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Differences in the Association between Use of Electronic Vaping Products and Subsequent Tobacco and Marijuana Use among US Youth

Zongshuan Duan

ABSTRACT

DIFFERENCES IN THE ASSOCIATION BETWEEN USE OF ELECTRONIC VAPING PRODUCTS AND SUBSEQUENT TOBACCO AND MARIJUANA USE AMONG US YOUTH

By

ZONGSHUAN DUAN

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Limited evidence shows that e-cigarette use is associated with subsequent cigarette and marijuana use among US adolescents. However, it remains unclear whether these associations differ by individual characteristics and state-level policies. This dissertation examines effect modification of biological sex on the association between e-cigarette use and subsequent cigarette use (Study One), effect modification of mental health conditions on the association between e-cigarette use and subsequent marijuana use (Study Two), and effect modification of state recreational marijuana laws on the association between e-cigarette use and subsequent marijuana use (Study Three).

Data were compiled from the first four waves (2013-2018) of the Population Assessment of Tobacco and Health (PATH) Study. Wave 1 to 3 were each considered as the baseline for its corresponding 12-month follow-up wave. The study population included adolescents (aged 12-17) who reported never using cigarettes or marijuana at baseline. Generalized estimating equations (GEE) were used to evaluate the associations and effect modifications.

Study One found that among baseline never cigarette smokers, baseline past-30-day e-cigarette use was significantly associated with past-30-day cigarette smoking at follow-ups. This association was significantly stronger for boys (aOR=6.17, 95% CI: 2.43–15.68) than for girls (aOR=1.10, 95% CI: 0.14–8.33). Study Two found that baseline e-cigarette use was significantly associated with marijuana use at 12-month follow-ups. Adolescents with severe internalizing (IMH) or externalizing mental health (EMH) problems were significantly more likely to initiate marijuana use. Additionally, e-cigarette users who reported more severe IMH symptoms were less likely to initiate marijuana use (aOR=3.04, 95% CI: 1.20–7.74), compared with those with less severe IMH problems (aOR=10.15, 95% CI: 4.72–21.81). Study Three found that the association between baseline past-30-day e-cigarette use and past-30-day marijuana use at follow-ups was significantly stronger for adolescents in states that legalized adult recreational marijuana use (aOR=18.39, 95% CI: 4.25–79.68) than those in states without such laws (aOR=5.09, 95% CI: 2.86–9.07).

The findings highlighted that efforts to curb youth cigarette and marijuana initiation may benefit from efforts to reduce youth vaping. Tailored interventions characterized by individual demographics and state policies are warranted for e-cigarette using adolescents.

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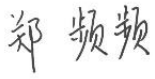

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Author's Statement Page

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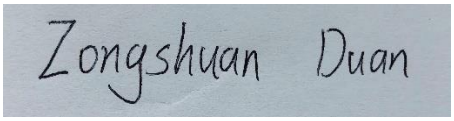

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Chapter 1: Literature Review and Statement of Purpose

Part A: Comprehensive Review

Use of cigarettes, marijuana, and e-cigarettes among US adolescents

The prevalence of combustible cigarette smoking declined substantially among adolescents in the United States in the first two decades of the 21st Century. Among high school students, the prevalence of current cigarette smoking had declined to 4.6% in 2020 from approximately 30% in 2000.[1 2]

Meanwhile, the Monitoring the Future (MTF) survey reported that while the prevalence of past-30-day marijuana use declined from 9.1% in 2000 to 6.5% in 2020 among 8th graders, and from 19.7% in 2000 to 16.6% in 2020 among 10th graders, the prevalence of past-30-day marijuana use among 12th graders rarely changed from 2000 (21.6%) to 2020 (21.1%).[3] Marijuana is the most used illicit substance among adolescents. The prevalence of past-30-day daily marijuana use for youth in grades 8th, 10th, and 12th were 1.1%, 4.4%, and 6.9%, respectively, in 2020.[4] Studies indicated that even though marijuana use among US youth had been declining at a slow rate over the past decade, the level of perceived harm associated with marijuana use had declined substantially.[3 5-7] The proportion of 12th-graders perceiving regular marijuana use as harmful had been declining substantially below 30% from approximately 80% in the 1990s.[3 7] The declining perceived risks among US adolescents coincided with recent movements of marijuana legalization, at least partially due to the fact that adolescents may interpret marijuana use as safe when more states legalize marijuana use as legitimate for medical or recreational purposes.[7 8] The steady level of marijuana use in recent years may be partially attributable to the declining trend of adolescent cigarette use; however,

without a further decline in cigarette smoking, it is concerning that the declining trend of adolescent marijuana use would reverse in the future.[7]

The remarkable achievements in youth cigarette control and the declining trend of marijuana use could be substantially undermined by the recently emerged innovative tobacco products. Even though combustible cigarettes remain the predominant tobacco product in the US marketplace, used mainly by adults, the US tobacco market landscape has become increasingly diversified due to the emergence of electronic cigarettes, with an increasing proportion of adolescents and young adults using innovative electronic cigarette products.[1] Electronic cigarettes, also known as e-cigarettes, electronic vaping products (EVPS), or electronic nicotine delivery systems (ENDS), has grown in popularity among adolescents since it entered the US market in 2007.[9] Estimates from the National Youth Tobacco Survey (NYTS) showed that in 2019, past-30-day (P30D) use of e-cigarettes was 27.5% among high school students and 10.5% among middle school students, increased from 1.5% and 0.6% in 2011, respectively.[10] In 2020, the prevalence of current e-cigarettes declined, with 19.6% of high school students and 4.7% of middle school students reporting using e-cigarettes in the past 30 days.[11] Consistently, the MTF survey also demonstrated the increasing prevalence of nicotine and marijuana vaping before 2019 among US adolescents.[12] In 2020, the prevalence of daily or near-daily nicotine vaping remained stable among 8th graders, but declined from 6.8% in 2019 to 5.6% in 2020 among 10th graders, and from 11.6% in 2019 to 8.3% in 2020 among 12th graders.[4] From 2019 to 2020, the percentage of youth reporting daily or near-daily marijuana vaping declined from 0.8% to 0.7% among 8th graders, from 3.0% to 1.7% among 10th graders, and from 3.5% to 2.5% among 12th graders.[4]

One primary concern of youth e-cigarette use is to increase the likelihood of future use of nicotine products and substances among adolescents,[13-15] even though current literature on the potential gateway effects of e-cigarettes are mixed.[16-19] The growing popularity of e-cigarettes among US youth, particularly among those who would be otherwise less likely to initiate cigarette and marijuana use, may have an impact on the current trends of youth cigarette use or substantially increase adolescent marijuana use. Therefore, it is of public health significance to monitor the longitudinal trends of youth use of e-cigarettes, cigarettes, and marijuana products, and understand the transitions from initial e-cigarette use to subsequent use of cigarettes and marijuana among US youth.

Putative association between e-cigarette use and subsequent cigarette use among US adolescents

Growing evidence from longitudinal studies documented a positive association between e-cigarette use and subsequent cigarette smoking initiation among adolescents,[20-23] leading to concerns that the increased e-cigarette use among youth may potentially addict a new generation to combustible cigarettes, resulting in a lifetime nicotine addiction.[24]

A meta-analysis reported that, among youth and young adults, the pooled adjusted odds ratio (aOR) for subsequent cigarette smoking initiation was 3.50 (95% CI: 2.38-5.16) among ever e-cigarette users compared with never e-cigarette users. In addition, it found that the pooled aOR for P30D cigarette smoking at follow-up was 4.28 (95% CI: 2.52-7.27) among baseline P30D e-cigarette users compared with those who did not use e-cigarettes in the past 30 days at baseline.[20] Leventhal et al. (2015) used a school-based cohort in ten public schools in Los Angeles and found that among high school students, baseline e-cigarette use was associated with a greater likelihood of use of any combustible tobacco product averaged across the 6-month and 12-month follow-up periods (aOR=

