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Original Contribution

Is nicotine vaping associated with subsequent initiation of cannabis or other substances from adolescence into young adulthood?

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Abstract

Prior studies estimating longitudinal associations between nicotine vaping and subsequent initiation of cannabis and other substances (eg, cocaine, heroin) have been limited by short follow-up periods, convenience sampling, and possibly inadequate confounding control. We sought to address some of these gaps using the nationally representative Population Assessment of Tobacco and Health Study (PATH) to estimate longitudinal associations between nicotine vaping and the initiation of cannabis or other substances among adolescents transitioning to adulthood from 2013 to 2019, adjusting for treatment-confounder feedback. Estimands like the longitudinal average treatment effect were not identified because of extensive practical positivity violations. Therefore, we estimated longitudinal incremental propensity score effects, which were identified. We found that reduced odds of nicotine vaping were associated with decreased risks of cannabis or other substance initiation; these associations strengthened over time. For example, by the final wave (2018-2019), cannabis and other substance initiation risks were 6.2 (95% CI, 4.6-7.7) and 1.8 (95% CI, 0.4-3.2) percentage points lower when odds of nicotine vaping were reduced to be 90% lower in all preceding waves (2013-2014 to 2016-2018), as compared with observed risks. Strategies to lower nicotine vaping prevalence during this period may have resulted in fewer young people initiating cannabis and other substances.

Key words: adolescents; emerging adults; cannabis; substance use; vaping; nicotine.

Introduction

Nicotine vaping prevalence increased among adolescents and young adults during the 2010s as a novel way to consume nicotine. In 2020, it decreased for the first time since national surveillance began[1-4]; however, 4.5% and 16.5% of middle and high school students, respectively, and 20% to 22% of young adults aged 18 to 22 years used e-cigarettes in the past month.[4-6] Some research has documented harmful longitudinal associations between nicotine vaping and cannabis use and the use of other substances, such as cocaine and heroin.[7-14] If such associations represent causal effects, they could operate through several hypothesized mechanisms, including (1) vaping nicotine may stimulate interest in using vaporizers to consume cannabis,[7,15-17] or (2) vaping nicotine may increase access to deviant peer networks, who may introduce youth to cannabis and other substances.[15,16,18,19] Regular use of cannabis and other substances may increase the risk of psychosis and behavioral and cognition problems,[20] physiological dependence,[21] some infectious diseases,[22,23] sleep problems,[24] worse interpersonal relationships,[25] poor job and school performance,[26] and unemployment.[27] If nicotine vaping leads to experimentation with cannabis or other substances, the latter may indirectly lead to these problems by increasing the risk of regular use.[28]

Nearly all reported associations between nicotine vaping and cannabis and other substance initiation are positive,[29,30] but many studies suffer from sources of bias expected to overestimate effects.[29] For example, a minority of studies controlled for known confounders, such as substance use history, friends' and family's influences on substance use, psychopathology, and work or school factors.[29,31-40] Additionally, most longitudinal studies did not use statistical methods that appropriately control for time-varying treatment-confounder feedback (so-called g methods[41]).[8,12,17,42]

Moreover, studies reporting positive longitudinal associations between nicotine vaping and the initiation of cannabis and other substances are limited to follow-up periods of less than 3 years among only adolescents or young adults,[12,29,43] instead of spanning the transition from adolescence to young adulthood. Following adolescents into adulthood is important because, although most substance initiation occurs in adolescence,[44] a substantial minority occurs in young adulthood,[6] which would be missed if studying only effects in adolescents. Longer-term longitudinal studies may also help address potential unmeasured confounding because adult studies rarely consider disruptive events in adolescence, such as parental divorce, as formative to adult substance use risks.[9,16,17,43,45,46]

Longer-term studies can also reveal the role of prior nonvaped tobacco product use (hereon, tobacco use) in nicotine vaping's effects during the transition from adolescence to adulthood. Smoking appears to be more strongly associated with incident

