quitting.

Table 1 (*continued*)
Baseline Sociodemographic and Smoking History Characteristics of Recent versus Long-term Quitters

	Recent Quitter[a] % or Mean (SD)	Long-Term Quitter[b] % or Mean (SD)	Total[c] % or Mean (SD)	Test of Difference[d]
	N = 2260	N = 2526	N = 4786	(p-value)
Smoking History Characteristics				
Number of Cigarettes per Day before Stopping Smoking	(N = 2149)	(N = 2414)	(N = 4563)	< .001
Mean (SD)	11.46 (8.37)	13.03 (9.64)	12.29 (9.10)	
Months Since Stopped Smoking	(N = 2251)	(N = 2519)	(N = 4770)	< .001
Mean (SD)	4.28 (3.37)	64.06 (68.07)	35.85 (57.81)	
Years Smoked Regularly before Stopping	(N = 2162)	(N = 2454)	(N = 4616)	< .001
Mean (SD)	7.82 (8.89)	10.52 (9.96)	9.26 (9.57)	
Age First Smoked Regularly before Stopping	(N = 1992)	(N = 2203)	(N = 4195)	.009
Mean (SD)	18.17 (3.20)	17.90 (3.40)	18.03 (3.31)	
Regular Brands of Cigarettes				
Cigarettes Smoked Regularly before Stopping were Menthol	(N = 1767)	(N = 1954)	(N = 3721)	< .001
%	44.14	36.69	40.23	

Note.
Abbreviations: SD, Standard Deviation
Sample sizes for individual variables may be less than column heads due to missing data.
[a] Recent Quitters had stopped from smoking within the last 12 months at baseline.
[b] Long-term Quitters had stopped from smoking 12 or more months ago at baseline.
[c] Total included Recent (N = 2260) and Long-term (N = 2526) Quitters who provided valid (non-missing) data.
[d] ANOVA was conducted to obtain p-values for continuous variables and chi-square tests were conducted to obtain p-values for categorical variables.
[e] Non-Hispanic Asian included: Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, or Other Asian
[f] Non-Hispanic Other Race included: American Indian or Alaskan Native, Native Hawaiian, Guamanian or Chamorro, Samoan, or Other Pacific Islander (or 2 or more races)

Data Analysis

The proportion of respondents who reported smoking at both the 9- and 12-month assessments was calculated, as it may be suggestive of persistent smoking approaching the end of the 12-month observation period.

Repeated-measure logistic regression models (generalized estimating equations [GEE]) assessed the associations of baseline sociodemographics, baseline smoking history, and time-varying JUUL use characteristics with past 30-day smoking over all non-missing follow-up observations. Regressors were first tested in individual (univariate) models, and then in a single fully-adjusted model that included all regressors. All models included time (continuous; months from baseline); both linear and quadratic terms were applied to evaluate change over time. GEE models allow for multiple observations per person, and for individuals to vary in the number of observations.[41] Odds ratios and 95% confidence intervals were computed using a 2-tailed alpha of .05. To test if associations of regressors and switching differed by FES status (Recent vs Long-term Quitters), an additional model was tested that included interaction terms for each regressor by FES status.

Additional analyses were conducted among FES who provided valid smoking data at all 6 follow-up assessments (referred to as a complete case analysis; N = 1589) to assess sustained smoking patterns. The

Table 2
Association of Sociodemographic, Smoking Characteristics and JUUL Use with Resumption of Smoking over the 12-month Period

Regressors	Univariate Models OR (95% CI)	Fully Adjusted Model OR (95% CI)[a]
Sociodemographic Characteristics		
Age Category		
21 to 24	Ref	Ref
25 to 29	0.71 (0.58, 0.87)**	0.88 (0.71, 1.10)
30 to 39	0.48 (0.39, 0.59)***	0.73 (0.56, 0.96)*
40 or older	0.42 (0.33, 0.53)***	0.59 (0.39, 0.90)*
Sex		
Male	Ref	Ref
Female	1.07 (0.91, 1.26)	1.13 (0.96, 1.34)
Transgender	1.68 (0.69, 4.09)	1.04 (0.45, 2.40)
Race/Ethnicity		
Non-Hispanic White	Ref	Ref
Non-Hispanic Black	1.59 (0.97, 2.59)	1.31 (0.80, 2.14)
Non-Hispanic Asian	1.49 (1.05, 2.13)*	1.35 (0.93, 1.97)
Non-Hispanic Other	1.49 (1.05, 2.10)*	1.29 (0.91, 1.84)
Hispanic Ethnicity	1.49 (1.15, 1.94)**	1.22 (0.94, 1.58)
Marital Status		
Married	Ref	Ref
Divorced, Separated or Widowed	1.06 (0.77, 1.46)	0.98 (0.70, 1.37)
Never Married	2.02 (1.69, 2.43)***	1.41 (1.14, 1.75)**
Education		
High School Graduate or Less Education	Ref	Ref
Some College or Associate Degree	1.03 (0.85, 1.25)	1.11 (0.91, 1.35)
Bachelor's Degree or More Education	0.81 (0.65, 1.01)	0.92 (0.73, 1.17)
Smoking Characteristics at Baseline		
Regular Brands of Cigarettes Smoked before Quitting were Menthol Cigarettes		
No	Ref	Ref
Yes	1.01 (0.87, 1.19)	0.84 (0.72, 0.99)*

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complete-case analyses provide additional insights into patterns of smoking behavior over multiple assessments by requiring the maximum the number of observations for each individual, allowing for counting the number of follow-ups at which smoking is reported, and tracking of trends over time in the same respondents. All statistical analyses were conducted using SAS® Version 9.4 (Cary, NC).

RESULTS

Sample Characteristics

In the overall analytic sample (N = 4786), participants were, on average, 32.31 years of age (SD = 11.29). The majority reported being male (64.2%), non-Hispanic white (79.8%) and having never been married (55.9%); the largest proportion reported attending some college (42.8%) with an-

Table 2 (*continued*)
Association of Sociodemographic, Smoking Characteristics and JUUL Use with Resumption of Smoking over the 12-month Period

Regressors *Smoking Characteristics at Baseline*	Univariate Models OR (95% CI)	Fully Adjusted Model OR (95% CI)[a]
Former Established Smoker Subtype		
Long-term Quitter	Ref	Ref
Recent Quitter	2.83 (2.41, 3.33)***	2.44 (2.05, 2.90)***
No. Cigarettes Smoked per Day before Quitting	0.97 (0.96, 0.98)***	0.98 (0.97, 0.9963)*
Years Smoked Regularly Before Quitting	0.98 (0.97, 0.99)***	1.02 (1.0012, 1.03)*
Age First Smoked Regularly Before Quitting	1.03 (1.01, 1.05)**	1.03 (1.01, 1.06)*
Time-varying Effects		
No. Days Used JUUL in Past 30 Days[b]	0.983 (0.978, 0.989)***	0.982 (0.976, 0.988)***
No. Times Used JUUL per Day[b]	0.994 (0.989, 0.999)*	0.9979 (0.9929, 1.0029)
Time effect, months (linear)[c]	1.02 (1.003, 1.03)***	1.01 (0.99, 1.02)

Note.
Fully adjusted model: N = 2923 participants, 12,275 observations. Participants with missing covariates were excluded.
Any past 30-day smoking outcome defined as reporting past 30-day smoking at any of the 6 follow-up assessments.
[a] Adjusted for baseline sociodemographic (age, sex, race/ethnicity, marital status and education), JUUL System use frequency and quantity, and baseline smoking characteristics.
[b] Time-varying covariate.
[c] Time was coded as a continuous variable, in months. A quadratic time term was non-significant (p = .29) when tested in a separate model.
*** parameter estimates significant with p < .05**
**** parameters significant with p < .01**
***** parameters significant with p < .001**

nual household income of less than USD 50,000 (46.0%; Table 1). The overall sample of FES, on average, smoked regularly for 9.26 years (SD = 9.57), started smoking regularly at age 18.03 (SD = 3.31), smoked 12.29 cigarettes per day (SD = 9.10) before quitting smoking and last smoked an average of 35.85 months ago (SD = 57.81). Approximately 40% of FES who used to have a regular brand of cigarettes reported that they smoked mentholated cigarettes when they were smoking (Table 1).

With the exception of sex, there were statistically significant differences between recent and long-term quitters in all sociodemographic characteristics (p*s* < .001; Table 1). On average, recent (vs long-term) quitters were significantly younger and more likely to have never married. Greater proportions of long-term (vs recent) quitters were non-Hispanic white, completed at least some college, and reported USD 50,000 or more in annual household income.

Recent and long-term quitters also differed significantly in all smoking history characteristics (p*s* < .01; Table 1). Before quitting smoking, long-term quitters, compared to recent quitters, on average, smoked more cigarettes per day, smoked regularly for more years, started smoking regularly at a younger age, and a smaller proportion smoked mentholated cigarettes.

Predictors of Resumption of Smoking

Table 2 displays unadjusted and adjusted associations of sociodemographic, smoking history, and JUUL use characteristics across follow-up with smoking across the 12-month period. In univariate models, nearly all baseline sociodemographic and smoking history characteristics and time-varying JUUL use characteristics were significantly associated with resumption of smoking. After adjusting for all covariates, marital status and age were the

Table 3
Smoking Outcomes at Each Follow-up Assessment, Stratified by Recent and Long-term Quitters[a]

Follow-Up Assessment	Past 30-Day Smoking[d] %	Proportion of P30D Now Smoking Not at All[e,f] %	Proportion of P30D Now Smoking Every or Some Days[e,g] %	Cigarette Consumption in Those Smoking Every Day or Some Days[h]	
				No. Days Smoked in P30D[i] Mean (SD)	CPD in P30D[j] Mean (SD)
			Recent Quitter[b]		
Month 1	16.59	52.42	47.58	7.19 (7.24)	1.15 (2.49)
	N = 1688	N = 269	N = 269	N = 127	N = 127
Month 2	18.10	45.26	54.74	7.91 (7.93)	1.32 (2.57)
	N = 1685	N = 285	N = 285	N = 153	N = 151
Month 3	17.69	41.81	58.19	9.15 (8.82)	1.98 (5.46)
	N = 1679	N = 287	N = 287	N = 166	N = 164
Month 6	16.89	41.10	58.90	10.01 (9.75)	2.25 (4.23)
	N = 1474	N = 236	N = 236	N = 139	N = 137
Month 9	19.33	45.23	54.77	11.06 (10.08)	2.00 (3.72)
	N = 1526	N = 283	N = 283	N = 154	N = 152
Month 12	19.91	38.83	61.17	11.32 (9.78)	2.81 (5.83)
	N = 1517	N = 291	N = 291	N = 178	N = 178
			Long-term Quitter[c]		
Month 1	7.04	57.35	42.65	10.24 (9.82)	2.03 (3.27)
	N = 1988	N = 136	N = 136	N = 58	N = 58
Month 2	6.40	50.85	49.15	9.47 (9.14)	1.95 (3.10)
	N = 1923	N = 118	N = 118	N = 58	N = 58
Month 3	7.04	51.49	48.51	8.38 (8.34)	1.69 (3.10)
	N = 1931	N = 134	N = 134	N = 65	N = 65

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only significant sociodemographic predictors; never-married participants were more likely to smoke than married participants, and those over 30 were less likely to smoke than 21-24-year-olds. Among the smoking-history variables, those who started smoking at a later age, who smoked more heavily and for longer were more likely to smoke, and those smoking menthol were less likely.

After adjustment for all other variables, recent quitters had more than double the odds of smoking than did long-term quitters (OR = 2.44, 95% CI: 2.05-2.90). The number of days participants used JUUL in the 30 days preceding the assessment was significantly associated with reduced odds of smoking resumption (OR = 0.98, 95% CI: 0.976-0.988): for each one-day increase in frequency of JUUL use, odds of smoking resumption decreased by 2%. The adjusted model indicated that the risk of smoking did not increase over time. Associations in the complete case sample were consistent with these results (Supplemental Table S2).

With the exception of the cigarettes smoked per day when smoking × FES status interaction term ($p = .01$), no regressor × FES status interaction terms

Table 3 (*continued*)
Smoking Outcomes at Each Follow-up Assessment, Stratified by Recent and Long-term Quitters[a]

Follow-Up Assessment	Past 30-Day Smoking[d] %	Proportion of P30D Now Smoking Not at All[e,f] %	Proportion of P30D Now Smoking Every or Some Days[e,g] %	Cigarette Consumption in Those Smoking Every Day or Some Days[h]	
				No. Days Smoked in P30D[i] Mean (SD)	CPD in P30D[j] Mean (SD)
Month 6	8.41	53.19	46.81	10.41 (9.54)	1.68 (2.40)
	N = 1725	N = 141	N = 141	N = 66	N = 66
Month 9	9.21	50.32	49.68	11.45 (10.59)	2.78 (7.22)
	N = 1759	N = 155	N = 155	N = 76	N = 76
Month 12	9.12	41.94	58.06	9.68 (10.17)	1.92 (3.50)
	N = 1733	N = 155	N = 155	N = 90	N = 90

Note.
Abbreviations: P30D, Past 30-Day; SD, Standard Deviation; CPD, Cigarettes Per Day
Ns shown represent the available Ns for the specified survey item, and varied for particular measures because of missing data.
[a] Sample included all who provided past 30-day smoking data at the relevant follow-up assessment.
[b] Recent Quitters had stopped from smoking within the last 12 months at baseline.
[c] Long-term Quitters had stopped from smoking 12 or more months ago at baseline.
[d] % of participants who responded "yes" to "In the past 30 days, have you smoked a cigarette, even one or two puffs?"
[e] Those who responded "yes" to "In the past 30 days, have you smoked a cigarette, even one or two puffs?" were asked "Do you now smoke cigarettes…Every day/Some days/Not at all." Total Ns may not add up to P30D count due to missing data.
[f] % of past 30-day smokers who responded "Not at all" to "Do you now smoke cigarettes …".
[g] % of past 30-day smokers who responded "Every day" or "Some days" to "Do you now smoke cigarettes …"
[h] Those who indicated now smoking "Not at all" were not asked how many days they had smoked or how many cigarettes they had smoked on those days. Thus the data on days smoked and cigarettes per day are from the subset who indicated they were now smoking "Every day" or "Some days," and provided valid (non-missing) data.
[i] # days smoked in past 30 days = "On how many of the past 30 days did you smoke cigarettes?" Total Ns may not add up to "Every Day/Some Days" count due to missing data.
[j] CPD in past 30 days = "On average, on those days you smoked, how cigarettes did you usually smoke each day? A pack usually has 20 cigarettes in it."; [CPD*number of smoking days in past 30 days]/30. Total Ns may not add up to "Every Day/Some Days" count due to missing data.

were significant (p*s* > .11). A subsequent model stratified by smoking status (recent vs long-term quitters) indicated only a small difference in the association of cigarettes smoked per day and smoking across follow-up (OR = 0.98 vs OR = 0.97). These results indicate that except for quantity of smoking associations of sociodemographic, smoking and JUUL use characteristics and switching did not significantly differ by FES status.

Cigarette Smoking across the Follow-up Period

Overall, 29.6% of FES reported past 30-day smoking at ≥1 follow-up assessment during the 12-month period: 39.8% of recent quitters and 20.5% of long-term quitters. The prevalence of sustained smoking resumption, defined as reporting past 30-day smoking at both 9- and 12-month follow-ups, was 6.5% in recent quitters and 2.8% in long-term quitters.

Among recent quitters, the prevalence of past 30-day smoking ranged from 16.6% to 19.9% across the follow-up period (Table 3). Among recent quitters who reported smoking in the past 30 days, 38.8% to 52.4% (across follow-ups) reported they did not currently smoke (ie, reported now smoking "not at all"). Recent quitters who re-

Table 4
JUUL Use at Each Follow-up Assessment, Stratified by Recent and Long-term Quitters[a]

Follow-Up Assessment	Past 30-Day JUUL Use[d] %	Proportion of P30D Now Using JS Not at All[e,f] %	Proportion of P30D Now Using JS Every or Some Days[e,g] %	JS Use Frequency in Those Using JS Every Day or Some Days[h]	
				No. Days Used JS in P30D[i] Mean (SD)	No. of JS Sessions per Day in P30D[j] Mean (SD)
			Recent Quitter[b]		
Month 1	98.77	1.36	98.64	26.29 (6.79)	12.96 (14.65)
	N = 1709	N = 1687	N = 1687	N = 1629	N = 1623
Month 2	96.30	1.65	98.35	25.74 (7.41)	12.85 (14.00)
	N = 1703	N = 1640	N = 1640	N = 1569	N = 1564
Month 3	94.89	1.55	98.45	25.27 (8.01)	13.07 (13.79)
	N = 1701	N = 1614	N = 1614	N = 1542	N = 1537
Month 6	93.40	1.66	98.34	24.09 (8.95)	12.70 (14.22)
	N = 1485	N = 1387	N = 1387	N = 1317	N = 1309
Month 9	91.65	2.26	97.74	24.10 (8.80)	12.58 (13.59)
	N = 1545	N = 1416	N = 1416	N = 1349	N = 1346
Month 12	88.40	3.32	96.68	23.51 (9.42)	11.77 (11.96)
	N = 1534	N = 1356	N = 1356	N = 1273	N = 1268
			Long-term Quitter[c]		
Month 1	99.05	2.07	97.93	24.46 (7.93)	10.70 (12.14)
	N = 1995	N = 1976	N = 1976	N = 1896	N = 1887
Month 2	96.08	1.88	98.12	24.42 (8.56)	10.77 (12.61)
	N = 1938	N = 1862	N = 1862	N = 1792	N = 1783
Month 3	94.50	1.74	98.26	24.21 (8.67)	10.73 (12.54)
	N = 1945	N = 1838	N = 1838	N = 1756	N = 1746

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ported smoking in the past 30 days and smoking "some days" or "every day" reported smoking, on average, between 7.19 and 11.32 days in the past 30 days and 1.15 to 2.81 cigarettes per day across the 6 follow-ups.

Among long-term quitters, prevalence of past 30-day smoking ranged from 6.4% to 9.2% across the follow-up period (Table 3). Among long-term quitters who reported smoking in the past 30 days, 41.9% to 57.4% (across follow-ups) reported now smoking "not at all." Long-term quitters who reported smoking in the past 30 days and smoking "some days" or "every day" reported smoking, on average, between 8.38 and 11.45 days in the past 30 days and 1.68 to 2.78 cigarettes per day.

Patterns of smoking were similar in the complete case analysis (Supplemental Table S3), with slightly lower rates of smoking prevalence. Among participants in the complete case sample who reported smoking at ≥1 follow-up, the largest proportion reported smoking at only one follow-up assessment (14.8% of FES); this was more common among recent quitters (17.5%) than long-term quitters (12.6%; Supplemental Table S4). Fewer than 2%

Table 4 (*continued*)
JUUL Use at Each Follow-up Assessment, Stratified by Recent and Long-term Quitters[a]

Follow-Up Assessment	Past 30-Day JUUL Use[d] %	Proportion of P30D Now Using JS Not at All[e,f] %	Proportion of P30D Now Using JS Every or Some Days[e,g] %	JS Use Frequency in Those Using JS Every Day or Some Days[h]	
				No. Days Used JS in P30D[i] Mean (SD)	No. of JS Sessions per Day in P30D[j] Mean (SD)
Month 6	91.23	1.83	98.17	23.57 (9.09)	10.80 (12.28)
	N = 1734	N = 1582	N = 1582	N = 1508	N = 1503
Month 9	89.05	2.92	97.08	22.98 (9.50)	11.23 (13.16)
	N = 1772	N = 1577	N = 1577	N = 1490	N = 1488
Month 12	87.18	2.63	97.37	22.75 (9.53)	10.84 (12.47)
	N = 1747	N = 1523	N = 1523	N = 1446	N = 1441

Note.
Abbreviations: P30D, Past 30-day; JS, JUUL System; SD, Standard Deviation
Ns shown represent the available Ns for the specified survey item, and varied for particular measures because of missing data.
[a] Sample included all who provided past 30-day JUUL System use data at the relevant follow-up assessment.
[b] Recent Quitters had stopped from smoking within the last 12 months at baseline.
[c] Long-term Quitters had stopped from smoking 12 or more months ago at baseline.
[d] % of past 30-day JS Users were those who responded "yes" to "Have you used a JUUL in the past 30 days, even one or two puffs?"
[e] Those who responded "yes" to "Have you used a JUUL in the past 30 days, even one or two puffs?" were asked "Do you now use a JUUL…Every day/Some days/Not at all." Total Ns may not add up to P30D JS Use count due to missing data.
[f] % of past 30-day JS Users who responded "Not at all" to "Do you now use a JUUL…"
[g] % of past 30-day JS Users who responded "Every day" or "Some days" to "Do you now use a JUUL…"
[h] Those who indicated now using a JUUL "Not at all" were not asked how many days they had use a JUUL or how times they had used a JUUL on those days. Thus, the data on days used a JUUL and JUUL sessions per day are from the subset who indicated they were now using a JUUL "Every day" or "Some days", and provided valid (non-missing) data.
[i] # Days Used JS in P30D = "On how many of the past 30 days did you use a JUUL?" Total Ns may not add up to "Every Day/Some Days" count due to missing data.
[j] # of JUUL Sessions/Day = "On average, on those days you used a JUUL, how many times did you usually use a JUUL each day? Assume that one "time" consists of around 15 puffs, or 10 minutes." Total Ns may not add up to "Every Day/Some Days" count due to missing data.

of former smokers reported past 30-day smoking at all 6 follow-up assessments.

JUUL Use across the Follow-up Period

Overall, the prevalence of past 30-day JUUL use was high in both recent and long-term quitters, and remained so across all follow-ups – over 87% among both recent and long-term quitters (Table 4). Prevalence of past 30-day JUUL use among recent quitters decreased over time, from 98.8% at the one-month follow-up to 88.4% at the 12-month follow-up. A similar decline in prevalence of past 30-day JUUL use was observed in long-term quitters, decreasing from 99.1% at the one-month follow-up to 87.2% at the 12-month follow-up.

Among recent quitters who reported past 30-day JUUL use, the vast majority (96.7%-98.6%) reported using JUUL "some days" or "every day" across the follow-up period (Table 4). Recent quitters who reported using JUUL in the past 30 days and on "some days" or "every day" used JUUL, on average, between 23.51 and 26.29 days in the past 30 days and 11.77 to 13.07 times per day.

Similar JUUL use patterns were observed among

long-term quitters. Among those who reported past 30-day JUUL use, almost all long-term quitters (97.1%-98.3%) reported using JUUL "some days" or "every day" (Table 4). Long-term quitters who reported using JUUL in the past 30 days and on "some days" or "every day" used JUUL, on average, between 22.75 and 24.46 days in the past 30 days and 10.70 to 11.23 times per day.

As was the case for the smoking outcomes, there were few differences in JUUL use across follow-up between the all-available and the complete case samples (Supplemental Table S5).

DISCUSSION

Among former established smokers who purchased a JSK, rates of cigarette smoking were low and stable across the 12-month follow-up period following initial purchase. The stability of point-prevalence of smoking suggests that those reporting past 30-day smoking were not resuming ongoing smoking, as this would have led to cumulatively rising prevalence rates. The relatively low rates of smoking at both of the last 2 follow-ups (9 and 12 months) also suggests a low likelihood of continuing smoking or resumption of smoking.

Across follow-ups, participants who used JUUL more frequently were less likely to smoke, suggesting that increased JUUL use may contribute to the prevention of smoking resumption. This finding is consistent with conceptual models that propose that ENDS may act as a less harmful alternative source of nicotine to deter cigarette smoking.[42,43] The finding here is consistent with that among baseline smokers in ADJUSST, which showed that greater frequency of JUUL use was associated with increased switching away from smoking.[44] Although there was a statistically significant association of daily quantity of JUUL use and reduced odds of smoking resumption in the univariate model, after controlling for past 30-day frequency of JUUL use (and other characteristics) in the fully-adjusted model this association was no longer significant. Past 30-day frequency of JUUL use (vs daily quantity of use) may be more indicative of engagement with JUUL and central to preventing resumption of smoking. Measurement of daily quantity is also particularly difficult,[45,46] particularly as ENDS users may use ENDS intermittently in small amounts throughout the day. It is possible that a more precise measure of daily quantity would be more predictive.

In any case, the data indicate that more frequent use of JUUL was associated with lower risk of smoking. Importantly, the present study differs from most studies of ENDS use in that ENDS users were not defined on the basis of any past 30-day ENDS use, but rather the sample consisted of former smokers who had purchased a JSK, implying a commitment to using ENDS. This characteristic likely helps explain the substantial average frequency (averaging > 20 days per month) and quantity (averaging > 10 uses per day) of JUUL use, as well as its persistence (> 85% using JUUL at 12 months). Persistent ENDS use was also observed among successful quitters in a randomized smoking cessation trial with ENDS.[47] As nicotine use may carry some risks,[22] users may want to discontinue use after smoking abstinence is securely established; PATH data suggest that users are far more successful in quitting ENDS than in quitting smoking.[48]

Recent quitters had higher likelihood of smoking over the 12-month period; at the 12-month assessment, 19.9% of recent quitters reported smoking, compared to 9.1% of long-term quitters. This was expected, as the risk of relapse decreases with longer duration of abstinence.[7,10,20]

Despite challenges in directly comparing relapse rates from other data sources and populations, the observed smoking resumption rates at 12 months are on the lower end of the range of reported rates of resuming smoking among former smokers using ENDS in other studies, which range from 6% to ~ 40% using similar point-prevalence definitions of current smoking status.[28,49,50] Furthermore, several analyses of the Population Assessment of Tobacco and Health, a large nationally representative sample of the US population, have shown rates of smoking among former smokers who use ENDS to be generally higher or comparable to those observed in the current analysis, using similar point-prevalence definitions of current smoking status.

Whereas direct comparisons to PATH data are limited for several reasons (eg, population differences, definitions of relapse and ENDS use, and product differences), 31.9% of recent quitters who quit within the past 12 months and used ENDS regularly (ie, using ENDS some days or every day at baseline, ever used ENDS fairly regularly) were smoking cigarettes some days or every day one

year later.[31] Another analysis of the first 2 waves of PATH data showed a 9.3% rate of smoking at Wave 2 among past long-term quitters who had quit for at least 5 years and were using ENDS in Wave 1.[32] Another methodologic difference is related to ENDS history; the current study enrolled former smokers just as they were starting to use JUUL products, whereas the PATH analyses included former smokers who may have been using ENDS for some time, implicitly excluding those who had stopped using ENDS. Furthermore, because the current study only included JUUL purchasers (ie, ENDS users), it was not possible to compare non-ENDS users with ENDS users.

Avoiding smoking is a major concern for former smokers. The significant association between increased past 30-day frequency of JUUL use and reduced odds of smoking resumption suggests that more frequent JUUL use may reduce risk of smoking resumption among former smokers using JUUL. Some former smokers may still feel at risk for resumption of smoking and may adopt JUUL to help them avoid smoking. In the broader literature, findings from studies examining the association between ENDS use and smoking among former smokers have been inconsistent. Some studies report reduced likelihood of later smoking[51,52] and others suggest increased likelihood of smoking, at least in some populations.[32,33,35]

Comparing the current findings with results from these studies requires caution, particularly given differences in the comparison groups (ie, comparing ENDS users and non-users vs comparing more and less frequent ENDS users) and differences in study populations. For example, the assessment of the effect of ENDS use on relapse in studies of ENDS purchasers is complicated given the potential for "biasing by indication" – ie, the fact that the former smokers who purchase ENDS may do so because they believe they are at heightened risk for relapse. Consistent with this, analyses in PATH show that the former smokers who report using ENDS specifically to assist in abstinence were more likely to smoke.[53]

These results of this study are limited by several methodological issues. First, there was no comparison group of former smokers who did not use ENDS, which limits causal attributions for the effect of ENDS on resumption of smoking. Second, there was substantial loss to follow-up; bias due to differential loss to follow-up by smoking status may affect smoking outcome data in this study. However, a separate analysis of loss to follow-up provided in Shiffman et al[39] found no statistically significant differences in baseline characteristics between responders and those lost to follow-up and substantial rates of past 30-day abstinence from smoking in a former smoker sample recontacted after missing the 12-month assessment. Third, this study used self-reported data, which has inherent limitations in all survey research studies; smoking outcomes were not biochemically verified. Fourth, the study focused on individuals who volunteered to be in the study, which may limit the generalizability of findings. Additionally, use of non-cigarette tobacco products, motivational factors associated with relapse, and JUUL use expectancies were not included in the predictive models, and should be assessed in future research.

The study focused on individuals who purchased a JUUL Starter Kit, which implies a degree of commitment to using JUUL that goes beyond that of individuals who merely used JUUL or another ENDS in the previous 30 days. Thus, although the findings likely do not generalize to all JUUL "users" defined by that standard, they likely apply to individuals who undertake use of JUUL, who are of significant public health interest. Relatedly, the findings may not generalize to users of ENDS products other than JUUL.

Strengths of this study include the large sample size with a frequent cadence of follow-up assessments over a one-year period, which is uncommon for large-scale longitudinal observational studies. The frequent follow-up assessments provided granular temporal detail to examine the trajectory of cigarette smoking among former smokers over time. Furthermore, the study examined real-world purchasers and provides actual use data that is relevant to real-world adoption of the product. This study focused solely on former smokers who purchased JUUL; other manuscripts in this journal issue evaluate switching completely away from smoking among smokers who purchase JUUL[44,54] and smoking reduction among dual users.[55]

Conclusions

This longitudinal study of former established smokers who purchased a JSK found low and sta-

ble rates of combustible cigarette smoking across the 12-month follow-up period following initial purchase. More frequent past 30-day use of JUUL was associated with reduced odds of smoking resumption, suggesting that greater engagement with JUUL may have a protective effect against resumption of smoking in former smokers who purchased JUUL (ie, may aid former smokers in avoiding smoking relapse). Further research is needed to replicate this finding in other populations of former smokers. The point prevalence of smoking did not increase across follow-up assessments, suggesting there is not a growing cohort of former smokers who have resumed smoking after the purchase of the JUUL.

Human Subjects Approval Statement

The ADJUSST study was approved by the Advarra® Institutional Review Board; all participants completed an informed consent form and were compensated USD30 for each survey they completed.

Conflict of Interest Disclosure Statement

GML, NMH, NIG, LCS, and EMA are full-time employees of Juul Labs Inc. CH was a full-time employee of Juul Labs Inc during the time that this work was conducted. Through PinneyAssociates Inc, SS provides consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc. Within the last 2 years, PinneyAssociates Inc has consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction. Under contract to JUUL Labs Inc, the Centre for Substance Use Research, an independent research consultancy, designed the study and assessments and oversaw collection of data through Dacima Inc. CSUR managed, cleaned, and summarized the data. NMH performed the statistical analyses under the direction of GML. All of the authors contributed to writing and review of the paper, and had access to the data. The sponsor approved the research plan and provided comment on a near-final draft of the paper.

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SUPPLEMENTARY MATERIALS

Supplemental Results

Individuals who, when asked whether they are "now smoking every day, some days, or not at all" say they are now smoking "not at all" are typically classified as abstinent or non-smokers in studies of smoking trajectories.[1] In the ADJUSST study, respondents who said they were not smoking at all, but who had reported smoking in the past 30 days were considered to have smoked, and constituted a substantial fraction (sometimes the majority) of those who were considered to have smoked.

However, in ADJUSST, such respondents were not asked how many days they had smoked or how many cigarettes per day, and thus, did not contribute to the calculations of the sample's cigarette consumption. To gain insight into the smoking behavior of respondents who showed this response pattern, we turned to the PATH study,[2] which also asked both smoking-status questions (past 30-day smoking and now smoking "every day," "some days," or "not at all"), but did not use them to skip over further questions about frequency and quantity of smoking. Specifically, all past-30-day smokers were asked how many days in the past 30 days they smoked and how many cigarettes they smoked. Additionally, they were asked how long ago they had last smoked.

Thus, PATH provides data on the smoking behavior of these past-30-day but now-not-at-all (P30D-NNAA) smokers. We identified a sample of smokers with P30D-NNAA response patterns in PATH Wave 4, and who had also provided Wave 3 data. To parallel the analyses in the ADJUSST analysis of former smokers, we identified individuals who were former smokers at Wave 3 (the equivalent of ADJUSST baseline) and tallied their reported smoking behavior at Wave 4 (Table S1).

Wave-4 P30D-NNAA smokers who were former established smokers at baseline reported smoking 7.1 days in the past month, and averaging 2.7 cigarettes per day (Table S1). Less than one in 5 (18.3%) smoked frequently, defined as 20 or more days per month. A minority (37.6%) reported having smoked in the 7 days preceding the assessment.

In sum, the PATH data strongly suggest that former smokers who subsequently showed the P30D-NNAA response pattern (ie, reporting they smoked in the past 30 days, but reporting they now smoke not at all) are smoking little, smoking infrequently and a modest number of cigarettes. The majority report 7-day abstinence, suggesting they may consider themselves to have stopped smoking, which may help explain their 'not at all' response when asked to characterize their current smoking. In any case, these data from PATH, though on a different sample, and not addressing ENDS use, shed some light on how to interpret the P30D-NNAA response pattern.

Supplementary References

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Figure S1
Study Flow Chart

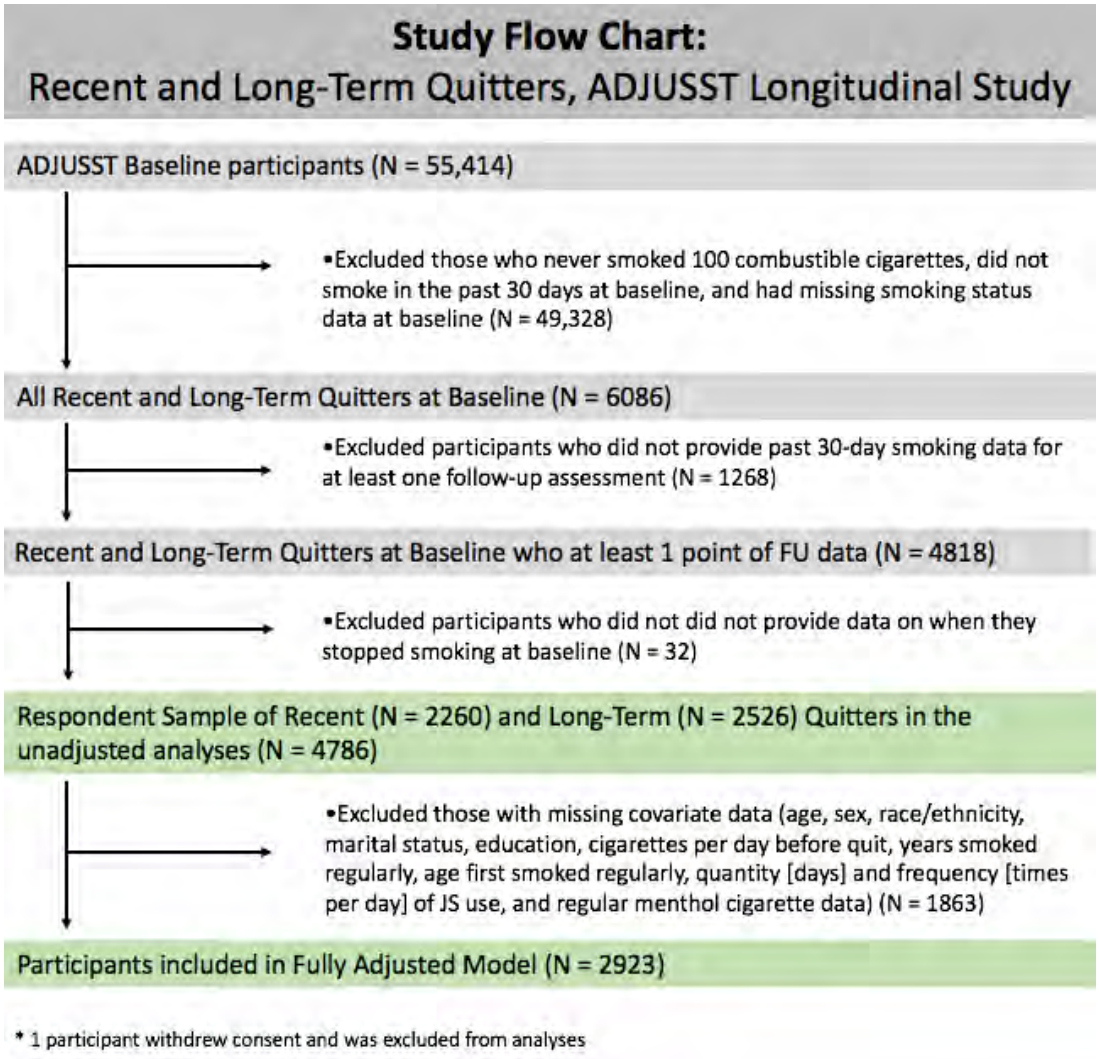

Table S1
Smoking Patterns Reported by Wave 4 Respondents in PATH Who Indicated They Had Smoked in the Past 30 Days and Also Indicated They Now Smoked "Not At All," Stratified by Their Year-ago Wave 3 Smoking Status

Reported Smoking Behavior 1 Year Later (Wave 4)	Smoking Status 1 Year Ago (Wave 3)					
	Former Established, Short-term (N = 72)			Former Established, Long-term (N = 79)		
	N	Mean or %	SD	N	Mean or %	SD
Overall CPD (mean, SD)	59	0.7	2.3	33	0.9	3.4
Days smoked past 30 days[a] (mean, SD)	70	3.1	5.4	77	1.6	4.3
Smoked ≥ 20 days in past 30 days[a] (%)	70	5.7%	—	77	1.3%	—
Smoked in past week (%)	72	35.2%	—	79	20.6%	—

Note.
Former Established, Short-term = Smoked < 12 months ago at Wave 3; at Wave 4 smoked in the past 30 days and "Now" smoke "Not at all."
Former Established, Long-term = At Wave 3 smoked ≥ 12 months ago; at Wave 4 smoked in the past 30 days and "Now" smoke "Not at all."
[a] Per PATH logic, respondents who indicated they smoked every day were assigned smoking 30 days out of 30.