2.73, 95% CI: 2.00-3.73).[21] Primack et al. (2015) used a national longitudinal cohort of youth and young adults and found that baseline e-cigarette use was significantly associated with progression to smoking (aOR=8.3; 95% CI: 1.2-58.6).[22] Chafee et al. (2018) used data from the first two waves of the PATH Study and found that compared with never e-cigarette users, those who had ever used e-cigarettes had a higher likelihood of progression to current established smoking, P30D cigarette smoking, and established cigarette smoking. In addition, the adjusted odds ratio indicated that e-cigarette ever use may be positively associated with current established smoking (aOR=1.80, 95% CI: 1.04–3.12). However, the association was borderline insignificant for established smoking (aOR=1.57, 95% CI: 0.99–2.49) and past-30-day smoking (aOR=1.32, 95% CI: 0.99–1.76).[23] Keller-Hamilton (2021) used a sample of adolescent boys from urban and Appalachian Ohio and found that compared to non-e-cigarette users, e-cigarette smoking adolescent boys were at an elevated likelihood of initiating subsequent cigarette smoking (RR=2.71, 95% CI: 1.89-3.87).[25]

Putative association between e-cigarette use and subsequent marijuana use among US adolescents

A growing body of longitudinal studies reported positive associations between e-cigarette use and subsequent marijuana use among US adolescents. A recently published meta-analysis based on eighteen cross-sectional and three longitudinal studies found that the pooled odds of marijuana use among adolescents who used e-cigarettes were 3.5 times the corresponding odds for non-e-cigarette users (aOR=3.47, 95% CI: 2.63–4.59); in addition, the pooled aOR based on three longitudinal studies was 2.43 (95% CI: 1.51–3.90).[26] Audrain-McGovern et al. (2018) used a school-based longitudinal sample in ten public high schools in Los Angeles and found that compared with never e-cigarette users, those who reported ever e-cigarette use was associated with an elevated likelihood of initiating marijuana use (aOR=3.63, 95% CI: 2.69-4.90) and current marijuana use in 24 months

(aOR=3.67, 95% CI: 2.51-5.36). Dai et al. (2018) used the first two waves of the PATH Study youth sample and found that relative to respondents who reported never using e-cigarettes, e-cigarette ever use was positively associated with subsequent marijuana use in 12 months (aOR=1.9, 95% CI: 21.4-2.5).[27] Evans-Polce et al. (2020) used data from the MTF panel of 12 graders in 2014 and 2015, and found that compared with respondents who didn't use e-cigarettes, e-cigarette only users were less likely to perceive any marijuana as risky at follow-up than nonusers (aOR=0.15, 95% CI: 0.04-0.65) and more likely to report past-30-day marijuana use (aOR=3.82, 95% CI: 1.45-10.04). In addition, Park et al. (2020) used latent class growth analyses with an online sample that followed over two years, and found that compared to adolescents who had never used e-cigarettes, respondents who used e-cigarettes were more likely to develop alcohol and marijuana use.[29]

Part B: Summary of limitations in previous studies

Despite the growing number of cohort studies investigating the prospective relationships between adolescent e-cigarette use and subsequent cigarette smoking and marijuana use, no study has examined how the longitudinal associations between baseline e-cigarette use and future cigarette or marijuana use may differ by individual characteristics, such as gender, race, age, socioeconomic status, and mental health condition. In addition, with more states legalizing recreational marijuana use for adults in recent years, the potential interactive impact of marijuana legalization on adolescent marijuana initiation in the context of the youth vaping epidemic has received minimal research attention. Few previous studies controlled mental health conditions and state-level policies in their models.

Putative sex difference in the association between e-cigarette use and subsequent cigarette smoking

Documented evidence suggests that the tobacco behaviors and addiction among adolescents are dependent upon their biological sex.[31] Unfortunately, to date, tobacco control policies and interventions have remained largely gender/sex blind, with limited recognition of the importance of understanding the sex differences in the mechanism and consequences of initiation and transition of tobacco products.[31 32] Biological sex is a significant dimension for nearly all public health areas,[33] and tobacco product use is no exception. Evidence from laboratory experiments with non-human subjects indicated that the neurobiological mechanisms underlying nicotine seeking and metabolism differ between males and females.[34 35] Due to the presence of higher level of estrogen, females metabolize nicotine faster and experience lower rewarding effects of nicotine than males.[36] Therefore, while men were more likely to smoke for the reinforcing stimulant effects of nicotine, women were more likely to smoke for other reasons, such as emotion regulation and reaction to nicotine-related cues.[37] Additionally, a meta-analysis based on social studies revealed that the norms associated with gender roles and the sex composition of adolescents' social networks might differentially affect their tobacco use initiation and use patterns.[38] In general, the traditional sex roles placed more restrictions on women's behaviors, and the norms also contributed to social pressures and expectations against women's cigarette smoking behaviors.[38 39] Due to variations in the factors contributing to gender differences in tobacco use, adolescent girls who use e-cigarette may have different patterns of transitioning to cigarette smoking, compared with their male counterparts. Consequently, the general associations between e-cigarette use and subsequent cigarette smoking initiation reported in previous studies may mask important sex differences, resulting in inaccurate predictions of the

impact of policies and interventions aiming to curb adolescent cigarette use. In addition to the important knowledge gap regarding the potential sex difference, many previous studies did not control for the effect of mental health conditions, which were found to be associated with the initiation of tobacco use among adolescents.[40-42] Despite the knowledge gap with sex differences, few studies controlled the effects of mental health conditions, which were identified to be associated with tobacco product use.[43 44]

Putative mental health differences in the association between e-cigarette use and subsequent marijuana use

Marijuana can be taken orally or smoked with other tobacco products. More recently, the using methods had expanded to vaping, blunting, or eating with different forms of resin extracts.[45] There is a documented relationship between marijuana and tobacco use, particularly for marijuana vaping and blunting.[46-49] Marijuana vaping among adolescents increased significantly in 2017 as this new way of using marijuana becomes more mainstream.[50] Tetrahydrocannabinol, which is short for THC, is the primary psychoactive ingredient in vaped marijuana.[51] Since August 2019, a multistate outbreak of e-cigarette, or vaping, product use–associated lung injury (EVALI) occurred in all 50 states with 2,602 reported cases and 57 confirmed deaths by January 2020.[52] All the EVALI patients reported using vaping products, and most patients reported using THC-containing products.[53] Blunting is another popular pattern of marijuana use, featured by emptying a cigar/cigarillo product to replace with cannabis.[54] A systematic review based mainly on observational/descriptive studies indicated that blunting might contribute to nicotine exposure and adverse health effects among adolescents, which may result in a developmental change in brain functions in adolescence and young adulthood, and lead to exclusive tobacco use patterns.[55]

The general associations between e-cigarette use and subsequent marijuana initiation reported in previous studies may mask how this association would differentiate for vulnerable populations, particularly for groups characterized by mental health problems. A recently published literature review indicated that mental health status was associated with elevated e-cigarette use among adolescents.[56] In addition, mental health problems are closely associated with the use of substance and nicotine products among adolescents and young adults.[57-60] Adolescent mental health problems were usually categorized as internalizing and externalizing mental health problems.[61] Internalizing problems are conceptualized as inner-directed and generating distress in the individual, featured with anxiety, depressive, and somatic symptoms; externalizing problems are described as outer-directed and generating discomfort and conflict in the surrounding environment, featured with impulsive, disruptive conduct, and substance use symptoms.[61 62] Evidence from longitudinal studies showed that externalizing problem behavior was a robust predictor of adolescent substance use, while the findings on the prospective associations between internalizing problems and substance use had been mixed.[63-67] In general, previous studies, mostly based on convenience samples, suggested that internalizing problems were moderately protective against substance use among adolescents, given that internalizing problems were protective against interacting with deviant peers to adopt substance use.[63 68] These findings indicated that mental health conditions, particularly internalizing problems, may modify the effects of initiation of marijuana use with other factors, such as e-cigarette use. More evidence from longitudinal studies is needed to determine which type of mental health problems may affect adolescents' initiation of marijuana use and examine if mental health problems may modify the effects of e-cigarettes on subsequent marijuana use among adolescents. In addition, most previous studies were individual-based and neglected the potential confounding effects of

state-level marijuana legalization status, which were found to be associated with marijuana use, abuse, and dependence.[69-71]