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cannabis use than vaping.[29,47] However, 2 studies reported that vaping's association with cannabis use was attenuated among individuals who also used tobacco than individuals who did not,[13,17] which could be evidence of a ceiling effect (ie, the baseline risk of cannabis initiation among people with a history of tobacco use could be so high that vaping confers little additional risk).[13]

Finally, medium-term studies have been limited by small convenience samples[13,17]; therefore, studying effect heterogeneity of tobacco use in a larger representative sample over a longer time period could help clarify the group at greatest increased risk and most in need of public health attention.

Using a nationally representative longitudinal survey of tobacco use, the Population Assessment of Tobacco and Health Study (PATH), we sought to estimate the extent to which (1) nicotine vaping increases the risk of initiating cannabis or other substances as adolescents transition to young adults from 2013 to 2019, and (2) tobacco use history modifies those associations.

Methods

Population Assessment of Tobacco and Health Study (PATH)

Data come from waves 1 (baseline, 2013-2014) to wave 5 (2018-2019) of PATH, a nationally representative cohort study of US adolescents and adults with the general purpose of evaluating tobacco use and tobacco-related health problems (eg, respiratory, dental).[48] PATH youth participants complete an annual survey about themselves, and a parent or guardian is asked to complete a survey mostly about their child. We were granted access to the restricted PATH data files, and Columbia University Medical Center Institutional Review Board approved this study.[49]

Data collection

Details about PATH's sampling strategy are given elsewhere.[48,49] Briefly, data were collected approximately annually (between 9 and 14 months) over the first 4 waves (Supplementary Table S1): wave 1 (2013-2014), wave 2 (2014-2015), wave 3 (2015-2016), and wave 4 (2016-2018).[48] Wave 5 (2018-2019) data were collected about 2 years after wave 4 data. Youth and adults completed specific instruments about themselves, including demographics, health, and substance use behaviors. Additionally, parents or guardians of youth completed an instrument mostly about their child. Youth who reached 18 years old completed an adult interview.

Study population

Figure 1 shows how we derived our analytic sample ($n = 9571$) from PATH's wave 1 cohort of 13 651 youth.

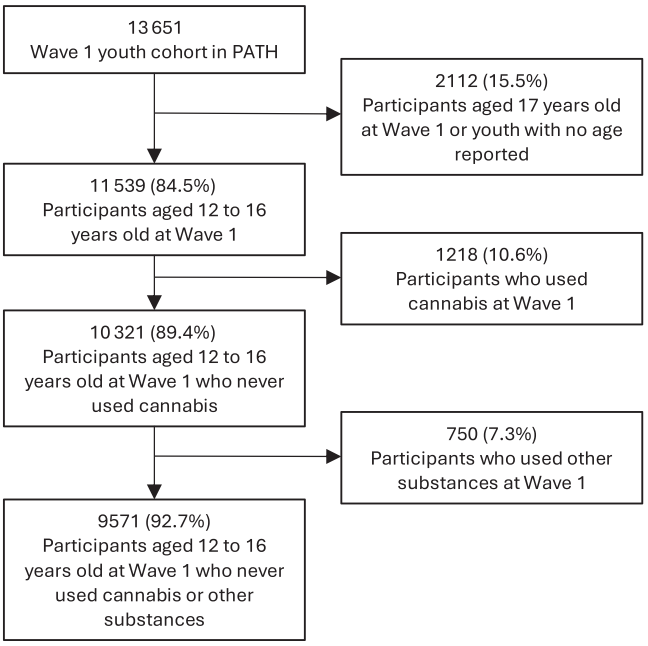

Figure 1. Flow diagram depicting how an analytical sample size of 9571 was derived from the Population Assessment of Tobacco and Health Study baseline cohort of 13 651 youth.