Table S2
Association of Sociodemographic, Smoking and JUUL Use Characteristics with Resumption of Smoking over the 12-month Period in Complete Case Sample

Regressors	Fully Adjusted Model OR (95% CI)[a]	
Sociodemographic Characteristics		
Age Category		
21 to 24	Ref	
25 to 29	1.11	(0.77, 1.59)
30 to 39	0.88	(0.57, 1.36)
40 or older	0.52	(0.27, 1.01)
Sex		
Male	Ref	
Female	1.43	(1.08, 1.89)*
Transgender	1.74	(0.63, 4.79)
Race/Ethnicity		
Non-Hispanic White	Ref	
Non-Hispanic Black	2.25	(1.17, 4.31)*
Non-Hispanic Asian	1.73	(1.02, 2.94)*
Non-Hispanic Other	1.00	(0.59, 1.71)
Hispanic Ethnicity	1.41	(0.92, 2.16)

(continued on next page)

Table S2 (*continued*)
Association of Sociodemographic, Smoking and JUUL Use Characteristics with Resumption of Smoking over the 12-month Period in Complete Case Sample

Regressors	Fully Adjusted Model OR (95% CI)[a]
Sociodemographic Characteristics	
Marital Status	
Married	Ref
Divorced, Separated or Widowed	1.04 (0.63, 1.73)
Never Married	1.34 (0.96, 1.85)
Education	
High School Graduate or Less Education	Ref
Some College or Associate Degree	1.34 (0.96, 1.86)
Bachelor's Degree or More Education	1.06 (0.72, 1.55)
Smoking Characteristics at Baseline	
Regular Brands of Cigarettes Smoked before Quitting were Menthol Cigarettes	
No	Ref
Yes	0.94 (0.72, 1.23)
Former Established Smoker Subtype	
Long-term Quitter	Ref
Recent Quitter	2.52 (1.93, 3.28)***
No. Cigarettes Smoked per Day before Quitting	0.99 (0.97, 1.01)
Years Smoked Regularly Before Quitting	1.02 (0.99, 1.05)
Age First Smoked Regularly Before Quitting	1.00 (0.94, 1.06)
Time-varying Effects	
No. Days Used JUUL in Past 30 Days[b]	0.98 (0.97, 0.99)**
No. Times Used JUUL per Day[b]	1.00 (0.99, 1.00)
Time effect, months (linear)[c]	1.00 (0.98, 1.02)

Note.
Fully adjusted model: N = 5818 observations; 1097 participants. Participants with missing covariates were excluded. Any past 30-day smoking outcome defined as reporting past 30-day smoking at any of the 6 follow-up assessments.
[a] Adjusted for baseline sociodemographic (age, sex, race/ethnicity, marital status and education), JUUL System use frequency and quantity, and baseline smoking characteristics.
[b] Time varying covariate.
[c] Time was coded as a continuous variable, in months. A quadratic time term was non-significant (p = .81) when tested in a separate model.
*** parameter estimates significant with p < .05**
**** parameters significant with p < .01**
***** parameters significant with p < .001**

Table S3
Smoking Outcomes at Each Follow-up Assessment, among Complete Cases, Stratified by Recent and Long-term Quitters[a]

Follow-up Assessment	Past 30-Day Smoking[d] % [N]	Proportion of P30D Now Smoking Not at All[e,f] % [N]	Proportion of P30D Now Smoking Every or Some Days[e,g] % [N]	Cigarette Consumption in Those Smoking Every Day or Some Days[h]	
				No. Days Smoked in P30D[i] Mean (SD) [N]	CPD in P30D[j] Mean (SD) [N]
			Recent Quitter[b] (N = 702)		
Month 1	16.24 [114]	47.71 [52]	52.29 [57]	7.04 (7.95) [56]	1.03 (1.89) [56]
Month 2	15.38 [108]	42.00 [42]	58.00 [58]	7.78 (7.62) [55]	1.11 (2.15) [54]
Month 3	16.10 [113]	47.32 [53]	52.68 [59]	9.50 (9.48) [58]	2.60 (8.37) [57]
Month 6	14.53 [102]	41.41 [41]	58.59 [58]	8.66 (9.50) [58]	2.14 (4.59) [56]
Month 9	17.38 [122]	52.10 [62]	47.90 [57]	11.89 (9.38) [56]	1.98 (4.19) [56]
Month 12	16.81 [118]	41.38 [48]	58.62 [68]	10.62 (8.92) [68]	2.03 (4.22) [68]
			Long-term Quitter[c] (N = 887)		
Month 1	6.43 [57]	61.82 [34]	38.18 [21]	11.24 (11.00) [21]	2.39 (3.35) [21]
Month 2	5.64 [50]	56.00 [28]	44.00 [22]	7.59 (7.68) [22]	1.61 (2.65) [22]
Month 3	6.65 [59]	46.55 [27]	53.45 [31]	8.23 (8.54) [31]	1.65 (3.06) [31]
Month 6	8.34 [74]	60.00 [42]	40.00 [28]	11.50 (9.54) [28]	1.89 (2.72) [28]
Month 9	8.00 [71]	59.70 [40]	40.30 [27]	11.23 (11.17) [26]	1.81 (2.51) [26]
Month 12	8.12 [72]	40.00 [28]	60.00 [42]	10.12 (9.59) [42]	1.90 (2.86) [42]

Note.
Abbreviations: P30D = Past 30-day; SD = Standard Deviation; CPD = Cigarettes Per Day
Ns shown represent the available Ns for the specified survey item, and varied for particular measures because of missing data.
[a] Sample included all who provided past 30-day smoking data at every follow-up assessment.
[b] Recent Quitters had stopped from smoking within the last 12 months at baseline.
[c] Long-term Quitters had stopped from smoking 12 or more months ago at baseline.
[d] % of participants who responded "yes" to "In the past 30 days, have you smoked a cigarette, even one or two puffs?"
[e] Those who responded "yes" to "In the past 30 days, have you smoked a cigarette, even one or two puffs?" were asked "Do you now smoke cigarettes…Every day/Some days/Not at all." Total Ns may not add up to P30D count due to missing data.
[f] % of past 30-day smokers who responded "Not at all" to "Do you now smoke cigarettes …".
[g] % of past 30-day smokers who responded "Every day" or "Some days" to "Do you now smoke cigarettes …"
[h] Those who indicated now smoking "Not at all" were not asked how many days they had smoked or how many cigarettes they had smoked on those days. Thus the data on days smoked and cigarettes per day are from the subset who indicated they were now smoking "Every day" or "Some days," and provided valid (non-missing) data.
[i] # days smoked in past 30 days = "On how many of the past 30 days did you smoke cigarettes?" Total Ns may not add up to "Every Day/Some Days" count due to missing data.
[j] CPD in past 30 days = "On average, on those days you smoked, how cigarettes did you usually smoke each day? A pack usually has 20 cigarettes in it." [CPD*number of smoking days in past 30 days]/30. Total Ns may not add up to "Every Day/ Some Days" count due to missing data.

Table S4
Number of Follow-up Assessments in which Past 30-day Smoking Status Was Reported among Complete Cases, Stratified by Recent and Long-term Quitters[a]

	Recent Quitter[b] % (N)	Long-Term Quitter[c] % (N)	Total % (N)
	(N = 702)	(N = 887)	(N = 1589)
Number of Follow-up Assessments in which Past 30-day Smoking Was Reported			
0 Follow-ups	56.55 (397)	76.66 (680)	67.78 (1077)
1 or More Follow-ups	43.45 (305)	23.34 (207)	32.22 (512)
1 Follow-up Only	17.52 (123)	12.63 (112)	14.79 (235)
2 Follow-ups Only	11.68 (82)	4.96 (44)	7.93 (126)
3 Follow-ups Only	6.41 (45)	3.49 (31)	4.78 (76)
4 Follow-ups Only	3.99 (28)	1.58 (14)	2.64 (42)
5 Follow-ups Only	2.71 (19)	0.23 (2)	1.32 (21)
6 Follow-ups Only	1.14 (8)	0.45 (4)	0.76 (12)

Note.
[a] Sample included all who provided past 30-day smoking data at every follow-up assessment.
[b] Recent Quitters had stopped from smoking within the last 12 months at baseline.
[c] Long-term Quitters had stopped from smoking 12 or more months ago at baseline.

Table S5
JUUL System Use at Each Follow-up Assessment, among Complete Cases, Stratified by Recent and Long-term Quitters[a]

Follow-up Assessment	Past 30-day JUUL Use[d] % [N]	Proportion of P30D Now Using JS Not at All[e,f] % [N]	Proportion of P30D Now Using JS Every or Some Days[e,g] % [N]	JS Use Frequency in Those Using JS Every Day or Some Days[h]	
				No. Days Used JS in P30D[i] Mean (SD) [N]	No. of JS Sessions per Day in P30D[j] Mean (SD) [N]
			Recent Quitter[b] (N = 702)		
Month 1	99.00 [695]	1.58 [11]	98.42 [684]	26.31 (6.91) [675]	13.12 (14.34) [675]
Month 2	97.01 [681]	2.20 [15]	97.80 [666]	25.40 (7.75) [653]	12.53 (13.54) [653]
Month 3	95.30 [669]	2.09 [14]	97.91 [655]	25.39 (7.92) [641]	13.15 (13.93) [639]
Month 6	93.02 [653]	1.53 [10]	98.47 [643]	24.15 (8.89) [631]	12.37 (13.45) [627]
Month 9	91.45 [642]	1.40 [9]	98.60 [633]	23.67 (9.01) [624]	12.45 (12.80) [623]
Month 12	87.89 [617]	2.59 [16]	97.41 [601]	23.73 (9.35) [589]	11.70 (11.86) [586]
			Long-term Quitter[c] (N = 887)		
Month 1	98.87 [877]	1.82 [16]	98.18 [861]	23.88 (8.25) [845]	10.59 (12.24) [844]
Month 2	95.94 [851]	2.00 [17]	98.00 [834]	24.26 (8.59) [825]	10.57 (12.56) [820]
Month 3	95.04 [843]	1.42 [12]	98.58 [831]	23.77 (8.84) [817]	10.27 (11.53) [813]
Month 6	91.66 [813]	2.09 [17]	97.91 [796]	23.36 (9.18) [777]	10.44 (11.54) [778]
Month 9	91.54 [812]	2.71 [22]	97.29 [790]	22.98 (9.38) [773]	11.14 (13.39) [772]
Month 12	89.52 [794]	2.90 [23]	97.10 [771]	23.03 (9.36) [756]	10.84 (12.75) [752]

Note.
Abbreviations: P30D = Past 30-day; JS = JUUL System; SD = Standard Deviation
Ns shown represent the available ns for the specified survey item, and varied for particular measures because of missing data.
[a] Sample included all who provided past 30-day smoking data at every follow-up assessment.
[b] Recent Quitters had stopped from smoking within the last 12 months at baseline.
[c] Long-term Quitters had stopped from smoking 12 or more months ago at baseline.
[d] % of past 30-day JS Users were those who responded "yes" to "Have you used a JUUL in the past 30 days, even one or two puffs?"
[e] Those who responded "yes" to "Have you used a JUUL in the past 30 days, even one or two puffs?" were asked "Do you now use a JUUL…Every day/Some days/Not at all." Total Ns may not add up to P30D JS Use count due to missing data.
[f] % of past 30-day JS Users who responded "Not at all" to "Do you now use a JUUL…"
[g] % of past 30-day JS Users who responded "Every day" or "Some days" to "Do you now use a JUUL…"
[h] Those who indicated now using a JUUL "Not at all" were not asked how many days they had use a JUUL or how times they had used a JUUL on those days. Thus, the data on days used a JUUL and JUUL sessions per day are from the subset who indicated they were now using a JUUL "Every day" or "Some days", and provided valid (non-missing) data.
[i] # Days Used JS in P30D = "On how many of the past 30 days did you use a JUUL?" Total Ns may not add up to "Every Day/Some Days" count due to missing data.
[j] # of JUUL Sessions/Day = "On average, on those days you used a JUUL, how many times did you usually use a JUUL each day? Assume that one "time" consists of around 15 puffs, or 10 minutes." Total Ns may not add up to "Every Day/Some Days" count due to missing data.

Smoking Trajectories of Adult Never Smokers 12 Months after First Purchase of a JUUL Starter Kit

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Objectives: We assessed adult never smokers' trajectories of smoking over 12 months after a first-time JUUL Starter Kit (JSK) purchase. **Methods:** Adult (≥ 21) never smokers (N = 3853) who purchased a JSK were recruited into an observational naturalistic study. Analyses distinguished those who had previously used ENDS (NS+E, N = 2848) from those who had not (NS-NE, N = 1005). Participants were invited to complete follow-up assessments at 1, 2, 3, 6, 9, and 12 months. "Smoking" was defined as any past-30-day smoking ("even a puff"). **Results:** Past-30-day smoking was reported by 5.01% of NS+E at month one, and 7.56% at month 12; for NS-NE, these were 10.23% and 12.35%. In both groups, < 5% reported smoking at both 9 and 12 months. Across follow-ups, 25%-49% of those reporting having smoked then said they were now smoking "not at all"; the remainder reported low frequency (10-12 days-per-month) and quantity (2-4 cigarettes-per-day) of smoking. Past-30-day use of JUUL remained at ≥ 80% across follow-ups. Each additional day-per-month of JUUL use decreased the odds of smoking by 1%. **Conclusions:** Some adult never smokers who purchased a JSK reported smoking during the succeeding year; smoking was light and intermittent. Participants who used JUUL more frequently were less likely to smoke.

Key words: electronic nicotine delivery systems (ENDS); e-cigarettes; JUUL; smoking; tobacco cessation
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Electronic nicotine delivery systems (ENDS) are likely to provide a significant potential benefit to public health by helping smokers, especially those who might not otherwise quit, to switch away from smoking.[1-4] Use of ENDS itself has risks, but these are likely to be much lower than those resulting from smoking;[4,5] thus, the biggest adverse effects of ENDS use comes from the potential of non-smokers moving on to smoke cigarettes, whose use carries much greater risk. At the same time, as the US Food and Drug Administration (FDA) has pointed out,[6] ENDS also can have adverse effects on public health to the extent that they are used by individuals who are not smoking and would not otherwise smoke.

Whether ENDS use leads to smoking has been extensively explored and debated in the context of youth use, without clear resolution. That youth who use ENDS are more likely to become subsequent smokers is established;[7-9] however, whether this is causal or due to confounding common factors – because of characteristics that may predispose individuals both to smoking and to ENDS use – is debated in the literature.[10-12]

The question of smoking after adoption of ENDS also arises with regard to adult never smokers who start using ENDS. The prevalence of past-30-day ENDS use among adults is low (eg, 2.3%),[13,14] though notably higher among young adults (eg, 5.3%).[13,15] In any case, the question of whether ENDS use is followed by cigarette smoking in adults is also important, and has been the subject

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of several studies. For example, McMillen et al[16] report that 7% of never smokers who were past-30-day ENDS users at Wave 1 of PATH (2013-2014) were past-30-day smokers a year later, higher than the rate among those not using ENDS. Studies also have focused on young adults, as young adulthood is the period associated with the highest prevalence of ENDS use,[17,18] and also associated with high risk for smoking initiation[19] and escalation.[20] Primack et al[21] estimated that 48% of young adult ever-users of ENDS smoked (criterion was even a puff) during the succeeding 18 months – a rate higher than that in non-users. Similarly, in college students, Loukas et al[22] reported that 40% of ever-ENDS users initiated smoking during an 18-month follow-up.

The studies of adults face the same hurdles to making causal attributions as have been noted for the youth data; Adults electing to use ENDS differ in many other ways from those not adopting ENDS,[23] and it is difficult to account for all the relevant differences. Additionally, studies typically start with a sample of existing ENDS users,[21,22] which may already have been subject to selection, in that those who had already progressed to smoking are out of the sampling frame, since they are no longer never smokers.

Additionally, studies of the association between ENDS use and smoking also have been criticized on the grounds that they have typically used limited measures of each behavior. Often, studies have examined the link between ever-use of ENDS and ever-use of cigarettes, representing low-threshold definitions of use. Other studies have looked at current use of ENDS (rather than "ever"), but defined it as any use at all in the past 30 days, which likely includes some casual use, such as trying a friend's ENDS.[24] Similar limitations apply to past-30-day smoking, which may indicate limited experimentation with cigarette smoking.[17,25-27] Prospective studies also have typically examined these behaviors only once over the course of a year.[16,21] Data on patterns over time and amounts of use also may be informative, helping to distinguish incident smoking that is intermittent and sporadic from that which appears to be taking on the continuity that may be associated with becoming a smoker.[2-5,28,29] Also, examining associations between the frequency or amount of ENDS use and subsequent smoking (analogous to a "dose-response" effect) also can provide relevant insight.[30-33]

This paper reports data from adult never smokers in the ADJUSST (Adult JUUL Switching and Smoking Trajectories) study,[34] a longitudinal naturalistic observational study that examined participants' smoking behavior in the course of a year after purchasing a JUUL Starter Kit (JSK). The JUUL System (henceforth "JUUL") is a pod-based closed-system ENDS brand with a nicotine salt formulation. The prevalence of past-30-day use of JUUL among adult never smokers has been estimated at 1.4% among young adults (18-24) and 0.1% among adults over 25.[14] The present analyses examine the prevalence of past-30-day smoking over 6 follow-up assessments across 12 months after a JSK purchase, including the frequency and quantity of smoking among those who report smoking. Use of JUUL is similarly tracked over time, and analyses examine the association of JUUL use and smoking. As some of these never smokers had already used ENDS before purchasing a JSK and entering the study, the analyses distinguish those with prior ENDS experience from those who were newly using ENDS.

METHODS

Participants

Participants were adults (21+) who were recruited at the time of a first JSK purchase (either at retail or online). These analyses focus on never smokers, defined as those who report having never smoked cigarettes at all (even a puff). Data were available from a total of 3853 never smokers who provided at least some follow-up data, comprising 73.6% of those who enrolled. A total of 1265 (24.2%) completed all 6 follow-ups. Shiffman et al[34] report that baseline demographic differences between those with complete data, partial data, and no data were uniformly small ($R^2s \leq 0.0025$). Of the 2628 (50.2%) who provided data at some but not all follow-ups, 71.1% completed at least 3 of the 6 follow-ups. Their pattern of missed follow-ups was not characterized by discontinuation, ie, completing follow-ups, but then dropping from the study and completing no subsequent follow-ups. Rather, 79.8% of those with partial data showed intermittent responding: they missed one or more follow-ups, but then returned at subsequent follow-ups. Most partial responders (83.1%) completed at least

one of the follow-ups in the second half of the year, at 6 months or later. Shiffman et al[34] also report that only 3.1% of 449 12-month-non-responders who were recontacted reported their non-response was due to having started smoking.

The sample was stratified according to whether they had reported having ever used ENDS prior to enrolling (2848 had previously used ENDS ["NS+E"], and 1005 had not used ENDS [NS-NE]; 40 enrollees did not have data on past ENDS use, and are not included). History or current use of other tobacco products, whether combusted (eg, small cigars, hookah) or non-combusted (eg, oral tobacco) was not assessed.

Procedures

The ADJUSST study design and methods are described in more detail in Shiffman et al.[34] Participants were recruited at the time of purchase of a JSK, which contained a JUUL device, a charging dock, and 4 JUULPods, and sold for approximately USD45-USD50. Those purchasing at retail were invited via a card in the package that read "Complete our online survey about vaping, smoking, and JUUL products and receive a USD30 Visa e-Gift Card." Those purchasing online were invited via a follow-up email that similarly described the study as a "JUUL customer online survey about JUUL vapor products, vaping and smoking." Participants qualified only if they enrolled and completed the baseline survey within 7 days of a first JSK purchase. Participants completed an informed consent form, which described the study as one "asking adults who have recently purchased a JUUL Starter Kit about their views and experiences of smoking cigarettes and using JUUL vapor products. We are looking to better understand the types of people who buy the JUUL Starter Kit, their reasons for using a JUUL, and what impact." The consent form indicated that JUUL Labs was the sponsor of the study, which was being conducted by the Centre for Substance Use Research (CSUR), an independent research firm. Participants were compensated USD30 for each survey.

Participants subsequently received emails inviting them to complete follow-up assessments 1, 2, 3, 6, 9, and 12 months after baseline. At each follow-up, respondents reported whether they had smoked in the past 30 days (even a puff). Those who indicated they had smoked were further asked: "Do you now smoke cigarettes… Every day, Some days, or Not at all." Only those who said they were smoking every day or some days were asked on how many days of the last 30 they had smoked, and how many cigarettes they consumed (on average) on those smoking days. Accordingly, for those who indicated they were now not smoking at all, persons for whom many analyses considered to be abstinent (eg, Glasser et al),[35] quantitative cigarette consumption data are missing. (Supplementary Material 1 uses data from PATH to provide some indication of their likely smoking behavior.)

A parallel set of questions assessed use of JUUL at each timepoint: any use (even a puff) in the past 30 days, now using every day, some days, or not at all; for those using every day or some days, the number of days used in the past 30, and the number of "uses" on days used, assessed using a question drawn from Foulds et al:[36] "On average, on those days you used a JUUL, how many times did you usually use a JUUL each day? Assume that one 'time' consists of around 15 puffs, or 10 minutes."

Data Analysis

Summary statistics are presented for sociodemographic characteristics, and univariate differences between NS+E and NS-NE are tested. Multivariable generalized estimating equations (GEE) analyses with sociodemographic and JUUL use variables as predictors estimated associations with the dichotomous response of past 30-day smoking at follow-ups. GEE methods allow for participants to have different numbers of observations, and account for the nesting of multiple observations within participants.[37] The GEE models included a dummy variable for prior ENDS use, testing the difference between NS+E and NS-NE groups. Separate GEE models tested trends over time (linear and quadratic trends) in the prevalence of past-30 day smoking and (separately) past-30-day use of JUUL. The study protocol specified assessing initiation among never smokers as a core study question, but, as this was considered a descriptive observational surveillance study, did not specify particular hypotheses or particular analyses. Tests were 2-tailed at alpha of .05.

The percent that reported past-30-day smoking at each follow-up was calculated, as was the per-

cent that reported smoking at one or more of the follow-ups. To capture a pattern of prevalence that may indicate continuing smoking, the percent of respondents that reported smoking at both the 9- and 12- month assessments (possibly suggestive of persistent smoking up to the end of the 12-month observation period) is also reported. (Participants smoking for at least one observation were classified as such, even if the other observation was missing.)

Among those who reported past-30-day smoking, tables present the percentage that reported they were now smoking "not at all" or "every day/some days," respectively. For those smoking every day/some days, tables show the mean number of days smoked in the past 30 days and the average cigarettes per day (CPD). Cigarette consumption data were not collected from those reporting now smoking not at all. Analyses of data from PATH (Supplementary Material 1) show that previous-Wave never smokers with this response pattern are likely to be smoking little, and have typically not smoked in the past week. Similar data are shown for JUUL use reported in the past 30 days at each follow-up.

The primary analyses use all available data (including respondents who did not complete all follow-ups). Supplemental analyses (Supplementary Material 2) consider complete cases, which have some advantages: maximizing the number of observations for each individual, allowing for counting the number of follow-ups at which smoking is reported, and allowing for tallying of smoking at consecutive follow-ups, as distinct from reports of smoking that are followed by reports of abstinence.

Analyses were conducted using SAS® software, Version 9.4 of the SAS System for Windows 10 Server.

RESULTS

Table 1 shows the demographic characteristics of the never smokers (stratified by ENDS use history). The sample averaged 24 years of age, and consisted predominantly of young adults, with almost 80% being 21-24 years old; those who had previously used ENDS were more likely to be 21-24 year old than those who had not (85% vs 63%). The sample was predominantly non-Hispanic white, but with representation of other ethnic backgrounds, including individuals identifying as Hispanic (15%). The largest fraction (41%) had not attended college, and most (86%) had never married.

Table 2 shows the relationship between these demographic variables and any past-30-day smoking at follow-up assessments. After adjustment for other variables, women were less likely to smoke than men (OR = 0.74), and older participants more likely to smoke (OR = 1.02 per year). The odds of past-30-day smoking increased slightly over time; the prevalence increased by 2.0-2.5% from Month 1 to Month 12.

Participants who used JUUL more frequently were less likely to smoke; the odds of smoking declined by 1% for every additional day per month JUUL was used. There was no effect of reported JUUL use sessions per day.

After adjusting for demographic differences (Table 1), those who had not previously used ENDS (NS-NE) had a higher likelihood of reporting past-30-day smoking during follow-ups, with a 53% higher odds of smoking than the prior ENDS-users (NS+E). Subsequent analyses examine these groups separately.

Never Smokers Who Had Previously Used ENDS (NS+E)

Table 3 (top panel) shows the prevalence among NS+E of past-30-day smoking at each follow-up, which increased by 2.6% over the year, from 5.0% at month 1 to 7.6% at month 12. Analysis indicated that the odds of smoking increased by 5% of the prior months' odds (OR = 1.05 [1.03,1.07]), though this decreased over time (quadratic effects, $p < .005$). Overall, 18.9% of the NS+E reported past-30-day smoking during at least one follow-up assessment. Reports of smoking at both 9 months and 12 months, an indicator of possible continuing or persistent smoking at the end of the observation period, occurred in 1.62% of NS+E.

Further analyses (Table 3) documented how much those reporting past-30-day smoking were smoking at each of the follow-ups. The table shows the percentage of past-30-day smokers who reported they were now smoking "not at all" and the percentage who responded either "every day" or "some days." For the latter groups only (the "not at all" group was not asked), the table also shows how often (days per month) and how much (cigarettes per day) they reported smoking in the pre-

Table 1
Baseline Sociodemographic Characteristics, Stratified by Prior ENDS Use

Sociodemographic Characteristics	Ever Used ENDS[a] Mean (SD) or % (N = 2848)	Never Used ENDS[b] Mean (SD) or % (N = 1005)	Total[c] Mean (SD) or % (N = 3853)
Age (Mean, [SD])	23.32 (5.52)	26.47 (8.59)	24.14 (6.61)
Strata (%)			
21 to 24	84.94	63.28	79.29
25 to 29	7.51	15.42	9.58
30 to 39	3.79	12.14	5.97
40 or older	3.76	9.15	5.16
Sex (%)			
Male	62.86	70.44	64.84
Female	36.72	27.96	34.43
Transgender	0.42	1.60	0.73
Race/Ethnicity (%)			
Non-Hispanic White	68.00	60.72	66.12
Non-Hispanic Black	6.51	7.44	6.75
Non-Hispanic Asian	5.48	11.05	6.92
Non-Hispanic Other[e]	5.67	4.49	5.36
Hispanic Ethnicity	14.35	16.30	14.85
Marital Status (%)			
Married	6.06	17.42	8.98
Divorced, Separated or Widowed	3.52	7.45	4.53
Never Married	90.42	75.13	86.50
Education (%)			
High school graduate or less	42.13	39.25	41.41
Some college or associate degree	41.85	35.24	40.21
Bachelor's degree or more	16.02	25.52	18.38
Annual Household Income (%)			
Less than USD 50,000	57.97	62.87	59.17
USD 50,000-USD 100,000	21.39	18.70	20.73
Greater than USD 100,000	20.64	18.43	20.10

Note.
Except for income, all variables differed between groups at p < .001
Abbreviations: ENDS = Electronic Nicotine Delivery System; SD = Standard Deviation
Ns varied due to missing data; Ns available for sociodemographic characteristics:
Age: Ever ENDS N = 2848; Never ENDS N = 1005
Sex: Ever ENDS N = 2827; Never ENDS N = 998
Race/Ethnicity: Ever ENDS N = 2628; Never ENDS N = 914
Marital Status: Ever ENDS N = 2757; Never ENDS N = 953
Education: Ever ENDS N = 2485; Never ENDS N = 823
Income: Ever ENDS N = 2277; Never ENDS N = 738
[a] Ever Used ENDS were those who reported having never smoked and having ever used any ENDS product at baseline.
[b] Never Used ENDS were those who reported having never smoked and having never used any ENDS product at baseline.
[c] Total included Ever ENDS Users and Never ENDS Users who provided data.
[d] Non-Hispanic Asian included: Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, or Other Asian.
[e] Non-Hispanic Other included: American Indian or Alaskan Native, Native Hawaiian, Guamanian or Chamorro, Samoan, or Other Pacific Islander (or 2 or more races).

Table 2
Generalized Estimating Equation Models Assessing the Outcome of Any Past 30-day Smoking Over the 12-month Period

Regressors	Univariate Models OR (95% CI)	Multivariable Fully Adjusted Model OR (95% CI)[a]
Sociodemographic Characteristics		
Age	1.03 (1.01, 1.04)***	1.02 (1.002, 1.03)*
Sex		
Male	Ref	Ref
Female	0.72 (0.58, 0.88)**	0.74 (0.60, 0.91)**
Transgender	1.38 (0.64, 3.00)	0.98 (0.43, 2.26)
Race/Ethnicity		
Non-Hispanic White	Ref	Ref
Non-Hispanic Black	0.99 (0.66, 1.5)	0.96 (0.63, 1.45)
Non-Hispanic Asian	1.54 (1.10, 2.15)*	1.34 (0.96, 1.87)
Non-Hispanic Other	1.24 (0.85, 1.81)	1.29 (0.89, 1.86)
Hispanic Ethnicity	1.17 (0.91, 1.52)	1.10 (0.85, 1.43)
Marital Status		
Married	Ref	Ref
Divorced, Separated or Widowed	1.32 (0.83, 2.09)	1.36 (0.84, 2.21)
Never Married	0.67 (0.49, 0.92)*	0.90 (0.63, 1.27)
Education		
High School Graduate or Less	Ref	Ref
Some College	0.83 (0.67, 1.01)	0.86 (0.70, 1.06)
Bachelor's Degree or More	1.12 (0.86, 1.45)	0.99 (0.76, 1.29)
Time-Varying Effects		
JUUL Use Frequency and Quantity		
# Days Used JUUL in Past 30 Days	0.99 (0.98, 0.996)**	0.99 (0.98, 0.997)**
# Times Used JUUL per Day	1.00 (0.99, 1.01)	1.00 (0.996, 1.01)
Time Effect, Months (linear)[b]	1.04 (1.03, 1.06)***	1.04 (1.02, 1.06)***
Prior ENDS Use		
Ever Used ENDS	Ref	Ref
Never Used ENDS	1.77 (1.45, 2.16)***	1.53 (1.23, 1.89)***

*** p < .05; ** p < .01; *** p < .001**

Note.
Fully adjusted model: N = 3015 participants, 12,403 observations. Participants with missing covariates excluded.
Abbreviations: ENDS = Electronic Nicotine Delivery System; OR = Odds Ratio; CI=Confidence Interval
[a] Adjusted for baseline sociodemographic (age, sex, race/ethnicity, marital status and education), JUUL use frequency and quantity.
[b] Time was coded as a continuous variable, in months. A quadratic time term was significant (p < .05) when tested in a separate model.

Table 3
Smoking Outcomes at Each Follow-up Assessment, by Prior ENDS Use[a]

Follow-Up Assessment	% P30D Smoking[d] %	% of P30D Now Smoking Not at All[e,f] %	Now Smoking Every Day or Some Days		
			% of P30D Now Smoking Every or Some Days[e,g] %	Cigarette Consumption in Those Smoking Every Day or Some Days[h]	
				# Days Smoked in P30D[i] Mean (SD)	CPD in P30D[j] Mean (SD)
Ever Used ENDS[b]					
Month 1- N = 2035	5.01	47.83	52.17	11.96 (10.76)	3.51 (6.30)
Month 2 - N = 2115	6.05	49.04	50.96	10.50 (10.29)	2.62 (5.36)
Month 3 - N = 2104	6.42	43.12	56.88	11.15 (10.17)	2.78 (5.43)
Month 6 - N = 1891	7.30	40.98	59.02	9.06 (9.46)	1.93 (5.01)
Month 9 - N = 1971	7.46	35.07	64.93	7.93 (8.83)	1.66 (4.88)
Month 12 - N = 1971	7.56	33.83	66.17	9.56 (9.75)	2.24 (5.42)
Never Used ENDS[c]					
Month 1 - N = 753	10.23	25.71	74.29	10.35 (9.94)	2.28 (4.45)
Month 2 - N = 750	9.60	24.62	75.38	11.02 (9.60)	2.45 (4.03)
Month 3 - N = 778	10.54	26.03	73.97	11.69 (10.40)	2.03 (2.97)
Month 6 - N = 696	10.78	25.00	75.00	10.71 (10.20)	2.32 (3.87)
Month 9 - N = 693	11.54	31.51	68.49	13.86 (10.68)	3.12 (5.57)
Month 12 -N = 672	12.35	27.40	72.60	10.69 (10.86)	2.72 (4.88)

Note.
Abbreviations: ENDS = Electronic Nicotine Delivery System; P30D = Past 30-Day; SD = Standard Deviation; CPD = Cigarettes Per Day
Ns shown represent the available Ns for the P30D smoked survey item.
Available Ns varied for particular measures because of survey item skip logic and missing data.
Ns range for those asked "Do you now smoke cigarettes…": Ever ENDS N = 92 to N = 134; Never ENDS N = 65 to N = 73
Ns range for # Days Smoked and CPD in P30D: Ever ENDS N = 45 to N = 86; Never ENDS N = 48 to N = 52
[a] Sample included all who provided past 30-day smoking data at the relevant follow-up assessment.
[b] Ever Used ENDS were those who reported having never smoked and having ever used any ENDS product at baseline.
[c] Never Used ENDS were those who reported having never smoked and having never used any ENDS product at baseline.
[d] % of participants who responded "yes" to "In the past 30 days, have you smoked a cigarette, even one or 2 puffs?"
[e] Those who responded "yes" to "In the past 30 days, have you smoked a cigarette, even one or 2 puffs?" were asked "Do you now smoke cigarettes…Every day/Some days/Not at all."
[f] % of past 30-day smokers who responded "Not at all" to "Do you now smoke cigarettes …".
[g] % of past 30-day smokers who responded "Every day" or "Some days" to "Do you now smoke cigarettes …"
[h] Those who indicated now smoking "Not at all" were not asked how many days they had smoked or how many cigarettes they had smoked on those days. Thus the data on days smoked and cigarettes per day are from the subset who indicated they were now smoking "Every day" or "Some days", and provided data.
[i] # days smoked in past 30 days = "On how many of the past 30 days did you smoke cigarettes?"
[j] CPD in past 30 days = "On average, on those days you smoked, how cigarettes did you usually smoke each day? A pack usually has 20 cigarettes in it." [CPD*number of smoking days in past 30 days]/30.

ceding 30 days. Across follow-ups, approximately one-third to one-half of those who reported past-30-day smoking at any given follow-up indicated they were now smoking "not at all." Among the remaining past-30-day smokers, days per month ranged from 12 at month 1 to 10 at month 12, and

Table 4
JUUL Use at Each Follow-up Assessment, Stratified by Prior ENDS Use[a]

Follow-Up Assessment	% P30D JUUL Users[d] %	% of P30D Now Using JUUL Not at All[e,f] %	Now Using JUUL Every Day or Some Days		
			% of P30D Now Using JUUL Every or Some Days[e,g] %	JUUL Use Frequency in Those Using JUUL Every Day or Some Days[h]	
				# Days Used JUULin P30D[i] Mean (SD)	# of JUUL Sessions per Day in P30D[j] Mean (SD)
Never Smokers					
Ever Used ENDS[b]					
Month 1 - N = 2060	95.19	2.50	97.50	20.60 (9.26)	9.78 (12.32)
Month 2 - N = 2141	92.01	2.74	97.26	20.12 (9.75)	9.42 (11.61)
Month 3 - N = 2147	89.52	2.91	97.09	19.42 (10.26)	9.23 (11.15)
Month 6 - N = 1924	86.80	4.13	95.87	19.28 (10.12)	9.73 (11.61)
Month 9 - N = 2006	85.39	3.97	96.03	19.21 (10.18)	9.44 (11.14)
Month 12 - N = 2009	82.58	4.10	95.90	18.49 (10.34)	9.30 (10.83)
Never Used ENDS[c]					
Month 1 - N = 766	86.42	2.27	97.73	19.82 (9.69)	9.76 (10.60)
Month 2 - N = 765	82.88	2.68	97.32	19.03 (10.30)	9.21 (11.94)
Month 3 - N = 792	81.69	1.85	98.15	19.32 (10.31)	9.61 (11.67)
Month 6 - N = 706	81.73	2.25	97.75	19.25 (10.18)	10.07 (12.15)
Month 9 - N = 713	81.07	2.08	97.92	19.05 (10.49)	9.39 (11.66)
Month 12 - N = 698	80.37	3.03	96.97	19.04 (10.48)	9.07 (10.70)

Note.
Abbreviations: ENDS = Electronic Nicotine Delivery System; P30D = Past 30-Day; JUUL = JUUL System; SD = Standard Deviation
Ns shown represent the available ns for the P30D JUUL System use survey item.
Available Ns varied for particular measures because of survey item skip logic and missing data.
Ns range for those asked "Do you now use a JUUL…": Ever ENDS N = 1659 to N = 1970; Never ENDS N = 561 to N = 662
Ns range for # Days Used JUUL and # of JUUL Sessions in P30D: Ever ENDS N = 1539 to N = 1880; Never ENDS N = 511 to N = 629
[a] Sample included all who provided past 30-day JUUL System use data at the relevant follow-up assessment.
[b] Ever Used ENDS were those who reported having never smoked and having ever used any ENDS product at baseline.
[c] Never Used ENDS were those who reported having never smoked and having never used any ENDS product at baseline.
[d] % of past 30-day JUUL Users were those who responded "yes" to "Have you used a JUUL in the past 30 days, even one or 2 puffs?"
[e] Those who responded "yes" to "Have you used a JUUL in the past 30 days, even one or 2 puffs?" were asked "Do you now use a JUUL…Every day/Some days/Not at all."
[f] % of past 30-day JUUL Users who responded "Not at all" to "Do you now use a JUUL…"
[g] % of past 30-day JUUL Users who responded "Every day" or "Some days" to "Do you now use a JUUL…"
[h] Those who indicated now using a JUUL "Not at all" were not asked how many days they had use a JUUL or how times they had used a JUUL on those days. Thus, the data on days used a JUUL and JUUL sessions per day are from the subset who indicated they were now using a JUUL "Every day" or "Some days," and provided data.
[i] # Days Used JUUL in P30D = "On how many of the past 30 days did you use a JUUL?"
[j] # of JUUL Sessions/Day = "On average, on those days you used a JUUL, how many times did you usually use a JUUL each day? Assume that one "time" consists of around 15 puffs, or 10 minutes."

cigarettes per day (CPD) ranged from 3.5 CPD at month 1 to 2.2 at month 12.