Putative effect modification of state recreational marijuana laws on the association between e-cigarette use and subsequent marijuana use

The youth marijuana vaping epidemic in the US coincides with an evolving landscape of marijuana regulations. Although marijuana remains as a Schedule 1 controlled substance under federal law, state-level policies legalizing marijuana use for medical and recreational purposes have been increasing rapidly in recent years. As of 2021, 33 states and Washington DC, Guam, Puerto Rico, and the Virgin Islands had legalized medical marijuana use, and 14 states and territories have approved adult non-medical use.[73] Despite the absence of an increase in marijuana use among US youth in recent years,[3] it's a matter of concern whether illicit marijuana use among youth may begin to increase soon as more states legalizing medical and recreational marijuana use.[7] Evidence shows that youth marijuana use rates may be affected by state and local marijuana policies.[74] Marijuana use among adolescents may be positively correlated with state medical and recreational marijuana laws, partially due to the fact that the trends of legalizing marijuana use in the US could allow illicit marijuana to become more available for adolescents.[70] State recreational marijuana laws have been demonstrated to be associated with marijuana use and other drug abuse among adolescents.[69-71] However, little is known about whether legalizing recreational marijuana use would interact with other risk factors of marijuana use and further elevate the likelihood of marijuana initiation among adolescents, particularly with regard to its interaction with e-cigarette use among adolescents. In addition to e-cigarette use, existing evidence showed that adolescents with mental health disorders were more likely to use nicotine and other substance, leading to substance addiction.[40 75 76] For

example, youth with internalizing mental health problems were more likely to suffer from depression and anxiety, and therefore more likely to use tobacco/marijuana to help cope with these symptoms.[60 77]

Part C: Description of public health significance of this dissertation

Given the research gaps and limitations of previous studies, empirical evidence on the potential health differences is urgently needed, particularly those characterized by biological sex, mental health conditions, and state marijuana legalization policies, between initial e-cigarette use and subsequent cigarette and marijuana use among American adolescents. Specifically, three studies are proposed in this dissertation, including

- Sex difference in the association between electronic cigarette use and subsequent cigarette smoking among US adolescents: findings from the PATH Study Waves 1–4.
- Effect Modification of Mental Health Problems in the Association between E-Cigarette Use and Subsequent Marijuana Use among US Adolescents.
- Effect modification of recreational marijuana legalization on the association between e-cigarette use and future marijuana use among US adolescents.

These studies aim to address the research gaps in health differences using data from four waves of nationally representative longitudinal PATH surveys. In addition, these studies aim to identify the potential subgroup differences characterized by sociodemographic factors, mental health conditions, and state-level tobacco and substance regulations.

These studies may provide empirical evidence to inform tobacco control strategies that may minimize the risks of e-cigarettes. More studies are needed to elucidate the trajectories in transition

behaviors from e-cigarette to cigarette use, including the effects of e-cigarette in cigarette smoking initiation among non-users. Although the baseline adolescent e-cigarette use was found to be prospectively associated with the putative initiation of e-cigarette use and marijuana use, these associations may not occur equally in all population subgroups, particularly those characterized by gender and mental health status. In addition, it is critically important to identify the underlying socio-economic drivers of these transition behaviors. More importantly, understanding how longitudinal effects of e-cigarette use on tobacco and substance use patterns are associated with potential sex differences can strengthen existing tobacco control efforts, particularly in developing focused interventions.

These studies will provide empirical evidence on how the longitudinal effects of e-cigarette use on cigarette and marijuana are associated with mental health disparities, can strengthen existing tobacco control efforts, particularly in developing focused interventions among venerable population groups.

Part D: Dissertation aims and specific study objectives

Dissertation aims: To determine whether baseline use of e-cigarettes is associated with subsequent progression to traditional cigarette smoking or marijuana use among US adolescents, and whether these associations may differ by individual characteristics and state policies.

Study One Objectives:

- To estimate the association between baseline e-cigarette use and subsequent cigarette smoking initiation among US adolescents who had never smoked cigarettes before.

- To examine whether cigarette use initiation differed by subgroup, characterized by age, gender, race/ethnicity, mental health conditions, and parental educational attainment.
- To evaluate sex differences in the effects of e-cigarette use on cigarette use initiation.

Study Two Objectives:

- To investigate the effect of baseline e-cigarette use on subsequent marijuana use initiation among youth who had never used marijuana before.
- To examine whether marijuana use initiation differed by subgroup, characterized by individual demographics and state recreational marijuana laws.
- To evaluate internalizing and externalizing mental health differences in the effects of baseline e-cigarette use on marijuana use initiation.

Study Three Objectives:

- To investigate the effect of baseline e-cigarette use on subsequent marijuana use initiation among youth who had never used marijuana before.
- To examine whether marijuana use initiation differed by subgroup, characterized by individual demographics and state recreational marijuana laws.
- To evaluate whether and to what extent the state recreational marijuana use law may modify the effects of baseline e-cigarette use on marijuana use initiation.

Reference

1. US Department of Health & Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General: Atlanta, GA: US Department of Health and Human Services, Centers for Disease …, 2014.
2. Gentzke AS, Wang TW, Jamal A, et al. Tobacco Product Use Among Middle and High School Students—United States, 2020. *Morbidity and Mortality Weekly Report* 2020;69(50):1881.
3. Johnston LD, Miech RA, O'Malley PM, et al. Monitoring the Future National Survey Results on Drug Use, 1975-2018: Overview, Key Findings on Adolescent Drug Use. *Institute for Social Research* 2019
4. Abuse NIoD. Monitoring the Future 2020 Survey Results 2020 [Available from: https://www.drugabuse.gov/drug-topics/related-topics/trends-statistics/infographics/monitoring-future-2020-survey-results accessed March 30 2021.
5. Miech R, Johnston L, O'Malley P, et al. Monitoring the future national survey results on drug use, 1975-2018: volume I, secondary school students, 2019.
6. Schulenberg J, Johnston L, O'Malley P, et al. Monitoring the Future national survey results on drug use, 1975-2018: Volume II, college students and adults ages 19-60, 2019.
7. Miech R, Johnston L, O'Malley PM. Prevalence and attitudes regarding marijuana use among adolescents over the past decade. *Pediatrics* 2017;140(6):e20170982.
8. DuPont RL, Voth EA. Drug legalization, harm reduction, and drug policy. *Annals of Internal Medicine* 1995;123(6):461-65.
9. US Department of Health & Human Services. E-cigarette use among youth and young adults. A report of the Surgeon General. *Atlanta, GA* 2016
10. Cullen KA, Gentzke AS, Sawdey MD, et al. E-Cigarette use among youth in the United States, 2019. *Jama* 2019;322(21):2095-103.
11. Wang TW, Neff LJ, Park-Lee E, et al. E-cigarette use among middle and high school students—United States, 2020. *Morbidity and Mortality Weekly Report* 2020;69(37):1310.
12. Miech R, Johnston L, O'Malley PM, et al. Trends in adolescent vaping, 2017–2019. *New England Journal of Medicine* 2019;381(15):1490-91.
13. Etter JF. Gateway effects and electronic cigarettes. *Addiction* 2018;113(10):1776-83.
14. Base NSE. E-Cigarettes and the Use of Conventional Cigarettes.
15. Bell K, Keane H. All gates lead to smoking: the 'gateway theory', e-cigarettes and the remaking of nicotine. *Social Science & Medicine* 2014;119:45-52.
16. Chapman S, Bareham D, Maziak W. The gateway effect of e-cigarettes: reflections on main criticisms. *Nicotine and Tobacco Research* 2019;21(5):695-98.
17. Shahab L, Beard E, Brown J. Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents: a cross-sectional, matched control study. *Tobacco Control* 2020
18. Morgenstern M, Nies A, Goecke M, et al. E-Cigarettes and the Use of Conventional Cigarettes: A cohort study in 10th grade students in Germany. *Deutsches Ärzteblatt International* 2018;115(14):243.
19. Khouja JN, Suddell SF, Peters SE, et al. Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis. *Tobacco Control* 2020