Data and estimand

We have the following longitudinal observed data: $O = (L_1, A_1, L_2, A_2, L_3, A_3, L_4, A_4, Y)$, the causal structure of which is depicted in Supplementary Figure S1. L_1 is a set of baseline confounders, measured at wave 1. A_t is nicotine vaping at wave t for $t \in \{1, 2, 3, 4\}$. L_2, L_3, and L_4 comprise sets of time-varying confounders at wave t ,and observed outcomes at wave $t-1$, Y for $t \in \{2, 3, 4\}$. Y is the observed outcome at wave 5.

One way to answer our research question would be to estimate longitudinal average treatment effects (ATEs)—the expected risk of cannabis initiation or other substance initiation had everyone versus no one in the population vaped every year. Identifying these effects requires several causal identification assumptions. One verifiable assumption is positivity, the nonzero probability of having each exposure history of interest (always vaped, never vaped), conditional on covariate values present in the population of interest (eg, nonzero propensity scores).[50] We tested this assumption and found evidence of practical positivity violations—that is, predicted probabilities that are very close to zero—in approximately 25% of individuals (Supplementary Figure S2).[29] The violations are likely due to the endogeneity of nicotine vaping (ie, nicotine vaping's strong relation to covariates in a propensity score model), which can result in small propensity scores and create problems for estimator performance in finite samples like ours. Due to these practical positivity violations, longitudinal ATEs were not chosen as this study's estimand.

Instead, we chose longitudinal incremental propensity score effects as our causal estimand.[51] This type of causal estimand qualitatively answered our research question, allowed for inference about the full population, and satisfied the positivity assumption by design.[51] The incremental propensity score effect is the observed risk of an outcome compared with its counterfactual risk had the odds of exposure been shifted across a range of values[51] and, using the above notation, can be denoted

$$E\left(Y_t - Y_t^{\delta \in (0.1, 0.9)}\right) \text{ for } t \in \{2, 3, 4, 5\}, \quad (1)$$

where δ is a ratio of the shifted to unshifted odds of nicotine vaping $\delta = \left(\frac{\frac{q_t(\bar{l}_t)}{1-q_t(\bar{l}_t)}}{\frac{\pi_t(\bar{l}_t)}{1-\pi_t(\bar{l}_t)}} \right)$ for all $t \in \{1, 2, 3, 4\}$, where $q_t(\bar{l}_t)$ and $\pi_t(\bar{l}_t)$ are the shifted and unshifted propensity scores (which are a function of covariate history, $\bar{l}_t$). In this study, $\delta < 1$, meaning $q_t(\bar{l}_t) < \pi_t(\bar{l}_t)$. Additionally, Y_t and $Y_t^{\delta \in (0.1, 0.9)}$ in expression 1 are the observed and potential outcomes at wave tt, respectively, where $Y_t^{\delta \in (0.1, 0.9)}$ are the potential outcomes that would have occurred had everyone's historical nicotine vaping odds been lower by an amount δ at all waves through wave $t-1$. Expression 1 is therefore the average difference by wave $t = \{2, 3, 4, 5\}$ between observed cannabis or other substance initiation risks $E(Y_t)$ and counterfactual risks

had nicotine vaping odds been 0.1 to 0.9 times the observed odds in all prior waves $E(Y_t^{\delta\in(0.1,0.9)})$ (90% to 10% lower). Importantly, appreciable incremental propensity score effects are qualitative evidence of a relationship between the exposure and the outcome. We refer readers to Supplementary Appendix S1 and Kennedy[51] for detailed explanations of guaranteed positivity for incremental propensity score effects.

Identification

We assumed no unmeasured time-invariant and time-varying confounding of nicotine vaping and outcomes to identify the estimand in expression 1 (ie, effects by waves 2, 3, 4, and 5).