Table 4 shows NS+E respondents' reports of past-30-day JUUL use over time. Almost all NS+E (95%) were using JUUL at month 1, and this declined over time, with the odds of JUUL use declining by 9% per month (linear OR = 0.91, 95% CI 0.90, 0.93), reaching 83% at month 12. The decline was steeper at first, and then slowed (quadratic effect $p < .001$). Almost all past-30-day JUUL users said they used JUUL every day or some days (vs "not at all"), with days per month ranging from 21 days at month 1 to 18 days at month 12, and uses per day ranging from 9.8 at month 1 to 9.3 at month 12.

Never Smokers Who Had Also Never Used ENDS (NS-NE)

Table 3 (bottom panel) shows the prevalence of past-30-day smoking at each follow-up, which increased by 2% over the year, from 10% at month 1 to 12% at month 12 among NS-NE. Analysis indicated that the odds of smoking increased each month by 3% of the prior months' odds (OR = 1.03 [1.01,1.06]). Overall, 26.5% of NS-NE reported past-30-day smoking during at least one follow-up assessment. A total of 3.6% reported past-30-day smoking at both 9 months and 12 months.

Across follow-ups, approximately one-fourth (25%-32%) of the NS-NE who reported they had smoked in the preceding 30 days then reported they were now smoking "not at all." Among those who reported smoking every day or some days, the average days per month smoked ranged from 10 days at month 1 to 11 days at month 12, and mean CPD day ranged roughly between 2 to 3 cigarettes per day.

Table 4 shows the reported use of JUUL across follow-ups among NS-NE. At each follow-up, substantial majorities (> 80%) of NS-NE reported past-30-day JUUL use. The proportion using JUUL declined over time from 86% to 80%, with the odds of JUUL use declining by 3% per month (linear OR = 0.97, 95% CI 0.95, 0.99). The decline was steeper at first, and then slowed (quadratic effect $p < .04$). Among those using JUUL every day or some days, the average use was 19 to 20 days per month, and 9 to 10 uses per day.

Complete-Case Analyses

Data from the subset of participants who provided data at all follow-ups (N = 915, 32% of the NS+E sample; N = 342, 34% of NS-NE) were analyzed in a similar fashion (Supplementary Material 2). Among NS+E, 20.4% reported smoking during at least one follow-up; only 1.3% reported smoking at the majority of follow-ups (4 or more). About one-fourth (27.3%) of those who reported any smoking during the study period ever reported smoking at any 2 consecutive follow-ups. Past-30-day smoking increased slightly by 1.8% between Month 1 and Month 12. Altogether 2.1% of the complete-case sample reported smoking at both the 9 and 12-month follow-ups.

Among NS-NE, 30.4% reported smoking during at least one follow-up; 4.7% reported smoking at the majority of follow-ups (4 or more). A little more than one-third (35.58%) of those who reported any smoking during the study period reported smoking at any 2 consecutive follow-ups. Past-30-day smoking increased slightly by 4.1% between Month 1 and Month 12. Altogether 5.0% of the complete-case sample reported smoking at both the 9 and 12-month follow-ups.

DISCUSSION

In this study, we examined in detail the occurrence of cigarette smoking in a sample of individuals who reported having never smoked a cigarette at the time they purchased a JSK and were followed for up to a year. The majority of these never smokers were young adults, consistent with prevalence data indicating that young adults – including never smokers – are more likely to use ENDS, including JUUL, than are older adults.[14,38]

Distinguishing never smokers according to their prior ENDS use proved to be instructive. In this sample, almost ¾ of the never smokers who purchased a JSK had already previously used ENDS. About one in 5 in this group reported some past-30-day smoking (even a puff) during the year after a JSK purchase. The observed patterns of smoking appeared to be light and intermittent.[39-41] Even when they reported having smoked in the past 30 days, one-third to one-half reported now smoking "not at all," a pattern that PATH data reveal to be associated with light smoking and with 7-day abstinence (Supplementary Material 1). Among those who did not give this "not at all" response, respon-

dents reported smoking on 10-12 days per month, on average, and averaging 2-4 cigarettes per day.

Similarly, light and intermittent smoking was observed among those who had not previously used ENDS – 10%-12% who reported past-30-day smoking at follow-ups. In this cohort, 30% reported past-30-day smoking at one or more follow-ups – most at only one follow-up (53% in the complete-case series). When they did report smoking, one-fourth or more indicated they were now smoking "not at all," and the rest reported smoking, on average, 10-14 days per month, and consuming an average of 2-3 cigarettes per day.

Thus, in both groups, the reported patterns of smoking were light and intermittent, and not suggestive of continuing smoking. If substantial portions of respondents were taking up ongoing smoking, the 30-day prevalence of smoking would rise steeply, because each timepoint would include those who initiated at previous follow-ups and continued to smoke, as well as new initiates. In contrast, the data show that the point-prevalence numbers increased just 2%-3% over the 12 months of observation, and less than 5% of the sample reported smoking at both the 9- and 12-month assessments, which might have indicated continuing smoking. Among those reporting smoking at the last observation at 12 months, one-fourth to one-third reported that they were now smoking "not at all," and those who did report smoking (every day or some days) reported smoking infrequently. Nevertheless, any smoking is of concern. Longer follow-ups would be useful for ascertaining the eventual trajectory of smoking in these groups.

On all measures included in this study, never smokers who had previously used ENDS were less likely to smoke. Across all follow-ups, they had 35% lower odds of smoking (inverse of the 1.53 odds ratio). It is likely that this difference is not causal, but reflects the historical trajectories that define these 2 never smoker groups. As there is an association between ENDS and smoking (causal or otherwise)[11,42-44] some never smokers who used ENDS may have already initiated smoking, but these smoking initiators would not be included in the present sample, which is limited to those who denied any smoking. Thus, the never smoking prior-ENDS-users who had not already smoked, and were in this sample, represent those with relatively lower predisposition to smoke, leading to the observation of relatively lower incidence of smoking in this group. This explanation is compatible with the finding in Prakash et al[45] that regular use of other ENDS at the time of the JSK purchase itself made no difference in 12-month smoking status.

This differential based on prior ENDS use is also important in considering comparisons to other studies of ENDS use in never smokers. Those studies typically follow a sample that at baseline is already using ENDS, but has never smoked.[8,9,16,21,33] In that sense, they are closest to the NS+E sample in the present analyses. In the study most closely paralleling the measures used in the present NS+E analyses, McMillen et al,[16] analyzing a sample using ENDS (past-30-day use) at Wave 1 of PATH, found that 7% reported past-30-day smoking a year later, close to the 7.6% observed in the present study. In samples of young adults, regardless of ENDS use, Perry et al[19] report smoking initiation rates of 3%-10% over 12 to 18 months.

However, comparisons to prior studies are difficult, because of differences in definitions of both the starting population and the subsequent outcome. Comparisons are also difficult because ADJUSST is unique in focusing on individuals based on a product *purchase*, rather than any *use*. A purchase likely reflects a greater engagement in ENDS use, as illustrated by the substantial persistence of JUUL use over the period. Indeed, PATH data show that device ownership is associated with more frequent use and persistent use of ENDS,[46] which also may be correlated with common factors[47] and a greater propensity to smoke.[11,42,48]

The present study did not include a comparison group of never smokers who were not using ENDS, whereas other observational studies with such comparison groups sought to make inferences about the role of ENDS in subsequent smoking by comparing the 2 groups, while trying to control for confounding factors. Lee and Fry[43] and Khouja et al[44] critique this approach. Besides lacking such a comparison group, the present study also lacked measures of common factors that might explain smoking among JUUL users.[12]

However, variations in frequency of ENDS use may provide some insights into the role of ENDS, even within a sample of users.[8,31-33,49,50] In this sample, more frequent use of JUUL was associated

with a significantly lower likelihood of smoking. The odds of smoking declined by 1% for each additional day of JUUL use, which would suggest that a daily user would have 30% lower odds of smoking (1% x 30) than a once-a-month user. This inverse dose-response suggests that JUUL use was not a causal factor in subsequent smoking, and may be more consistent with a "diversion" effect in which use of ENDS may divert susceptible individuals away from smoking.[51-53] Studies of different design will be needed to address this association better.

In this study, high prevalence of JUUL use was seen over the 12 months of observation, although it declined over time in both groups of never smokers. Longer follow-up would be needed to assess whether that trend continues. Predominant majorities of the respondents reported using JUUL out to 12 months, with average use on 20 of the preceding 30 days. Participants had purchased a JSK, which implies a substantial engagement with JUUL, as distinct from the more-commonly studied populations of "users" defined by any past-30-day use, which may reflect trial rather than substantial engagement in ENDS use. PATH data show that purchase of an ENDS device is associated with greater and longer use.[46]

Among those using JUUL every day or some days, uses per day averaged 9 to 10 uses per day, where a "use" was defined as use for about 10 minutes, or 15 puffs. A "use," defined in this way, is not equivalent to a cigarette, as pharmacokinetic data show that on a puff-for-puff basis, JUUL delivers considerably less nicotine than a cigarette.[54] No measure of within-day amount of use of ENDS, including that used in this study, has been definitively validated,[36,55,56] which may be why the measure of uses-per-day was unrelated to the risk of smoking, even as greater use-days-per-month was associated with lower risk of smoking.

In any case, the never smokers in this sample were engaged in ongoing use of JUUL over a substantial time period. Even though the health risks associated with ENDS are likely to be much lower than those of smoking,[3,4] ENDS use carries the risks associated with nicotine use[57,58] and possibly other risks associated with inhalation of other aerosol constituents.[58-60] Thus, use of JUUL or other ENDS exposes non-smokers to new risks, and is a concern. It has been suggested that if ENDS use diverts never smokers from taking up smoking, that could be a favorable risk trade-off (ie, harm reduction).[51-53] The potential adverse effects of use of ENDS by never smokers – both due to direct harms and considering the potential for progression to smoking – is considered in population models that conclude that the overall effect on population health is positive.[61] However, at an individual level it is not known who may be headed to initiation of smoking in the absence of ENDS. Accordingly, use of ENDS by never smokers should be discouraged.

Limitations and Strengths

The findings should be interpreted in light of the study's limitations. One of the most important is that the participants' history and/or current use of other tobacco products was not assessed. Use of other (non-ENDS) tobacco products is associated with subsequent smoking, to a much greater extent than ENDS use is.[22] Use of other tobacco products is associated with subsequent smoking,[22,62-65] and poly-use is common among ENDS users,[66] so it is likely that some of the sample was already using other tobacco products, but it is not known how many, or the extent to which that might account for their subsequent smoking.

As typical of surveys, the data are based on self-report, which may be subject to inaccuracy or bias. Consistent with other studies tracking smoking trajectories of ENDS users in PATH[67-69] and other surveys,[70-72] self-reports of smoking were not subject to biochemical verification. Importantly, unlike in treatment studies, no objective of smoking cessation was set, which should minimize acquiescence or social desirability biases. As in other studies, participants were volunteers who agreed to participate and be followed, and may not be representative of all never smokers who purchase a JSK. Furthermore, Rodu and Plurphanswat[46] found that some never smokers using ENDS did not own a device, so the sample is not representative of all never smokers who used ENDS. The sample consisted of adults 21 and older, the population that is now legally permitted to purchase ENDS such as JUUL, and may not represent the experience of underage users.

As in all longitudinal surveys, some enrollees missed some or all of the follow-up assessments (eg, an International Tobacco Control survey[73] lost 63% of respondents at the second follow-up), and

this can raise concern about whether participants might have smoked during those missing time periods. However, analyses showing that respondents and non-respondents had similar baseline profiles, and a finding that non-respondents rarely said they stopped responding because they had started smoking, suggest potential for bias would have been limited.[34] Nevertheless, the potential for bias due to non-response needs to be considered.

The sample for the study consisted entirely of people who purchased a JSK. There was no opportunity to contrast their behavior to others who did not purchase or use JUUL, which limits the inferences that can be made about the role of JUUL use in the observed instances of smoking. Moreover, individuals who self-select to purchase and use JUUL likely differ from the larger population of never smokers, including in characteristics associated with the risk of smoking.[11,12,43,48,74] It is not known how many of the participants might have smoked even if they had not adopted JUUL use. Studies that follow both users and non-users, and that assess predisposition to smoke, are better positioned to address such questions. Longer follow-ups that assess behavior over more than one year would also be useful.

The study participants had purchased a JSK, and thus, did not include or represent individuals who may have engaged in more casual use of JUUL. In that sense, this was a study of never smokers who made a substantial commitment to using JUUL, and in fact made substantial use of JUUL, and thus, represents the smoking behavior that occurred with such substantial use, and may not reflect what would be seen with more casual use.

The study also had a number of strengths. It included a large sample of never smokers using ENDS, and implemented multiple assessments over the course of 12 months, documenting patterns of smoking and JUUL use over time. The study also was able to characterize the frequency and quantity of smoking and of JUUL use, allowing for more detailed characterization of behavior. Further analyses examining trajectories of smoking and JUUL use in more detail would be useful.

Conclusions

In summary, our results showed that in a group of never smokers who self-selected to purchase a JUUL Starter Kit, some smoking occurred over the following 12 months, with patterns suggesting the smoking was light and intermittent. In this sample of purchasers, most participants engaged in JUUL use over the 12 months studied. More frequent JUUL use was associated with a modestly reduced risk of smoking.

Human Subjects Approval Statement

The study was approved by the Advarra® Institutional Review Board, a fully certified independent IRB (https://www.advarra.com/about-advarra/the-advarra-review-board/).

Conflict of Interest Disclosure Statement

SS, through PinneyAssociates Inc, provides consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc. Within the last 2 years, PinneyAssociates Inc has consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction. NMH is a full-time employee of Juul Labs Inc.

Under contract to JUUL Labs Inc, the Centre for Substance Use Research, an independent research consultancy, designed the study and assessments and oversaw collection of data through Dacima Inc. CSUR managed, cleaned, and summarized the data. NMH performed the statistical analyses under the direction of SS. Both authors contributed to writing and review of the paper, and had access to the data. The sponsor approved the research plan and provided comment on a near-final draft of the paper.

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SUPPLEMENTARY MATERIAL 1

Insights from PATH on Smoking Patterns in Year-Ago Never Smokers Who Say They Smoked in the Preceding 30 Days, but Say They Now Smoke "Not At All"

In the ADJUSST study, respondents who said they smoked in the past 30 days, but then said they now smoke "not at all" were not asked how many days they had smoked or how many cigarettes per day, and thus, did not contribute to the calculations of the sample's cigarette consumption at follow-up assessments. To gain insight into the smoking behavior of respondents who showed this response pattern, we turned to the Population Assessment of Tobacco and Health (PATH) study,[1] which also asked both smoking-status questions (past-30-day smoking and now smoking every day, some days, or not at all), but did not use them to skip over further questions about frequency and quantity of smoking. Whereas analyses of PATH often considered those who said they now do not smoke at all as non-smokers,[2] the survey actually collected data about their past-30-day smoking; they were asked how many days in the past 30 days they smoked and how many cigarettes they smoked, as well as being asked how long ago they had last smoked.

Thus, PATH provides data on the smoking behavior of these past-30-day but not-at-all (P30D-NAA) responders. To approximate the present sample who started the study as never smokers, we focused on PATH respondents who reported being never smokers at Wave 3, and who responded with P30D-NAA response patterns in Wave 4.

The table below shows the Wave 4 data reported by 72 such respondents. These year-ago never smokers with theP30D-NAA pattern reported smoking only 1.5 days per month, averaging 0.1 cigarettes per day. Only about one in 6 reported having smoked in the preceding 7 days.

In sum, the PATH data strongly suggest that year-ago never smokers with a current P30D-NAA response pattern (ie, reporting they smoked in the past 30 days, but reporting they now smoke not at all) are smoking little, smoking infrequently and smoking a modest number of cigarettes. The majority report 7-day abstinence, suggesting they may consider themselves to have stopped smoking, which may help explain their 'not at all' response when asked to characterize their current smoking at Wave 4. In any case, these data from PATH, though on a different sample, across a longer interval than most of our paper's assessments, and based on relatively small samples, and not addressing ENDS use, shed some light on how to interpret the P30D-NAA response pattern.

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Table S1
Smoking Patterns Reported by Wave 3 Never Smokers in PATH Who at Wave 4 Indicated They Had Smoked in the Past 30 Days, but also Indicated They Now Smoked "Not at All" (N = 72)

Wave 4 Smoking Behavior (1 Yr Later)	N	Mean	SD
Days smoked in the past 30 days[a]	72	1.5	4.1
Overall CPD[b]	38	0.1	0.2
	N	%	
% Report smoking past 7 days (%)	11	16.5	

Note.
Abbreviations: CPD = cigarettes per day; N = sample size; SD = standard deviation; Yr = year
[a] Per PATH logic, respondents who indicated they smoked every day were assigned smoking 30 days out of 30.
[b] Cigarettes per day in the past 30 days calculated from past 30 day CPD on days smoked and days smoked in the past 30 days. Missing for those who report smoking on zero days in the past 30 days.

SUPPLEMENTARY MATERIAL 2

Table S2
Smoking Outcomes at Each Follow-up Assessment, among Complete Cases,[a] Stratified by Prior ENDS Use

Follow-Up Assessment	% P30D Smoking[d] %	% of P30D Now Smoking Not at All[e,f] %	Now Smoking Every Day or Some Days		
			% of P30D Now Smoking Every or Some Days[e,g] %	Cigarette Consumption in Those Smoking Every Day or Some Days[h]	
				# Days Smoked in P30D[i] Mean (SD)	CPD in P30D[j] Mean (SD)
Ever Used ENDS[b] (N = 915)					
Month 1	4.15	37.14	62.86	10.82 (11.92)	3.64 (7.73)
Month 2	5.46	52.38	47.62	9.74 (11.72)	2.41 (6.82)
Month 3	4.26	38.71	61.29	11.94 (10.04)	4.02 (8.03)
Month 6	6.67	49.12	50.88	11.59 (11.10)	2.66 (7.07)
Month 9	6.34	35.29	64.71	8.65 (10.04)	2.25 (7.29)
Month 12	6.01	44.68	55.32	11.62 (10.40)	2.24 (5.90)
Never Used ENDS[c] (N = 342)					
Month 1	7.89	20.83	79.17	9.37 (10.16)	1.61 (2.80)
Month 2	9.06	15.38	84.62	12.14 (10.11)	2.88 (4.67)
Month 3	9.06	33.33	66.67	10.61 (9.73)	2.25 (3.31)
Month 6	10.82	33.33	66.67	10.25 (10.14)	2.35 (4.71)
Month 9	10.82	31.25	68.75	16.55 (11.42)	3.98 (6.75)
Month 12	11.99	34.29	65.71	12.82 (11.73)	3.91 (5.72)

Note.
Abbreviations: ENDS = Electronic Nicotine Delivery System; P30D = Past 30-Day; SD = Standard Deviation; CPD = Cigarettes Per Day
Available Ns varied for particular measures because of survey item skip logic and missing data.
Ns range for those asked "Do you now smoke cigarettes…": Ever ENDS N = 31 to N = 57; Never ENDS N = 24 to N = 35
Ns range for # Days Smoked and CPD in P30D: Ever ENDS N = 18 to N = 31; Never ENDS N = 17 to N = 22
[a] Sample included all who provided past 30-day smoking data at all 6 follow-up assessments.
[b] Ever Used ENDS were those who reported having never smoked and having ever used any ENDS product at baseline.
[c] Never Used ENDS were those who reported having never smoked and having never used any ENDS product at baseline.
[d] Percent (%) of participants who responded "yes" to "In the past 30 days, have you smoked a cigarette, even one or two puffs?"
[e] Those who responded "yes" to "In the past 30 days, have you smoked a cigarette, even one or two puffs?" were asked "Do you now smoke cigarettes…Every day/Some days/Not at all."
[f] % of past 30-day smokers who responded "Not at all" to "Do you now smoke cigarettes …".
[g] % of past 30-day smokers who responded "Every day" or "Some days" to "Do you now smoke cigarettes …"
[h] Those who indicated now smoking "Not at all" were not asked how many days they had smoked or how many cigarettes they had smoked on those days. Thus the data on days smoked and cigarettes per day are from the subset who indicated they were now smoking "Every day" or "Some days", and provided data.
[i] # days smoked in past 30 days = "On how many of the past 30 days did you smoke cigarettes?"
[j] CPD in past 30 days = "On average, on those days you smoked, how cigarettes did you usually smoke each day? A pack usually has 20 cigarettes in it."; [CPD*number of smoking days in past 30 days]/30.

Table S3
JUUL Use at Each Follow-up Assessment, among Complete Cases,[a] Stratified by Prior ENDS Use

Follow-Up Assessment	% P30D JS Users[d] %	% of P30D Now Using JS Not at All[e,f] %	Now Using JS Every Day or Some Days		
			% of P30D Now Using JS Every or Some Days[e,g] %	JS Use Frequency in Those Using JS Every Day or Some Days[h]	
				# Days Used JS in P30D[i] Mean (SD)	# of JS Sessions per Day in P30D[j] Mean (SD)
Ever Used ENDS[b] (N = 915)					
Month 1	95.41	3.09	96.91	20.30 (9.07)	9.35 (12.13)
Month 2	92.13	2.25	97.75	19.84 (9.72)	9.04 (11.57)
Month 3	89.29	2.57	97.43	19.29 (10.05)	9.00 (10.72)
Month 6	87.76	3.74	96.26	19.02 (10.00)	8.96 (11.13)
Month 9	86.45	2.40	97.60	18.64 (10.29)	8.56 (10.49)
Month 12	83.39	2.23	97.77	18.35 (10.27)	9.13 (11.21)
Never Used ENDS[c] (N = 342)					
Month 1	84.21	2.78	97.22	19.99 (9.48)	9.81 (10.12)
Month 2	82.46	2.48	97.52	19.01 (10.14)	9.03 (11.92)
Month 3	82.46	1.77	98.23	18.74 (10.27)	8.44 (10.27)
Month 6	78.65	1.86	98.14	19.88 (9.74)	10.23 (12.04)
Month 9	80.70	2.90	97.10	18.85 (10.59)	8.74 (9.07)
Month 12	78.36	3.73	96.27	18.96 (10.36)	8.71 (9.53)

Note.
Abbreviations: ENDS = Electronic Nicotine Delivery System; P30D = Past 30-Day; JS = JUUL System; SD = Standard Deviation
Available ns varied for particular measures because of survey item skip logic and missing data.
Ns range for those asked "Do you now use a JUUL…": Ever ENDS N = 763 to N = 873; Never ENDS N = 268 to N = 288
Ns range for # Days Used JS and # of JS Sessions in P30D: Ever ENDS N = 727 to N = 839; Never ENDS N = 247 to N = 276
[a] Sample included all who provided past 30-day smoking data at all 6 follow-up assessments.
[b] Ever Used ENDS were those who reported having never smoked and having ever used any ENDS product at baseline.
[c] Never Used ENDS were those who reported having never smoked and having never used any ENDS product at baseline.
[d] % of past 30-day JS Users were those who responded "yes" to "Have you used a JUUL in the past 30 days, even one or two puffs?"
[e] Those who responded "yes" to "Have you used a JUUL in the past 30 days, even one or two puffs?" were asked "Do you now use a JUUL…Every day/Some days/Not at all."
[f] % of past 30-day JS Users who responded "Not at all" to "Do you now use a JUUL…"
[g] % of past 30-day JS Users who responded "Every day" or "Some days" to "Do you now use a JUUL…"
[h] Those who indicated now using a JUUL "Not at all" were not asked how many days they had use a JUUL or how times they had used a JUUL on those days. Thus, the data on days used a JUUL and JUUL sessions per day are from the subset who indicated they were now using a JUUL "Every day" or "Some days", and provided data.
[i] # Days Used JS in P30D = "On how many of the past 30 days did you use a JUUL?"
[j] # of JUUL Sessions/Day = "On average, on those days you used a JUUL, how many times did you usually use a JUUL each day? Assume that one "time" consists of around 15 puffs, or 10 minutes."

Transitions in Smoking among Adults Newly Purchasing the JUUL System

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Objectives: In this study, we prospectively assessed changes in smoking a year after US adults' first-time purchase of a JUUL Starter Kit (JSK). **Methods:** Descriptive analyses assessed transitions in smoking status at 12 months among adult (age ≥21) JSK purchasers providing baseline and 12-month follow-up data (N = 27,164 [49.0% of baseline]), stratified by baseline smoking status. Baseline regular use of other ENDS was also considered. **Results:** Purchasers included baseline past 30-day smokers (65.2%), former smokers (12.0%), and never smokers (9.7%); over 90% were ever-smokers. One year later, the majority (58%) of those smoking at baseline reported no longer smoking. Former smokers or never smokers who were smoking at 12 months represented less than 2% of respondents. Former and current smokers who were regularly using other ENDS at baseline were less likely to report smoking at 12 months. **Conclusions:** Past 30-day smoking prevalence in a large longitudinal study of first-time JSK purchasers fell by more than half over 12 months. Analyzing the sample composition at purchase and transitions within subgroups defined by smoking status allows for a detailed understanding to help inform assessments of the population health impact of ENDS.

Key words: smoking; electronic nicotine delivery system; population health impact; JUUL; longitudinal study
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The increase in Electronic Nicotine Delivery System (ENDS) use in the United States (US) in recent years[1,2] has fueled extensive debate regarding the overall net population health impact of ENDS. Adult smokers may use ENDS as a means to transition away from cigarette smoking, and their resultant significant decrease in exposure to carcinogenic and toxic constituents[3-5] may benefit public health, especially if smokers who would not otherwise quit in the near term can successfully switch completely from smoking to ENDS use. Similarly, former smokers may utilize ENDS products to prevent a return to smoking. Conversely, adoption of ENDS products by non-smokers who would not otherwise have used tobacco products would have negative implications for population health.

To assess the net population impact of ENDS, it is crucial to understand: (1) the smoking status and history of adult ENDS users; and (2) changes in their smoking behaviors over time.[6,7] Although additional public health and public policy questions arise with regard to use by underage individuals,[8] it is also essential to assess these 2 key questions among adults, to characterize overall population impact more accurately.

Nationally representative cross-sectional prevalence studies indicate that the adult ENDS user

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population is largely comprised of current smokers or former smokers who recently quit smoking (eg, in the previous year, whom we refer to as "Recent Quitters"), rather than never smokers or long-term former smokers who have not smoked for over a year (whom we refer to as "Long-Term Quitters").[9-13] This is consistent with findings from previous studies indicating that the primary reason that adult ENDS users report for purchasing and using ENDS is to quit smoking or reduce their cigarette consumption.[14-16] In the Population Assessment of Tobacco and Health (PATH) study,[17] a nationally-representative longitudinal population study of tobacco product use, the distribution of adult ENDS users at each survey wave followed a similar pattern, with the majority reporting current (eg, past 30-day) or former smoking.[18,19]

There is limited longitudinal data on the smoking trajectories of adult ENDS users over time. Prior observational studies indicate that use of ENDS by adult smokers is associated with subsequent reduction of cigarette consumption or complete abstinence from smoking.[20,21] Analyses of a cohort of adult smokers (separate from the current study) who had newly purchased a JUUL Starter Kit (JSK; Juul Labs Inc; henceforth "JUUL"), a closed-system ENDS brand with a nicotine salt formulation, found that 47% of respondents reported switching (ie, no cigarette smoking in the past 30 days) 3 months after purchase of JUUL[22] and 54%[22] reported switching at 6 months. However, there remains a lack of longitudinal data assessing patterns of smoking over time in a broader and more diverse population of current, former, and non-smokers who report using these products, especially within the same study. To date, longitudinal analyses of the PATH study have provided the best data for assessing trajectories of smoking among key subgroups in the population.[18,19,23,24] However, most recently published PATH analyses rely on data collected from 2013-2016. Given the dynamic nature of the ENDS marketplace and the evolution of products over time, more contemporary data are needed to enhance the understanding of transitions among users of newer ENDS products.

The Adult JUUL Switching and Smoking Trajectories (ADJUSST) Study, an in-market surveillance study of adult JUUL users (methods described elsewhere; see Shiffman et al, in this issue)[25] characterizes the history and smoking trajectories among new purchasers of a widely-used ENDS product, JUUL, in greater detail than is traditionally captured in surveys. Past research has traditionally characterized ENDS users based on smoking status (ie, current, former, and never smokers) and used this as the basis to assess 3 key types of transitions over time: (1) complete switching away from smoking; (2) resumption of smoking among former smokers; and (3) initiation of smoking among never users.[26]

Several companion papers in this issue analyze in greater detail particular subpopulations, namely established smokers,[27] dual users,[28] former smokers,[29] and never smokers.[30] The purpose of this paper is to provide an overarching picture of how smoking changed in the entire sample of JUUL purchasers over the course of a year. This whole-population perspective is essential for understanding the population impact of JUUL and other ENDS. In the course of analyzing the full range of JUUL purchasers, this paper also summarizes information on subpopulations that are not addressed in the companion papers, such as current and former experimental smokers (ie, those who ever-smoked, but did not smoke over 100 cigarettes). Considering all of these subgroups, and distinguishing the heterogeneous population of JUUL purchasers by smoking history and smoking status at the time of purchase is essential to understanding the trajectories of smoking following adoption of ENDS such as JUUL.[31-35] Like previous approaches to analyzing longitudinal transitions in tobacco product use, the paper uses descriptive visualization tools to identify common transitions and their relative frequency.[24]

METHODS

Participants

A sample of adults of legal purchasing age (age ≥ 21 years) residing in the US were invited to participate in a longitudinal prospective cohort survey of tobacco product use upon purchasing a JUUL Starter Kit (JSK) in a retail store or online via the manufacturers' ecommerce platform, beginning in June 2018.[25] Study inclusion criteria were: (1) age ≥ 21 years; (2) purchased a JSK for the first time within the past 7 days; and (3) permanent residency in the USs. Employees of Juul Labs Inc or PAX Labs Inc were excluded. The present analysis focused on 27,164 adults who provided data on

relevant measures at both baseline and 12-month follow-up. Analyses by Shiffman et al[25] (this issue) showed groups defined by differential completion of follow-ups differed little in demographics or baseline smoking profiles; re-contact with some non-responders also indicated that non-response was not related to smoking outcomes, suggesting limited bias due to non-response.[25]

Procedure

The study was a naturalistic observational surveillance study. There was no intervention; participants purchased products on their own as they wished, and received no instructions or advice, nor was any behavioral objective defined for them.

Individuals who purchased a JSK at retail were invited via a recruitment card found in the packaging. Those who purchased a JSK via the online ecommerce platform were invited to participate via a post-purchase study recruitment email. The study was described as "a survey about vaping, smoking, and JUUL products" and offered $30 compensation.

All surveys were administered online. The data collection was overseen by the Centre for Substance Use Research (Glasgow, Scotland; www.csures.com) and conducted by Dacima (https://www.dacimasoftware.com). The Advarra® Institutional Review Board, an accredited IRB (https://www.advarra.com), approved the study. All participants provided written informed consent to participants in "an online survey of your views and experiences of smoking cigarettes and using JUUL vapor products" whose purpose was "to better understand the types of people who buy the JUUL Starter Kit, their reasons for using a JUUL, and what impact, if any, using a JUUL has on cigarette smoking." Participants were compensated with a $30 Visa gift card for the baseline and each follow-up survey they completed.

After completing a baseline survey, participants were invited by email to complete surveys at several timepoints up to 12 months; each follow-up survey remained open for up to 10 days after the initial email invitation was sent. The invitations noted: "You are eligible to take this survey whether or not you still use a JUUL, and whether or not you still smoke cigarettes," and reminded participants of the $30 compensation and the confidentiality of their information. Additional details regarding the overall study methodology are described in another publication in this issue[25] and in 2 publications reporting a separate, parallel study of adult smokers who purchased the JSK.[22]

Measures

Baseline smoking. As described in Shiffman et al,[25] baseline smoking status was assessed based on key questions assessing ever smoking, number of cigarettes smoked in lifetime, past 30-day smoking, now smoking 'every day/some days/not at all', and time since last smoked. Baseline smoking status definitions were adapted from those used in previous literature[36,37] and constructed to be mutually exclusive and comprehensively exhaustive in characterizing the adult JUUL purchaser population based on the smoking status variables above (Table 1).

Participants who reported ever smoking cigarettes, having smoked ≥ 100 cigarettes in their lifetime, smoking in the past 30 days, and 'now' smoking 'every day' or 'some days' were defined as "Past 30-day Established Smokers." Goldenson et al[27] provide detailed analyses of this group. Participants who reported ever smoking cigarettes, having smoked ≥ 100 cigarettes in their lifetime, smoking in the past 30 days, and 'now' smoking 'not at all' were defined as "Past 30-day Established Smokers Now Smoking 'Not at all';" persons who reported ever smoking cigarettes, smoking less than 100 cigarettes in their lifetime, and smoking in the past 30 days were defined as "Past 30-day Experimental Smokers."

Because the expected risk of smoking relapse among former smokers is substantially different in the first year of quitting versus afterward,[31,32] we divided former established smokers into "Recent Quitters," who stopped smoking cigarettes in the last 12 months, and "Long-Term Quitters," who stopped smoking cigarettes over 12 months previously (see Le et al[29]).

Participants who ever smoked cigarettes, but had smoked fewer than 100 cigarettes in their lifetime, and did not smoke a cigarette in the past 30 days were defined as "Former Cigarette Experimenters." We considered these under the rubric of "Never Established Smokers" (Rather than "Former Smokers") because some authors have not considered this group to have been smokers.[23,38] Participants

Table 1
Distribution of Baseline Smoking Status in Analytic Sample

Baseline Smoking Status	Definition	N (%)[a] (N = 27,164)
Past 30-day Smokers		17,701 (65.2)
Past 30-day Established Smokers	Ever smoked cigarettes, even one or 2 puffs; and Smoked 100 or more cigarettes in their entire life; and Smoked in past 30 days; and Now smoke 'Every day' or 'Some days'	11,919 (43.9)
Past 30-day Established Smokers Now Smoking "Not at all"	Ever smoked cigarettes, even one or 2 puffs; and Smoked 100 or more cigarettes in their life; and Smoked in past 30 days; and Now smoke 'Not at all'	2603 (9.6)
Past 30-day Experimental Smokers	Ever smoked cigarettes, even one or 2 puffs; and Smoked less than 100 cigarettes in their entire life; and Smoked in past 30 days;	3179 (11.7)
Former Established Smokers		3250 (12.0)
Recent Quitters	Ever smoked cigarettes, even one or 2 puffs; and Smoked 100 or more cigarettes in their life; and Have not smoked in past 30 days; and Quit smoking within the past 12 months	1517 (5.6)
Long-Term Quitters	Ever smoked cigarettes, even one or 2 puffs; and Smoked 100 or more cigarettes in their life; and Have not smoked in past 30 days; and Quit smoking more than 12 months ago	1733 (6.4)
Never Established Smokers		6213 (22.9)
Former Experimental Smokers	Ever smoked cigarettes, even one or 2 puffs; and Smoked less than 100 cigarettes in their life; and Did not smoke a cigarette in the past 30 days	3549 (13.1)
Never Smokers	Never smoked cigarettes, even one or 2 puffs	2664 (9.8)

Note.
[a] All percentages reflect proportion of total sample (N = 27,164) that provided smoking status data at 12 months.

who never smoked a cigarette, not even one or 2 puffs, were defined as "Never Smokers" (see Shiffman et al[30]).