20. Soneji S, Barrington-Trimis JL, Wills TA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. *JAMA pediatrics* 2017;171(8):788-97.
21. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *Jama* 2015;314(7):700-07.
22. Primack BA, Soneji S, Stoolmiller M, et al. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. *JAMA pediatrics* 2015;169(11):1018-23.
23. Chaffee BW, Watkins SL, Glantz SA. Electronic cigarette use and progression from experimentation to established smoking. *Pediatrics* 2018;141(4)
24. Health UDo, Services H. E-cigarette use among youth and young adults: A report of the Surgeon General. 2016
25. Keller-Hamilton B, Lu B, Roberts ME, et al. Electronic cigarette use and risk of cigarette and smokeless tobacco initiation among adolescent boys: A propensity score matched analysis. *Addictive Behaviors* 2021;114:106770.
26. Chadi N, Schroeder R, Jensen JW, et al. Association between electronic cigarette use and marijuana use among adolescents and young adults: a systematic review and meta-analysis. *Jama Pediatrics* 2019;173(10):e192574-e74.
27. Dai H, Catley D, Richter KP, et al. Electronic cigarettes and future marijuana use: a longitudinal study. *Pediatrics* 2018;141(5)
28. Evans-Polce RJ, Veliz PT, Boyd CJ, et al. E-cigarette and cigarette use among US adolescents: Longitudinal associations with marijuana use and perceptions. *American journal of preventive medicine* 2020;58(6):854-57.
29. Park E, Livingston JA, Wang W, et al. Adolescent E-cigarette use trajectories and subsequent alcohol and marijuana use. *Addictive Behaviors* 2020;103:106213.
30. National Academies of Sciences E, Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. 2017
31. Amos A, Greaves L, Nichter M, et al. Women and tobacco: a call for including gender in tobacco control research, policy and practice. *Tobacco control* 2012;21(2):236-43.
32. Solomon A. Gender, women, and the future of tobacco control. *Drugs and Alcohol Today* 2020
33. Ismail SA, McCullough A, Guo S, et al. Gender-related differences in care-seeking behaviour for newborns: a systematic review of the evidence in South Asia. *BMJ global health* 2019;4(3):e001309.
34. Pogun S, Yararbas G. Sex differences in nicotine action. Nicotine psychopharmacology: Springer 2009:261-91.
35. Piper ME, Cook JW, Schlam TR, et al. Gender, race, and education differences in abstinence rates among participants in two randomized smoking cessation trials. *Nicotine & Tobacco Research* 2010;12(6):647-57.
36. Benowitz NL, Lessov-Schlaggar CN, Swan GE, et al. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clinical Pharmacology & Therapeutics* 2006;79(5):480-88. doi: 10.1016/j.clpt.2006.01.008

37. Cosgrove KP, Wang S, Kim S-J, et al. Sex differences in the brain's dopamine signature of cigarette smoking. *Journal of Neuroscience* 2014;34(50):16851-55. doi: 10.1523/JNEUROSCI.3661-14.2014
38. Jacobs W, Goodson P, Barry AE, et al. The role of gender in adolescents' social networks and alcohol, tobacco, and drug use: a systematic review. *Journal of School Health* 2016;86(5):322-33.
39. Waldron I. Patterns and causes of gender differences in smoking. *Social science & medicine* 1991;32(9):989-1005.
40. Riehm KE, Young AS, Feder KA, et al. Mental health problems and initiation of e-cigarette and combustible cigarette use. *Pediatrics* 2019;144(1)
41. Upadhyaya HP, Deas D, Brady KT, et al. Cigarette smoking and psychiatric comorbidity in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry* 2002;41(11):1294-305.
42. Audrain-McGovern J, Rodriguez D, Kassel JD. Adolescent smoking and depression: evidence for self-medication and peer smoking mediation. *Addiction* 2009;104(10):1743-56.
43. Talley AE, Turner B, Foster AM, et al. Sexual minority youth at risk of early and persistent alcohol, tobacco, and marijuana use. *Archives of sexual behavior* 2019;48(4):1073-86.
44. Memedovich KA, Dowsett LE, Spackman E, et al. The adverse health effects and harms related to marijuana use: an overview review. *CMAJ open* 2018;6(3):E339.
45. Hudak J. Marijuana: a short history: Brookings Institution Press 2016.
46. Ramo DE, Liu H, Prochaska JJ. Tobacco and marijuana use among adolescents and young adults: a systematic review of their co-use. *Clinical psychology review* 2012;32(2):105-21.
47. Schauer GL, Berg CJ, Kegler MC, et al. Assessing the overlap between tobacco and marijuana: Trends in patterns of co-use of tobacco and marijuana in adults from 2003–2012. *Addictive behaviors* 2015;49:26-32.
48. Keyes KM, Vo T, Wall MM, et al. Racial/ethnic differences in use of alcohol, tobacco, and marijuana: Is there a cross-over from adolescence to adulthood? *Social Science & Medicine* 2015;124:132-41.
49. Pulvers K, Ridenour C, Woodcock A, et al. Marijuana use among adolescent multiple tobacco product users and unique risks of dual tobacco and marijuana use. *Drug and alcohol dependence* 2018;189:80-89.
50. Dai H. Self-reported marijuana use in electronic cigarettes among US youth, 2017 to 2018. *Jama* 2020;323(5):473-74.
51. Moore C, Rana S, Coulter C. Simultaneous identification of 2-carboxy-tetrahydrocannabinol, tetrahydrocannabinol, cannabinol and cannabidiol in oral fluid. *Journal of Chromatography B* 2007;852(1-2):459-64.
52. Siegel DA, Jatlaoui TC, Koumans EH, et al. Update: interim guidance for health care providers evaluating and caring for patients with suspected e-cigarette, or vaping, product use associated lung injury—United States, October 2019. *Morbidity and Mortality Weekly Report* 2019;68(41):919.
53. Blount BC, Karwowski MP, Shields PG, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *New England Journal of Medicine* 2020;382(8):697-705.

54. Giovenco DP, Miller Lo EJ, Lewis MJ, et al. “They’re pretty much made for blunts”: product features that facilitate marijuana use among young adult cigarillo users in the United States. *Nicotine & Tobacco Research* 2017;19(11):1359-64.
55. Schauer GL, Rosenberry ZR, Peters EN. Marijuana and tobacco co-administration in blunts, spliffs, and mulled cigarettes: A systematic literature review. *Addictive Behaviors* 2017;64:200-11.
56. Becker TD, Arnold MK, Ro V, et al. Systematic review of electronic cigarette use (vaping) and mental health comorbidity among adolescents and young adults. *Nicotine & Tobacco Research* 2020
57. Esmaeelzadeh S, Moraros J, Thorpe L, et al. Examining the association and directionality between mental health disorders and substance use among adolescents and young adults in the US and Canada—a systematic review and meta-analysis. *Journal of clinical medicine* 2018;7(12):543.
58. Zaman T, Malowney M, Knight J, et al. Co-occurrence of substance-related and other mental health disorders among adolescent cannabis users. *Journal of addiction medicine* 2015;9(4):317-21.
59. Bond L, Butler H, Thomas L, et al. Social and school connectedness in early secondary school as predictors of late teenage substance use, mental health, and academic outcomes. *Journal of Adolescent Health* 2007;40(4):357. e9-57. e18.
60. Groenman AP, Janssen TW, Oosterlaan J. Childhood psychiatric disorders as risk factor for subsequent substance abuse: a meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry* 2017;56(7):556-69.
61. Achenbach TM, Ivanova MY, Rescorla LA, et al. Internalizing/externalizing problems: Review and recommendations for clinical and research applications. *Journal of the American Academy of Child & Adolescent Psychiatry* 2016;55(8):647-56.
62. Brown BB, Prinstein MJ. Encyclopedia of adolescence: Academic Press 2011.
63. Scalco MD, Colder CR, Hawk Jr LW, et al. Internalizing and externalizing problem behavior and early adolescent substance use: A test of a latent variable interaction and conditional indirect effects. *Psychology of Addictive Behaviors* 2014;28(3):828.
64. Colder CR, Frndak S, Lengua LJ, et al. Internalizing and externalizing problem behavior: A test of a latent variable interaction predicting a two-part growth model of adolescent substance use. *Journal of abnormal child psychology* 2018;46(2):319-30.
65. Miettunen J, Murray G, Jones P, et al. Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. *Psychological medicine* 2014;44(8):1727-38.
66. Pedersen MU, Thomsen KR, Heradstveit O, et al. Externalizing behavior problems are related to substance use in adolescents across six samples from Nordic countries. *European child & adolescent psychiatry* 2018;27(12):1551-61.
67. Audrain-McGovern J, Rodriguez D, Testa S, et al. Adolescent E-Cigarette Onset and Escalation: Associations With Internalizing and Externalizing Symptoms. *Journal of Adolescent Health* 2020
68. Colder CR, Scalco M, Trucco EM, et al. Prospective associations of internalizing and externalizing problems and their co-occurrence with early adolescent substance use. *Journal of abnormal child psychology* 2013;41(4):667-77.