Measures

Outcomes

There were 2 binary outcomes, each assessed in the past 12 months by each follow-up wave: (1) cannabis initiation was defined as any use of THC, grass, pot, or weed, and (2) other substance initiation was defined as any nonmedical use of prescription drugs, such as Ritalin, Adderall, painkillers, sedatives, or tranquilizers, or the use of methamphetamine, speed, heroin, inhalants, solvents, hallucinogens, cocaine, or crack. Once participants endorsed cannabis or other substances, they were considered to have initiated for the duration of the study. Despite alcohol being psychoactive, addictive, and prohibited for anyone under 21 years old, alcohol initiation was not considered an outcome. Alcohol initiation usually precedes nicotine vaping initiation, or both are initiated concurrently,[52,53] which, as others have found,[54] makes estimating nicotine vaping's effects on alcohol initiation challenging. Instead, we considered alcohol use to be a confounder.

Exposure

At wave 1, participants answered whether they used e-cigarettes in the past 12 months. E-cigarettes were described as devices that look like regular cigarettes but are battery-powered and produce vapor instead of smoke. At waves 2 through 4, participants answered whether they used electronic nicotine products in the past 12 months. Electronic nicotine products were described as e-cigarettes, e-cigars, e-pipes, e-hookahs, and personal vaporizers, as well as vape pens and hookah pens that are battery-powered, use nicotine fluid rather than tobacco leaves, and produce vapor instead of smoke. Participants were shown generic pictures of the products. We refer to affirmative responses to these questions as nicotine vaping, a binary variable, throughout.

Confounders

We considered problem behavior theory,[55] interactive theory,[56] common liability theory,[57] and drug, set, and setting,[58] as well as prior research to guide confounder selection. According to these sources, the most important confounders were one's substance use history, friends' and family's influences on substance use, psychopathology, and school or employment factors.[29] Measured baseline confounders were age, sex, racialized/ethnic group, household income, parental education, and sensation-seeking. Measured time-varying confounders, most of which were also measured at baseline, included nonvaping tobacco use, alcohol use, living with both parents, tobacco used/allowed in the home, psychopathology, and school performance. All measured confounders, their operationalizations, relevant theories, and constructs from relevant theories appear in Supplementary Table S2, and the waves at which they were measured can be seen in Supplementary Table S3. None of the operationalizations or constructs are from validated scales. An outcome variable at previous waves that was not considered the outcome of an analysis (eg, other substance use) was considered a time-varying confounder for the longitudinal effect on the outcome being analyzed at a later wave (eg, cannabis initiation).

Effect modifiers

We considered any history of tobacco use (including concurrent use) other than nicotine vaping to be a potential effect modifier. For example, participants whose nicotine vaping was evaluated in wave 4 were categorized as having tobacco use history if they used tobacco in wave 1, 2, 3, or 4. Otherwise, they were categorized as having no tobacco use history. Tobacco products included cigarettes, cigars, cigarillos, pipes, hookah, and smokeless tobacco.

Statistical analysis

Missing data

Missing exposure data increased from 0.5% in wave 1 to 27.7% in wave 4, and missing data for both outcomes increased from about 13% in wave 2 to about 28% in wave 5 (Supplementary Tables S4-S6). In the cohort in which cannabis initiation was the outcome, the median proportion of missingness of the 31 covariates at wave 1 was 0.8% (IQR, 0.4-1.1). Median covariate missingness proportions were 13.7% (IQR, 13.4-14.1, $n = 25$) at wave 2, 16.6% (IQR, 16.1-28.6, $n = 25$) at wave 3, and 20.6% (IQR, 20.3-41.3, $n = 25$) at wave 4. Missingness of individual covariates is shown in Supplementary Table S3. We estimated missing data with multiple imputation by chained equations (R package mice) under the missing at random assumption (MAR).[59] MAR is an unverifiable assumption that missing data are dependent only on observed data. We imputed 15 data frames and combined estimates using Rubin's rules (R package Amelia).[60,61]