These 7 smoking status categories were consolidated to form 3 composite smoking status groups for analysis of transitions among: (1) Past 30-day Smokers; (2) Former Established Smokers; and (3) Never Established Smokers (Former Cigarette Experimenters and Never Smokers).

Participants who reported currently smoking every day or some days were asked 2 questions that assessed frequency (number of days smoked in past month) and quantity of smoking (based on number of cigarettes smoked per day on days smoked) at baseline.

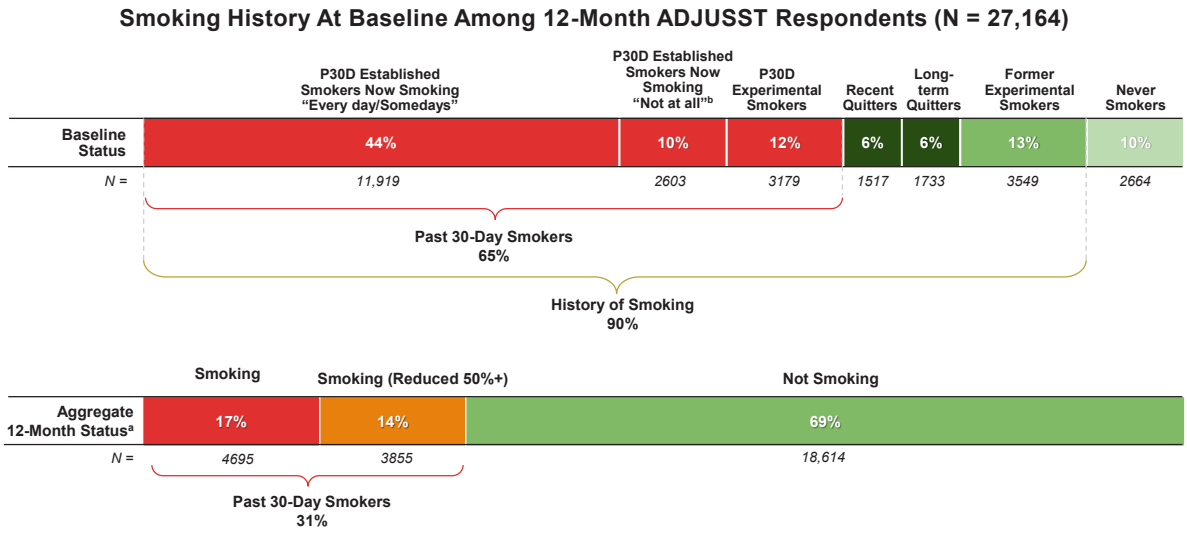
Baseline ENDS use. Participants also were asked about use of other ENDS at the time of their first-time JSK purchase, with the question "In the 30 days before you purchased your JUUL Starter Kit, were you using any another brand of e-cigarette/vapor product fairly regularly?"

Use of other tobacco products. Neither history nor current use of other tobacco products was assessed.

Smoking and cigarette consumption at 12-month follow-up. At the 12-month follow-up assessment, the primary outcome was past 30-day smoking status. Participants who reported smoking every day or some days at that time were asked the same 2 questions that assessed frequency and quantity of smoking as at baseline.

Change in cigarettes smoked per day. Among

Figure 1
Baseline Status and 12-month Smoking Status (Past 30 Days; P30D) among All Participants



Note.
The figure shows the distribution of smoking status and history at baseline, and the smoking status at 12 months. The data are based on 27,164 participants who provided data at 12 months.
[a] The analysis focused on 27,164 adults who provided valid data on all relevant study measures at both baseline and 12-month follow-up.
[b] Participants who reported past 30-day smoking at baseline or follow-up but did not provide valid data on cigarette consumption were classified as "Smoking" as cigarette reduction could not be assessed for these individuals; it is likely that some proportion of these smokers also reduced their CPD.

participants who reported past 30-day smoking at baseline and also at 12-month follow-up, change in daily cigarette consumption (cigarettes per day × [days smoked in past 30 days/30]) was computed to determine whether or not there was a ≥ 50% reduction in this measure at 12 months. Change in cigarette consumption could not be assessed among those who reported past 30-day smoking but reported now smoking "Not at all" at either baseline or 12-month follow-up, as these respondents were not asked about cigarette consumption. Analyses of PATH data, reported in the online supplement to this paper suggest that such respondents were likely smoking very little, but, for these analyses, they were conservatively classified as having not reduced their cigarette consumption by ≥ 50% (Table S1); See Selya et al[28] for more detail on changes in cigarette consumption in ADJUSST.

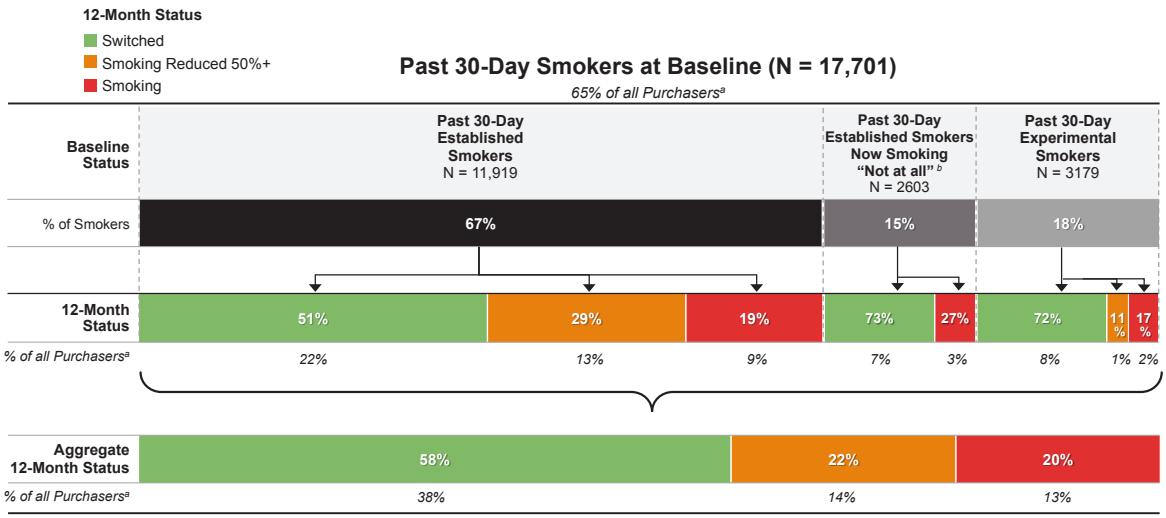
Data Analysis

Primary analyses were descriptive. The analytic sample consisted of participants with data on smoking status at baseline and 12 months. All analyses were conducted using Python 3.7, Tableau 2020.1, or SAS 9.4.

Smoking status at 12 months was classified as: (1) not smoking (ie, no smoking in the past 30 days, not even a puff); (2) smoking (past 30 days) but having reduced cigarette consumption by ≥ 50% compared to baseline (smoking but reduced); or (3) smoking (past 30 days) and not reduced by ≥ 50%. As noted above, participants who reported past 30-day smoking at baseline or follow-up but who did not provide data on cigarette consumption were conservatively classified as smoking without reduction.

To visualize transitions in smoking from baseline to 12 months across all groups, a Sankey diagram was created.[39] This flow diagram, where the width of the arrow of each transition is proportional to the number of participants moving from one status to another (eg, smoking to no longer smoking),

Figure 2
Baseline Status and 12-month Smoking Status among Baseline Past 30-day Smokers



Note.
The figure shows the distribution of smoking history at baseline for participants who reported past 30-day smoking at baseline, and their smoking status at 12 months (among those who provided data at 12 months). The top ribbon shows the distribution according to smoking history and status at time of purchase. The middle ribbon shows the 12-month smoking status of each of these groups. the bottom ribbon shows the overall 12-month smoking status for the Past 30-day Smokers as a whole. The same layout applies to Figures 3 and 4.
Smoking reduction could not be assessed among Other Past 30-day Established Smokers at baseline, because their baseline cigarette consumption was not captured in the survey; among these, those who reported past 30-day smoking at follow-up were classified as "Smoking."
[a] % of all purchasers is proportion of total sample (N = 27,164).
[b] Participants who reported past 30-day smoking at baseline or follow-up but did not provide valid data on cigarette consumption were classified as "Smoking" as cigarette reduction could not be assessed for these individuals; it is likely that some proportion of these smokers also reduced their CPD.

identifies the most frequent transitions and overall changes at 12 months.

To provide further characterization of 12-month smoking status by pre-purchase behavior, the 12-month past 30-day smoking status of each baseline-smoking group was sub-stratified according to whether respondents had reported regularly using other ENDS at the time of a JSK purchase. Odds ratios and 95% confidence intervals were generated, comparing 12-month past 30-day smoking prevalence between those who were and were not using other ENDS at baseline.

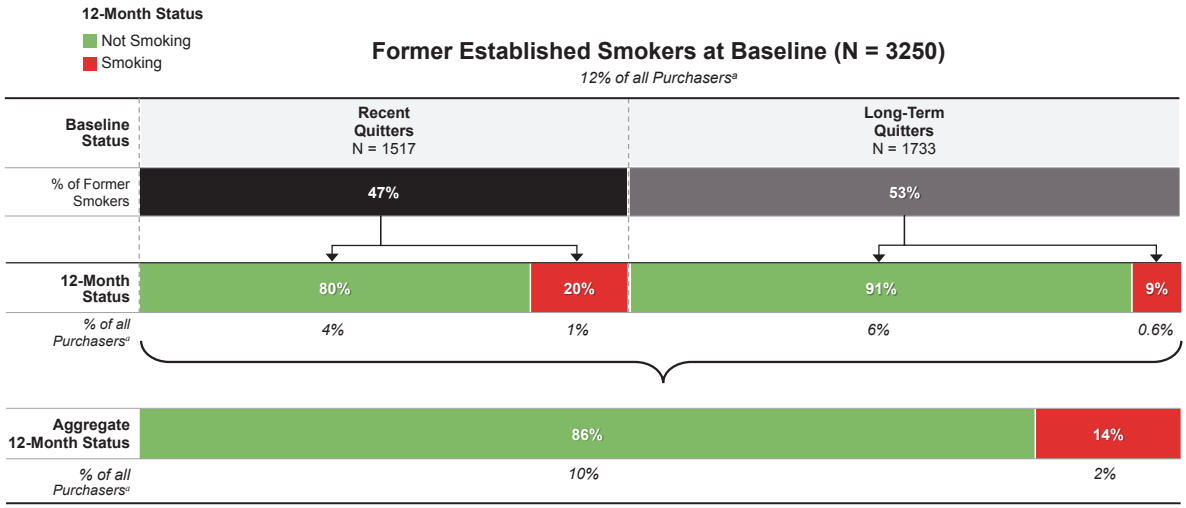
RESULTS

Baseline Composition of Adult JUUL Purchasers

The overall analytic sample (N = 27,164; 49.0% of baseline participants) had a mean age of 29.9 years (SD = 10.3), the majority self-reported as male (58.7%) and non-Hispanic white (74.4%; Table S2). Almost two-thirds had never married (65.5%), 70.1% reported completing at least some college, and 54.7% reported annual household income of less than $50,000 (sociodemographics stratified by smoking status are displayed in Table S1).

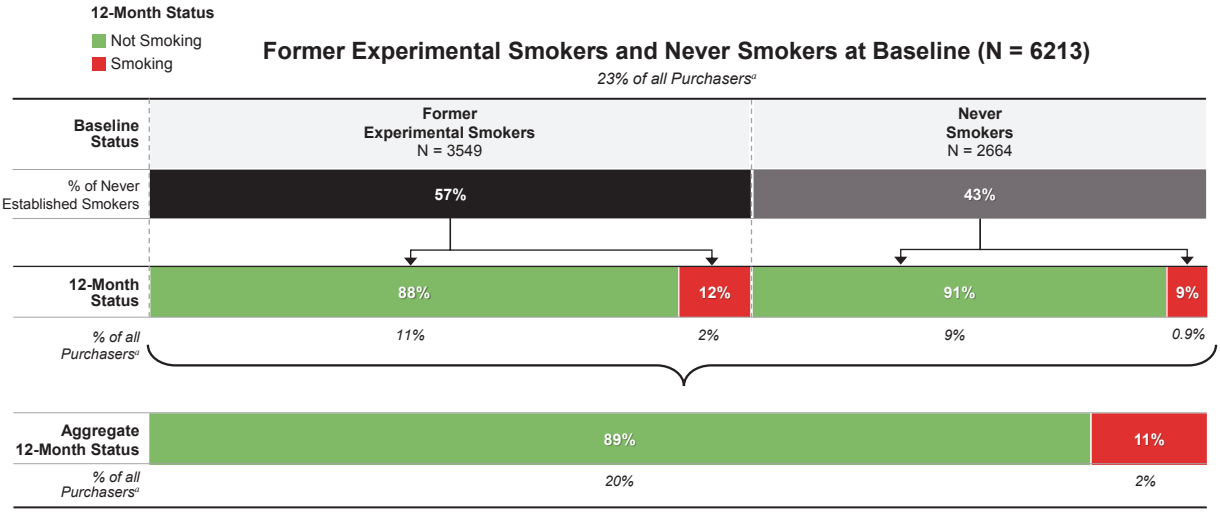
As Table 1 shows, at time of JSK purchase (ie, baseline) 65.2% were Past 30-day Smokers, 12.0% were Former Established Smokers and 22.9% were Never Established Smokers. Overall, 90.2% of the adult purchaser population had previous experience with smoking at time of JUUL purchase; 9.8% were Never Smokers. The largest subgroup, and the vast majority of the Past 30-day Smokers group, were Current Established Smokers (N

Figure 3
Baseline Status and 12-month Smoking Status among Baseline Former Established Smokers



Note.
The figure shows the distribution of former established smokers' quit duration (recent: < 1 year); long-term: ≥ 1 year) at baseline and their smoking status at 12 months (among those who provided data at 12 months). See notes for Figure 2.
*** % of all purchasers is proportion of total sample (N = 27,164).**

Figure 4
Baseline Smoking Status and 12-month Smoking Status among Baseline Never Established Smokers



Note.
The figure shows the participants who were never established smokers (either former experimental smokers or never-smokers) at baseline and their smoking status at 12 months (among those who provided data at 12 months). See notes for Figure 2.
Percentages in italics represent each group as a percentage of the total JSK purchaser population with 12-month follow-up data (N = 27,164).

Table 2
Past 30-day Smoking at 12 months, by Baseline Smoking Status and Regular Use of Other ENDS

Baseline smoking status	Proportion of Each Group Who Were Using ENDS Regularly at Baseline[a] (%)	Past 30-day Smoking at 12 Months, by Baseline Use of ENDS		
		Proportion Reporting Past 30-day Smoking at 12 Months among Those Regularly Using ENDS at Baseline[a] (%)	Proportion Reporting Past 30-day Smoking at 12 Months among Those Not Regularly Using ENDS at Baseline[a] (%)	OR[b] (95% CI)
Past 30-day Smokers				
Past 30-day Established Smokers	23.4	47.0	53.0	**0.78** (0.71 , 0.87)
Past 30-day Established Smokers Now Smoking "Not at All"	30.9	25.1	31.0	**0.74** (0.58 , 0.95)
Past 30-day Experimental Smokers	31.6	29.4	32.6	0.86 (0.68 , 1.09)
Former Established Smokers				
Rcent Quitters	50.0	16.6	24.3	**0.62** (0.45 , 0.87)
Long-Term Quitters	69.6	7.4	11.7	**0.61** (0.40 , 0.91)
Never Established Smokers				
Former Experimental Smokers	38.5	13.1	12.8	1.03 (0.76 , 1.38)
Never Smoker	29.2	6.4	7.3	0.87 (0.49 , 1.54)

Note.
[a] Based on the question "In the 30 days before you purchased your JUUL Starter Kit, were you using any another brand of e-cigarette/vapor product fairly regularly?"
[b] Reference category: Not regularly using ENDS at baseline. Bolded odds ratios indicate statistically significant differences between those using and not using other ENDS

= 11,919; 43.9% of the total sample). The other 2 subgroups of Past 30-day Smokers (Past 30-Day Established Smokers Now Smoking "Not at all," and Experimental Smokers) comprised 21.3% of the sample.

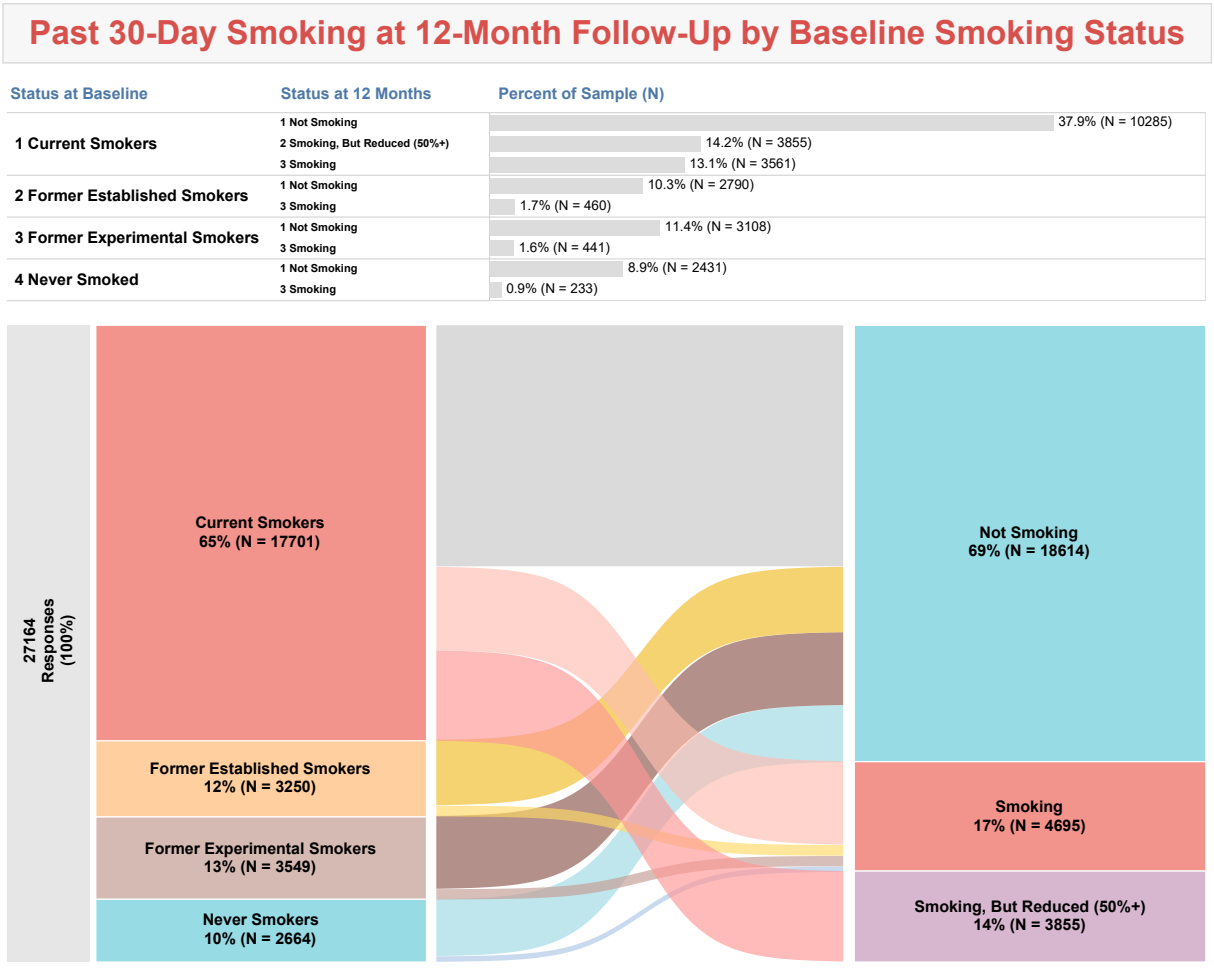
Those not smoking at the time of purchase made up a smaller proportion of the sample. Among Former Established Smokers, slightly less than half (46%; 5.6% of overall sample) were Recent Quitters, with the remaining 54% (6.4% of overall sample) having quit for over 12 months. The majority (57%; 13.1% of overall sample) of the Never Established Smokers had previously smoked, and the remainder (43%; 9.8% of overall sample) had not.

Descriptive Transitions Analysis: Tree Diagrams of Smoking Behavior at 12 Months

Figures 1-4 show tree diagrams displaying transitions at 12-month follow-up among each baseline smoking status group. Figure 1 summarizes the smoking status of the sample at baseline (just after JSK purchase) and their smoking status after one year. The top 'ribbon' is a summary of baseline smoking status using the categories described in Methods. The bottom ribbon summarizes smoking status in the entire sample 12 months later.

Figures 2-4 summarize the baseline and 12-month smoking status in major baseline smoking groups, ie, baseline Past 30-day Smokers, Former Established Smokers, and Never Established Smokers,

Figure 5
Sankey Diagram of Past 30-day Smoking at 12 Months by Baseline Smoking Status



Note.
The Sankey diagram shows the flows or transitions in participants' smoking status between baseline and 12 months (among those who provided data at 12 months). All Percentages are based on proportion of total sample with baseline and 12-month data (N = 27,164)

respectively. One year after initiating JUUL use, 58% of baseline Past 30-day Smokers reported not smoking in the past 30 days. This was true of over 70% of both Past 30-day Smokers Now Smoking "Not at All" and Past 30-day Experimental Smokers, and of 51% of the Past 30-day Established Smokers. Of those who continued to smoke (every day or some days) at follow-up, more than half reported that they had reduced their cigarette consumption by over 50% (orange segment).

Among Former Established Smokers (Figure 3), 14% reported smoking at 12-month follow-up, with substantial variation by time since quitting – smoking was reported by 20% of Recent Quitters and 9% of Long-term Quitters. The Former Established Smokers who reported past 30-day smoking at 12 months comprised 2% of the overall purchaser sample.

Among Never Established Smokers (Figure 4), 11% reported past 30-day smoking at follow-up (9% among Never Smokers and 12% among Former Experimental Smokers). Never Smokers smoking at 12 months comprised < 1% of the adult purchaser population.

Regular Use of Other ENDS at Baseline and Association with Smoking at 12 Months

Regular use of ENDS was common at baseline among Former Established Smokers (69.6% of Long-Term Quitters and 50.0% of Recent Quitters); fewer Past 30-day Smokers (31.6% of Current Cigarette Experimenters, 30.9% of Past 30-day Established Smokers Now Smoking "Not at All" and 23.4% of Current Established Smokers) and Never Established Smokers (38.5% of Former Experimental Smokers and 29.2% of Never Smokers) reported regularly using other ENDS at baseline. Smoking at 12 months was generally less common among those already regularly using ENDS prior to the JSK purchase, and this association was significant among Former Established Smokers and the Past 30-Day Established Smokers (Table 2).

Descriptive Transitions Analysis: Sankey Diagram of the Adult JUUL Purchaser Sample

Figure 5 provides a Sankey diagram summarizing the relative magnitude of transitions by smoking status. Across the entire sample, 69% of respondents were not smoking at 12-month follow-up. Among the 31% who were smoking at 12 months, the majority (87%) were smoking at baseline, 5% were baseline former smokers, 5% were baseline former experimental smokers and 3% were baseline never smokers.

The most common transition observed was from past 30-day ('current') smoking at baseline to no longer smoking at follow-up, reported by 38% of respondents. The 2 next most common transitions were from baseline some day or every day smoking to: (1) smoking but with cigarette consumption reduced by at least 50% (14% of sample); and (2) continued smoking without a ≥ 50% reduction in cigarette consumption (13%). The least common transition was from never smoking at baseline to past 30-day smoking at follow-up (0.9% of sample).

DISCUSSION

In this paper, we report on smoking behavior in a large sample of new adult JUUL purchasers 12 months after purchase. Over 90% of purchasers reported ever-smoking at baseline, most (65%) reporting smoking in the 30 days preceding purchase. A comparatively smaller proportion were former smokers, either Former Established Smokers (12%) or Former Experimental Smokers (13%). The smallest subgroup were Never Smokers (10%).

One year later, 58% of those who were smoking (past 30 days) at baseline (including over half of Past 30-day Established Smokers) were no longer smoking. Among those who did continue to smoke every day or some days, the majority had reduced their cigarette consumption by at least 50%. Less than 3% of all purchasers were baseline Former Smokers (2%) and Never Smokers (0.9%) who reported smoking at 12 months. From the time of initial purchase to 12 month later, the overall prevalence of past 30-day smoking fell by more than half, from 65% to 31%.

The findings presented herein provide insight into transitions among different populations of adults purchasing JUUL products, and demonstrate the importance of accounting for heterogeneity within smoking status subgroups when characterizing ENDS users. For example, whereas 58% of Past 30-day Smokers reported not smoking at follow-up, these rates varied by whether smokers were Past 30-day Established Smokers (51%), Past 30-day Experimental Smokers (72%) or Past 30-day Established Smokers who reported they were currently smoking "not at all" (73%) at baseline. The established smokers likely includes those who face greater difficulty in switching,[19,40-42] whereas Past 30-day Established Smokers Now Smoking "Not at all" may include smokers who may have switched away from cigarettes more easily, such as just before, at, or immediately following purchase of JUUL. Although we cannot determine if or exactly when Past 30-day Established Smokers who now reported smoking "not at all" stopped smoking (ie, whether this occurred after JSK purchase but prior to completing the baseline survey, or in the past month and prior to JSK purchase), it is likely that some of these respondents were smokers who switched just after initiating JUUL use. Data from PATH study suggest that this response pattern is typically associated with past 7-day smoking abstinence (Table S2). Similarly, we observe that those who stopped smoking more recently are more likely to resume smoking, consistent with previous research on risk of relapse, even without ENDS use.[32,33]

The heterogeneity of the adults who purchased a JSK was also evident in consideration of their pre-existing use of other ENDS. The prevalence of 'fairly regularly' use of other ENDS at baseline ranged from roughly one-fourth – among past 30-day Established Smokers – to more than two-thirds among Long-Term Quitters. These individuals appear to have been changing brands of ENDS, rather than initiating regular ENDS use for the first time. This was particularly common among the Former Established Smokers, suggesting that some of these may have been smokers who had switched to ENDS, and were continuing that trend with JUUL. Similarly, the use of other ENDS by Never Smokers and Former Experimenters indicate that these individuals were not initiating or re-initiating tobacco or nicotine use with JUUL, but continuing a pre-existing use pattern. Further exploration of these variations is warranted.

Among baseline Established Past 30-day and Former Established Smokers, those who regularly used ENDS at baseline were less likely to be smoking one year later. This may be related to the fact that, in this study, the proportion of smokers who switched away from smoking increased over time.[27,28,43] It may be that those already using ENDS before the JSK purchase were further along in a process of substituting ENDS for smoking. Consistent with this possible interpretation, no such effect was observed among those not smoking at baseline.

Comparisons between the present study and other studies following ENDS users are challenging. ADJUSST followed individuals who had purchased a JUUL Starter Kit, which would seem to imply a substantial demonstrated interest in ENDS use, in contrast to studies that identify ENDS users on the basis of any use in the preceding 30 days. Despite such differences, a comparison of the smoking history of ENDS users in this study and in the population-representative PATH study suggests that there are similarities, in that ENDS users in PATH waves are primarily current or former smokers.[18] However, there are also substantial differences: the proportion of dual users in PATH Wave 1 (those both smoking and using ENDS, perhaps most analogous to the Current Established Smokers in ADJUSST) who were no longer smoking one year later was significantly lower (12.1%) than in the current study (51%, Figure 2). This may be due to both underlying differences in the definitions of ENDS use, as noted, as well as differences in the types of ENDS available for use during PATH Wave 1 data collection (2013-14). It has been noted that ENDS products themselves, and smokers' approach to using them, may have evolved, "As an emerging product on the US market in 2013-2014, the novelty of e-cigarettes may have prompted some people to try them out of curiosity, perhaps without any intention for sustained use;"[23] indeed, PATH reported high rates of discontinuing ENDS use.[23] In contrast, over 89% of Past 30-day Established Smokers in the ADJUSST sample were still using JUUL at 12 months.[27] Some of the change also may reflect product evolution. Evidence suggests that early ENDS products were unsatisfying for smokers,[44] and recent-generation devices are more satisfying.[45-47]

The analyses presented focus on changes in cigarette smoking, which is by far the most hazardous form of tobacco or nicotine use.[48] To the extent that use of ENDS such as JUUL can help users avoid smoking, their individual health, and public health, is likely to benefit.[3] That said, ENDS use itself carries some risks, and would represent an increment in risk for those not using tobacco.[5] If the use of ENDS were to cause an increase in the likelihood of progressing to smoking (ie, "gateway" – which is controversial[49,50]), this would particularly represent an increase in risk.

Thus, smoking initiation among never smokers and resumption of smoking among former smokers would adversely impact population health, if these individuals would not have otherwise smoked. Smoking in these cohorts were the least common transitions observed among JUUL users in this study, and substantial proportions of these cohorts were already regularly using ENDS when they purchased a JSK. Importantly, in-depth analyses of these Never Smoker[30] and Former Established Smoker[29] cohorts find reported smoking is neither frequent nor persistent among these groups (ie, the majority who smoked at any point across the 12-month study period reported past 30-day smoking at just one of the 6 follow-up assessments).

Any reported smoking by never smokers is problematic, especially if it goes beyond infrequent and impersistent use and becomes established smoking.

A comprehensive understanding of behaviors across each subgroup within current, former, and never smokers is necessary to account for both the risks and benefits of ENDS product use to population health. Net population health impact modeling included in this issue incorporates these transitions from ADJUSST, along with PATH data, to model the impact of both beneficial and harmful transitions, with extensive sensitivity testing to account for varying the prevalence of these behaviors beyond what is reported in this analysis.[51]

There are several key strengths to this paper and the ADJUSST study, including the large sample size, longitudinal nature of the data, recency of data collection, use of standard questions to define smoking status, and availability of data from point of initial product purchase. However, there are also several limitations, some relating to generalizability – the sample consisted of adults who had recently purchased a JSK on their own, and arguably, would be representative of that population. However, the results would likely not generalize to a broader population of ENDS users, such as those in cohorts defined by any use on the past 30 days, which can include casual trial.[52] By the nature of the sample, participants were using JUUL, a particular ENDS whose nicotine delivery exceeds that of some ENDS, though not others;[53,54] therefore, generalizability to other ENDS is unknown.

As with any study, the sample consisted of volunteers, who may differ from users who do not participate in research. Also, as is common with other naturalistic observational follow-up studies,[26] interpretation may be limited by the fact that the data are self-report, and that there is participant attrition. Analyses of missing data in the sample, reported in-depth elsewhere in this issue,[25] show that non-responders resembled responders at baseline, and, when reached in a recontact study, reported similar smoking status at 12 months as respondents, suggesting minimal bias due to nonresponse. Nonetheless, it is possible that nonrespondents were more likely to be smoking, and that the true smoking prevalence is higher than reflected in these reports.

This study was observational in nature and did not include a comparison group of individuals not using JUUL, much less randomized individuals to use of JUUL, limiting our ability to establish causality for the descriptive transitions presented here. Recently published randomized trials that assessed use of ENDS[55-57] for smoking cessation and a trial in which smokers were randomized to use of JUUL[58] found increased odds of no longer smoking among adult smokers assigned to use ENDS (or JUUL); these trials can better inform causal attributions.

Finally, neither the baseline assessment nor the follow-ups asked about the use of tobacco products other than cigarettes and ENDS. Thus, it is possible that some respondents were tobacco users, even smokers (eg, little cigars) at baseline or at follow-ups, and this is not accounted for in our findings. The analyses also did not consider participants' history of quitting or prior use of nicotine replacement medications.

Conclusion

In this observational longitudinal surveillance study, 90.2% of adult JUUL purchasers reported some smoking history at time of purchase; two-thirds had been smoking in the preceding 30 days. The majority of purchasers who were smokers at baseline were no longer smoking at 12 months. Initiation of smoking among Never Established Smokers and resumption of smoking by Former Established Smokers was rare, with each transition being reported by 1%-2% of the sample. Data, such as those in the current study, that assess transitions in populations of adult ENDS users provide the foundation for population health modeling and are necessary to elucidate the net population health impact of ENDS products.

Human Subjects Approval Statement

This study was approved by the Advarra® Institutional Review Board.

Conflict of Interest Disclosure Statement

SP was a full-time employee of Juul Labs Inc during the time that this work was conducted. YX, NIG, and RW are full-time employees of Juul Labs Inc. Through PinneyAssociates Inc, SS and RG provide consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc. Within the last 2 years, PinneyAssociates Inc has consulted for British American Tobacco and Reynolds American

Inc and subsidiaries on tobacco harm reduction. Under contract to JUUL Labs Inc, the Centre for Substance Use Research, an independent research consultancy, designed the study and assessments and oversaw the work of Dacima Inc, that hosted the survey and collected the data. CSUR managed, cleaned, and summarized the data.

SP, RW, RG and SS conceptualized the study and analysis plan. YX and NIG performed the statistical analyses under the direction of SP and SS, and all authors interpreted results. All of the authors contributed to writing and review of the paper, and had access to the data. The sponsor approved the research plan and provided comment on a near-final draft of the paper.

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Table S1
PATH Wave 4 Past 30-day Smokers Currently Smoking "Not at All" Stratified by Wave 3 Smoking Status

	Never Smoker (N = 72)			Former Smoking Experimenter (N = 160)			Former Established Smoker, Long-Term Quitter (N = 79)			Former Established Smoker, Recent Quitter (N = 72)			Current Smoking Experimenter (N = 96)			Current Established Smoker (N = 223)		
Wave 4 smoking behavior (1 year later)	**N**	**Mean or %**	**SD**	**N**	**Mean or %**	**SD**	**N**	**Mean or %**	**SD**	**N**	**Mean or %**	**SD**	**N**	**Mean or %**	**SD**	**N**	**Mean or %**	**SD**
Days smoked in the past 30 days,[a] Mean	72	1.5	4.1	160	1.7	3.8	77	1.6	4.3	70	3.1	5.4	95	2.3	4.3	219	7.1	9.6
Overall CPD,[b] Mean	38	0.1	0.2	99	0.1	0.4	33	0.9	3.4	59	0.7	2.3	75	0.2	0.7	190	2.7	4.9
Past 7-day Smoking (%)	11	16.5	—	39	25.0	—	16	20.6	—	25	35.2	—	35	36.9	—	84	37.6	—

Note.
Abbreviations: CPD, cigarettes per day.
Denominators or sample size may be less than column heads due to missing data.
[a] Per PATH logic, respondents who indicated they smoked every day were assigned smoking 30 days out of 30.
[b] Cigarettes per day in the past 30 days calculated from past 30-day CPD on days smoked and days smoked in the past 30 days. Missing for those who report smoking on zero days in the past 30 days.

Table S2
Sample Sociodemographic Characteristics by Smoking Status

Sociodemographic Characteristics	Past 30-day Established Smokers Now Smoking Every Day or Some Days (N = 11,919)	Past 30-day Established Smokers Now Smoking "Not at all" (N = 2603)	Past 30-day Experimental Smokers (N = 3179)	Recent Quitters (N = 1517)	Long-term Quitters (N = 1733)	Former Experimental Smokers (N = 3549)	Never Smokers (N = 2664)	Total (N = 27,164)
Age, years, Mean (SD)	32.6 (10.6)	30.4 (10.0)	27.1 (9.3)	28.8 (9.3)	35.3 (11.2)	25.3 (7.8)	24.1 (6.5)	29.9 (10.3)
Sex								
Male	54.5 (6452)	60.6 (1563)	59.5 (1879)	63.1 (951)	65.9 (1130)	61.5 (2169)	64.0 (1693)	58.7 (15837)
Female	44.9 (5315)	38.9 (1002)	39.9 (1260)	36.2 (546)	33.8 (580)	38.0 (1340)	35.1 (929)	40.7 (10972)
Transgender	0.6 (65)	0.5 (13)	0.6 (18)	0.7 (10)	0.2 (4)	0.6 (20)	0.8 (22)	0.6 (152)
Race/Ethnicity								
Non-Hispanic White	77.9 (8688)	78.7 (1898)	67.3 (1974)	75.6 (1060)	82.0 (1316)	68.0 (2273)	66.2 (1630)	74.4 (18839)
Non-Hispanic African-American	3.1 (347)	3.8 (91)	4.7 (138)	3.3 (46)	2.2 (35)	5.2 (174)	7.1 (174)	4.0 (1005)
Non-Hispanic Asian	5.8 (642)	4.0 (96)	7.5 (220)	5.1 (71)	4.7 (75)	5.8 (194)	7.2 (178)	5.8 (1476)
Hispanic Ethnicity	8.6 (956)	8.9 (214)	15.7 (462)	10.2 (143)	7.0 (112)	15.3 (511)	14.3 (352)	10.9 (2750)
Non-Hispanic Other Race	4.7 (518)	4.7 (114)	4.8 (141)	5.9 (82)	4.2 (67)	5.7 (191)	5.3 (130)	4.9 (1243)
Marital Status								
Married	28.8 (3386)	25.2 (650)	16.0 (496)	22.8 (339)	43.1 (736)	12.9 (447)	9.4 (241)	23.6 (6295)
Never Married	56.6 (6647)	62.3 (1605)	76.4 (2371)	68.1 (1014)	44.7 (764)	82.5 (2865)	86.1 (2209)	65.5 (17475)
Divorced, Separated or Widowed	14.6 (1715)	12.5 (321)	7.6 (236)	9.1 (136)	12.2 (208)	4.6 (161)	4.5 (115)	10.9 (2892)
Highest Level of Education Completed								
High school graduate or less education	28.3 (3156)	29.5 (719)	33.8 (960)	29.8 (410)	19.1 (308)	30.4 (959)	40.1 (916)	29.9 (7428)
Some college or associate degree	43.2 (4821)	45.4 (1107)	39.3 (1116)	44.7 (614)	43.3 (700)	41.9 (1325)	41.3 (942)	42.7 (10625)
Bachelor's degree or more education	28.5 (3183)	25.1 (613)	26.9 (764)	25.5 (351)	37.7 (609)	27.7 (875)	18.6 (425)	27.4 (6820)
Annual Household Income								
Less than $50,000	53.9 (5573)	54.6 (1233)	62.1 (1638)	55.6 (696)	37.7 (551)	55.8 (1610)	59.1 (1239)	54.7 (12540)
$50,000-$100,000	29.8 (3079)	29.6 (667)	23.2 (612)	28.2 (353)	33.5 (489)	24.3 (701)	20.9 (438)	27.6 (6339)
Greater than $100,000	16.3 (1688)	15.8 (357)	14.8 (390)	16.2 (202)	28.9 (422)	20.0 (576)	20.0 (420)	17.7 (4055)

Note.
Values represent % (N) unless noted otherwise.
Based on enrollees with 12-month smoking status data. Denominators or sample size may be less than column heads due to missing data.