69. Cerdá M, Wall M, Keyes KM, et al. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug and alcohol dependence* 2012;120(1-3):22-27.
70. Cerdá M, Wall M, Feng T, et al. Association of state recreational marijuana laws with adolescent marijuana use. *JAMA pediatrics* 2017;171(2):142-49.
71. Cerdá M, Mauro C, Hamilton A, et al. Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA psychiatry* 2020;77(2):165-71.
72. Caulkins JP, Kilmer B, Kleiman MA. Marijuana Legalization: What Everyone Needs to Know®: Oxford University Press 2016.
73. National Conference of State Legislatures. State Medical Marijuana Laws 2019 [Available from: https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx accessed Jan 29 2020.
74. Ammerman S, Ryan S, Adelman WP, et al. The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics* 2015;135(3):e769-e85.
75. Green VR, Conway KP, Silveira ML, et al. Mental health problems and onset of tobacco use among 12-to 24-year-olds in the PATH study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2018;57(12):944-54. e4.
76. Duan Z, Wang Y, Huang J. Sex Difference in the Association between Electronic Cigarette Use and Subsequent Cigarette Smoking among US Adolescents: Findings from the PATH Study Waves 1–4. *International Journal of Environmental Research and Public Health* 2021;18(4):1695.
77. Zahn–Waxler C, Klimes–Dougan B, Slattery MJ. Internalizing problems of childhood and adolescence: Prospects, pitfalls, and progress in understanding the development of anxiety and depression. *Development and psychopathology* 2000;12(3):443-66.

Chapter 2: Study One

Sex difference in the association between electronic cigarette use and subsequent cigarette smoking among US adolescents: findings from the PATH Study Waves 1–4

Abstract

E-cigarettes are the most-used tobacco products among US adolescents. Emerging evidence suggests that adolescents using e-cigarettes are at elevated risk for initiating cigarette smoking. However, whether this risk may differ by sex remains unknown. This study analyzed data from Wave 1 to 4 of the Population Assessment of Tobacco and Health (PATH) Study, a nationally representative longitudinal survey. Generalized estimation equations (GEE) were performed to estimate the associations between baseline e-cigarette use and subsequent cigarette smoking, controlling for sociodemographic characteristics, mental health conditions, and other tobacco use. Effect modifications by sex were examined. Multivariate analyses showed that, among baseline never cigarette smokers, past-30-day e-cigarette use at baseline waves was significantly associated with past-30-day cigarette smoking at follow-up waves (aOR=3.90, 95% CI: 2.51–6.08). This association was significantly stronger for boys (aOR=6.17, 95% CI: 2.43–15.68) than for girls (aOR=1.10, 95% CI: 0.14–8.33). Additionally, using other tobacco products, older age, and having severe externalizing mental health problems at baseline were significantly associated with an increased likelihood of cigarette smoking at follow-up. The prospective association between e-cigarette use and cigarette smoking differs by sex among US adolescents. Sex-specific tobacco control interventions may be warranted to curb the youth tobacco use epidemic.

Introduction

Cigarette smoking among US youth has declined substantially since the mid-1990s.[1] Among 12th-grade students, the prevalence of past-30-day (P30D) cigarette smoking decreased steadily from 28.3% in 1996 to 7.5% in 2020.[2 3] However, e-cigarettes are becoming increasingly popular among adolescents, including those who are not susceptible to smoking cigarettes.[4-6] In 2020, 19.6% of high school students and 4.7% of middle school students reported using e-cigarettes in the past 30 days.[7] A growing body of evidence documented a positive association between e-cigarette use and subsequent cigarette smoking initiation among tobacco-naïve adolescents,[8-10] leading to concerns that the increased e-cigarette use among youth may potentially addict a new generation to combustible cigarettes, resulting in a lifetime nicotine addiction.[4] A recent meta-analysis combined the findings of 9 longitudinal studies and reported that, among youth and young adults, the pooled adjusted odds ratio (aOR) for subsequent cigarette smoking initiation was 3.62 (95% CI, 2.42-5.41) among ever e-cigarette users compared with never e-cigarette users. In addition, it found that the pooled aOR for P30D cigarette smoking at follow-up was 4.28 (95% CI, 2.52-7.27) among baseline P30D e-cigarette users compared with those who did not use e-cigarettes in the past 30 days at baseline.[8]

Despite the growing number of studies investigating the prospective relationships between adolescent e-cigarette use and subsequent cigarette smoking, no study had examined how this association may differ by sex. The tobacco use behaviors and nicotine addiction among adolescents are dependent upon their sex.[11] Unfortunately, to date, tobacco control policies and interventions have remained largely sex blind, with limited recognition of the importance of understanding the sex differences in the mechanism and consequences of tobacco products' initiation and transition.[11 12]

Sex is a significant dimension for nearly all public health areas,[13] and tobacco use is no exception. Evidence from laboratory experiments with non-human subjects indicated that the neurobiological mechanisms underlying nicotine seeking and metabolism differ between males and females.[14 15] Due to the presence of higher levels of estrogen, females metabolize nicotine faster and experience lower rewarding effects of nicotine than males.[16] Therefore, while men were more likely to smoke for the reinforcing stimulant effects of nicotine, women were more likely to smoke for other reasons, such as emotion regulation and reaction to nicotine-related cues.[17] Additionally, a meta-analysis based on social studies revealed that the norms associated with adolescent boys and girls, and the sex composition of adolescents' social networks might differentially affect their tobacco adoption and use behaviors.[18] In general, the traditional social norms placed more restrictions on women's tobacco use behaviors, and the norms also contributed to social pressures and expectations against women's smoking behaviors.[18-20] Due to variations in the factors contributing to sex differences in tobacco use, adolescent girls who use e-cigarettes may have different patterns of transitioning to cigarette smoking, compared with their male counterparts. Consequently, the general associations between e-cigarette use and subsequent cigarette initiation reported in previous studies may mask important sex differences, resulting in inaccurate predictions of the impacts of policies and interventions aiming to curb adolescent tobacco use.

In addition to the important knowledge gap regarding the potential sex difference, many previous studies did not control for the effect of mental health conditions, which were found to be associated with the initiation of tobacco use among adolescents.[21-23] Our study aims to address these critical research gaps. Specifically, we used the youth cohort from the first four waves of the Population Assessment of Tobacco and Health (PATH) Study to investigate whether the longitudinal

association between initial e-cigarette use and subsequent cigarette smoking initiation would differ by sex, controlling for individual's sociodemographic characteristics, use of other tobacco products, and mental health conditions. We hypothesize that this association would differ by sex. Additionally, we hypothesize that significant differences exist in cigarette smoking initiation between subgroups characterized by individual factors.