Statistical analysis

We estimated survey-weighted incremental propensity score effects by waves 2 to 5. These effects are the expected differences in observed cannabis and other substance initiation risks versus those risks had nicotine vaping odds been incrementally lower than observed in the previous waves. We used the R package Incremental-dropout's estimation.sample.splitting function and the SuperLearner machine learning algorithm to estimate propensity scores, risk differences, and 95% confidence intervals for the latter.[62] SuperLearner weights candidate algorithms' predictions by how much they minimize cross-validated loss functions (eg, mean squared error in linear regression models).[63-65] In cross-validation, data are split into k folds (ie, equal splits of the data) using $k - 1$ folds to train the data and the remaining "hold-out" fold to predict. It is used to avoid overfitting.[65,66] In our study, $k = 5$, so each algorithm predicted 5 parameters and 5 loss functions, one for each hold-out fold.[65,66] Candidates in our SuperLearner library were an intercept-only model (SL.mean), generalized linear models (SL.glm), and multivariate adaptive regression splines (SL.earth). Standard errors were estimated by taking the square root of the sample variance of the influence function. We modified estimation.sample.splitting's code to accommodate survey sampling weights.[62]

We also estimated possible effect modification by tobacco use by subtracting risk difference estimates (to calculate differences in risk differences). We calculated standard errors for differences in risk differences by taking the square root of the sum of squared

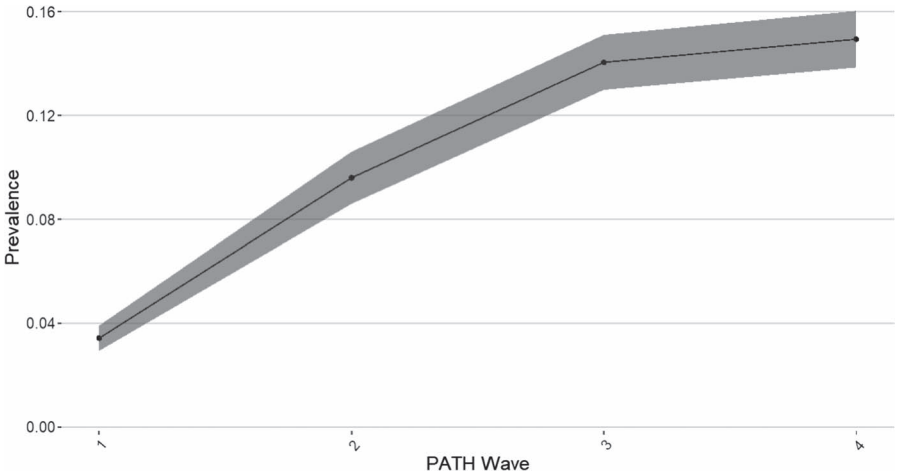

Figure 2. Nicotine vaping prevalence across Population Assessment of Tobacco and Health Study waves 1 through 4 ($n = 9571$ baseline participants 12-16 years old).

standard errors of each risk difference $\left(\sqrt{RD_1^2 + RD_2^2}\right)$, which could be anticonservative if estimates were not independent.[67]

All analyses were weighted using wave 1 survey sampling weights because we used multiple imputation to impute data for all wave 1 youth through wave 5.

Results

Distributions of exposure and confounders at baseline

Of the 9571 participants in the analytic cohort, only 3.4% vaped nicotine products in the past year (Supplementary Table S7) at baseline (2013-2014), which may reflect the public's relatively low awareness of e-cigarettes in 2013, the inclusion of middle school–aged children in the sample, and the removal of anyone with prevalent cannabis or other substance use at wave 1 from the analytic cohort. Past-year nicotine vaping prevalence increased from 3.4% in wave 1 to 10% in wave 2, 14% in wave 3, and 15% in wave 4 (Figure 2).