Supplemental Results

Additional Analysis of Past 30-day Smokers Currently Smoking "Not at All"

In the ADJUSST study, respondents who reported that they smoked in the past 30 days, and that they now smoke "not at all" were not asked how many days they had smoked in the past 30 days or how many cigarettes they smoked per day, and thus were not included in calculations of the sample's cigarette consumption, either at baseline or at follow-up assessments. To gain insight into the smoking behavior of respondents who showed this response pattern, we turned to the PATH study[1] which also asked both smoking-status questions (past-30-day smoking and now smoking every day, some days, or not at all), but did not use them to determine presentation of further questions about past 30-day frequency and daily quantity of smoking. Specifically, all respondents who were asked how many days in the past 30 days they smoked and how many cigarettes they smoked. Additionally, they were asked how long ago they had last smoked.

Thus, PATH provides data on the smoking behavior of these past 30-day but not-at-all (P30D-NAA) responders. We identified a sample of smokers with P30D-NAA response patterns in PATH Wave 4, who had also provided Wave 3 data. To parallel the analyses in the ADJUSST study, we stratified individuals by their smoking status at Wave 3 (the equivalent of ADJUSST baseline), and tallied their reported smoking behavior at Wave 4. Table S1 shows the results.

Except for those who were Current established smokers at Wave 3, all Wave-4 P30D-NAA reported smoking less than 5 days per month and less than one cigarette per day. Wave-3 established smokers reported smoking 7.1 days per month at Wave 4, smoking 2.7 cigarettes per day. Only a minority of P30D-NAA, generally about one quarter to one third, reported they had smoked in the previous seven days.

In sum, the PATH data strongly suggest that respondents with the P30D-NAA response pattern (ie, reporting they smoked in the past 30 days, but reporting they now smoke not at all) are smoking very little, smoking infrequently and a modest number of cigarettes. The majority report 7-day abstinence, suggesting they may consider themselves to have stopped smoking, which may help explain their 'not at all' response when asked to characterize their current smoking. In any case, these data from PATH, though based on a different and relatively small sample, and not addressing ENDS use, shed some light on how to interpret the P30D-NAA response pattern.

Supplemental Reference

1. Hyland A, Ambrose BK, Conway KP, et al. Design and methods of the Population Assessment of Tobacco and Health (PATH) study. *Tob Control.* 2017;26(4):371-378.

Changes in Dependence as Smokers Switch from Cigarettes to JUUL in Two Nicotine Concentrations

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Objectives: In this study, we assessed changes in dependence as smokers transitioned from cigarette smoking to exclusive use of the JUUL System ("JUUL"), contrasting users of 5.0% versus 3.0% nicotine concentration pods. **Methods:** Overall, 5246 adult (age ≥ 21) established smokers (> 100 cigarettes lifetime) who purchased a JUUL device completed online surveys at baseline, when smoking, and one and 3 months later; 1758 reported no past-30-day smoking ('switching') at one or both timepoints. Analyses compared dependence on cigarettes (at baseline) and JUUL (at follow-up), as assessed by the 4-item PROMIS scale (Range: 0-4). **Results:** Switching increased from Month 1 (18.3%) to Month 3 (28.6%); switchers at one month (Difference = 0.23) and 3 months (0.24) showed lower mean baseline cigarette dependence. Dependence decreased significantly (p*s* < .001) from baseline cigarette dependence to JUUL dependence at both one (from 1.82 to 1.59) and 3 months (1.97 to 1.73); changes did not significantly differ between users of 5.0% and 3.0% (p*s* > .43). Dependence on JUUL did not change significantly from Month 1 to Month 3. **Conclusions:** Dependence decreased as smokers transitioned from smoking to exclusive use of JUUL, similarly for users of both nicotine concentrations. Smokers who switch to JUUL may reduce their nicotine dependence..

Key words: dependence; electronic nicotine delivery system; smoking; switching; JUUL
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Cigarette smoking continues to be the leading cause of preventable mortality in the developed world.[1] Smoking behavior is persistent, with limited rates of cessation.[2] This difficulty in the cessation of smoking is largely attributable to smokers' nicotine dependence, a chronic and relapsing condition that robustly predicts continued smoking.[3] However, nicotine itself is not a major factor in smoking-related harm, which is attributable to exposure to the numerous combustion-related toxins in cigarette smoke.[4]

Electronic nicotine delivery systems (ENDS) deliver nicotine without burning tobacco, and thus, enable smokers to obtain nicotine while reducing such exposures.[4] The US Food and Drug Administration (FDA) and other public health and tobacco control experts have stated that the ability to sustain some degree of dependence, so that smokers can transfer their dependence on highly-toxic cigarettes to ENDS, is a crucial aspect of ENDS' ability to promote switching away from cigarettes.[5,6] At the same time, there is concern that ENDS may perpetuate or increase smokers' nicotine dependence.[7-9] This raises the question of the degree of dependence associated with ENDS use, and the changes in dependence as smokers transition from smoking to ENDS use.

Assessing dependence on ENDS, and comparing

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it to dependence on cigarettes, is psychometrically challenging.[10] A number of studies have reworded questionnaires developed and validated for assessment of cigarette dependence, applying them to assessment of ENDS dependence, and using them to compare ENDS and cigarette dependence.[11-13] Studies using such measures consistently report that dependence on ENDS is lower than dependence on cigarettes – for example, a scale combining items from multiple cigarette dependence scales found that dependence on ENDS was lower than dependence on cigarettes (assessed retrospectively),[12] and Liu et al[13] reached a similar conclusion from analysis of several individual items used to assess cigarette dependence. The National Academies of Science Engineering and Medicine reviewed this literature and also concluded that dependence on ENDS was lower than dependence on cigarettes.[4]

However, most of the measures that have been used in such comparisons have not been validated psychometrically for assessing ENDS dependence and for comparing it to cigarette dependence. Such cross-product application and comparability is not a given; for example, Strong et al[14] found that a number of items from existing, validated measures of cigarette dependence, administered in the Population Assessment of Tobacco and Health (PATH) were not valid for comparing different tobacco/nicotine products, ie, they did not meet the criterion of measuring the same thing in the same way, such that the scores could be compared quantitatively.[15]

Analyses of data from the PATH Study, using the Tobacco Dependence Index (TDI), a dependence measure that did demonstrate cross-product validity and invariance,[14,16] have found that dependence on ENDS is lower than dependence on cigarettes,[13,14,16] including among dual users.[16] This finding is consistent with a study of dual users that used the brief 4-item scale developed by the Patient-Reported Outcomes Measurement Information System (PROMIS) group[17] (adapted for ENDS).[18] However, one psychometric analysis of the 4-item PROMIS scale (currently under review) indicated that its validity for assessing ENDS dependence was limited. Specifically, the measure was found to be valid for assessing dependence on cigarettes both in smokers and in dual users, but was only valid for assessing ENDS dependence in exclusive ENDS users, not in dual users, where the scale failed a test of factorial validity, precluding comparisons of ENDS and cigarette dependence in dual users.[19]

ENDS are a diverse product category, with variations in many factors, including nicotine delivery. The JUUL System (Juul Labs Inc) ENDS – henceforth "JUUL" – are among the most widely used ENDS, accounting for the majority of ENDS purchases in conventional retail outlets.[20] JUUL uses nicotine-salt based e-liquids, which have been speculated to have higher dependence potential.[21,22] Hence, when evaluating dependence it may be important to consider particular product characteristics including nicotine concentration and formulation.

Two studies have examined rates of switching away from smoking (defined as past-30-day smoking abstinence) in adult established smokers who newly purchased JUUL.[23,24] Both found that the proportion of smokers switching away from smoking increased over time, and that heavier smokers were less likely to switch. The larger of the studies, using the PATH TDI, found that smokers with higher cigarette dependence were less likely to subsequently switch, and that those who did switch (vs dual users) were distinguished by greater dependence on JUUL, both cross-sectionally and prospectively.[24] The latter finding is consistent with 2 analyses of PATH showing that exclusive users of ENDS demonstrate higher dependence on ENDS than do dual users.[16,25] These findings are consistent with the concept that dependence on ENDS can facilitate switching, perhaps through the transfer of dependence from cigarettes to ENDS.[5,6]

Such between-subjects analyses comparing smokers to ENDS users may be confounded by uncontrolled interindividual differences between these self-selected groups. Furthermore, they only provide a snapshot of dependence at a single point in time. Prospective longitudinal data are required to evaluate whether smokers' dependence changes when they transition from smoking to use of ENDS. The current longitudinal study assessed prospective within-person changes in dependence as adult smokers switched completely from smoking to use of JUUL.

An additional question is whether the nicotine concentration of the e-liquid in ENDS such as JUUL affects the potential for dependence. Pharmacokinetic assessments of tobacco and nicotine-

delivering products demonstrate that that higher levels of nicotine delivery are associated with increased dependence potential.[26] To address this with respect to JUUL, the current study compared changes in dependence for those switching to the 2 different JUULpod nicotine concentrations – 5.0% (59 mg/mL) and 3.0% (35 mg/mL) – which have been demonstrated to differ in nicotine delivery.[27]

Accordingly, the primary aims of this study were to assess: (1) changes in dependence as smokers transitioned from cigarette smoking to exclusive use of JUUL; and (2) whether such changes differed between switchers using JUUL in 5.0% and 3.0% nicotine concentrations. In the course of addressing these questions, analyses also assessed differences in smoking characteristics between smokers who did (vs did not) switch, including the association of baseline cigarette dependence and future switching.

METHODS

Participants

US and Canadian adults who recently purchased a JUUL in a retail store or online via the manufacturers' ecommerce platform were invited to join a longitudinal study beginning in January 2019. Eligibility criteria included: (1) age ≥ 21 years; (2) permanent resident of either the United States or Canada; and (3) purchased a JUUL Device Kit or Starter Kit for the first time within the 3 days prior to receiving an invitation to participate in this study. Participants employed by or related to an employee of Juul Labs Inc or PAX Labs Inc were ineligible. Participants provided informed consent and were compensated for their participation. The analytic sample was restricted to established smokers (smoked ≥ 100 cigarettes in lifetime, smoked in the past 30 days, currently smoke 'some days', or 'every day') at baseline who provided follow-up data at one and 3 months.

Procedure

Participants were recruited in 2 ways: (1) study invitation cards were inserted into the packaging of JUUL Device Kits and JUUL Starter Kits; (2) individuals who purchased a JUUL Starter Kit via the online ecommerce platform were invited via a post-purchase study recruitment email. Each invitation carried a unique code that could only be used once. Additionally, to prevent duplicate enrollment, the survey system detected and rejected duplicate logins from the same IP (Internet Protocol) address. Participants completed the baseline survey and subsequently received email invitations to complete follow-up assessments one and 3 months after the baseline assessment. They were not provided with products, but purchased and used them on their own; continuing participation and compensation were not contingent in any way on JUUL use or smoking behavior. All data collection was overseen by the Centre for Substance Use Research (Glasgow, Scotland; www.csures.com), and conducted by Dacima (https://www.dacimasoftware.com/). As Supplemental Figure 1 shows, 10,447 smokers enrolled, 2526 completed one of the 2 follow-ups, and 5246 completed both the one- and 3-month follow-ups.

Measures

Past 30 day JUUL use at follow-up. At the follow-up assessments, past 30-day JUUL use was assessed with the question: "Have you used a JUUL vaporizer in the past 30 days, even one or 2 puffs?" (yes/no). Past 30-day JUUL users were asked how many days of the past 30 they had used JUUL, and how many JUULpods total they had used in the past 30 days, and JUUL dependence questions.

Primary JUUL nicotine concentration used at one-month and 3-month follow-ups. Participants reported the number of JUULpods they used in each flavor and nicotine concentration in the past 30 days (open-ended, continuous). Participants' primary JUUL nicotine concentration (5.0% or 3.0%) was operationalized as the nicotine concentration used most in the past 30 days (ie, the concentration with greatest number of JUULpods). This was computed separately at one and 3 months, as participants could change their use patterns, and thus, their primary concentration over time. Some participants did not have a primary nicotine concentration because they reported using an equal number of JUULpods in each concentration; they were excluded from comparisons by nicotine concentrations at the relevant timepoint. Observations missing the data needed to determine a primary nicotine concentration (N = 13 at one month and N = 65 at 3 months) and the few cases where a

Table 1
Differences in Baseline Smoking Characteristics and Dependence by Switching at One-month and 3-month Follow-up Assessments

Baseline Smoking Characteristics Mean (SD)	Switched at One-month (N = 958)	Not Switched at One-month (N = 4288)	Difference[a] p-value
No. Days Smoked in Past 30 Days	20.94 (10.69)	25.88 (7.83)	< .0001
No. Cigarettes Smoked per Day	10.09 (11.41)	13.87 (12.60)	< .0001
Duration of Regular Smoking, years	14.39 (10.44)	18.66 (12.08)	< .0001
Cigarette Dependence (PROMIS)	2.82 (1.10)	3.15 (0.95)	< .0001
	Switched at 3-months (N = 1498)	**Not Switched at 3-months (N = 3748)**	**Difference[a] p-value**
No. Days Smoked in Past 30 Days	22.77 (9.93)	25.86 (7.89)	< .0001
No. Cigarettes Smoked per Day	11.57 (12.50)	13.82 (12.41)	< .0001
Duration of Regular Smoking, years	15.76 (11.01)	18.74 (12.15)	< .0001
Cigarette Dependence (PROMIS)	2.97 (1.05)	3.14 (0.96)	< .0001

Note.
[a] Differences tested with independent samples t-tests.

1.5% nicotine concentration (available only in Canada) was reported as primary (N = 11 at one month, N = 22 at 3 months) also did not enter into the analyses by nicotine concentration.

Smoking/switching at follow-ups. At each follow-up, participants were asked: "In the past 30 days, have you smoked a cigarette, even one or 2 puffs?" (Yes/No). Reporting "No" past 30-day smoking was designated as "switching." Past-30-day abstinence from smoking has been used in past literature (including PATH) to assess and classify subsequent smoking status in follow-ups of smokers using ENDS.[28]

Cigarette and JUUL dependence. The 4-item PROMIS Nicotine Dependence scale,[29-31] assessing cigarette dependence was administered at baseline. A modified version of the scale adapted for ENDS[17] and reworded to assess dependence on JUUL was completed at follow-up assessments: (1) "I find myself reaching for a JUUL vaporizer without thinking about it." (2) "I drop everything to go out/go online and buy more JUULpods." (3) "I use a JUUL vaporizer more before going into a situation where vaping is not allowed." and (4) "When I haven't been able to use a JUUL vaporizer for a few hours, the craving gets intolerable." All items were answered on 5-point response scales (from 0 ["Never"] to 4 ["Almost always"]); means were used in analysis. A psychometric analysis indicated that the scale was valid for comparison of dependence for smokers and for exclusive JUUL users, but not for JUUL dependence among dual users.[19] Accordingly, analyses focus on JUUL dependence among participants who were not smoking at follow-up (ie, switchers).

Data Analysis

To characterize the dependence measures, Pearson correlations were computed between JUUL dependence and past 30-day JUUL use frequency (days in the past 30) and quantity (number of pods used in past 30 days; log transformed to reduce skewness), at each timepoint. Correlations were computed between cigarette dependence and subsequent JUUL dependence at one and 3 months.

Analyses of changes in dependence were limited by psychometric considerations to those who switched completely to JUUL at each respective follow-up. To document the implications of this selection for baseline cigarette dependence, t-tests compared the baseline cigarette dependence scores and other smoking characteristics for switchers and

Table 2
Sociodemographic, Smoking, and JUUL Use Characteristics of Analytic Sample

Sociodemographic Characteristics	N (%) or Mean (SD)	Number Available[a]
Country		1758
Canada	419 (23.8)	
United States	1339 (76.2)	
Age, years, Mean (SD)	35.93 (10.93)	1758
Sex		1758
Male	984 (56.0)	
Female	767 (43.6)	
Transgender	7 (0.4)	
Race/Ethnicity		1755
Non-Hispanic White	1286 (73.3)	
Non-Hispanic Black	38 (2.2)	
Non-Hispanic Asian	211 (12.0)	
Non-Hispanic Other Race	83 (4.7)	
Hispanic Ethnicity	137 (7.8)	
Marital Status		1753
Married	693 (39.5)	
Divorced, Separated or Widowed	269 (15.3)	
Never Married	791 (45.1)	
Highest Level of Education Completed		1750
High school graduate or less education	389 (22.2)	
Some college or associate degree	750 (42.9)	
Bachelor's degree or more education	611 (34.9)	
Smoking Characteristics		
No. Days Smoked in Past 30 Days, Mean (SD)	22.33 (10.14)	1758
No. Cigarettes Smoked per Day, Mean (SD)	11.29 (12.65)	1758
Duration of Regular Smoking, years, Mean (SD)	15.34 (10.87)	1676
Age Started Smoking Regularly, years, Mean (SD)	18.54 (4.22)	1678
Cigarette Dependence (PROMIS), Mean (SD)	1.93 (1.06)	1722

(continued on next page)

non-switchers at one and 3 months, respectively.

Three primary analyses were conducted: (1) dependent t-tests assessed changes in dependence from baseline cigarette smoking to JUUL dependence among complete switchers at one- and 3-month follow-ups, separately, because smokers'

Table 2 (*continued*)
Sociodemographic, Smoking, and JUUL Use Characteristics of Analytic Sample

Sociodemographic Characteristics	N (%) or Mean (SD)	Number Available[a]
JUUL Use Characteristics at One Month		
No. Days Used JUUL in Past 30 Days, Mean (SD)	27.76 (5.79)	958
Primary users of 3.0% nicotine concentration	26.85 (5.97)	60
Primary users of 5.0% nicotine concentration	28.16 (5.32)	806
No. of JUUL pods used in the past 30 days, Mean (SD)	17.86 (17.22)	952
Primary users of 3.0% nicotine concentration	16.17 (13.09)	60
Primary users of 5.0% nicotine concentration	17.53 (14.33)	806
JUUL Use Characteristics at 3 Months		
No. Days Used JUUL in Past 30 Days, Mean (SD)	26.96 (7.02)	1498
Primary users of 3.0% nicotine concentration	26.57 (7.03)	160
Primary users of 5.0% nicotine concentration	27.36 (6.67)	1198
No. of JUULpods used in the past 30 days, Mean (SD)	19.36 (22.65)	1481
Primary users of 3.0% nicotine concentration	17.49 (14.04)	160
Primary users of 5.0% nicotine concentration	18.74 (15.06)	1198

Note.
Total N = 1758
[a] Number of participants or observations with non-missing data available for the respective variable.
Sample restricted to Current Established Smokers at Baseline who were exclusive JUUL Users at either the one-month or 3-month follow-up assessment and completed both follow-up assessments. Sample sizes for JUUL-use variables based on those using JUUL and reporting details of their use. Subsets for primary users of 3.0% and 5.0% based on those reporting primary use of these nicotine concentrations.

switch status could change between follow-ups; (2) multi-level linear models (MLM) assessed whether such changes in dependence varied by primary nicotine concentration (ie, whether there was a time × nicotine concentration interaction), contrasting participants primarily using the 3.0% or 5.0% nicotine concentration products at the one-month, and 3-month follow-up, separately, as participants could change their primary nicotine concentration between follow-ups, and could switch at one follow-up but not the other; (3) among smokers who switched at both the one-month and 3-month follow-ups (N = 698) MLM models assessed changes in dependence across all 3 timepoints (baseline, Month 1, Month 3), comparing each follow-up to baseline and also comparing Month 3 to Month 1 (nicotine concentration could not be considered in this 3-timepoint analysis because of sample size and changes in concentration across follow-ups).

All statistical analyses were performed using R version 4.0.2 (Vienna, Austria)[32] with alpha = .05 (2-tailed).

RESULTS

Switching and Baseline Smoking Characteristics

The dependence analyses focused on smokers who switched completely at each follow-up. At Month 1, 18.3% of smokers (958/5246) reported switching away from smoking to exclusive JUUL use (no smoking in the past 30 days, JUUL use in the past

Table 3
Association of JUUL System Dependence and Frequency and Intensity of JUUL System Use at One-month and 3-month Follow-up Assessments

JUUL Dependence One-month and 3-month Follow-up Assessment	Past 30-day Frequency of JUUL System Use	Number of JUUL System Pods used in the past 30 days[a]
	r (95% CI)	r (95% CI)
One Month	0.20 (0.14, 0.26)	0.35 (0.29, 0.40)
3 Months	0.26 (0.22, 0.31)	0.34 (0.29, 0.38)

Note.
CI = Confidence Interval; r = Correlation Coefficient
[a] Log-transformed to correct skewness.
Past 30-day frequency of JUUL System use: One-month, N = 958; 3-month, N = 1498.
Number of JUULpods used in the past 30 days: One -month, N = 952; 3-month, N = 1481.

30 days). At Month 3, the proportion that switched increased to 28.6% (1498/5246). The increase was statistically significant (McNemar test, $p < .001$), reflecting the fact that 797 Month-1 smokers had switched at Month 3, whereas only 224 Month-1 switchers had reverted to smoking at Month 3.

Table 1 shows the baseline smoking characteristics of those who had or had not switched completely at one and 3 months, respectively. Those who switched at either timepoint were consistently lighter smokers with shorter smoking histories. Notably, switchers were significantly less cigarette-dependent at baseline, implying that the sample of switchers subject to further analysis of JUUL dependence represent less cigarette-dependent smokers.

Characteristics of the Sample with JUUL Dependence Data

A total of 1798 participants had switched at either follow-up, or both, and provided valid data on JUUL dependence. Approximately three-fourths of these (76.2%) were American, and the average age was 35.93 years (Table 2). The largest proportion was male (56.0%), non-Hispanic white (73.3%), never married (45.1%), and attended some college (42.9%). At baseline, on average, participants reported smoking on about two-thirds of the past 30 days, smoking 11.29 cigarettes per day, initiating regular smoking at around age 18, and having regularly smoked for 15 years.

JUUL Use at Follow-up Assessments and Association with JUUL Dependence

At one month, participants who switched reported, on average, using JUUL 27.76 days (SD = 5.79) out of the past 30 days and using 17.86 JUULpods (SD = 17.22) in the past 30 days (Table 2). At 3 months, participants averaged using JUUL 26.96 days (SD = 7.02) out of the past 30 days and

Table 4
Changes from Baseline Dependence on Combustible Cigarettes to JUUL System Dependence at One- and 3-month Follow-ups among Exclusive JUUL Users at Follow-up

Follow-up Assessment	Cigarette Dependence at Baseline	JUUL Dependence at Follow-up	Difference	Paired t-test
	M (SD)	M (SD)	M	p-value
One Month (N = 958)	1.82 (1.10)	1.59 (0.86)	0.23	< .001
3 Months (N = 1498)	1.97 (1.10)	1.73 (0.82)	0.24	< .001

Table 5
Changes in Dependence from Baseline across Follow-up

Cigarette Dependence at Baseline	JUUL Dependence at One Month	JUUL Dependence at 3 Months
1.86 (1.09)[a]	1.60 (0.85)[b]	1.67 (0.86)[b]

Note.
[a, b] Means with different letter superscripts differ significantly from each other. Those sharing a superscript were not significantly different from each other.
N = 698 participants who had switched to exclusive JUUL use at both one month and 3 months.
Dependence values that do not share the same superscript significantly differ (p < .05).

using 19.36 JUULpods (SD = 22.65) in the past 30 days. At both follow-ups these use parameters were similar for primary users of 3.0% and 5.0% nicotine concentrations (Table 2).

At both one month and 3 months, JUUL dependence was significantly associated with both frequency and quantity of JUUL use, though the correlations were limited in magnitude (r*s* = 0.20-0.35; Table 3).

Dependence on JUUL was moderately related to prior dependence on cigarettes, at both timepoints (1 month: r = 0.44; 3 months: r = 0.38).

Change in Dependence from Baseline Cigarette Smoking to JUUL One and 3 Months Later

As Table 4 shows, among participants who switched completely at the one-month follow-up, levels of dependence decreased significantly from their cigarette dependence at baseline to their dependence on JUUL at one month. Similarly, dependence decreased significantly from baseline cigarette dependence to JUUL dependence at Month 3.

This pattern was also observed among the 698 smokers who switched at both timepoints: JUUL dependence was significantly lower at both Month 1 and Month 3 compared to cigarette dependence at baseline. JUUL dependence did not change significantly between Month 1 and Month 3 (Table 5).

Change in Dependence from Baseline Cigarette Smoking to JUUL Dependence, by Nicotine Concentration Used

At one month, 866 switchers were primarily using either 3.0% or 5.0% nicotine concentrations,

Table 6
Changes from Baseline Dependence on Combustible Cigarettes to JUUL System Dependence at One- and 3-month Follow-ups among Exclusive JUUL Users at Follow-up by Nicotine Concentration

Follow-up Assessment	Primary JUUL Nicotine Concentration	Cigarette Dependence at Baseline	JUUL Dependence at Follow-up	Difference	Primary Nicotine Concentration × Dependence Interaction
		M (SD)	M (SD)	M	p-value
One-month (N = 866)	5.0%	1.85 (1.10)	1.62 (0.84)	0.23	.78
	3.0%	1.77 (1.10)	1.50 (0.90)	0.27	
3-month (N = 1301)	5.0%	1.98 (1.04)	1.75 (0.81)	0.23	.43
	3.0%	1.93 (1.01)	1.63 (0.78)	0.30	

and thus, entered into analyses by nicotine concentration; 93.1% were using 5.0% nicotine concentration. At 3 months, 1301 were using either 5.0% or 3.0%; 87.5% were using 5.0% nicotine concentration pods. Transitions in primary nicotine concentration across months were not uncommon. Among those who had switched completely at either timepoint (ie, those in analyses by nicotine concentration), 26.6% reported a change in primary nicotine concentration at both timepoints. Some (8.6%) transitioned between the 3.0% and 5.0% primary nicotine concentrations (with proportionately more going from 5.0% at Month 1 to 3.0% at Month 3), while others (11.1%) transitioned between having and not having a primary nicotine concentration (equally in each direction). As a result, participants' classification by nicotine concentration often differed between the Month 1 and Month 3 follow-up assessments, and the sample sizes in each cohort varied in the analyses that follow.

The MLM modeling of interaction effects showed that the decreases from cigarette dependence to JUUL dependence did not significantly differ between users of 3.0% and 5.0% nicotine JUUL; this was true at both one month ($p = .78$) and 3 months ($p = .43$; Table 6).

DISCUSSION

This longitudinal study assessed changes in dependence among adult smokers who switched from smoking to exclusive use of JUUL one month and/or 3 months after their initial JUUL purchase, respectively. These smokers showed a significant decline in dependence, from their initial dependence on cigarettes at baseline to their dependence on JUUL one and 3 months later. Moreover, the declines were similar whether participants primarily used JUUL in the higher available nicotine concentration (5.0%) or the lower one (3.0%).

On the raw-score metric of the PROMIS scale, the observed differences were small; among Month-3 switchers, the decline from baseline cigarette dependence and JUUL dependence was 0.23 on the 0-4 scale. However, analyses showed that switching away from smoking at 3 months, an important behavioral transition with likely public health significance, was predicted by even smaller mean differences of just 0.17 in baseline PROMIS scores, on the same, quantitatively-comparable scale. Analyses of the TDI in PATH similarly indicated that small differences in dependence scores were behaviorally meaningful, both cross-sectionally and prospectively.[16,33] Small numerical difference on these scales appear to index meaningful differences in dependence and in subsequent behavioral outcomes.

The observed decreases in dependence as smokers switched from cigarettes to JUUL should be interpreted in light of the fact that these were assessed among smokers who had switched completely away from smoking. Analyses in this sample, and those in a separate sample of JUUL purchasers, show that smokers who switch started with lower baseline cigarette dependence.[24] An analysis of switching among smokers who purchased JUUL, using the PATH TDI scale, showed that smokers who switched subsequently had higher JUUL dependence than did dual users.[24] Taken together, these findings suggest that the present sample would represent a smaller decrease in dependence than would be observed among dual users (ie, from a lower baseline level of cigarette dependence to a relatively higher JUUL dependence, compared to dual users). Additionally, the sample was comprised of smokers who purchased JUUL and were using it frequently (almost daily), which would also suggest higher dependence than might be observed in more intermittent or casual users.

The results of this study are consistent with previous cross-sectional analyses of the PATH study showing that adults exclusively using ENDS demonstrated lower dependence than exclusive cigarette smokers.[14,16] The present study extends our understanding by assessing within-subject *changes* in dependence over time in the same individuals. This longitudinal design inherently controls for interindividual variation, and suggests that dependence declines as smokers transition from smoking to JUUL use. The present data also extend the findings from the whole range of ENDS products evaluated in PATH to JUUL, a nicotine-salt-based ENDS, finding that dependence on JUUL is lower than dependence on cigarettes.

We also found that the decline from cigarette to JUUL dependence among smokers switching completely from smoking to JUUL use did not significantly differ among participants using JUUL in

higher (5.0%) versus lower (3.0%) nicotine concentrations. There was no evidence of compensation among those using the lower-nicotine products, as their reported quantity and frequency of JUUL use were similar. However, it should be kept in mind that participants self-selected the nicotine concentration they used. The data on baseline cigarette dependence by participants' selected nicotine concentration (Table 5) suggests that smokers who were more dependent on cigarettes tended to select the higher nicotine concentration JUUL. Whereas the study did not collect data on how smokers decided which nicotine concentration to use, this observation may indicate that, whether intuitively or with explicit intention, smokers may have made apt self-selection decisions based on their level of dependence on cigarettes. Future research is needed to improve understanding of users' self-selection of nicotine concentrations for ENDS products.

Although the present sample of adult smokers purchasing JUUL reported somewhat-lighter-than-average smoking at baseline, the sample demonstrated levels of baseline cigarette dependence in the range of those in the population. The sample on which the PROMIS measure was developed, which was sampled and weighted to be representative of US adult smokers, averaged a score of 2.0 on the PROMIS scale.[30] Even the smokers who reported subsequently switching (and hence were less-dependent) demonstrated baseline dependence levels close to this score.

The literature offers several potential explanations for why dependence on ENDS (including JUUL) may be lower than dependence on cigarettes. Decades of abuse liability research[1,26,34,35] and more recent population-based analyses[14,16,25] demonstrate that cigarettes are the most addictive tobacco product. Cigarettes contain numerous additives and compounds other than nicotine (eg, ammonia, acetaldehyde, levulinic acid, urea) that have been speculated to contribute to dependence.[36-38] Cigarette smoking also involves a wide variety of multi-sensory stimuli that may contribute to its addictiveness, and smokers in this study typically had years of experience and conditioning to the rituals of smoking.[39,40] Hence, it is possible that dependence on JUUL and other ENDS might increase with experience and exposure to ENDS. It also has been observed that cigarettes in effect force smokers into bouts of puffing (because, once lit, a cigarette will burn down, so must be smoked within about 10-12 minutes), which would lead to substantial peaks in blood nicotine levels. In contrast, some users of ENDS use sporadically or "graze" throughout the day, with smaller bouts distributed more sparsely,[41,42] which would be expected to result in lower peak nicotine levels, even at the same total intake. This may play a role in the reduced dependence on ENDS.

Pharmacokinetic data suggest that the use of the JUUL by smokers results in nicotine delivery that, on average, is substantially less than cigarettes, even in the higher 5.0% concentration,[27,43,44] (although dual users may obtain more nicotine)[45] which in turn delivers significantly more nicotine than the JUUL 3.0%.[27] Additionally, the difference in nicotine delivery between the 5.0% nicotine concentration JUUL product and cigarettes is, on average, much larger than the difference between these 2 JUUL variants.[46] Our data suggest that despite the higher nicotine delivery of the 5.0% (vs 3.0%) JUUL, self-selected users of each experience similar decreases in dependence when transitioning from cigarettes to JUUL.

One implication of the finding that dependence on JUUL is lower than dependence on cigarettes is that smokers who switch completely from smoking to JUUL use (and likely use of other ENDS as well) may find that stopping JUUL use is easier than stopping smoking. Indeed, an analysis of PATH data found that ENDS users who made a deliberate attempt to quit ENDS were twice as likely to succeed compared to cigarette smokers trying to quit smoking, and over a one-year period ENDS users were more than 4 times more likely than cigarette smokers to stop using ENDS (vs stopping smoking).[33]

Data among participants who switched at both Month 1 and Month 3 suggest that JUUL dependence did not change significantly between Month 1 and Month 3 in this continuing-switcher group. Given the evidence that higher JUUL dependence is associated with switching,[47] and the conceptual framework suggesting that a certain degree of dependence is necessary to facilitate smokers' switching away from cigarettes,[5,6] it is possible that such continuing dependence is important to maintaining switching.

It is notable that the proportion of smokers who switched away from smoking increased substantially from Month 1 (18%) to Month 3 (29%). Continuing increases in switching were observed in 2 other large studies of JUUL purchasers, where the majority of smokers reported switching at 6 months[23] or 12 months.[24] This is a different pattern than is observed in smoking cessation studies, where abstinence declines steeply over time,[2] highlighting that the process of switching with ENDS may be quite different than smoking cessation, as traditionally construed. As seen in another analysis of switching with JUUL,[24] some smokers, especially those with more extensive smoking history, take longer to switch away from smoking, suggesting a gradual growth process. It may be that smokers need time to adapt to JUUL as a substitute for cigarette smoking. Another manuscript in this journal issue found that smokers concurrently using JUUL (dual users) substantially reduced their cigarette consumption,[48] so it also may be that smokers work their way to complete switching through a process of gradual cigarette reduction.[49] Importantly, another study of JUUL purchasers found that most were not ready to quit at the time of purchase (defined as planning to quit within 30 days),[24] but nevertheless achieved high switching rates over time, again suggesting that there may be a gradual process for achieving switching. The process of switching away from smoking with ENDS may be different than the process of a smoking-cessation attempt. A similar observation was made by Glasser et al,[50] who noted that smokers may initially adopt ENDS products for a variety of reasons, not necessarily as an aid to cessation in a formal quit attempt, observing a key distinction between intervention trials and naturalistic follow-ups of ENDS adopters such as in the present study.

Our results should be interpreted in light of several limitations. The sample was comprised of smokers who purchased JUUL, and the results may not generalize to other ENDS products. Pharmacokinetic data indicate that nicotine delivery from JUUL is comparable to that of some other marketed ENDS, but higher than others.[45,51-53] In any case, the present data suggest that switching to exclusive use of the nicotine-salt-based JUUL resulted in a decline in dependence compared to smokers' baseline cigarette dependence. The findings here are based on adult smokers 21 and older, and their applicability to youth or to users of other tobacco products is not addressed by these data.

Respondents all purchased the JUUL and volunteered to participate, and may not be representative of the overall population of JUUL users, which is often defined on the basis of any past-30-day use. Some who enrolled in the study did not respond at follow-ups, which could introduce bias in the follow-up samples. It is important to keep in mind that in this naturalistic study, smokers self-selected which nicotine concentration to use. Thus, comparisons based on the nicotine concentration used are between different groups of smokers who made different decisions about which nicotine concentration to use, which complicates the comparison. However, the analyses focused on within-subjects changes over time, comparing cigarette dependence and JUUL dependence in the same individuals. All analyses were based on self-reports, and thus, subject to inherent limitations. Participants completed the baseline survey up to 3 days after their initial JUUL purchase, and it is possible that their smoking behavior might have changed in that time period.

Strengths of the study included its naturalistic design among smokers who made a decision to use and purchase JUUL, and the use of a dependence scale that has been validated to assess both cigarette and JUUL dependence, and for comparison between the 2.