Methods

Study sample and design

Data were collected from 2013 through 2018 and analyzed in 2020. This study used a youth cohort sample (aged 12-17) compiled from Wave 1 (Sept 2013 to Dec 2014), Wave 2 (Oct 2014 to Oct 2015), Wave 3 (Oct 2015 to Oct 2016), and Wave 4 (Dec 2016 to Jan 2018) of the PATH Study, an ongoing nationally representative cohort study conducted by the US National Institutes of Health (NIH) and the Food and Drug Administration (FDA).[24 25] A four-stage stratified probability sample was selected to represent the noninstitutionalized population in the US.[25] Among households that were screened, the weighted response rates for the youth cohort were 78.4% (Wave 1), 87.3% (Wave 2), 83.3% (Wave 3), and 79.5% (Wave 4), respectively.[26 27] In the PATH data, multiple imputations were performed on the variables such as sex, age, and use of tobacco products to address the missing data bias. Further details regarding the study design and sampling methods are published elsewhere,[25] and are described in the PATH Study Public-Use Files user guide.[26] This study involved only secondary data analysis of the PATH survey data, which contained no personally identifiable information, and was exempt for ethical review by the Georgia State University Institutional Review Board (IRB

Number: H20183; Reference Number: 357029). This article follows the reporting guideline for cohort studies of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[28]

In this study, we followed a validated approach used by the data management and research team of the PATH study to stack covariates in the baseline wave with cigarette smoking status at its corresponding follow-up wave study.[29-31] In this study, Wave 1, Wave 2, and Wave 3 were each considered as the baseline wave for its corresponding 12-month follow-up wave. The youth all-wave weights for the Wave 1 cohort were used to produce nationally representative estimates. The all-wave weights were assigned only to Wave 1 respondents and the shadow sample of individuals aged 9-11 at Wave 1 who completed interviews at all waves while they were 12-17 years old.[27] The target population of this study included youth respondents who reported never having used cigarettes at baseline waves. At each baseline wave, participants were asked, “Have you ever tried cigarette smoking, even one or two puffs”, and those who responded “No” were identified as baseline never cigarette smokers.

Measures

The primary outcome was the self-reported P30D cigarette smoking status at 12-month follow-up waves among never cigarette smokers at baseline waves. In the follow-up surveys, baseline never cigarette smokers who reported having smoked at least one cigarette in the past 30 days at follow-up waves were coded as P30D cigarette smokers. Additionally, respondents who tried cigarette smoking, even one or two puffs in between baseline and 12-month follow-up, were defined as ever cigarette smokers.

The primary exposure variable was the P30D use of e-cigarettes at baseline waves. In each baseline wave, never cigarette smokers who reported having used any e-cigarettes in the past 30 days were categorized as baseline P30D users of e-cigarettes.

Covariates were potential confounding variables selected based on previous literature,[8 10 29 32] including the following two domains. 1) Sociodemographic factors and other tobacco products use status at baseline waves: age (12-14 or 15-17), sex (male or female), race/ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, or Non-Hispanic Other), parental education (less than high school, high school graduate, some college or associate degree, and bachelor's degree or above), and P30D use of other tobacco products (defined as using cigar, hookah, or smokeless tobacco in the past 30 days). Sexual orientation (straight vs. homosexual, bisexual, or other), which was only available for participants aged 14 and above, was used to examine the bivariate associations with outcome variables but not included in the regression analysis. 2) Intrapersonal factors: the internalizing and externalizing mental health problems over the past 12 months at baseline waves. The PATH study included four items measuring internalizing problems and seven items measuring externalizing problems (Table 2.1). In this study, we followed a validated approach to sum up the scores for internalizing and externalizing problems, where the severity of mental health problems was categorized into low (0-1), moderate (2-3), and high severity (4 for internalizing problems or 4-7 for externalizing problems).[33 34]

Statistical analysis

All data management and analyses were conducted using Stata 15 (College Station, TX. StataCorp). The youth cohort all-wave weights were applied to account for the complex sample design features and produce nationally representative estimates. The balanced repeated replication

(BRR) approach with Fay's adjustment of 0.3 was used to compute statistical precision for all estimations.[25 29] We reported the weighted prevalence of outcomes at follow-up waves and their weighted associations with covariates at baseline waves. Generalized estimating equations (GEE) with unstructured covariance were used to estimate the associations between the outcomes and exposure variables, controlling for individual sociodemographic characteristics, use of other tobacco products, and mental health conditions. Additional GEE models were fitted to examine the potential effect modifications of sex on the association between P30D e-cigarette use at baseline and P30D cigarette smoking at 12-month follow-up. Subgroup analyses, separately for adolescent boys and girls, were conducted to compare the associations between e-cigarette use and subsequent cigarette smoking. Additionally, sensitivity analyses, based on the same set of analyses mentioned above in which the outcome measures were replaced with ever cigarette smoking, were conducted. All statistical tests were two-sided with the significance level set to 0.05.

Results

Sample and demographic characteristics

Our study sample included 5,001 youth never cigarette smokers at Wave 1, 6,637 at Wave 2, and 8,177 at Wave 3. The enrollment and exclusion procedures are illustrated in Figure 2.1.

Among youth who reported never having used cigarettes at Wave 1, the weighted prevalence of P30D e-cigarette use was 0.4%; almost all (96.7%) respondents were between age 12 and 14; 49.2% of the respondents were girls; 53.4% were Non-Hispanic White, 14.1% were Non-Hispanic Black, and 23.0% were Hispanic; 0.4% used other tobacco products in the past 30 days; and 18.1% and 29.5% of them experienced high severity of internalizing and externalizing mental health

problems in the past year, respectively. Among youth who reported never having used cigarettes at Wave 2, 0.9% of them used e-cigarettes in the past 30 days; over three quarters (77%) of them were between age 12-14; 49.2% were girls; 52.5% were Non-Hispanic White, 13.9% were Non-Hispanic Black, and 23.9% were Hispanic; 0.6% used other tobacco products in the past 30 days; and 19.7% and 28.8% experienced high severity of internalizing and externalizing mental health problems in the past year, respectively. Among youth who reported never having used cigarettes at Wave 3, 1.5% used e-cigarettes in the past 30 days; approximately two-thirds of them were between age 12-14; 48.9% were girls; 51.7% were Non-Hispanic White, 13.6% were Non-Hispanic Black, and 24.6% were Hispanic; 0.7% used other tobacco products in the past 30 days; and 21.3% and 29.1% experienced high severity of internalizing and externalizing mental health problems in the past year, respectively. Detailed descriptive statistics of other characteristics are presented in Table 2.2.

Past-30-day cigarette smoking at 12-month follow-up waves

As shown in Table 2.3, among adolescents who reported P30D e-cigarette use at baseline waves, the prevalence of P30D cigarette smoking was 4.0% (95% CI: 0.5%-27.7%) at Wave 2, 12.6% (95% CI: 5.1%-27.6%) at Wave 3, and 9.1% (95% CI: 4.9%-16.4%) at Wave 4, respectively. By contrast, among adolescents who did not use e-cigarette at baseline waves, the prevalence of P30D cigarette smoking was 1.2% (95% CI: 0.9%-1.6%) at Wave 2, 0.8% (95% CI: 0.6%-1.2%) at Wave 3, and 1.4% (95% CI: 1.1%-1.7%) at Wave 4, respectively. In addition, generally, the weighted prevalence of self-reported P30D cigarette smoking at follow-up waves was higher among adolescents who were older, sexual minorities, and having severe internalizing or externalizing mental health problems at baseline waves.

Multivariate analyses

As shown in Table 2.4, after adjusting for individual characteristics, adolescents who reported P30D e-cigarette use at baseline waves were significantly more likely to report P30D cigarette smoking in the follow-up waves (aOR=3.90, 95% CI: 2.51–6.08; P<0.001) (Model 1). Older age, P30D use of other tobacco products, severe externalizing mental health problems at the baseline waves were also statistically significantly associated with elevated odds of P30D cigarette smoking at follow-up waves, everything else being constant. In addition, being Non-Hispanic Black or Other and having parents with a bachelor's degree or above were associated with reduced odds of P30D cigarette smoking at follow-up waves. As shown in Model 2, the interaction between P30D e-cigarette use and sex, noted as "P30D e-cigarette use by Sex", was statistically significant (exponent of the estimated coefficients 3.18, 95% CI: 2.21-4.57), which indicated that the associations between cigarette smoking status at 12-month follow-up waves and P30D e-cigarette use at baseline waves were significantly different between adolescent boys and girls.

Table 2.5 showed the results of the subgroup analyses stratified by sex. For boys, P30D cigarette smoking at 12-month follow-up waves was statistically significantly associated with P30D e-cigarette use at baseline waves (aOR=6.17, 95% CI: 2.43-15.68; P<0.001), controlling for individual characteristics. However, for girls, the corresponding association was not statistically significant (aOR=1.10, 95% CI: 0.14–8.33; P=0.154), controlling for other covariates.