The sample was about two-thirds non-Hispanic White and included slightly more boys (52%) than girls (47%). Two-thirds of parents were currently married. About 40% of youth reported that a parent or guardian lived separately from them. About 20% to 32% of youth reported mild behavioral or mood problems, while slightly fewer reported a willingness to break rules (18%) and do frightening things (15%). Over 30% of respondents reported that tobacco is used by someone other than the youth in the home and that tobacco is not prohibited in the home.

Nicotine-vaping youth were more likely to be non-Hispanic White, male, and from lower-income households than non-nicotine-vaping youth (Supplementary Table S8). They were also more likely to have parents who were unmarried and had less educational attainment and who would not be upset if the youth used tobacco. Nicotine-vaping youth were more likely to report some types of behavioral or mood problems and sensation-seeking predisposition, tobacco use in the past month, residing with someone who used tobacco in the home, and lifetime alcohol use.

Longitudinal incremental propensity score effects

By wave 2, the observed cannabis initiation risk was 0.5 percentage points (95% CI, 0.2-0.8) higher than it would have been had nicotine vaping odds been 90% lower in wave 1 (δ= 0.1) (Figure 3). By waves 3 and 4, the observed risk was 2.3 (95% CI, 1.3-3.2) and 4.6 (95% CI, 3.3-5.8) percentage points higher than it would have been had nicotine vaping odds been 90% lower in prior waves. By wave 5, the observed risk was 6.2 percentage points (95% CI, 4.6-7.7) higher than it would have been had nicotine vaping odds been 90% lower in prior waves.

By wave 2, the observed other substance initiation risk was 0.2 percentage points (95% CI, 0.0-0.4) higher than it would have been had nicotine vaping odds been 90% lower in wave 1 (δ= 0.1) (Figure 3). By waves 3 and 4, the observed risk was 0.4 (95% CI, –0.5 to 1.4) and 1.2 percentage points (95% CI, 0.0 to 2.4) higher than it would have been had nicotine vaping odds been 90% lower in prior waves, respectively. By wave 5, the observed risk was 1.8 percentage points (95% CI, 0.4-3.2) higher than it would have been had nicotine vaping odds been 90% lower in prior waves.

The incremental propensity score effect on cannabis initiation by wave 5 was stronger among participants who had a history of tobacco use than those who did not (Figure 4). Among individuals with and without a history of tobacco use, the observed wave 5 cannabis initiation risks were 9.4 (95% CI, 6.1-12.7) and 4.3 (95% CI, 3.5-5.1) percentage points greater than the risks would have been had nicotine vaping odds been 90% lower in prior waves, respectively (Figure 3). The difference in risk differences was 5.1 (95% CI, –5.3 to 15.4) percentage points. The effect on other substance initiation by wave 5 also appeared to vary by tobacco use history (Figure 4). Among individuals with and without a history of tobacco use, the observed wave 5 other substance initiation risks were 3.6 (95% CI, 0.2-7.0) and 0.8 (95% CI, 0.0-1.5) percentage points greater than the risks would have been had nicotine vaping odds been 90% lower in prior waves, respectively. The difference in risk differences was 2.8 (95% CI, –0.8 to 6.6) percentage points.

Discussion

We examined whether evidence supports effects of nicotine vaping on the initiation of cannabis or other substances during a 6-year period of increasing nicotine vaping popularity among youth aging into young adulthood. Two observations emerged from our analysis. First, a lower propensity of nicotine vaping was associated with reduced longitudinal risks of cannabis and other substance initiation among the selected subsample that excludes youth who had used cannabis or other substances by wave 1. Second, wave 5 associations comparing observed with