Conclusions

This prospective study of adult smokers who switched completely to JUUL found that dependence declined as smokers transitioned from cigarette smoking to exclusive use of JUUL, and that the declines did not differ significantly by JUUL nicotine concentration of 5.0% or 3.0%.

Human Subject Approval Statement

This study was approved by Advarra Institutional Review Board (Approval no. 00030928, November 21, 2018).

Conflict of Interest Disclosure Statement

NIG, CH, and EMA are full-time employees of Juul Labs Inc. Through PinneyAssociates, SS provides consulting services on tobacco harm reduc-

tion on an exclusive basis to Juul Labs Inc. Within the last 2 years, PinneyAssociates has consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction.

Under contract to JUUL Labs Inc, the Centre for Substance Use Research, an independent research consultancy, designed the study and assessments and oversaw collection of data through Dacima, Inc. CSUR managed, cleaned, and summarized the data. CH performed the statistical analyses under the direction of SS and NG. All of the authors contributed to writing and review of the paper, and had access to the data. The sponsor approved the research plan and provided comment on a near-final draft of the paper.

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Improving Retailer Compliance for Tobacco Purchases: Pilot Study Findings

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Objectives: Those underage should not use tobacco products, including electronic nicotine delivery systems. A technologically-based solution developed by Juul Labs Inc to restrict underage access seeks to automate transactions, structurally mandate age-verification, and limit the quantity of JUUL products purchased per transaction. A pilot of this standards-based approach, referred to as RACS™ (Retail Access Control Standards), was conducted to assess efficacy. **Methods:** RACS was implemented at 171 stores within 3 retail chains selling tobacco products in 3 states. "Secret shopper" compliance audits, in which a mystery shopper attempted to purchase JUUL products, were conducted at participating stores before and after implementation of RACS, to test compliance with age-verification and product-quantity limits. Audit failure rates were compared pre- and post-RACS implementation to assess effectiveness. Comparisons were made overall, by chain, state, and failure type. **Results:** A total of 3990 audits were conducted. We found large, statistically significant reductions ($p < .001$) in failure rates for age-verification and compliance with product-quantity limits after implementing RACS, as compared to pre-RACS rates, declining to near zero. **Conclusions:** Utilizing enhanced access controls can be part of a comprehensive, evidence-based tobacco-control strategy to address underage use of all tobacco products, including JUUL.

Key words: electronic nicotine delivery system; youth prevention; retailer access control standards; JUUL; retailer compliance for tobacco purchases
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Restricting access to tobacco products of individuals under the legal age of purchase (henceforth "youth") is a critical element of tobacco control policy in the United States (US). Following the significant increases in youth use of electronic nicotine delivery systems (ENDS) in recent years,[1] policymakers, regulators, and manufacturers have taken several actions to prevent the sale of ENDS products to minors and restrict access in places where ENDS products are sold.[2] In 2016, the US Food and Drug Administration (FDA) extended its authority beyond combustible cigarettes and smokeless tobacco to include all tobacco products, for the first time restricting the purchase of ENDS to individuals aged 18 years or older. The ruling also required a photo identification (ID) to verify the age of individuals who are under the age of 27 years.[3] Other notable initiatives included state-level tobacco retail licensing laws,[4] the implementation of assurances of voluntary compliance between states and corporate retailers,[5] and legislation requiring age-verification to enter vaping shops.[6] An important development is

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the 2019 passage of federal legislation that raised the minimum-purchasing age for the sale of all tobacco products, including ENDS, from 18 to 21 years nationally.[7] Whereas many restrictions aim to reduce underage access through age-verification initiatives, their effectiveness depends on ground-level compliance by retailers and retail clerks or cashiers. Data suggest that retailers often violate these youth access laws and regulations. Roesler et al[8] demonstrated that nearly 49.8% of tobacco and vape shops failed to check IDs for individuals under 27 years old, and 44.7% of these stores sold products to underage decoys in 2018. Violations were higher for ENDS products than for combustible cigarettes.[8] With regards to the sale of ENDS products specifically, in 2018, the FDA issued warning letters and fines to at least 1300 brick-and-mortar and online retailers that sold ENDS products to minors.[9] In a 2020 study of vape shops in 6 metropolitan statistical areas in the US, Berg et al[10] reported that while 95% of these shops displayed minimum-age signage, only 35.6% of mystery shoppers were asked for ID upon entry and 23.4% upon purchase.

Consistent with this, studies find that underage ENDS users do report obtaining ENDS through purchase. Nationally representative prevalence surveys showed that 15%-30% of youth below the minimum-purchasing age for tobacco products reported purchasing ENDS products directly from retail settings.[11] Similar numbers have been reported for underage purchase of JUUL-brand ENDS products (henceforth: "JUUL") users.[12] These findings confirm limited retailer compliance with age-verification requirements. Restricting access at the point-of-sale among those who are underage is particularly important as these direct purchasers are more likely to be frequent and even daily ENDS users.[13-15]

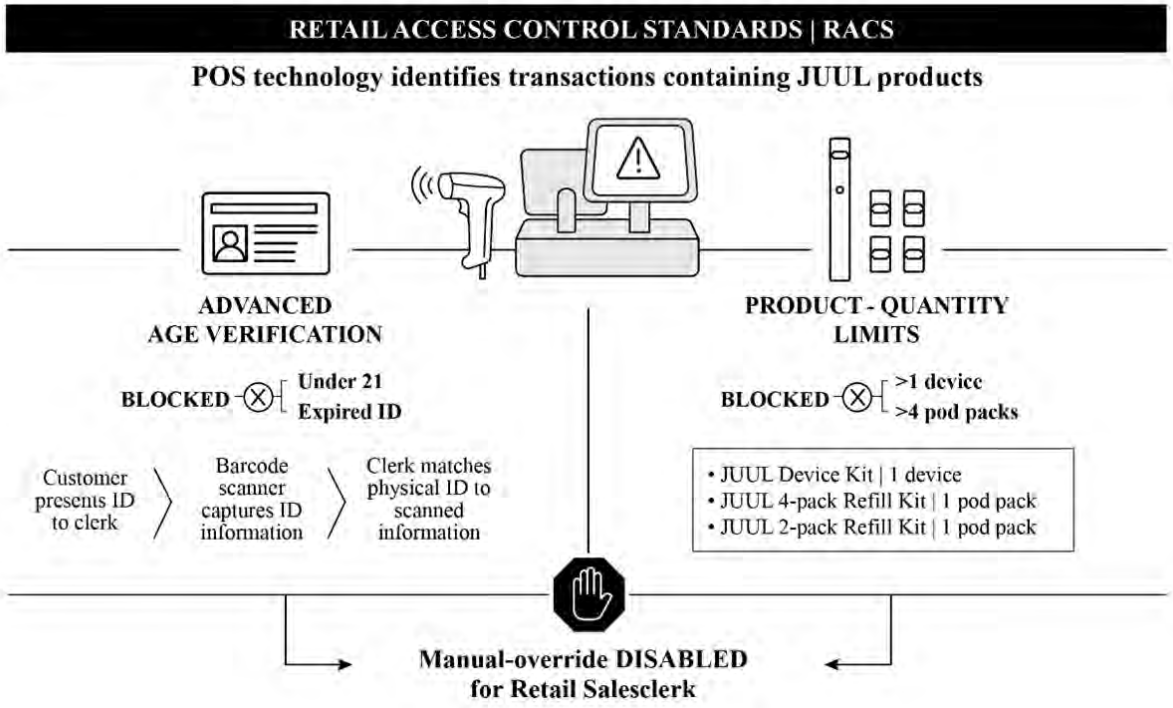
Other underage ENDS users obtain ENDS from other individuals, who are often termed "social sources."[8,12,14,16,17] About half of these social sources are friends.[18,19] This suggests that these social sources could also be impeded by an effective application of age-verification requirements, as most adolescents' friends are same-age peers who would be ineligible to purchase.[20] Moreover, some "social sourcing" actually consists of second-order purchases; that is, youth report buying them from someone else,[12] who has presumably purchased them from a retailer. This suggests that reducing bulk purchases, where a person buys quantities that seem to exceed the needs of personal use and may indicate purchase for sharing or resale, could potentially also block additional sources of youth access to ENDS. These findings suggest that reducing underage purchase of ENDS and bulk purchase of high quantities could help address product leakage to minors.

To address underage purchase, the FDA has recommended that manufacturers and retailers employ effective sales and distribution restrictions.[21] An emerging body of evidence suggests that retail point-of-sale-based measures can be effective in reducing underage access to tobacco products.[22] However, Krevor et al[23] found no effect of equipping retail locations with an ID scanner that was separate from the retailers' POS systems, based on comparing pre- vs post-implementation mystery shopper audits. They suggested that a system better integrated into the sale work-flow might be needed. To this end, Juul Labs Inc (JLI) has developed a standards-based program, tied to the retailer's point-of-sale system, for the sale of the JUUL products that is integrated with the retailers' point-of-sale systems, blocking conclusion of a sale unless an ID is scanned. This program is called RACS™ (Retail Access Control Standards). RACS automatically controls transactions involving JUUL products from beginning to end, ensuring that the retailer verifies the purchaser's age and ID validity and also limits the amount of product that can be purchased to reduce the potential for a purchaser to buy for distribution to others.[23]

RACS has been developed as a standards-based trade program for retailers, software vendors, and other industry stakeholders to adopt within pre-existing point-of-sale-system technology or acquire through new point-of-sale-system technology. A RACS-compliant point-of-sale system (as shown in Figure 1):

- Enforces a mandatory, automated standard (below) for completing a purchase of JUUL; that is, the point-of-sale system will not allow the purchase transaction to complete until the requirements are met.
- Override the block to completing the transaction requires manager approval.
- Requires the electronic scanning of a government-issued ID to verify age. Once an ID is scanned, RACS uses the information encod-

Figure 1
RACS™ Process in Retail Setting



ed in the ID barcode to:

- Check that age in the scanned ID meets the local requirement for minimum purchase age. (Subsequently updated to implement the national minimum age of 21.)
- Check that the ID is not expired.
- Present the clerk with limited information on the point-of-sale display screen, such as the name on the ID, to facilitate detecting modified IDs.
- Limits the amount of JUUL product that can be purchased (ie, currently one JUUL Device and/or 4 packages of JUUL pods per transaction).

In this paper, we report on findings from an initial pilot of RACS implementation in the retail setting, across a small sample of convenience store chains with multiple stores. This pilot was designed as a pragmatic proof-of-concept test to assess the technology and its potential effectiveness of the RACS technology in restricting sales of JUUL products without presentation and verification of an ID (regardless of the apparent age of the consumer), and bulk purchases of JUUL products.

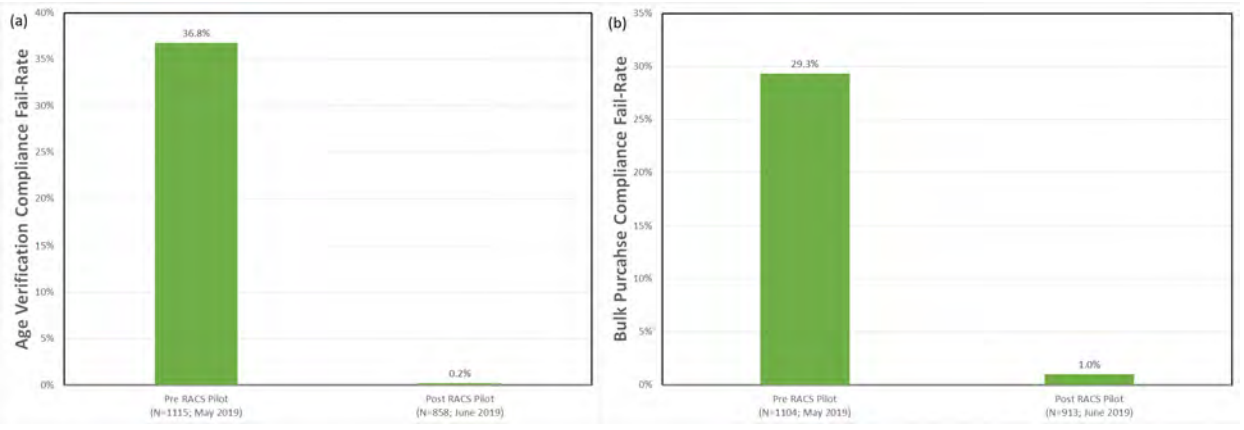
METHODS

Design

The study used a pre-post implementation design, testing the appropriate application of age verification (AV) and bulk purchasing limits (BP) before and again after the implementation of RACS at the participating retail stores. As described below, AV and BP policies were tested separately. The key outcome was the proportion of attempted purchases that failed to pass appropriate checks, for AV and BP, before and after RACS implementation.

Three regional convenience store chains that sell tobacco products, including JUUL products, were recruited to participate in this program, based on their receptivity to pilot new technology and ability to execute in a timely manner. A total of 171 retail stores in 4 distinct metropolitan areas in Pennsylvania, North Carolina, and South Carolina participated. Two retailers had sites in Pennsylvania; the

Figure 2
Overall Age Verification and Bulk Purchase Failure Rates Pre- and Post-RACS Pilot



Note.
(a) Age Verification Failure Rates
(b) Bulk Purchase Failure Rates

third had sites in the Carolinas. This was intended as a pragmatic proof-of-concept test of implementation, not as a generalizable study representative of the US retail landscape.

Implementation

At participating retailers, the point-of-sale systems were updated to comply with RACS. The RACS software is compliant with existing ID scanners, so no changes to the retailer's existing barcode scanners were necessary. JLI created sample training material to explain how the point-of-sale system would operate with the RACS features. Participating retailers trained their employees (training new employees as they were added) on RACS, using materials developed by JLI. To model realistic implementation, training was handled by the retailers, without JLI's direct participation.

As detailed above, a RACS-compliant point-of-sale system included 3 key elements: (1) required presentation and electronic scanning of a government-issued ID to verify age and that the ID was not expired; (2) limited the amount of product that could be purchased in a single transaction; and (3) prevented the completion of a sale if the requirements were not met and restricted manual override by retail salesclerks.

Procedures and Outcome Measures

Compliance was assessed by sending "secret shoppers" to participating stores to attempt to purchase JUUL products. Secret shoppers were provided by a vendor of such services, who assigned participating "shoppers" who were available to visit a participating store; JLI had no role in selecting the secret shoppers. Secret shoppers were required to be age 21 or older. Each individual shopper was randomly assigned a type of check (AV or BP) for their secret shop visit; the 2 kinds of audit were conducted separately.

For AV checks, secret shoppers entered the store and requested JUUL products but did not present an ID. If asked for ID, they would tell the retailer that they did not bring an ID. If they were able to complete the transaction, it was considered an AV failure. Secret shoppers recorded the nature of the failure (eg, the clerk not scanning ID during the transaction, the clerk scanning the clerk's own ID, or other activities that did not follow age verification requirements).

For BP checks, secret shoppers asked to purchase a quantity of JUUL product exceeding the bulk purchasing limits. They could present an ID if asked. If a BP failure occurred, the process (eg, allowing a single transaction above the purchase

Table 1
Stratified Results Comparing AV and BP Failures Pre- versus Post-RACS Implementation

			AGE-VERIFICATION					BULK PURCHASE LIMITS				
			Pre-RACS		Post-RACS		p-value* (pre-post change)	Pre-RACS		Post-RACS		p-value* (pre-post change)
Retail Chain	State	Number of Stores	Number of Audits	Failure Rate	Number of Audits	Failure Rate		Number of Audits	Failure Rate	Number of Audits	Failure Rate	
OVERALL		171	1115	36.8%	858	0.2%	1.1e-36	1104	29.3%	913	1.0%	1.5e-22
1	A	32	190	24.7%	152	0.0%	2.3e-11	217	21.2%	128	0.0%	1.5e-09
	B	30	185	27.6%	170	0.6%	6.6e-14	162	25.3%	143	0.0%	1.5e-10
2	C	53	359	32.3%	245	0.0%	1.8e-15	349	10.6%	308	0.0%	3.4e-07
3	C	56	381	51.4%	291	0.3%	5.9e-26	376	53.2%	334	2.7%	1.9e-22

Note.
*** p-values, expressed in scientific notation, are for the change in audit failure rates from pre- to post-RACS implementation, based on a linear probability model with robust errors clustered at the store level, and fixed effects for retail chain and state. The overall change represents all audits and reflects the overall effect of RACS implementation; other rows reflect the pre-post changes within each retail-chain-state stratum, as an assessment of the robustness and generalizability of the effect within the strata.**

limits, or the store clerk splitting the purchase into several transactions) was recorded.

Pre-implementation audits were made from May 13, 2019 to May 26, 2019. After a period to allow for implementation, post-implementation checks were conducted from June 10, 2019 to June 22, 2019. (Implementation was expected to be completed by June 10, but was not completely done by that date. Accordingly, 504 audits conducted on June 10 had to be dropped, and were not considered further. This resulted in a smaller number of audits in the post-implementation phase than pre-implementation.) Post-implementation compliance audits continued until each retail location received roughly equal number of pre- and post-audits for AV and BP compliance, respectively.

Data Analysis

Audit failure rates for AV and BP, separately, were calculated and compared pre- and post- RACS implementation overall and further stratified by retailer chain and state. Our regression analyses utilized linear probability models, to estimate the effects of RACS on the failure rate of AV and BP audits (separately). That is, the model tested if the probability of an audit failure varied according to whether the audit occurred before versus after RACS implementation. The model controlled for the retail chain and state fixed effects. Robust errors were clustered at the store level to correct for potential correlation of multiple observations from each store. The primary analysis of interest assessed the overall change from before to after RACS implementation, across all stores. As a robustness-check, models also assessed the pre-post difference within each stratum defined by the combination of retail chain and state. Details of the regression model can be found in the Supplement A. All analyses were conducted in Tableau v. 2020.1 (Tableau Software, King of Prussia, PA) and Stata 16.1 (College Station, TX).

RESULTS

A total of 3990 compliance checks, conducted at 171 participating stores, were analyzed. This included 2219 in the pre-RACS period and 1771 in the post-RACS period. Figure 2 presents failure rates overall across stores pre- and post-RACS implementation, separately for AV (Panel a) and BP (Panel b). Prior to implementing RACS, the overall AV failure rate across stores was 36.8% (N = 1115 audits). During the test, the failure rate was reduced to 0.2% (N = 858 audits), and this reduction was statistically significant ($p < .001$). The primary reason provided by secret shoppers for AV failures that occurred in the post-RACS period was the clerk scanning their own ID when the secret shopper indicated that they did not bring a valid ID.

Similarly, the overall BP failure rate across stores was 29.3% (N = 1104) in the pre-period and was reduced to 1.0% (N = 913) in the post period. This change was also statistically significant ($p < .001$). Post-implementation BP failures primarily occurred due to initially incorrect system configuration during the retailer's roll out of RACS to participating stores.

As a robustness check of the audit failure reductions seen in the overall sample, Table 1 reports failure rates of pre- and post-RACS periods within each possible retailer and state combination. The reductions in both AV and BP failure rates were tested and demonstrated highly significant in all strata (Table 1).

DISCUSSION

Tobacco products, including ENDS such as JUUL, should be accessible only to adults of legal-purchase age. Nonetheless, as the data have shown, those who are underage still have been able to access ENDS, contributing to use among adolescents. The core objective of RACS is to reduce underage access to, and ultimately use of, JUUL products through traditional retail channels, by addressing main underage access points – lack of age-verification among retailers and bulk purchase with subsequent distribution – as channels by which youth obtain JUUL products. This pilot study was intended as a proof-of-concept to assess the feasibility and potential effect of automated controls at the point-of-sale to improve retailer compliance with laws and regulations regarding age-verification and also limit bulk purchases that may also be a source of youth access.

The results provided preliminary, promising evidence that enhanced access controls such as RACS could enforce age-verification and limit bulk purchase at retail. Based on 3990 point-of-sale audits, we found large and statistically significant reductions in the failure rates for AV and BP after the implementation of RACS. Failures to require ID for age verification declined to near zero once RACS was implemented. Similarly, bulk purchases exceeding the single-purchase limits also dropped to near zero after implementation. Furthermore, these findings were consistent across retail chains and states. These positives findings contrast to those of Krevor et al.[23] The key difference may be the integration of RACS into the point-of-sale systems, making ID scanning an automatic part of the retail sales workflow.

It is interesting to compare these results with the findings of FDA's compliance-check inspections for age-verification.[4] (There is no legal limit on bulk purchase, and thus, the FDA's audit program does not cover BP.) As described in the Supplement B, the FDA's data on AV failures for the year prior to the RACS pilot (May 2018-May 2019) resulted in lower estimates than reported here (14% overall, and 3.8% for one of the retailers in the RACS pilot). This is not surprising, as the FDA's audits differ in material ways. Importantly, FDA's compliance-check inspection program often uses shoppers who are underage (ages 16-17) to make illegal purchases, whereas RACS did not (as it would be illegal). Retail clerks may be more likely to ask for ID when the shopper is clearly too young. Thus, the 2 metrics are not comparable. Nonetheless, the FDA rates serve as a general benchmark of the existing level of AV failures in retail – a benchmark that the post-implementation RACS data improved upon.

These preliminary findings suggest that a technological approach can be both feasible and effective in reducing underage access to, and therein, lowering the potential for underage use of tobacco products. The findings are in line with previous research demonstrating the efficacy of retail-based measures to control youth access to tobacco products.[4,25-31] Our study is distinct in that we have developed and tested a novel, technologically-based solution that has the flexibility to be adopted within pre-existing point-of-sale-system technology or acquired through new point-of-sale-system technology, which may facilitate its adoption in the existing retail system.

There are several limitations of this pilot study. First, the follow-up compliance measures were taken shortly after RACS implementation, and as such, our results may not generalize to the long-term effectiveness of RACS. Second, the pilot study was limited to assessing stores that implemented RACS pre- and post-implementation. There was no control group of stores to compare in the same time period; as such, we cannot attribute the entire decline in failure rates in the post-RACS period to the implementation of the program, as other ongoing trends relevant to compliance may have contribut-

ed to this reduction. Third, the pilot study assessed compliance only for JUUL products, and did not implement RACS or assess its effect on other tobacco products (eg, cigarettes, cigars, other ENDS, smokeless tobacco products) or other products that are age-restricted (eg, alcohol and some caffeinated beverages). Implementing RACS, even just for JUUL products, may affect how retailers conduct age-verification for non-JUUL products, and the pilot data did not speak to these broader impacts. Lastly, retail chains participated based on their interest in RACS, so the sample of retailers may not be representative of all relevant retail outlets.

Future studies are needed to improve understanding of the effect of solutions such as RACS on restricting youth access to tobacco products. It is important to note that this pilot study was designed to test the effectiveness of RACS to control access, rather than to assess explicit changes in retailer behavior or reductions in underage purchase attempts. Additional research is needed to demonstrate that implementing sales and distribution controls has a downstream impact on youth access.

The pilot study also provides some insight on potential improvements that could enhance this type of solution. For instance, the few age-verification failures we observed in our study after the implementation of RACS were due to store clerks using their own IDs to complete a transaction. Improvements in education, training, compliance monitoring, and technological developments, might address this gap in the enforcement of age-verification.

Further technological developments might also improve the system's capabilities. JLI's current RACS program limits the amount of product that can be purchased in a single transaction, but does not store purchasers' information, which precludes blocking individuals from conducting multiple transactions across different retailers to acquire a bulk amount of the product. To circumvent this issue, network-based approaches could be developed to enable automated product-quantity limits across retailers that sell JUUL products by using unique, anonymized identifiers to track purchases across different retailers. The RACS system does verify the validity of scanned IDs by ensuring that the information on the face of the ID matches what is encoded in the barcode on the back of the ID, but it is possible that, eventually, a net-connected solution could further validate IDs by cross-referencing publicly available records or other data sources to identify fake IDs.

We note that RACS and other technological solutions are only a part of a broader range of sales and distribution restrictions and marketing controls that can be pursued in tandem by manufacturers, retailers, policymakers, and regulators. The 2019 law[25] raising the minimum-purchasing age of tobacco products to 21 years also should lead to a reduction in direct retail purchases by youth users, as well as a reduction in social sourcing among high schoolers, as few, if any, can now legally purchase ENDS products.[27] These interventions can most effectively limit access when applied for all tobacco products. Additional manufacturer actions recommended by the FDA, include "screening retailers, in advance of establishing or renewing distribution agreements, based on the strength of the retailers' age verification policies; [and] establishing and publicizing a hotline for anonymous reporting of noncompliant sales"[21] also may be effective as part of a portfolio of access controls that could reduce underage use. But, as noted here, an automated solution that requires age-verification and limits the amount of product that can be purchased can ensure effective compliance.

The favorable results of this pilot study have informed efforts that are underway to implement RACS and additional solutions premised on enhanced access controls nationally across all retailers of JUUL products. Currently, electronic ID scanning (updated to meet the national Tobacco-21 minimum legal age for purchase) has been implemented at over 50,000 retail outlets selling JUUL products. Through future software updates, automated product-quantity limits to restrict bulk purchases ultimately will be implemented as well. Moreover, legislative or regulatory policies that incorporate such requirements (eg, electronic scanning of IDs) can help facilitate and accelerate adoption, so long as technology is readily available across retailers and reasonable timelines for implementation are considered.

Conclusions

In this proof-of-concept pilot test of RACS, implementation nearly eliminated failures of compliance with age-verification and failures to enforce

bulk-purchasing limits. This suggests that broader implementation of this type of enhanced access controls can effectively reduce transactions that could be sources of underage access to tobacco products. Brick-and-mortar retail continues to be an access point for ENDS products among those who are underage – either for lack of age-verification or bulk purchases of product that, in turn, are resold or shared among underage users. Automated, technological solutions at the retailer's point-of-sale to restrict sales of tobacco products, including JUUL products, to adult consumers aged 21 years or older may help reduce underage use. Given the feasibility of such solutions, these requirements (eg, electronic scanning of IDs) could be implemented through public policy to address underage use as part of a comprehensive, evidence-based strategy.

Human Subjects Statement

Institutional Review Board approvals were not required, as no human subjects were involved in this manuscript.

Conflict of Interest Statement

TC, AZ, JJ, and PK are full-time employees of Juul Labs Inc. SP was a full-time employee of Juul Labs Inc during the time that this work was conducted. Through PinneyAssociates Inc, SS provides consulting services on tobacco harm reduction on an exclusive basis to Juul Labs Inc. Within the last 2 years, PinneyAssociates Inc has consulted for British American Tobacco and Reynolds American Inc and subsidiaries on tobacco harm reduction.

TC performed the statistical analyses under the direction of SP and SS. All of the authors contributed to writing and review of the paper, and had access to the data. The sponsor approved the research plan and provided comment on a near-final draft of the paper.

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Supplement A

Regression Models

We use linear probability model regressions to estimate the effects of the implementation of RACS on the failure rate of complying age verification or bulk purchase limit requirements and report corresponding p-values in Table 1 of the paper:

$$y_{irst} = \alpha RACS_{it} + \beta_r + \gamma_s + \varepsilon_{irst},$$

where y_{irst} is an indicator variable that takes value 1 if audit i recorded a failure (AV or BP) in chain r in state s in time t and 0 otherwise. $RACS_{it}$ is a dummy that takes the value 1 if audit i in time t occurred after the implementation of RACS and 0 otherwise, and α is our interested coefficient for the overall average treatment effect. Retailer and state fixed effects have been controlled by β_r and γ_s, respectively. Robust errors are clustered at the store level to correct for potential correlation of multiple observations from each store. Moreover, the linear probability model allows us to estimate the effects of RACS for each possible retailer-state combination as:

$$y_{irst} = \sum_{rs} \alpha_{rs} RACS_t + \beta_r + \gamma_s + \varepsilon_{irst},$$

where α_{rs} provides estimates for different retailer-state combinations. In this pilot, we have in total 4 of them, which are Retailer 1 State A, Retailer 1 State B, Retailer 2 State C, and Retailer 3 State C.

The standard regression results are summarized in the following table, with first 2 columns for AV and last 2 columns for BP. Column (1) and (3) report overall effects as 36.4% reduction in AV failure rate and 28.8% reduction in BP failure rate. Column (2) and (4) provide estimated effects for each possible chain-state stratum as a robustness check.

Table S1
Regression Results on AV and BP Failure Rates

	(1) AV	(2) AV	(3) BP	(3) BP
Overall Effects				
RACS	-0.364*		-0.288*	
	(0.0222)		(0.0254)	
Effects within Chain-state Strata				
RACS*1(Retailer 1 and State A)		-0.247*		-0.212*
		(0.0345)		(0.0331)
RACS*1(Retailer 1 and State B)		-0.270*		-0.253*
		(0.0330)		(0.0371)
RACS*1(Retailer 2 and State C)		-0.323*		-0.106*
		(0.0368)		(0.0200)
RACS*1(Retailer 3 and State C)		-0.511*		-0.505*
		(0.0407)		(0.0446)
Observations	1973	1973	2017	2017
Adjusted R^2	0.220	0.236	0.219	0.270

Note.
The parameters approximate the change in the proportion of audits that failed, from pre- to post-RACS. All specifications have controlled for chain and state fixed effects. Robust standard errors (in parentheses) are clustered at the store level. Asterisks * indicate p < .00001. See Table 1 in the paper for actual p-values.

Supplement B

US Food and Drug Administration (FDA) Undercover Buy Inspections

To monitor retailers' compliance with Federal tobacco laws and regulations, the FDA conducts its own secret shopper compliance check program, called Undercover Buy Inspections, for age verification.[1] The FDA is permitted to use legally underage shoppers to conduct inspections, and does so. These minors, trained for the purpose and working with commissioned FDA inspector, attempt to purchase regulated tobacco product without identifying themselves to retailers.[2] The FDA takes corrective action when violations occur, including warning letter, Civil Monetary Penalty, or No-Tobacco Sale Order.

To provide an external measure of benchmark, we obtained data on AV failures both overall and for comparable convenience store retailers for the full year prior to the RACS pilot (May 2018-May 2019; to achieve a reliable estimate and damp out any seasonal effects) from the FDA database.[1] Any instance of a warning letter, Civil Monetary Penalty (CMP), or No-Tobacco Sale Order issued by FDA upon secret shop inspection for age verification was counted as a failure. Failure rates were calculated from the data overall, for the subset of convenience stores and gas stations to be analogous to stores in our sample, and specifically for Retailer 1, as insufficient data were available to calculate a failure rate for the other chains.

The table below shows the age verification failure rates reported by the FDA in the year prior to the RACS pilot, which was 13.5% overall, 14.4% among convenience stores and gas stations only, and 4.0% for retailer 1. Although these failure rates are lower than our pre-RACS-implementation AV failure rates, the FDA rates are still much higher than the post-RACS AV failure rates, as shown in Figure 2(a) of the paper. As the FDA does not mandate product purchasing limits, no similar data for BP failures were available to assess.

Unfortunately, it is not possible to get robust estimates for the post-period from the FDA system. To get pre-period estimates, we analyzed a full year of FDA audit data. This was not possible for the post-test, for 2 reasons. First, the onset of E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI) in August 2019 had a major impact on ENDS risk perceptions and sales, disrupting valid trending. Subsequently, the FDA was forced to stop its program in March 2020 due to COVID-19.

It is worth noting 2 crucial differences between the FDA Undercover Buy Inspections and the secret shopper program we employed for this pilot as: (1) the FDA is permitted to use legally underage shoppers to conduct age verification tests (while manufacturers are not, and therefore RACS did not), and (2) the FDA age verification program is designed to test adherence to the federal standard for checking ID if a shopper appears to be below age 27, rather than meeting the requirements of advanced AV under RACS. Due to the 2 crucial differences between the FDA Undercover Buy Inspections and this pilot, we did not perform any statistical comparisons, but we nonetheless use this measure as a relevant benchmark of existing failure rates for underage purchases. The comparison between the post-RACS age verification failures, which were near zero, and the pre-RACS FDA audit failures are consistent with the conclusion that RACS improved compliance with age verification.

Supplementary References

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Table S2
FDA Undercover Buy Inspections Age Verification Failure Rate, May 2018 to May 2019

Variable Name Original	N	Number of Passes	Number of Fails	Failure Rate
FDA: All Retailers	151,300	130,894	20,406	13.5%
FDA: Convenience Stores and Gas Stations	48,152	41,299	6853	14.2%
FDA: Retailer 1	354	340	14	4.0%

Modeling the Population Health Impact of ENDS in the U.S.

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Objectives: Our objective was to improve understanding of the population health impact of electronic nicotine delivery systems (ENDS) availability in the US via computational modeling. **Methods:** We present an agent-based population health model (PHM) that simulates annual smoking, ENDS use, and associated mortality for individual agents representing the US population, both adults and youth, between 2000 and 2100. Model transitions were derived from key population surveys and a large longitudinal study of JUUL purchasers. The mortality impact of ENDS is modeled as excess risk relative to smoking. Outcomes are compared between a cigarettes-only Base Case and a Modified Case where ENDS are introduced in 2010. Model validation demonstrates that the PHM simulates population-level behavior and outcomes realistically. **Results:** The availability of ENDS in the US is projected to reduce smoking and prevent 2.5 million premature deaths by 2100 in the Modified Case. Sensitivity analyses show that a significant population health benefit occurs under all plausible scenarios. **Conclusions:** Our results suggest the availability of ENDS is likely to result in a significant health benefit to the US population as a whole, after accounting for both beneficial and harmful uses.

Key words: population health modeling; agent-based model; electronic nicotine delivery system; smoking; harm reduction
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Although smoking prevalence in the United States (US) has declined over the past 5 decades, about 34 million US adults, nearly one in 7, are still current, established cigarette smokers.[1] Smoking represents a major public health concern and the leading preventable cause of mortality in the US, resulting in approximately 480,000 premature deaths each year.[2-5]

Over the last decade, electronic nicotine delivery systems (ENDS) have emerged as a potential harm reduction alternative for smokers to obtain satisfying levels of nicotine without using combustible cigarettes.[6-8] A growing body of evidence points towards significant rates of complete switching away from combustible cigarettes to ENDS by adult smokers,[8-11] exposing them to reduced levels of carcinogens and toxicants compared to cigarette smoking.[7,12-15] Whereas the exact long-term health effects of ENDS use are not yet known, reviews of the available scientific evidence suggest that they may be much less harmful than combustible cigarettes.[14,16,17] For example, the UK Royal College of Physicians concluded "[a]lthough it is not possible to quantify the long-term health risks associated with e-cigarettes precisely, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products, and may well be substantially lower than this figure."[17] As such, ENDS may present a promising new tool in the arsenal of tobacco control in-

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terventions to reduce the harm caused by cigarette smoking.[6,18-21]

Besides their potential benefit, ENDS are also a source of potential harm. Although their use is likely much less harmful than that of combustible cigarettes, it is not without risks.[7,12,15-17] The best outcome for any smokers is complete cessation of tobacco and nicotine use. Moreover, concerns exist about ENDS use by groups that would not have otherwise smoked, even in the absence of ENDS.[7,17,20-22] Examples of these undesirable uses are diversion of would-be quitters, initiation among non-nicotine users, and progressions of non-smokers from ENDS use to cigarette smoking.

A particular area of concern has been a high level of ENDS use among youth (those under age 18) and young adults (ages 18 to 24) in the US in recent years,[23-25] as ENDS have become the most frequently used tobacco product among those underage. Likewise, concerns exist about transitions from ENDS use to cigarette use by some users who would not have started smoking otherwise.[21] A number of studies have indicated the potential for such progressions and found correlations between ENDS use and subsequent cigarette smoking, raising the possibility of a 'gateway effect'.[7,26,27] Other authors have found that smoking prevalence has continued to fall, including among youth and young adults, even while ENDS use has increased[28-30] and some studies have even raised the possibility of a diversion effect.[31] Overall, these remain highly active areas of research with critical implications for public health.

Given the potential for ENDS to be a source of both benefit and harm, it is important to assess the overall population-level impact of ENDS based on the "risks and benefits to the population as a whole, including users and nonusers of the tobacco product."[32] Population modeling via computational and statistical techniques is well-suited to enable such an assessment.[20,21,33-37] It offers a systematic, quantitative method for integrating empirical data on population demographics, tobacco product use and transitions, and tobacco-related health risks, and projecting the population impact under a variety of scenarios. As such, population modeling has been used by public health researchers,[20,21,33-38] the majority of which have found a positive population mortality impact of ENDS availability (see also 'Discussion'), and in recent regulatory applications in line with recommendations from the US Food and Drug Administration (FDA).[32,39]

The evolving tobacco product landscape (eg, changes in availability and use of ENDS), changing regulatory policies (eg, the December 2019 increase of the federal minimum purchasing age of tobacco products to 21[40] or the January 2020 FDA guidance to change enforcement discretion for non-tobacco, non-menthol flavored cartridge-based ENDS products to remove such products from the US market[41]), and remaining uncertainties of the long-term health effects of ENDS use present additional challenges for a reliable assessment of the population health impact. Population modeling can address these via extensive sensitivity testing of key model inputs and by exploring of a wide variety of possible future scenarios.[20,21]

In this paper, we present an agent-based population health model (PHM) that models the impact of a category of ENDS on cigarette smoking and population mortality in the US between the years 2000 and 2100, considering both beneficial and harmful impacts of ENDS. The PHM is based on an agent-based modeling framework and code base originally developed by Muhammad-Kah et al (as summarized in Lee at al[42]). After defining a Base Case with only cigarettes available and a Modified Case with cigarettes and ENDS, we derive transition rates from surveys such as the National Health Interview Survey (NHIS),[29] the National Youth Tobacco Survey (NYTS),[43] and the Population Assessment of Tobacco and Health (PATH),[44] as well as a more recent, large-scale, longitudinal study of first-time purchasers of a JUUL Starter Kit (Adult JUUL Switching and Smoking Trajectories [ADJUSST]) Study, described in Shiffman et al.[45] The JUUL System – henceforth "JUUL" – is a pod-based closed-system ENDS brand with a nicotine salt formulation. We use model validation to compare the prevalence of smoking and ENDS use retrospectively projected by the PHM to historic data for the years 2000 to 2019, demonstrating the model's ability to simulate real-world tobacco use trends. To address uncertainties around key transition rates and the long-term health effects of ENDS use, we conduct extensive sensitivity testing and scenario analyses.