To evaluate whether the association between e-cigarette use and subsequent cigarette smoking is robust to outcome measures, sensitivity analyses in which cigarette smoking was measured by ever cigarette smoking, rather than P30D cigarette smoking at 12-month follow-up waves, were conducted. The results of the sensitivity analyses were presented in Table 2.6, Table 2.7, and Table 2.8. Consistent with results presented in Table 2.3, results in Table 2.6 show that, at each

follow-up wave, the prevalence of ever cigarette smoking was higher among adolescents who reported P30D e-cigarette use at corresponding baseline wave, compared with those who did not. In addition, results in Table 2.7 were similar to those in Table 2.4 regarding the adjusted associations between ever cigarette smoking at 12-month follow-up waves and characteristics at baseline waves. Notably, the interaction term between e-cigarette use and sex (P30D e-cigarette use by Sex) was also statistically significant, consistent with the results in Table 2.4. Furthermore, the results of subgroup analyses in Table 2.8 showed that the adjusted ORs between ever cigarette smoking at 12-month follow-up waves and P30D e-cigarette use at baseline waves were 5.81 (95% CI: 3.34-10.13; P<0.001) and 2.31 (95% CI: 0.98-5.41; P=0.052) for adolescent boys and girls, respectively.

Discussion

This study aimed to examine whether and to what extent sex would affect the associations between initial e-cigarette use and subsequent cigarette smoking among American adolescents (aged 12-17). Although the longitudinal associations between e-cigarette use and subsequent cigarette smoking had been documented,[8-10] no previous studies examined the potential difference in this relationship by sex. Our results revealed, consistent with previous studies, that e-cigarettes use at baseline waves was significantly associated with P30D cigarette smoking at 12-month follow-up waves. More importantly, our study added to the current knowledge base by revealing that this association was significantly stronger for boys than for girls. The differential patterns were consistently observed regardless of whether the follow-up cigarette smoking status was measured by past 30-day use or ever use. The consistency indicates that sex differences in the association between initial P30D e-cigarette use and subsequent cigarette smoking are robust to outcome measures.

The differential effects characterized by sex may be partially attributable to the different levels of nicotine dependence between boys and girls. Our study showed that among P30D e-cigarette users, the number of days using e-cigarettes in the past 30 days was higher for boys than for girls (Table 2.9). The difference may indicate that among adolescents who used e-cigarettes, the level of nicotine dependence was likely to be higher for boys than girls. This finding is consistent with a recent literature review concluding that boys tended to use e-cigarettes more frequently than girls.[35] Since youth with higher nicotine dependence levels were presumably more likely to transition to cigarette smoking, the difference in nicotine dependence between e-cigarette using boys and girls may explain why e-cigarette using boys were more likely to advance to cigarette smoking than e-cigarette using girls.[10] In addition to use frequency, several other potential reasons may explain why boys may be more likely to develop nicotine dependency than girls from vaping. First, evidence showed that females metabolized nicotine faster than males due to estrogen.[16] The differential metabolism rates by sex suggest that females are more likely to experience higher adverse sensitivity and lower rewarding effects of nicotine than their male counterparts.[36-38] Consequently, e-cigarette using girls may be less likely to develop nicotine dependency and less susceptible to transition to cigarette smoking. In addition, the sources of acquisition for e-cigarettes may be different between girls and boys. A study in Connecticut showed that compared with boys, girls were more likely to obtain e-cigarettes from their peers,[39] suggesting more social and less frequent e-cigarette use among girls; hence the difference in transitioning to cigarette smoking. The sex differences in the association between baseline e-cigarette use and subsequent cigarette initiation suggest that policies/interventions aiming to combat the youth vaping epidemic may reduce subsequent cigarette smoking among the US youth population, particularly among adolescent boys. For example, a vaping

cessation media campaign that specifically targets at boys may reduce e-cigarette use among boys, and consequently, making them less likely to transition from e-cigarettes to cigarettes.

Our results also show that internalizing and externalizing mental health problems were prospectively associated with cigarette smoking initiation, controlling for sociodemographic covariates and use of e-cigarettes and other tobacco products. Our findings were consistent with other published studies,[21 40] suggesting that a wide range of mental health problems could be considered as predictors of cigarette smoking among adolescents. Early screening for mental health problems combined with targeted mental health interventions (e.g., school counseling, preventive efforts through primary care providers) may help reduce cigarette smoking among vulnerable youth.[41 42] Additionally, we found that older age, being Non-Hispanic White, and using other tobacco products were significantly associated with subsequent cigarette smoking in our study, consistent with findings reported in previous studies.[8 10 29 32] Notably, the magnitude of the association between P30D e-cigarette use at baseline waves and subsequent cigarette smoking was comparable to the association between P30D other tobacco use at baseline waves and subsequent cigarette smoking, indicating the importance of e-cigarette use in predicting subsequent cigarette smoking among US adolescents. Continued surveillance of e-cigarette and other tobacco product use among youth is therefore warranted.

This study is subject to several limitations. First, self-reported use of e-cigarettes, cigarettes, and other tobacco products may introduce recall bias and social desirability bias.[43] Future studies may consider using the PATH Study biomarker data files to examine the tobacco use status and verify the study hypotheses. Second, the small sample size of adolescent e-cigarette users in the PATH study prevented us from conducting a mediation analysis to further examine whether the sex

differences could be partially attributed to different nicotine dependence levels between boys and girls. Future studies are needed to further explore the mechanisms of the differential effects characterized by sex and other potential characteristics. Third, the association between e-cigarette use at baseline waves and subsequent cigarette smoking identified in this study did not represent a true causal relationship. However, our study did control for a wide range of potential confounding factors and established a temporal relationship and chronological sequence between e-cigarette use and subsequent cigarette smoking, addressing most, if not all, of the concerns and criticisms on the current literature regarding the potential gateway effect of e-cigarettes to cigarette smoking.[5 44-46] Furthermore, future studies may control other potential confounding factors, which may include a wide range of interpersonal and intrapersonal factors, product factors, and policy factors. In addition, further analyses using mediation analysis approach or factor analysis and structural equation modeling may be needed to explore the potential mechanism between baseline e-cigarette use and subsequent cigarette smoking initiation among US adolescents.

Conclusions

This study's findings highlighted the important sex differences in the longitudinal association between initial e-cigarette use and subsequent cigarette smoking among US adolescents. Efforts to curb the adolescent vaping epidemic may have added benefits to reduce cigarette initiation, particularly among adolescent boys. Sex-specific tobacco control interventions may be warranted to reduce youth tobacco use. In addition, targeted tobacco control interventions, focusing on youth with severe mental health conditions, are warranted. Finally, continued efforts are needed to monitor

tobacco and cigarette transitions among youth, particularly among vulnerable and high-risk youth subpopulations.