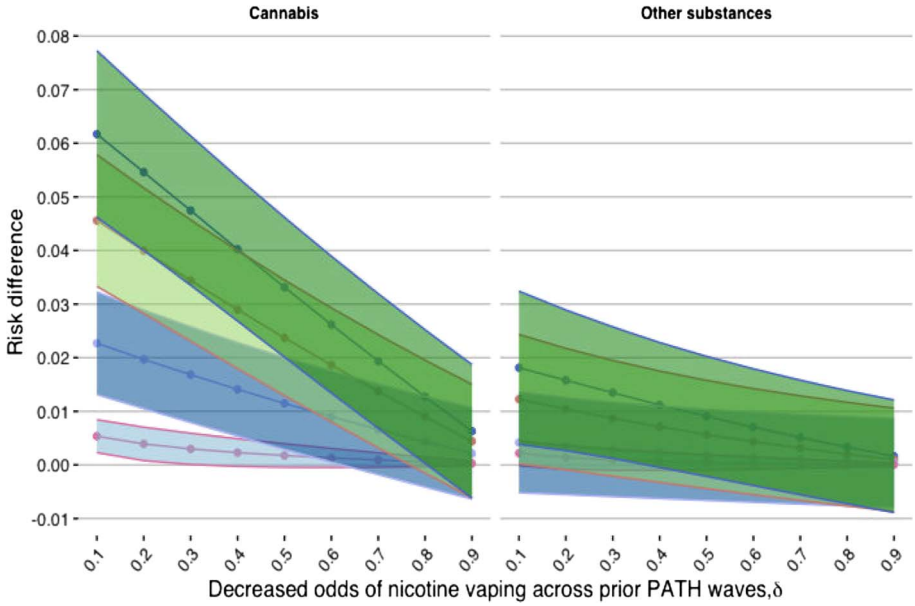

Figure 3. Risk differences and 95% confidence intervals comparing past-year observed cannabis initiation risks and past-year observed other substance initiation risks by each follow-up wave with those risks had nicotine vaping odds been 10% to 90% lower in prior waves (δ= 0.9 to δ= 0.1, respectively), controlling for baseline confounding for effects by wave 2 and baseline and time-varying confounding for effects by waves 2 through 5 (n = 9571 baseline participants 12-16 years old). Example: Where δ= 0.1 on plot, risk difference shown is $E\left(Y_t - Y_t^{\delta=0.1}\right)$.

90% lower nicotine vaping odds appeared qualitatively stronger comparing those with a history of tobacco use to those without one in terms of cannabis and other substance initiation but were not significantly different.

Our results are compatible with others' findings that nicotine vaping is associated with subsequent initiation of cannabis and other substances.[12,15,43] We also expanded upon others' findings. Our study period was 3 years longer than the next longest study, and it spanned the transitional period from adolescence into young adulthood for most participants. The extent to which our estimates can be interpreted as causal effects partially depends on the degree to which we controlled for confounding. To the extent the data allowed, we controlled for time-invariant and time-varying confounders specified in substance use theory and prior studies, which likely affected nicotine vaping and the outcomes during the transitional period (eg, living arrangements, academic performance).[31-40,55,56,68-73] Based on the extent to which we adequately controlled for confounding, our findings may be evidence that nicotine vaping has long-term effects on cannabis and other substance initiation as adolescents age into adulthood. They may also be evidence that lowering nicotine vaping prevalence may have reduced the number of people who later initiated cannabis or other substances. Our study does not address whether lowering nicotine vaping prevalence would have prevented subsequent cannabis and other substance use among people who had previously used these substances.

In contrast with previous research,[13,17] we found no statistically significant evidence for effect modification by history of tobacco use on cannabis or other substance initiation. Although we note that our statistical estimand is not directly comparable