METHODS

Model Structure and Outcome Measures

The PHM simulates cigarette smoking and ENDS use for a hypothetical population of individuals (*agents*) by modeling annual transitions between different tobacco use states. Such agent-based models are appropriate tools for the analysis of tobacco use given their potential to capture the heterogeneity across individuals and to evaluate population-level outcomes based on aggregating individual-level behaviors over time.[36,42,46] By keeping track of each agent's history of smoking and ENDS use, and estimating the associated individual mortality impact of time spent in each tobacco use state, the PHM is able to project tobacco product use prevalence and mortality over time on an individual as well as a population-level aggregated basis. Agents in the PHM are non-interacting, ie, our model is more similar to a highly granular cohort or microsimulation model than a "full" agent-based model with complex inter-agent interactions.[42]

We focus on combustible cigarettes and ENDS as the only tobacco products in the simulation to address the specific question (impact of ENDS), while reducing complexity. Transitions between other categories of tobacco products (eg, smokeless tobacco, heated tobacco) and ENDS in the US have been varied or negligible.[47] This simplification is consistent with other population modeling work.[20,35,48,49]

At initialization, a population of 282,000,000 agents, representing the US population, is generated based on the distribution of age, sex, and cigarette smoking history in the US in the year 2000 as measured by US Census, NHIS, and NYTS.[29,43,50] Starting in the year 2000 allowed us to validate the model by comparing (retrospective) model projections to historic data between 2000-2019.

The PHM advances in one-year time steps, during which each agent has a mortality probability and a probability of transitioning out of their current tobacco product use state into a new one. These probabilities are based on each agent's individual attributes and tobacco use history. At the end of each one-year time step, new agents are added to the model to account for births and immigration.[50,51]

Primary outcome measures are the annual and cumulative premature deaths, defined here as deaths between the ages 35 and 85, and the annual prevalence of tobacco product use. Premature deaths are a measure of population mortality commonly used in the study of tobacco use and harm reduction.[34,42,48,52] (We note here that the exact value of the age cutoffs – eg, choosing precisely 85 as the upper limit – impacts the numerical values of projections but does not meaningfully alter the overall direction and magnitude of findings.) These outcome measures in the PHM can be computed for the population as a whole or for specific subgroups (eg, by age or sex).

Scenarios: Base Case and Modified Case

To explore the overall population-level health impact of ENDS in the US, the PHM compares 2 different scenarios, both starting in the year 2000: a *Base Case*, in which only combustible cigarettes are available, and a *Modified Case*, in which ENDS are introduced after the year 2010, when their use became more prevalent.

The difference in cumulative premature deaths between the Base Case and the Modified Case gives a measure for the net population health impact of ENDS. Both scenarios are run until the year 2100 to account for long-term health effects of tobacco use, which can take decades to manifest. This approach is consistent with other population modeling work, including by Apleberg et al,[38] Levy et al,[34,35] and Warner and Mendez.[20] The PHM also compares prevalence of exclusive smoking, exclusive ENDS use, and dual use between the 2 scenarios.

Tobacco Use States and Transition Rates in the Base Case

In the Base Case, agents can be never, current, or former cigarette smokers (Figure 1, Panel A). The PHM considers 'current use' of cigarettes to mean any use in the past 30 days combined with having smoked at least 100 cigarettes in one's lifetime, a common criterion for established smoking. (The PHM focuses on established smoking as the overwhelming driver of smoking-related mortality. Experimental smoking can be important for behavioral analyses, but its impact on mortality is expected to be minor, except to the extent that it leads to established smoking.) Initiation of smoking, ie, transitioning from being a never (established) smoker to being a current established cigarette

Table 1
Adult Transition Rates in the Base Case and Modified Case in 2019

Case	From	To	Transition	Rate	Data Source(s)
Base	NU	CC	Smoking Initiation	1.8%[a] [18-24 y/o]	CISNET/NHIS
Modified	NU	CC	Smoking Initiation	1.3% [18-24 y/o]	PATH + CISNET/NHIS
Modified	NU	CD	Dual Use Initiation	0.2% [18-24 y/o]	PATH + CISNET/NHIS
Modified	NU	CE	ENDS Initiation	1.8% [18-24 y/o]	ADJUSST + PATH
Modified	CE	CCFE	ENDS To Smoking	1.6%	ADJUSST + PATH
Modified	CE	CD	ENDS To Smoking	9.9%	ADJUSST + PATH
Modified	CEFC	CCFE	Smoking Relapse (from ENDS)	1.5%	ADJUSST + PATH
Modified	CEFC	CD	Smoking Relapse (from ENDS)	8.6%	ADJUSST + PATH
Modified	CC	CEFC	Full Switching (from Smoking)	2.4%	ADJUSST + PATH
Modified	CCFE	CEFC	Full Switching (from Smoking)	3.2%	ADJUSST + PATH
Modified	CC	CD	Transition to Dual Use	1.5%	ADJUSST + PATH
Modified	CCFE	CD	Transition to Dual Use	1.8%	ADJUSST + PATH
Modified	CD	CEFC	Full Switching (from Dual Use)	34.0%	ADJUSST + PATH
Modified	CD	CCFE	Transition to Exclusive Smoking	16.0%	ADJUSST + PATH
Base	CC	FC	Smoking Cessation	2.9% [a]	CISNET/NHIS
Modified	CC	FC	Smoking Cessation	3.0% [a]	CISNET/NHIS + PATH
Modified	CCFE	FD	Smoking Cessation	3.0% [a]	CISNET/NHIS + PATH
Modified	CD	FD	Dual Use Cessation	3.0% [a]	CISNET/NHIS + PATH
Modified	CE	FE	ENDS Cessation	6.0%	ADJUSST + PATH
Modified	CEFC	FD	ENDS Cessation	6.0%	ADJUSST + PATH

Note.
See Figure 1 for full list of abbreviations
[a] Transition rate varies by age and/or sex. The number shown is the average across all applicable ages and sexes.

smoker, is possible for agents aged 12-24. This cut-off is a commonly used[36] simplifying assumption based on data showing that initiation of cigarette smoking and new tobacco use in never regular users is substantially less likely after 24 years of age.[53]

Regarding 'former use', we note that relapse rates among smokers trying to quit are high and most do not succeed at long-term abstinence.[54] For those that are able to quit for 2 or more years, relapse rates reduce drastically.[55] The latter (sub)group members, who have made a sustained behavior change, are what the PHM considers former smokers. Consequently, the transition rate for current to former smokers is based on only the share of smokers that successfully quit for 2+ years, and the reverse transition rate is set to zero (as short-term relapse is already captured in the reduced cessation rate). This approach is consistent with other work in the literature.[21,48,53]

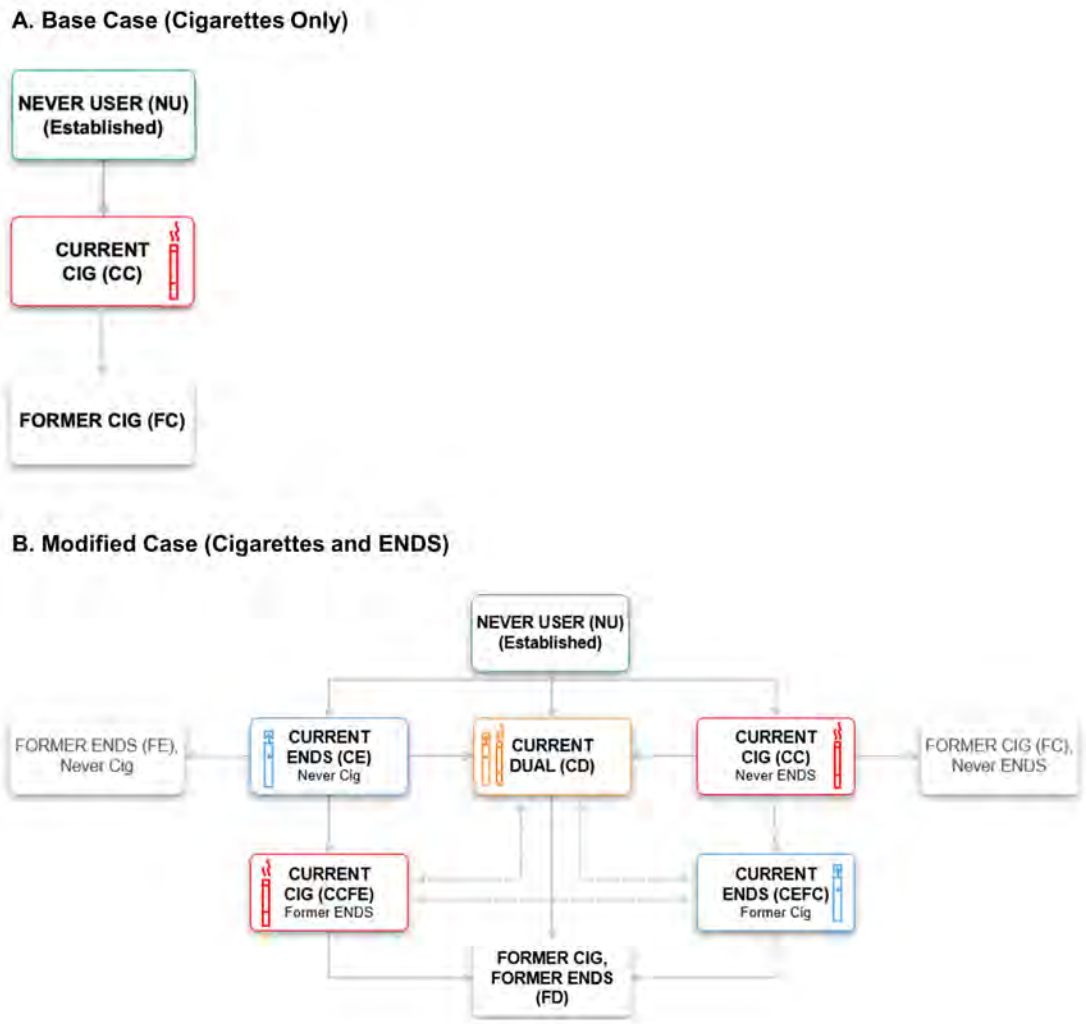
Smoking initiation and cessation rates in the Base Case are taken from analysis of NHIS data conducted by the Cancer Intervention and Surveillance Modeling Network (CISNET).[56] Annual rates are applied from 2000 until 2010, at which point the 2010 rates are used going forward to model the (hypothetical) Base Case scenario where ENDS were never introduced.

As examples, see Table 1 for adult transition rates in the year 2019 and Supplemental Table S1 for youth transition rates in the year 2019.

Tobacco Use States and Transition Rates in the Modified Case

In the Modified Case, there are 9 tobacco use states and consequently a larger number of possible transitions (Figure 1, Panel B). Similar to smoking, the PHM considers 'current ENDS use' among adults to mean any past 30-day use and having 'ever fairly regularly used ENDS' (as the equivalent of

Figure 1
Tobacco Use States (Rectangles) and Possible Transitions (Arrows) in the PHM



the 100+ cigarettes lifetime criterion). For youth, any past 30-day ENDS use is considered current use in the PHM, even though data indicate that the majority of this use is infrequent and experimental.[23,43,57-59] Transition rates into ENDS use are scaled in linearly over 5 years beginning in 2011.

Similar to the Base Case, initiation of tobacco use (here, smoking or ENDS use) is possible for ages 12-24. For cessation of established smoking and ENDS use, we again consider long-term successful cessation only. Switching between tobacco products and cessation of any past 30-day use (in the case of youth ENDS use) is permitted on a yearly basis. In addition to CISNET/NHIS and NYTS, 2 additional data sources are considered for transition rates: Waves 1 to 4 from PATH with over 49,000 respondents covering years 2013 to 2018 (transition rates primarily use waves 3 to 4, with the earlier waves being used for calibration and analyses of specific patterns, such as the relationship between device ownership and established use),[44] as well as the retail portion (which represents the vast majority of sales volume) of a large-scale, one-year longitudinal study of adult JUUL purchasers

(ADJUSST) covering years 2018 to 2019 with over 22,000 respondents.[45,60]

Using ADJUSST for adult transition rates means we are able to incorporate more recent data than available in PATH up to Wave 4. Specifically, this is meant to capture use behavior of JUUL, which in recent years was the largest ENDS brand in the US and accounted for a meaningful portion of all ENDS use,[61,62] and possibly other, newer ENDS products. In other words, the PHM models a category of ENDS products whose use patterns and behavioral transitions is meant to reflect the most recent generation of ENDS products on the US market – with JUUL, the largest single brand, as one particular example. Incorporating ADJUSST data led to slightly higher initiation among never users, a significantly higher share of full switching compared to dual use, and lower rates of "switching back" from ENDS use to dual use or exclusive smoking. Additional details of calculations are in the Supplement Section 1, (Additional Details on Transition Rate Calculations). The design and methods of ADJUSST, including analyses of response bias, are described in detail in Shiffman et al[45] and additional papers analyzing different subgroups, such as current smokers,[11] dual users,[63] former smokers,[64] never smokers,[65] and transitions among the overall sample of respondents.[60]

For youth use, transition rates were derived from PATH Waves 3 to 4, which coincided with a significant increase in ENDS use among youth.[43,66] However, because the PATH-derived ENDS initiation rates were much lower than what was needed to reproduce ENDS use prevalence as reported in NYTS, they were scaled up significantly to calibrate youth prevalence of ENDS use against NYTS data from 2011–2019, while scaling down by half as much the subsequent transitions to not artificially inflate youth smoking rates. Analyses of PATH were also used to model the share of past 30-day youth ENDS users that go on to become established adult ENDS users once they turn 18.

Table 1 shows adult transition rates in the year 2019 and corresponding youth transition rates are included in the Supplemental Table S1.

Modeling the Impact of Tobacco 21 and Underage Use Prevention Efforts

The federal minimum-purchasing age for tobacco products was raised to 21 years of age in December 2019.[40] Both the Base Case and the Modified Case include an estimate for the future impact of this policy change. The Modified Case also includes an estimate for the future impact of a broader range of underage tobacco use prevention efforts, in line with proposals and guidance from the FDA, academic researchers, and industry to resemble a plausible future regulatory landscape. These efforts include restrictions of available flavors in ENDS, limited marketing activities, and increased retail access controls.[67]

The potential impacts were expressed as reduction in initiation rates of ENDS use and smoking for youth and young adults, phased in from 2020 to 2025. The PHM assumes reductions of 25% (youth) and 15% (young adults) for smoking initiation rates (Base Case and Modified Case) and 65% (youth) and 35% (young adults) for ENDS initiation rates (Modified Case) over those 5 years. We derived these assumption as plausible scenarios based on an increasing, but still limited, body of research and evidence concerning the impact of such interventions.[34,68-70] Considerable uncertainty about the precise outcomes remains, which in part can be addressed via sensitivity testing. Encouragingly, 2020 data from NYTS show a faster reduction in youth use of ENDS than assumed in the PHM.[25,43]

Agent Mortality and Excess Relative Risk

The annual mortality risk for each individual agent as a function of age, sex, and smoking history (including years of smoking and years since quitting smoking) is derived from a Kaiser Permanente Cohort Study[71,72] and the Human Mortality Database,[73] including adjustments for projected future mortality improvements. This mortality modeling framework is based on one developed by Muhammad-Kah et al, as summarized in Lee et al.[42]

The excess mortality risk of ENDS is modeled via Excess Relative Risk (ERR) as a percentage of that of cigarette smoking, which is common in the literature.[48] The PHM uses an ERR of 5%, based on an estimate used by regulators as well as other modelers.[15-17] As the precise long-term health risks of ENDS are not yet known, sensitivity testing is used to explore a wide range of ERRs. Stopping use of a tobacco product in the model slowly decreases

the excess mortality risk with accumulating years of cessation.[42]

Dual use of combustible cigarettes and ENDS is treated as having the same excess morality risk as smoking. Some studies have raised concerns about the health risks associated with dual use,[74,75] while others have indicated that many dual users reduce their daily cigarette consumption significantly[42,63,76,77] and that such reductions may be associated with similarly large reductions in smoking-related biomarkers of exposure.[33] Overall, more evidence is needed to understand the mortality impact of dual use.[7]

Additional details on the mortality model are provided in Supplement Section 4 (Mortality Model). Supplemental Figure S2 illustrates cumulative survival probability curves for agent with various smoking and ENDS use histories.

Model Validation

Evaluating the ability of models to 'predict' known outcomes retrospectively increases confidence in their predictions about future outcomes.[78] Whereas such validation cannot guarantee the accuracy of model forecasts, it demonstrates the validity of the model as compared to known data and its ability to realistically simulate behavior and outcomes on a population-level. We conducted validation of the PHM's prevalence estimates for smoking and ENDS use across different age groups between 2000 and 2019 as well as overall projections of future population size and mortality.

Sensitivity Analyses

Sensitivity testing around model inputs, such as the ERR and key transition rates (eg, initiation, switching), is useful to assess the robustness of the projected outcomes and identify critical drivers. This is particularly important as population modeling is a highly useful tool to explore the likely direction and magnitude of population health impacts and trends, but – given existing data limitations and necessary model simplifications – usually not a reliable way of forecasting precise outcomes.

Implementation

The PHM was implemented in MATLAB® version 9.7 (MathWorks, Inc.). The current code base is derived from a version by Muhammad-Kah et al.[42] Computations reported on in this paper were run via parallel execution in Google Cloud Platform.

RESULTS

Smoking and ENDS Use Prevalence

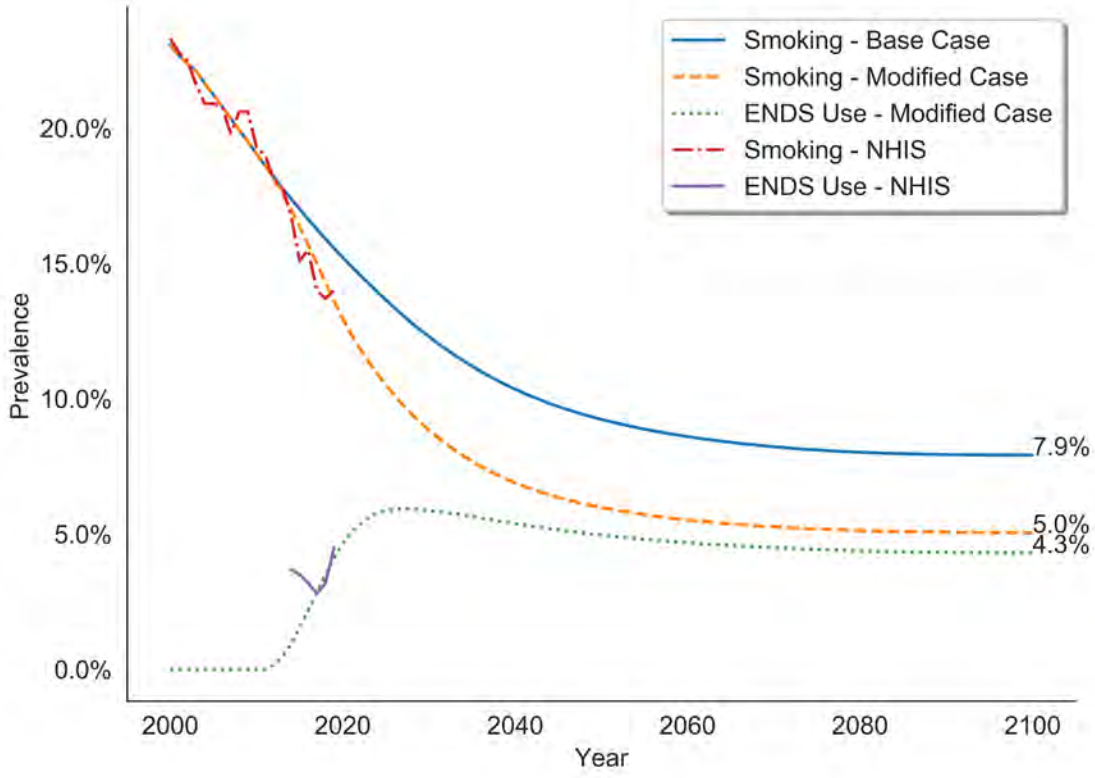
Figure 2 shows the prevalence of adult smoking and adult ENDS use from 2000 to 2100. Initially, adult smoking prevalence drops from ~ 23% in 2000 to ~ 19% in 2010. Subsequently, the Base Case and Modified Case diverge, with smoking decreasing more quickly in the latter after the introduction of ENDS, to ~ 14% in 2020. The Modified Case aligns well with actual NHIS data, which is currently available until 2019.[79] (We note that 2019 NHIS data only became available after completion of the PHM, thus providing a stronger validation test for our model than comparing against previously known data.)

Looking forward, the PHM projects smoking rates to decline further in both cases, but again more rapidly in the Modified Case. After leveling out, the Modified Cases shows a 37% reduction in adult smoking prevalence compared to the Base Case (5.0% vs 7.9%), corresponding to about 10.5 million fewer adult smokers. Much of this reduction builds throughout the first decades of ENDS availability (up until ~ 2040), as existing smokers switch to ENDS.

Adult ENDS use initially rises to above 5%, before reducing slightly and leveling off at 4.3%. The projection aligns well with NHIS data for the most recent years up until 2019, while somewhat underestimating earlier use around 2014-2015. Recall that the PHM assumes a linear increase in ENDS use after 2010 as a simplification, while in reality the adoption of ENDS in the US appears to have occurred in a number of waves.[29,44]

Some of the ENDS use overlaps with smoking in the form of dual use. Although this ratio varies somewhat through the simulation as ENDS get introduced and find adoption, it settles at about one-fifth of overall ENDS use in the long-term steady state, or an overall population prevalence of slightly below 1%. In Figure 2, such an individual would be counted in both the smoking and the ENDS use prevalence. Overall, the PHM projections imply that the prevalence of any product use (cigarettes or

Figure 2
Projected Adult Tobacco Prevalence in the Base Case and the Modified Case



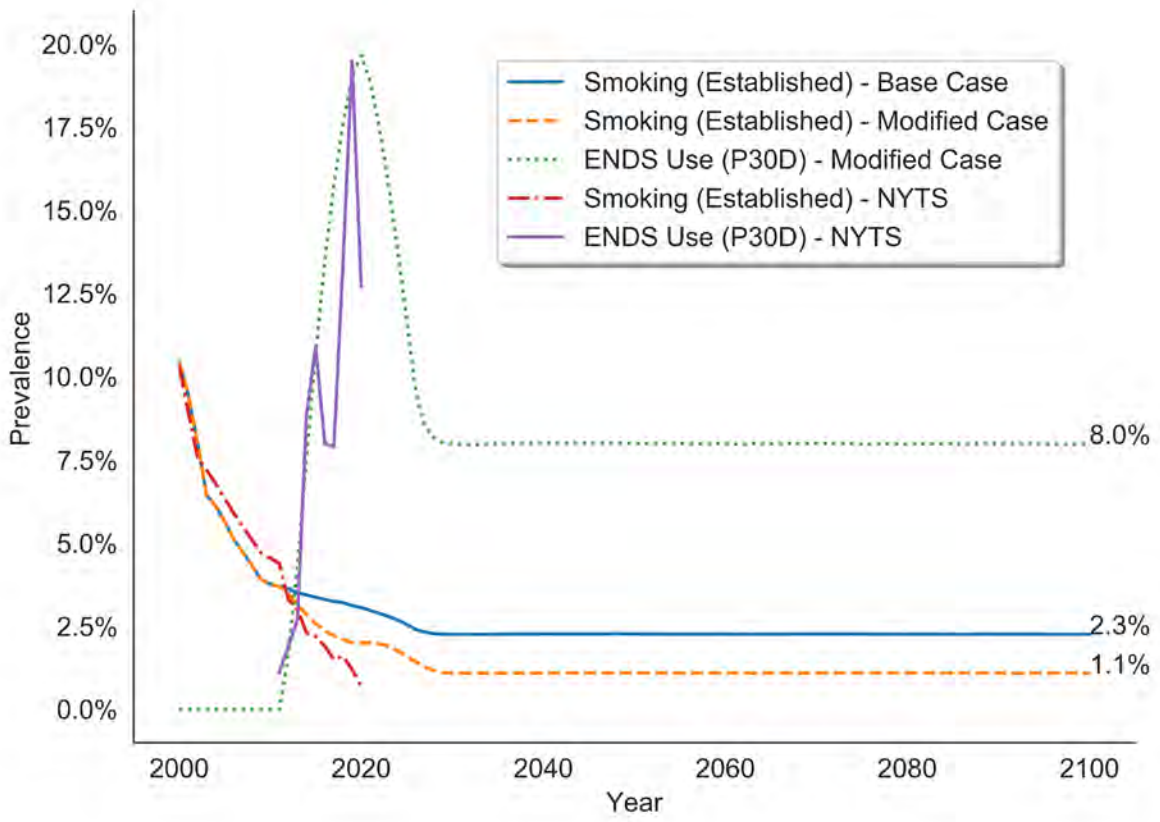
Note.
Smoking and ENDS use are defined as having used in the past 30 days and having met the lifetime established criterion ('100+ cigarettes' for smoking, 'ever fairly regularly used' for ENDS).
NHIS reference data shown as available until 2019.

ENDS) in the adult population increases slightly in the Modified Case compared to the Base Case.

Figure 3 shows the analogous prevalence of (established) smoking and any (past 30-day) ENDS use for youth ages 12-17 from 2000 to 2100. The retrospective model projections for youth smoking again align well with the historical data based on NYTS until about 2010, showing rapid declines from above 10% to below 5%. Subsequently, the Base Case and the Modified Case (to a lesser extent, ie, better tracking historical data). This is likely due to conservative assumption made in the derivation of model rates. However, both cases directionally show further reductions in established youth smoking into the 1%-2% range, in alignment with NYTS.

Youth ENDS use prevalence in the PHM initially rises rapidly from 2011-2020, up to almost 20% past 30-day use. The magnitude and direction match overall NYTS trends, with the exception that the model uses a simplified linear scaling in of ENDS transitions rates and as such does not reproduce the interim up-and-down pattern, just as with adult ENDS use. After 2020, projected youth ENDS use in the PHM drops as a result of underage use prevention efforts (including Tobacco 21), before leveling out at 8.0%. The model is again intended to be conservative in its assumptions; recently released data from NYTS 2020 show a 35% reduction in youth ENDS use from 2019 to

Figure 3
Projected Youth (Age 12-17) Tobacco Prevalence in the Base Case and the Modified Case



Note.
Smoking is defined as having used in the past 30 days and having met the lifetime established criterion ('100+ cigarettes'). ENDS use is defined as having used in the past 30 days.
NYTS reference data shown as available until 2020.

2020,[25] a more rapid decline than in the Modified Case. (These data became available after completion of the PHM.)

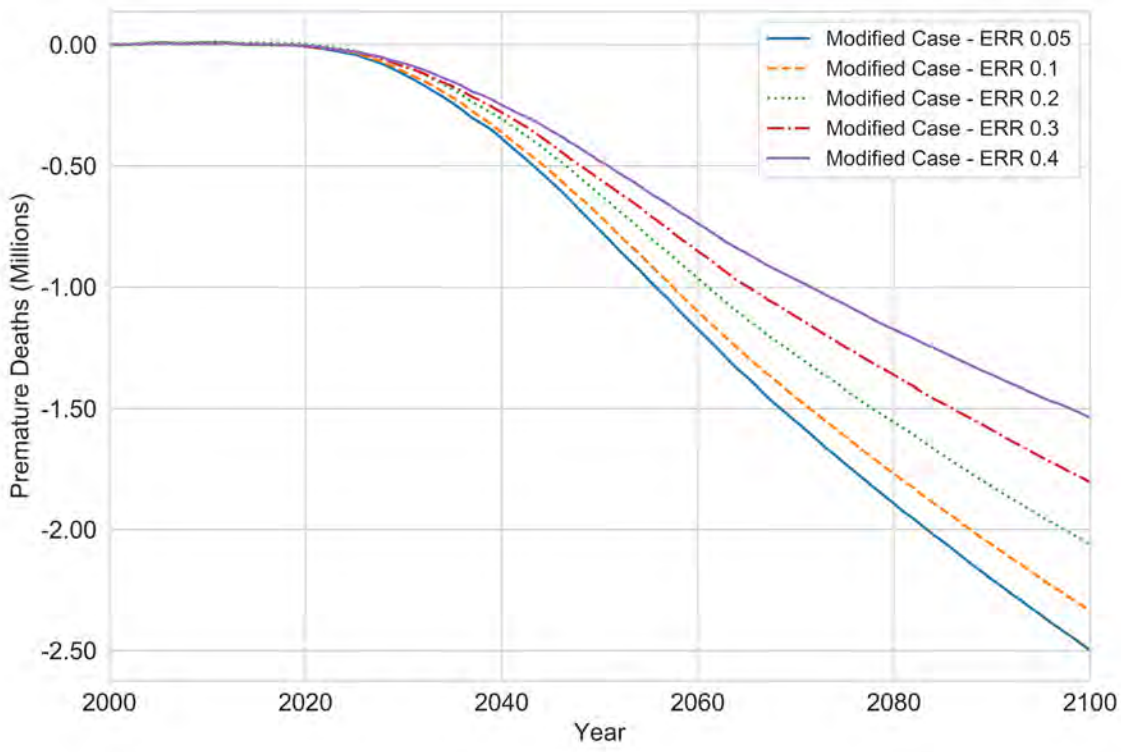
Mortality Impact and Sensitivity Testing

The PHM projects a reduction in tobacco-related premature deaths in the Modified Case (with cigarettes and ENDS available) compared to the Base Case (with only cigarettes available) of 2.5 million fewer premature deaths by the year 2100, after accounting for the mortality impact of both cigarette smoking and ENDS use. The reduction in overall mortality is primarily due to the substantial reduction in adult smoking prevalence in the Modified Case, as described above.

Sensitivity testing of key input parameters is important to established robustness of model findings. Figure 4 presents the difference in cumulative premature deaths in the Modified Case compared to the Base Case under varying ERRs between 5% and 40% (ie, ENDS use being 5% to 40% as harmful as smoking). Even at the (unrealistic) top end of this range, the Modified Case shows a net population benefit of 1.5 million fewer premature deaths.

Figure 5 shows sensitivity analyses conducted by changing key transitions in the model. Panels A, B, and C demonstrate outcomes when varying rates of switching compared to initiation, ENDS-to-Smoking transitions, and resumption of smoking by ENDS users. A positive net population health

Figure 4
Difference in Cumulative Premature Deaths Between the Modified Case and the Base Case for Varying Excess Relative Risk (ERR) Values



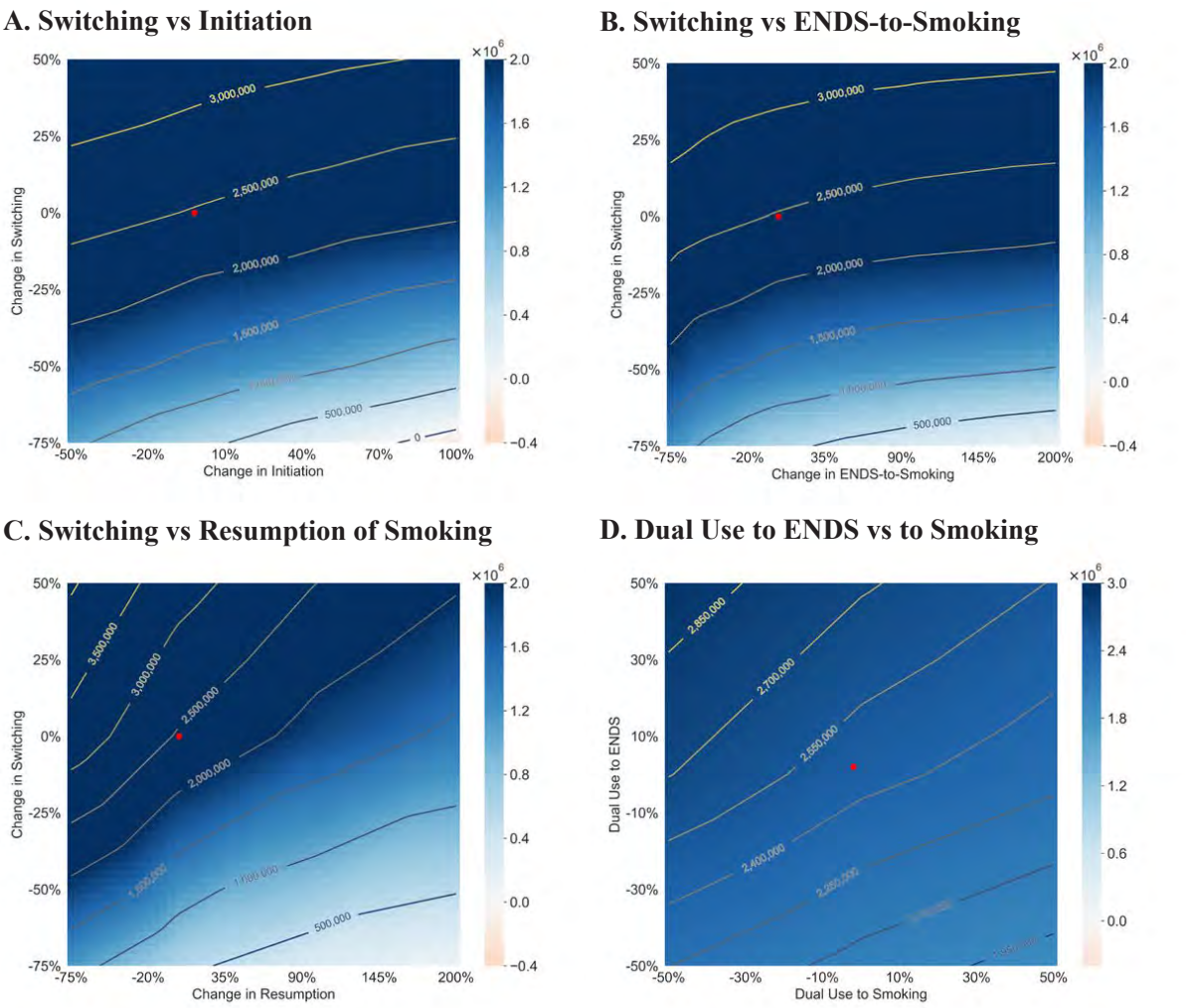
impact arises in all but the most extreme scenarios. The extent of full (and sustained) switching is the largest driver of mortality reductions. Panel D in Figure 5 reports the impact of varying rates of dual users transitioning to either exclusive ENDS use or exclusive cigarette smoking.

As youth use of ENDS has been a key concern and ENDS use prevalence has varied year-after-year, we performed additional sensitivity testing of different levels of future youth use of ENDS. For example, in a counterfactual scenario with continued 2019 NYTS levels of 19.7% past 30-day ENDS use among youth age 12-17, the net impact would be reduced to 2.2 million premature deaths averted.

Youth smoking prevalence after 2011 is lower in the Modified Case than in the Base Case. Whereas this appears directionally consistent with historical trends, we conducted a sensitivity test with increased youth smoking initiation in the Modified Case to match the prevalence of the Base Case. This removed about 150,000 premature deaths avoided or ~ 6% of the total difference between the Modified Case and the Base Case. Thus, this effect is meaningful, but represents a small portion of the overall benefit in the Modified Case.

In summary, we performed extensive sensitivity testing, including: (1) increasing the ERR up to values of 40% (Figure 4 for the Modified Case, Supplement Figure S1 for a scenario with reduced ENDS cessation rates to match smoking cessation rates); (2) varying combinations of multiple transition rates to explore important scenarios (eg, varying levels of smokers switching from ENDS to cigarettes compared to different levels of ENDS use initiation; Figure 5); (3) varying each transition

Figure 5
Sensitivities Testing: Premature Deaths Averted by the Year 2100 When Varying Key Transition Rates in The Modified Case



A. Varying rates of smokers switching compared to varying rates of never users initiating;
B. Varying rates of smokers switching compared to varying rates of ENDS users transitioning to smoking;
C. Varying rates of smokers switching compared to varying rates of switchers resuming cigarette smoking;
D. Varying rates of dual users switching to exclusive ENDS use compared to dual users moving to exclusive cigarette smoking.

Note.
The axes denote the change in the relevant rates compared to the Modified Case in the PHM. The red point in each subfigure shows the Modified Case with a difference of 2.5 million premature deaths averted.

rate individually to explore the overall sensitivity of outcomes (Supplemental Table S2); and (4) exploring tipping points at which the PHM projects little or no net population benefit (Figure 5).

Additional sensitivity testing results are included in Supplement Section 3 (Additional Sensitivity Testing Results).

DISCUSSION

Our model projects that the availability of ENDS products in the Modified Case leads to 2.5 million premature deaths averted by the year 2100. This is driven primarily by reductions in cigarette use, with adult smoking prevalence declining 37% in the Modified Case compared to the Base Case. Sensitivity analyses show that an overall reduction in population mortality occurs in all but the most extreme scenarios. Varying individual or combinations of transition rates in the PHM illustrates key drivers of outcomes and their relative impact.

As a number of public health and tobacco-control researchers have used population modeling to understand the potential impact of ENDS products on public health,[20,21,33-37,42,49,52] it is illustrative to compare our results to theirs. Consistent with the PHM, the majority of researchers find a positive population health impact of ENDS in all or most realistic scenarios, often with similar findings in terms of magnitude and key drivers of outcomes.[20,33,34,36]

Cherng et al[36] found that over a 60-year period, adult smoking prevalence could decrease by multiple percentage points if ENDS significantly increased the likelihood of switching (eg, by ~ 0.8 percentage points for a 20% increase to baseline rates of smokers moving away from cigarettes and ~ 3.1 percentage points for a 100% increase), compared to our finding of a ~ 2.9 percentage point decrease. Levy estimated that after accounting for the impact of tobacco-control policies, ENDS product use has been associated with an 8%-20% reduction in cigarette smoking prevalence in the US since they became available.[80] The PHM shows a comparable finding of a ~ 13% reduction in cigarette smoking by 2020 in the Modified Case compared to the Base Case.

Regarding population mortality, Levy et al[34] modeled 'what if' scenarios, including extreme cases where all cigarette smoking is being replaced with ENDS. The range of outcomes under various scenarios suggests 1.6-6.6 million fewer premature deaths over an 80-year time frame. The PHM's estimates fall near the lower end of this range in a Modified Case that results in a 37% reduction in smoking prevalence rather than a complete substitution. Similarly, Mendez and Warner[49] used a population model to assess the impact of ENDS use on population mortality in the US between 2018 and 2100 under a large number of scenarios. They found that in 99% of scenarios, ENDS use led to positive life-years saved, and that "[m]ost scenarios result in millions of individuals quitting smoking due to vaping." Prior work by the same authors had come to similar conclusions with regards to a likely positive impact of ENDS use on population mortality.[20]

The fact that a range of models varying in methods, data sources, and assumption reach similar conclusions can be seen as further evidence for such findings.[42] Overall, model projections should not be interpreted as precise forecasts, but rather seen as a tool to estimate the general direction and magnitude of population health outcomes as well as the range of potential impact of specific products, interventions and policies.[20,34,49]

Limitations and Strengths

The results and implications of this study should be understood with several limitations. First, the PHM only accounts for cigarette smoking and ENDS use. It does not explicitly model the use of other tobacco products such as cigars, cigarillos, pipes, smokeless tobacco, or heated tobacco. Although transitions between these and ENDS in the US have been varied or negligible,[47] and their use may have been uncommon enough or not directly impacting transition rates beyond what is implicitly account for,[81] this does represent a simplification compared to reality. It allows us to focus on the specific question of interest – ie, the impact of ENDS availability on cigarette smoking and its associated mortality – while keeping the model simple enough to derive input parameters from empirical data. As such, this simplification is common and often unavoidable in population modeling.[20,34,35,42,48,49]

Second, in the interest of model simplicity and due to a lack of granular, reliable data on what interactions are relevant and how precisely they affect transitions rates,[42] agents in the current version of the PHM are non-interacting. Network effects are only incorporated to the extent they are captured

implicitly in the transition rates. Including explicit inter-agent terms would be an interesting future extension of the PHM.

Another limitation is that we assumed homogeneity within ENDS in terms of use behavior and health risk. In reality, ENDS availability may differ meaningfully, for example with regards to transitions from/to cigarette smoking or relative risk profiles. As we have used a number of data sources specific to JUUL (eg, the ADJUSST study),[45] the PHM would be expected to be most applicable to JUUL and ENDS with similar use behavior and health risks, but as a result it may not accurately model the impact of other types of ENDS.

The majority of model inputs are empirically-derived from recent, large-scale longitudinal or repeated cross-sectional studies. However, in some cases, parameters were estimated with small sample sizes, leading to statistical uncertainty, or had to be augmented with assumptions, such as in the exact level of future impact of underage use prevention measures. We have attempted to be conservative in such situations. Our focus was on establishing robustly whether the availability of ENDS in the US is likely to have a positive net benefit on population health, rather than to create the best possible point estimate. Sensitivity testing helps to analyze the associated uncertainties.

ENDS use behavior in the US population has varied considerably over the last years, and is impacted by changes to product availability (eg, flavors), and unexpected exogenous perturbations such as EVALI and COVID-19.[82,83] In addition, existing ENDS in the US are undergoing a Pre-Market Tobacco Application process, at the conclusion of which the FDA will decide which products will be authorized to stay on market. Furthermore, it is impossible to anticipate the exact nature of behavioral, policy, and product changes for the next 8 decades. However, a long time-horizon such as in the PHM is necessary to ensure that the model fully captures the long-term health impacts of tobacco product initiation among young adults and youth today.[21,36] For simplicity, we have held transition rates in the Base and Modified Scenarios constant throughout the future simulation period (after 2025), similar to other published models.[21,48] Given the steady accumulation of premature deaths avoided between the Modified Case and the Base Case (Figure 4), future changes in rates might impact the order of magnitude of the mortality difference, but are unlikely to change the overall finding of a net benefit. By accounting for historically low youth smoking rates even in the Base Case, we are careful not to attribute undue benefit to the Modified Case by comparing it to scenarios with unrealistically high future smoking prevalence.

As a final limitation, the PHM does not currently estimate morbidity risk, primarily due to a lack of granular, long-term epidemiological data for the morbidity impact of ENDS use.[7] This would be a natural extension as more data and evidence become available. Another future extension to the model outcome measure could be life-years lost (in addition to the premature deaths measure that is the focus of this paper).

There are several additional strengths to the modeling approach utilized in the PHM: transitions in the model account for the full range of uses, including for those potentially increasing risk. Validation of modeling results against historical cigarette smoking and ENDS prevalence rates demonstrate that the PHM sensibly reflects population-level and within-subgroup use behavior. Finally, extensive sensitivity analyses enable an understanding of the key drivers of outcomes and demonstrate robustness of the directional finding of a significant positive net benefit under a wider range of possible scenarios.

Conclusions

The population model presented in this paper projects that – after considering both potentially beneficial and potentially harmful transitions and based on the available evidence to date – the (continued) availability of ENDS in the US is likely to have a positive impact on population mortality. In the Modified Case with ENDS available, 2.5 million premature deaths are prevented by the year 2100 compared to the Base Case with only cigarettes available. Sensitivity testing shows that a substantial mortality reduction occurs under a wide range of plausible scenarios and allows the illustration of drivers of outcomes. This might assist policymakers and public health researchers in understanding trade-offs and key goals in regulating ENDS, such as encouraging complete switching by adult smokers who would not otherwise stop use of all tobacco products and combating underage use and initiation.

We note that our findings depend on the model, its input data, and its assumptions. While we have aimed to derive transition rates empirically from large-scale behavioral surveys, to validate prevalence projections against historical data, and to benchmark our findings against existing work, significant uncertainties remain. Further research into the long-term health effects and population health impact of ENDS is needed.

Human Subjects Approval Statement

This work utilizes data from the ADJUSST study, which was approved by Advarra Institutional Review Board (Approval no. 00030928, November 21, 2018).

Conflict of Interest Disclosure Statement

RW, CZ, and YX are full-time employees of Juul Labs Inc. KD and SP were full-time employees of Juul Labs Inc during the time that this work was conducted.

RW, SP and KD conceptualized this study. SP, CZ and YX performed statistical analyses, and KD maintained and ran the model code. RW and CZ drafted the manuscript. All authors reviewed the manuscript and contributed to interpretations of the results. Juul Labs Inc approved the research plan and provided comment on a near-final draft of the paper.

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SUPPLEMENTARY MATERIAL

Additional Details on Transition Rate Calculations

We primarily utilized CISNET's[1] analyses of NHIS data (adult and youth),[2] analyses of PATH data (adult and youth),[3] and analyses of ADJUSST data (adult)[4] to calculate transition rates for the PHM. NHIS and PATH are well-known public health surveys widely used for the study of tobacco product use behavior and transitions. ADJUSST is a large-scale longitudinal study of cigarette and JUUL System (a pod-based closed-system ENDS brand (henceforth "JUUL") product use behavior among adult (age 21+) first-time JUUL Starter Kit purchasers through 12 months from mid-2018 to mid-2019.[5]

CISNET's analyses directly provide transition rates of the kind useful for the PHM. For PATH, we calculated representative rates using the latest available data from Waves 3 to 4 based on the tobacco use states provided in Supplement Section 5 below. We also calculated rates for Waves 1 to 2 as a sanity check. As mentioned in the main paper, ENDS initiation rates for youth were scaled up to better match NYTS prevalence up until 2019.[6]

Because ADJUSST reflects smoking and ENDS use behavior among JUUL Starter Kit purchasers,[5] but is not nationally representative, a number of calculations are needed to derive transition rates for the PHM, comparable to those derived from CISNET/NHIS and PATH. Specifically, we used the retail portion of ADJUSST, as retail sales account for > 90% of JUUL sales volume. For transition rates among ENDS and dual users in the model, we were able to use one-year follow-up data directly. For transitions rates that required estimation of rates within other population groups, such as uptake of JUUL use among existing smokers or initiation of JUUL use among non-tobacco users, the following provides an outline of how rates were scaled from the survey population to the overall population.

Based on available sales and market share data, such as from syndicated data sources like IRI and Nielsen, combined with average consumption data, and in directional agreement with prevalence data,[7] we estimated that the number of annual new adult established JUUL product users during the relevant time frame ranged from 1,250,000 to 2,000,000. The retail portion of ADJUSST include 16,262 respondents at one-year follow up, out of which 13,747 were in one of the 2 JUUL product use states (exclusive JUUL product use or dual use of JUUL products and cigarettes). With the assumption that survey respondents are representative of all new adult JUUL product users, every one respondent in the survey represents between 91 $\left(=\frac{1{,}250{,}000}{13{,}747}\right)$ and 146 $\left(=\frac{2{,}000{,}000}{13{,}747}\right)$ new annual JUUL product users in the population.

There were 2311 respondents who went from CC (smokers who had never been established ENDS users) to CEFC (current JUUL users, former smokers) and 779 who went from CCFE (smokers who had previously been established ENDS users) to CEFC. With the scaling factors of 91-146, this indicates that between 210,137 and 336,219 CC smokers and between 70,834 and 113,334 CCFE smokers switched (as per model definition) from cigarettes to JUUL products annually.

Given that there were an estimated 29,000,000 exclusive adult smokers in the US population, based on CDC estimates of about 34,000,000 million adult smokers, out which we assume approximately 5,000,000 to be dual smokers and ENDS users,[8] this gave an estimated rate of annual switching among

US smokers of between 1.0% $(= \frac{210{,}137 + 70{,}834}{29{,}000{,}000})$ and 1.6% $(= \frac{336{,}219 + 113{,}334}{29{,}000{,}000})$. Based on the relative prevalence of CC and CCFE in PATH Wave 3, we assume that 80% of these 29,000,000 adult smokers are CC, and the other 20% are CCFE, resulting in the corresponding ratios of 0.9%-1.4% as the range of transition rates for CC to CEFC, and 1.2%-2.0% as the range of estimated transition rates for CCFE to CEFC.

The transition rates estimated are for JUUL products only. We estimate that JUUL had a category share of between 35%-50%, based on the sources above and prevalence data, and multiplied these rates by 2 to get a category-wide transition rate.[7] This gives 1.8%-2.9% for CC to CEFC and 2.4%-3.9% for CCFE to CEFC. The model uses the midpoint of these ranges as transition rates, ie, 2.4% for CC to CEFC, and 3.2% for CCFE to CEFC (Table 1, main paper).

Similar calculations were made for dual use, initiation among those ages 22-24 (which was then scaled up to the age range 18-24), cessation of ENDS use, and so on. We then compared rates from PATH, ADJUSST and CISNET/NHIS (where applicable), finding generally reasonable agreement in the order of magnitude, with the exceptions that incorporating ADJUSST data led to slightly higher initiation among

Table S1
Youth Transition Rates in the Base Case and Modified Case in 2019

Case	From	To	Transition	Rate	Data Source(s)
Base	NU	CC	Smoking Initiation	2.0%[a]	CISNET/NHIS
Modified	NU	CC	Smoking Initiation	0.2%	PATH
Modified	NU	CD	Dual Use Initiation	0.1%	PATH
Modified	NU	CE	ENDS Initiation	15.4%	PATH, NYTS
Modified	CE	CCFE	ENDS To Smoking	1.2%	PATH, NYTS
Modified	CE	CD	ENDS To Smoking	2.8%	PATH, NYTS
Modified	CEFC	CCFE	Smoking Relapse (from ENDS)	24.3%	PATH
Modified	CEFC	CD	Smoking Relapse (from ENDS)	14.1%	PATH
Modified	CC	CEFC	Full Switching (from Smoking)	0.0%	PATH
Modified	CCFE	CEFC	Full Switching (from Smoking)	3.2%	PATH
Modified	CC	CD	Transition to Dual Use	23.5%	PATH
Modified	CCFE	CD	Transition to Dual Use	28.9%	PATH
Modified	CD	CEFC	Full Switching (from Dual Use)	2.4%	PATH
Modified	CD	CCFE	Transition to Exclusive Smoking	29.4%	PATH
Base	CC	FC	Smoking Cessation	3.0%[a]	CISNET/NHIS
Modified	CC	FC	Smoking Cessation	3.5%[a]	CISNET/NHIS
Modified	CCFE	FD	Smoking Cessation	3.5%[a]	CISNET/NHIS
Modified	CD	FD	Dual Use Cessation	3.5%[a]	CISNET/NHIS
Modified	CE	FE	ENDS Cessation	37.7%	PATH
Modified	CEFC	FD	ENDS Cessation	37.7%	PATH

Note.
See Figure 1 for full list of abbreviations.
[a] Transition rate varies by age and/or sex. The number shown is the average across all applicable ages and sex.

never users, a significantly higher share of full switching by smokers, and lower rates of "switching back" from ENDS use to dual use or exclusive smoking. For cessation of ENDS use, the model rate used, while higher than that for smoking, is lower than those observed in either PATH or 10A.

Obviously, transition rates in the population cannot be known with certainty and are subject to changes over time. As we discuss in the main paper and in Supplement Section 3 below, we conducted model validation compared to historical data for the years 2000-2019 and extensive sensitive testing to gain further confidence that our model rates describe population-level trends well and that key model findings are robust to existing uncertainty around individual or groups of transition rates.

Additional Sensitivity Testing Results

Table S2 shows the impact of increasing and lowering each transition rate in the Modified Case by 50%. This is not to imply that these are the confidence intervals, or that the altered parameters are realistic, but rather, to illustrate the degree to which model projected outcomes are sensitive to variations in each rate and which rates are associated with positive or negative changes to population mortality.

Direct smoking cessation – smokers quitting smoking, no involvement with ENDS – is the single most impactful behavior on outcomes. However, because cessation rates are almost identical between the Base Case and the Modified Case, they have minimal impact on mortality differences between both cases.

Stopping the use of ENDS by ENDS users who were former smokers is also impactful, and this is mostly due to potential resumption of cigarette smoking by ENDS users (rather than the potential harm of ENDS use directly).

Switching from cigarette smoking to exclusive ENDS use has a large impact on model outcomes. This is expected, as this transition is the primary driver of benefit.

Moving from cigarette smoking to dual use has no immediate impact on each agent's mortality in the PHM, but as indicated by data, dual use often is a transitional step towards subsequently switching completely from combustible cigarettes.[9] Accordingly, sensitivity testing shows that greater benefit is observed as the transition rate from combustible cigarettes to dual use increases.

Initiation of cigarette smoking and initiation of ENDS use in combination with subsequent transitions to smoking or dual use are drivers of potential harm in the model. Similarly, resumption of cigarette smoking after ENDS use and failed switching – ie, transitioning from dual use back to exclusive smoking – have significant negative impact in the model. (Obviously, to derive accurate real-world interpretations, these transitions, as well as switching, etc, have to be interpreted against the backdrop of what would have happened in a scenario without ENDS availability, ie, the counterfactual.)

A separate analysis in Figure S1 illustrates the impact of varying ERR in a scenario where ENDS cessation rates in the Modified Case are reduced to match those for combustible cigarettes in the Modified Case. The mortality difference with a 5% ERR is then 1.9 million premature deaths averted (from 2.5 million), and a tipping point would be reached at an ERR of approximately 55%.

Mortality Model

Our mortality model is a variant of one developed by Muhammad-Kah et al.[10] The mortality hazard is modeled based on 2 data sources, the Kaiser Permanente (KP) Medical Care Program Cohort Study and the Human Mortality Database (HMD). The base equation for the hazard function is:

$$h(age, \text{YSM}, \text{YQSM}, \text{YENDS}, \text{YQENDS})$$

$$= e^{\alpha_{HMD,2000} * \theta_{HMD,2000} + \beta_{HMD,2000} * \text{age} + \gamma_{KP,NU\&CC} * \text{YSM} + \delta_{KP,NU\&CC} * \text{YSM} * \text{age} + \varepsilon_{KP,CC\&FC} * \text{YQSM}}$$

$$* \left(ERR\left(e^{\gamma_{KP,NU\&CC} * \text{YENDS} + \delta_{KP,NU\&CC} * \text{YENDS} * \text{age} + \varepsilon_{KP,CC\&FC} * \text{YQENDS}} - 1\right) + 1\right)$$

Table S2
Impact of Varying Each Transition Rate +/-50%

Transition			Transition Rate (Modified Case)		With 50% Lower Rate		With 50% Higher Rate	
Type	From	To	Adult (Regular ENDS Use)	Youth (P30D ENDS Use)	Premature Deaths Averted	Difference to Modified Case	Premature Deaths Averted	Difference to Modified Case
Cessation	Smoker	Neither	3%[a]	3.5%[a]	1,372,396	-1,117,990	3,262,103	771,717
Cessation	ENDS User (Former Smoker)	Neither	6%	37.7%	1,993,509	-496,877	2,745,510	255,124
Cessation	Smoker (Former ENDS)	Neither	3%[a]	3.5%[a]	2,066,230	-424,156	2,743,496	253,110
Cessation	Dual User	Neither	3%[a]	3.5%[a]	2,380,589	-109,797	2,535,247	44,861
Cessation	ENDS User	Neither	6%	37.7%	2,347,607	-142,779	2,509,944	19,558
Switching	Smoker	ENDS	2.4%	0%	2,002,169	-488,217	2,799,371	308,985
Switching	Dual User	ENDS	34.0%	2.4%	2,014,771	-475,615	2,691,965	201,579
Switching	Smoker (Former ENDS)	ENDS	3.2%	3.2%	2,232,985	-257,401	2,620,518	130,132
Adding ENDS	Smoker	Dual Use	1.5%	23.5%	2,304,274	-186,112	2,611,437	121,051
Adding ENDS	Smoker (Former ENDS)	Dual Use	1.8%	28.9%	2,396,430	-93,956	2,502,003	11,617
ENDS-to-Smoking	ENDS User	Dual Use	9.9%	2.8%	2,545,732	55,346	2,379,431	-110,955
ENDS-to-Smoking	ENDS User	Smoking	1.6%	1.2%	2,503,754	13,368	2,425,461	-64,925
Initiation	Never User	Dual Use	0.2%[b]	0.1%	2,470,817	-19,569	2,419,827	-70,559
Initiation	Never User	ENDS	1.8%[b]	15.5%	2,701,766	211,380	2,246,605	-243,781
Initiation	Never User	Smoking	1.3%[a,b]	0.2%	2,695,591	205,205	2,220,814	-269,572
Dual Use-to-Smoking	Dual User	Smoking	16.0%	29.4%	2,588,766	98,380	2,359,358	-131,028
Relapse	ENDS User (Former Smoker)	Smoking	1.5%	24.3%	2,698,477	208,091	2,271,175	-219,211
Relapse	ENDS User (Former Smoker)	Dual Use	8.6[a]	14.1%	2,823,152	332,766	2,180,399	-309,987

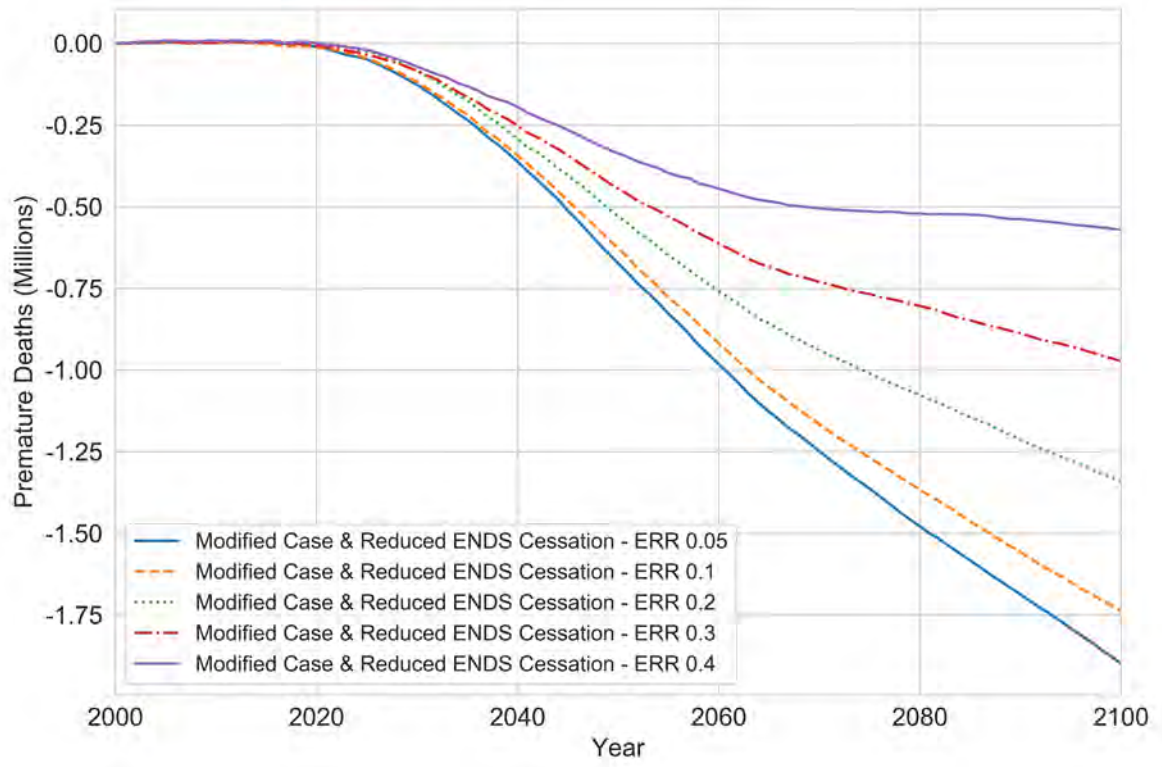
Note.
[a] Transition rate varies by age. The number shown is the average across all applicable ages
[b] Among individuals age 18-24 only

Here, YSM is the number of years of smoking, YQSM is the years of smoking cessation, YENDS is years of ENDS use, and YQENDS is years of ENDS cessation.

Applying the Lee-Carter model to mortality data from the HMD for the years 1950 to 2017 obtains a forecast of annual age- and gender-specific mortality improvement factors.[10] We then add these factors to the mortality model as:

$$h(age, \text{YSM}, \text{YQSM}, \text{YENDS}, \text{YQENDS}, \text{t}) =$$

Figure S1
Difference in Cumulative Premature Deaths Between the Modified Case and the Base Case for Varying ERR Values for a Scenario with Lowered ENDS Cessation Rates



$$((e^{\alpha_{HMD,2000} * \theta_{HMD,2000} + \beta_{HMD,2000} * \text{age} + \gamma_{KP,NU\&CC} * \text{YSM} + \delta_{KP,NU\&CC} * \text{YSM} * \text{age} + \varepsilon_{KP,CC\&FC} * \text{YQSM}}$$

$$* \left(ERR\left(e^{\gamma_{KP,NU\&CC} * \text{YENDS} + \delta_{KP,NU\&CC} * \text{YENDS} * \text{age} + \varepsilon_{KP,CC\&FC} * \text{YQENDS}} - 1\right) + 1\right)) * LC_{age,t}$$

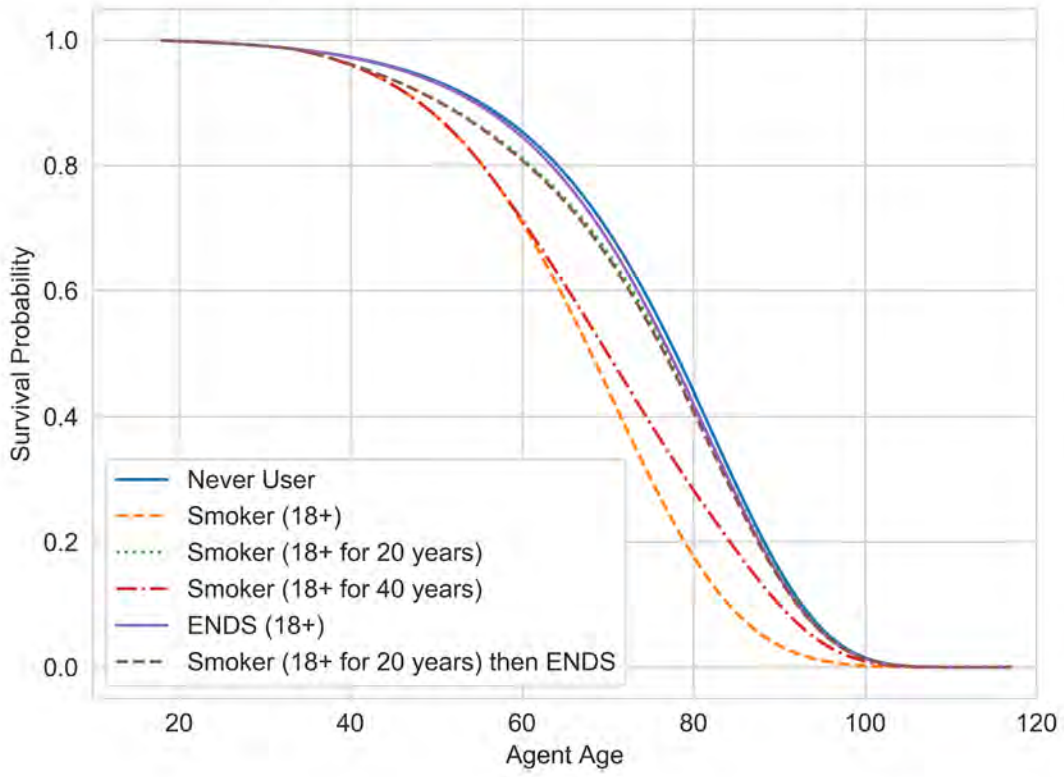
where t is the simulation year and $LC_{age,t}$ is the mortality improvement factor. The hazard rate is then converted to the mortality probability using

$$(age, \text{YSM}, \text{YQSM}, \text{YENDS}, \text{YQENDS}, \text{t}) = 1 - e^{-h(age, \text{YSM}, \text{YQSM}, \text{YENDS}, \text{YQENDS}, \text{t})}$$

Figure S2 shows examples of individual agent cumulative survival curves as a function of agent age as derived from the mortality model. A smoker initiating at age 18 faces an increased health risk over time. This individual's chance of death by or before age 60, if they continue smoking (orange line), is almost twice that of a never tobacco user (blue line). Quitting smoking stops the accumulation of health damage, and over time, reduces some of the excess mortality risk through years of cessation (green and red lines).

Switching to an ENDS with a 5% ERR, although not as beneficial as quitting altogether, still provides a major potential health benefit in terms of reduced excess mortality (brown line). A never smoker who initiates and continues ENDS use at age 18 also faces an increased mortality risk, but much less so than that of a smoker (purple line).

Figure S2
Survival Curves for Individual Agents with Different Tobacco Use Histories



Definitions of Tobacco Use States in the PHM

Below are the tobacco use states utilized in the PHM. The descriptions capture the concept for each and are slightly adjusted to the definitions and available data for each data source for prevalence and transitions between states (eg, as discussed in the paper, the PHM only considers long-term successful cessation for transitions from CC to FC and CE to FE).

Adult Tobacco Use States

- ***Current cigarette smoker (CC).*** Has smoked in the last 30 days, has smoked 100 or more cigarettes in their lifetime, has never used ENDS fairly regularly.
- ***Former cigarette smoker (FC).*** Has not smoked cigarettes for the past 30 days, has smoked 100 or more cigarettes in their lifetime, has never used ENDS fairly regularly.
- ***Current ENDS user and former smoker (CEFC).*** Has not smoked cigarettes for the past 30 days, has smoked 100 or more cigarettes in their lifetime, has ever used ENDS fairly regularly and has used ENDS fairly regularly in the past 30 days.
- ***Current ENDS user (CE).*** Has used ENDS fairly regularly in the past 30 days and has ever used ENDS fairly regularly, has not smoked 100 or more cigarettes in their lifetime.
- ***Former ENDS user (FE).*** Has ever used ENDS fairly regularly, has not used ENDS fairly regularly

in the 30 days, has smoked less than 100 cigarettes in their lifetime.

- ***Current smoker and former ENDS user (CCFE).*** Has smoked in the last 30 days, has smoked 100 or more cigarettes in their lifetime, has ever used ENDS fairly regularly, has not used ENDS fairly regularly in the past 30 days.
- ***Current dual user (CD).*** Has smoked in the last 30 days, has used ENDS fairly regularly in past 30 days, and smoked 100 or more cigarettes in their lifetime and ever used ENDS fairly regularly.
- ***Former dual user (FD).*** Has not smoked cigarettes for the past 30 days, has smoked 100 or more cigarettes in their lifetime, has ever used ENDS fairly regularly, has not used ENDS fairly regularly in the past 30 days.

Youth Tobacco Use States

- ***Cigarette smoker (CC).*** Has smoked cigarettes in past 30 days, has smoked 100 or more cigarettes in their lifetime, has never used ENDS.
- ***Former cigarette smoker (FC).*** Has not smoked cigarettes in past 30 days, has smoked 100 or more cigarettes in their lifetime, has never used ENDS.
- ***Current ENDS user and former smoker (CEFC).*** Has not smoked cigarettes in past 30 days, has smoked 100 or more cigarettes in their lifetime, and has used ENDS in the past 30 days.
- ***ENDS user (CE).*** Has used ENDS in the past 30 days and has not smoked 100 or more cigarettes in their lifetime.
- ***Former ENDS user (FE).*** Has ever used ENDS, has not used ENDS in the past 30 days, and has not smoked 100 or more cigarettes in their lifetime.
- ***Current smoker and former ENDS user (CCFE).*** Has ever used ENDS, has not used ENDS in the past 30 days, has smoked cigarettes in the past 30 days, and has smoked 100 or more cigarettes in their lifetime.
- ***Current dual user (CD).*** Used both cigarettes and ENDS in past 30 days, and has smoked 100 or more cigarettes in their lifetime.
- ***Former dual user (FD).*** Has ever used ENDS and has smoked 100 or more cigarettes in their lifetime, has not used either cigarettes or ENDS in the past 30 days.

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Closing Perspective on the Special Issue on JUUL

Karl O. Fagerström, PhD

Objective: This article provides an overview of this theme issue of the *American Journal of Health Behavior* dedicated to electronic nicotine delivery systems (ENDS), with a special focus on JUUL. **Methods:** The author summarizes key findings from included papers and offers an evaluative perspective on ENDS as tools for smoking cessation versus the prospect of their appeal to previous non-smokers. **Results:** Delineation of certain metrics (eg, defining who is a smoker) and clarification about an acceptable level of unintended consequences weighed against harm reduction confound conclusions about the public health role of ENDS/JUUL. **Conclusion:** Until agreement on key definitions and performance of well-controlled studies, a system that promotes ENDS/JUUL use among smokers but discourages their use by never-smokers is a regulatory challenge.

Key words: e-cigarettes; electronic nicotine delivery systems (ENDS); JUUL; nicotine; harm reduction
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This special issue on electronic nicotine delivery systems (ENDS), and JUUL, in particular, includes many interesting studies. Among them is a prospective study where buyers of a JUUL starter kit were asked to participate in an investigation with several follow-ups at one, 2, 3, 6, 9, and 12 months. The researchers collected multiple baseline data that are reported in 7 different papers in this issue. Such a prospective study has its advantages, but also disadvantages, because the decision to participate may not be random and independent of important variables. The first paper is a relatively representative study of the use of ENDS and smoking in the US.[1] The issue also includes an intervention study whose objective was to limit access of JUUL to underage users.[2] An additional paper reports on a modeling study to identify the public health impact of JUUL under different scenarios.[3]

What has intensified the debate about ENDS, especially JUUL, is the fact that these systems are being used by non-smoking young adults; that said, in one study, only one percent of current JUUL users were classified as never-smokers.[1] However, for this study, one must take into consideration the metric used for determining "smoking status" – ie, "any smoking within the past 30 days." Among middle-aged and older smokers, this definition could mean regular and daily smoking; however, for adolescents and young adults, it could mean experimental smoking with no progression to regular, harmful smoking.

The other and more positive side of the argument is the help ENDS give smokers who are attempting to quit smoking. Significant associations with ENDS use and smoking cessation is seen in several analyses.[4] About 50% of frequent JUUL purchasers had stopped smoking at 12-month follow-up. This figure is based on self-report only, with no objective verification of smoking status of the type often used in smoking cessation trials. When a more restrictive definition is used, like switching (to ENDS) – ie, no smoking at all for the 30 days prior to both the 9- and 12-month assessments – the figure is reduced to approximately 30%. Still, 30% is a figure rarely seen even among motivated smokers receiving treatment for smoking cessation, and certainly not when smokers like ones in these studies attempt to quit on their own. The long-term success rate in such attempts is often only about 5%.[5] The reason for this seemingly high effectiveness in real-world use is probably the close similarity to traditional cigarettes. JUUL especially seems to be able to deliver nicotine in a pharmacokinetic profile similar to that of traditional cigarettes,[6] but overall, ENDS mimic smoking behavior more closely than

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other treatments. Another feature of ENDS use is that there is no abrupt quitting needed. Instead, users have a possibility to discover for themselves how the product works and how it should be used, building trust, acceptance, and dependence where the product is concerned. A notable finding from several studies is that switching (to ENDS) or stopping smoking steadily increases over time.[4,7-8] This has rarely been seen in smoking cessation studies except from those with varenicline that mandated no abrupt quitting in the beginning of the treatment and found success rates to increase over time.[9] Maybe there is a lesson to be learned here. The effect of using and getting used to a product and quitting gradually needs to be researched more thoroughly. As with most other treatments, success in stopping seems to be higher among less dependent smokers and those who rate their dependence higher on JUUL.[4,10]

One of the papers in this issue examines dependence on JUUL compared with baseline cigarette dependence.[10] The dependence rating was lower with JUUL than with cigarettes, but the time on JUUL was shorter than that of cigarettes. What the dependence rating would be if time on JUUL and cigarettes were the same remains a question still to be studied.

The findings from several studies in this issue clearly point to JUUL as an effective smoking cessation tool which has not been seen so convincingly in other studies where other ENDS products mostly have been used.[11]

The problem for regulators and the anti-tobacco community seems to be how much unintended consequence, ie, uptake among never-smokers and progression to smoking, can be allowed. Is one percent, 2%, or 5% of JUUL users acceptable, or, is it an absolute number in a population that is critical? How much use of ENDS, or for that matter, other pure nicotine products (eg, NRT and non-tobacco pouches) is acceptable is a decision that ought to be based on its harmfulness. There are reasons to believe that pure nicotine products, conditioned that they do not expose users to toxic flavors and other by-products, have little or no risk for increased mortality, as found with Swedish snus in the Global Burden of Disease Study.[12] Because cigarettes are so much more harmful, one should be less disturbed by ENDS-only use by never-smokers than by dual use or exclusive smoking by persons with a history of smoking. Maybe the public health modeling demonstrated in this study can help answer this question.[3]

The "tricky goal" to work towards seems to be to find a regulatory system that promotes ENDS and JUUL use for smokers, and at the same time keeps ENDS entirely away from never-smokers. In one intervention study, having mandated age verification and a limit to the quantity of JUUL products that could be purchased per transaction seemed to reduce the potential for underage purchase of JUUL.[2] The critical question with never-smokers' use of ENDS is, of course, what would these individuals have done if JUUL or other pure nicotine products had not existed? Well-controlled studies yielding an answer to this question likely will never be done. Therefore, the decisions not only will be fact-driven, but also opinion-driven. Because it is unlikely that humankind will give up drugs, nicotine included, the findings from the studies presented in this issue suggest that ENDS, and JUUL in particular, can be an acceptable substitute for more harmful cigarette alternatives.

Disclaimer

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