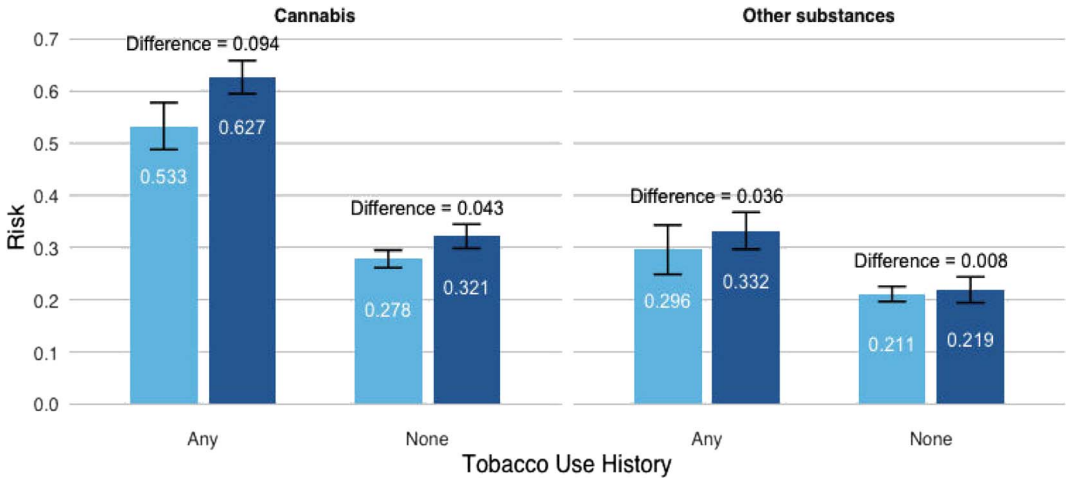

Figure 4. Observed wave 5 cannabis initiation and other substance initiation risks (and 95% confidence intervals) and those risks had nicotine vaping odds been 90% lower in prior waves, as well as differences in those risks, stratified by history of tobacco use at waves 1 through 4 and controlling for baseline and time-varying confounding (n = 9571 baseline participants 12-16 years old).

with those from prior studies, there may be explanations for why our estimate for effect modification did not reach statistical significance. First, tobacco use could have happened years prior to vaping, which may diminish the strength of the effect. Second, the finite sample contained a small number of participants who had a tobacco use history, which could lead to imprecise effect estimates. Despite the absence of statistically significant evidence for effect modification, the association with cannabis use was qualitatively stronger among participants who had versus did not have a tobacco use history, which is also contradictory with prior research. To our knowledge, no prior studies evaluated effect modification between vaping and tobacco use on other substance use.

Our study encountered some limitations. First, misclassification due to social desirability was likely because participants self-reported sensitive topics. In this study, social desirability can cause a correlation between reasons for misreporting different substance use behaviors, such as stigma and illegality of substance use for individuals under a particular age[74]; however, PATH used audio computer-assisted self-interviewing and computer-assisted personal interviewing, and participants were assured that responses were confidential to avoid socially desirable responses. A second limitation is unmeasured confounders, such as friends' substance use, parents' smoking during the prenatal period or childhood or adolescence, parental supervision, and neighborhood risks (eg, density of vape shops). Direct measures of these constructs were absent; however, we comprehensively controlled indirect measures (eg, someone else uses tobacco in the home, house rules about tobacco in the home, would use e-cigarettes if a best friend offered, noticed e-cigarette advertising). Third, missing data was an issue. To mitigate potential bias, we imputed missing data under the MAR assumption, which was possibly inadequate if they were dependent on unmeasured data.

In summary, we found evidence consistent with nicotine vaping's positive effects on cannabis and other substance initiation among adolescents as they aged into adulthood from 2013 to 2019. Public health interventions designed to decrease nicotine vaping prevalence include an increase in the age to legally purchase nicotine products,[75] bans on nicotine vaping flavors aimed at youth consumers,[76] the US Food and Drug Administration ban of JUUL products,[77] and vaping restrictions where other tobacco products are not allowed. A comprehensive strategy of limiting cannabis and other substance initiation may include these interventions and other levers that blunt the effects of nicotine vaping on cannabis and other substance initiation; these levers may be identified through further investigation of potential effect modifiers and mediators.

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Supplementary material

Supplementary material is available at the *American Journal of Epidemiology* online.

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Conflict of interest

The authors declare no conflicts of interest.

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