Reference

1. US Department of Health & Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General: Atlanta, GA: US Department of Health and Human Services, Centers for Disease …, 2014.
2. Johnston LD, Miech RA, O'Malley PM, et al. Monitoring the Future National Survey Results on Drug Use, 1975-2018: Overview, Key Findings on Adolescent Drug Use. Institute for Social Research, 2019.
3. NIDA. Study: Surge of teen vaping levels off, but remains high as of early 2020 2020 [Available from: https://www.drugabuse.gov/news-events/news-releases/2020/12/study-surge-of-teen-vaping-levels-off-but-remains-high-as-of-early-2020 accessed January 27 2021.
4. US Department of Health & Human Services. E-cigarette use among youth and young adults: A report of the Surgeon General, 2016.
5. Khouja JN, Suddell SF, Peters SE, et al. Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis. *Tobacco Control* 2020 doi: 10.1136/tobaccocontrol-2019-055433
6. Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tobacco control* 2019;28(2):146-51.
7. Wang TW, Neff LJ, Park-Lee E, et al. E-cigarette use among middle and high school students—United States, 2020. *Morbidity and Mortality Weekly Report* 2020;69(37):1310.
8. Soneji S, Barrington-Trimis JL, Wills TA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. *JAMA pediatrics* 2017;171(8):788-97. doi: 10.1001/jamapediatrics.2017.1488
9. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *Jama* 2015;314(7):700-07.
10. Primack BA, Soneji S, Stoolmiller M, et al. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. *JAMA pediatrics* 2015;169(11):1018-23.
11. Amos A, Greaves L, Nichter M, et al. Women and tobacco: a call for including gender in tobacco control research, policy and practice. *Tobacco control* 2012;21(2):236-43.
12. Solomon A. Gender, women, and the future of tobacco control. *Drugs and Alcohol Today* 2020 doi: 10.1108/DAT-02-2020-0005
13. Regitz-Zagrosek V. Sex and gender differences in health: Science & Society Series on Sex and Science. *EMBO reports* 2012;13(7):596-603. doi: 10.1038/embor.2012.87
14. Pogun S, Yararbas G. Sex differences in nicotine action. Nicotine psychopharmacology: Springer 2009:261-91.
15. Schmidt HD, Rupprecht LE, Addy NA. Neurobiological and neurophysiological mechanisms underlying nicotine seeking and smoking relapse. *Molecular neuropsychiatry* 2018;4(4):169-89. doi: 10.1159/000494799
16. Benowitz NL, Lessov-Schlaggar CN, Swan GE, et al. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clinical Pharmacology & Therapeutics* 2006;79(5):480-88. doi: 10.1016/j.clpt.2006.01.008

17. Cosgrove KP, Wang S, Kim S-J, et al. Sex differences in the brain's dopamine signature of cigarette smoking. *Journal of Neuroscience* 2014;34(50):16851-55. doi: 10.1523/JNEUROSCI.3661-14.2014
18. Jacobs W, Goodson P, Barry AE, et al. The role of gender in adolescents' social networks and alcohol, tobacco, and drug use: a systematic review. *Journal of School Health* 2016;86(5):322-33.
19. Waldron I. Patterns and causes of gender differences in smoking. *Social science & medicine* 1991;32(9):989-1005. doi: 10.1016/0277-9536(91)90157-8
20. Piper ME, Cook JW, Schlam TR, et al. Gender, race, and education differences in abstinence rates among participants in two randomized smoking cessation trials. *Nicotine & Tobacco Research* 2010;12(6):647-57. doi: 10.1093/ntr/ntq067
21. Riehm KE, Young AS, Feder KA, et al. Mental health problems and initiation of e-cigarette and combustible cigarette use. *Pediatrics* 2019;144(1) doi: 10.1542/peds.2018-2935
22. Upadhyaya HP, Deas D, Brady KT, et al. Cigarette smoking and psychiatric comorbidity in children and adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry* 2002;41(11):1294-305. doi: 10.1097/00004583-200211000-00010
23. Audrain-McGovern J, Rodriguez D, Kassel JD. Adolescent smoking and depression: evidence for self-medication and peer smoking mediation. *Addiction* 2009;104(10):1743-56. doi: 10.1111/j.1360-0443.2009.02617.x
24. National Institutes of Health National Institute on Drug Abuse, Products FDACfT. Population Assessment of Tobacco and Health (PATH) Study [United States] Public-Use Files: Inter-university Consortium for Political and Social Research [distributor], 2020.
25. Hyland A, Ambrose BK, Conway KP, et al. Design and methods of the Population Assessment of Tobacco and Health (PATH) Study. *Tobacco control* 2017;26(4):371-78.
26. Inter-university Consortium for Political and Social Research. Population Assessment of Tobacco and Health (PATH) Study [United States] Public-Use Files ICPSR Public-Use Files User Guide 2019 [updated August 13, 2019. Available from: https://www.icpsr.umich.edu/files/NAHDAP/documentation/ug36498-all.pdf accessed Jan 21 2021.
27. United States Department of Health & Human Services, National Institutes of Health, National Institute on Drug Abuse, et al. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files: Inter-university Consortium for Political and Social Research [distributor], 2020.
28. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Annals of internal medicine* 2007;147(8):573-77.
29. Kasza KA, Edwards KC, Tang Z, et al. Correlates of tobacco product initiation among youth and adults in the USA: findings from the PATH Study Waves 1–3 (2013–2016). *Tobacco Control* 2020;29(Suppl 3):s191-s202.
30. Kasza KA, Edwards KC, Tang Z, et al. Correlates of tobacco product cessation among youth and adults in the USA: findings from the PATH Study Waves 1–3 (2013–2016). *Tobacco Control* 2020;29(Suppl 3):s203-s15.

31. Edwards KC, Kasza KA, Tang Z, et al. Correlates of tobacco product reuptake and relapse among youth and adults in the USA: findings from the PATH Study Waves 1–3 (2013–2016). *Tobacco Control* 2020;29(Suppl 3):s216-s26.
32. Stanton CA, Sharma E, Seaman EL, et al. Initiation of any tobacco and five tobacco products across 3 years among youth, young adults and adults in the USA: findings from the PATH Study Waves 1–3 (2013–2016). *Tobacco Control* 2020;29(Suppl 3):s178-s90. doi: 10.1136/tobaccocontrol-2019-055573
33. Conway KP, Green VR, Kasza KA, et al. Co-occurrence of tobacco product use, substance use, and mental health problems among adults: findings from Wave 1 (2013–2014) of the Population Assessment of Tobacco and Health (PATH) Study. *Drug and Alcohol Dependence* 2017;177:104-11.
34. Conway KP, Green VR, Kasza KA, et al. Co-occurrence of tobacco product use, substance use, and mental health problems among youth: findings from wave 1 (2013–2014) of the population assessment of tobacco and health (PATH) study. *Addictive behaviors* 2018;76:208-17.
35. Kong G, Kuguru KE, Krishnan-Sarin S. Gender differences in US adolescent e-cigarette use. *Current addiction reports* 2017;4(4):422-30.
36. Perkins KA. Acute responses to nicotine and smoking: implications for prevention and treatment of smoking in lower SES women. *Drug and alcohol dependence* 2009;104:S79-S86. doi: 10.1016/j.drugalcdep.2008.10.022
37. Sofuoglu M, Mooney M. Subjective responses to intravenous nicotine: Greater sensitivity in women than in men. *Experimental and clinical psychopharmacology* 2009;17(2):63. doi: 10.1037/a0015297
38. Rubinstein ML, Shiffman S, Rait MA, et al. Race, gender, and nicotine metabolism in adolescent smokers. *Nicotine & tobacco research* 2013;15(7):1311-15. doi: 10.1093/ntr/nts272
39. Kong G, Morean ME, Cavallo DA, et al. Sources of electronic cigarette acquisition among adolescents in Connecticut. *Tobacco regulatory science* 2017;3(1):10-16. doi: 10.18001/TRS.3.1.2
40. Green VR, Conway KP, Silveira ML, et al. Mental health problems and onset of tobacco use among 12-to 24-year-olds in the PATH study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2018;57(12):944-54. e4.
41. Flay BR. School-based smoking prevention programs with the promise of long-term effects. *Tobacco Induced Diseases* 2009;5(1):6. doi: 10.1186/1617-9625-5-6
42. Kulig JW. Tobacco, alcohol, and other drugs: the role of the pediatrician in prevention, identification, and management of substance abuse. *Pediatrics* 2005;115(3):816-21. doi: 10.1542/peds.2004-2841
43. Coughlin SS. Recall bias in epidemiologic studies. *Journal of clinical epidemiology* 1990;43(1):87-91.
44. Chapman S, Bareham D, Maziak W. The gateway effect of e-cigarettes: reflections on main criticisms. *Nicotine and Tobacco Research* 2019;21(5):695-98. doi: 10.1093/ntr/nty067
45. Shahab L, Beard E, Brown J. Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents: a cross-sectional, matched control study. *Tobacco Control* 2020 doi: 10.1136/tobaccocontrol-2019-055283

46. Morgenstern M, Nies A, Goecke M, et al. E-Cigarettes and the Use of Conventional Cigarettes: A cohort study in 10th grade students in Germany. *Deutsches Ärzteblatt International* 2018;115(14):243. doi: 10.3238/arztebl.2018.0243

Figure 2.1. Flowchart for participants included in final analysis.

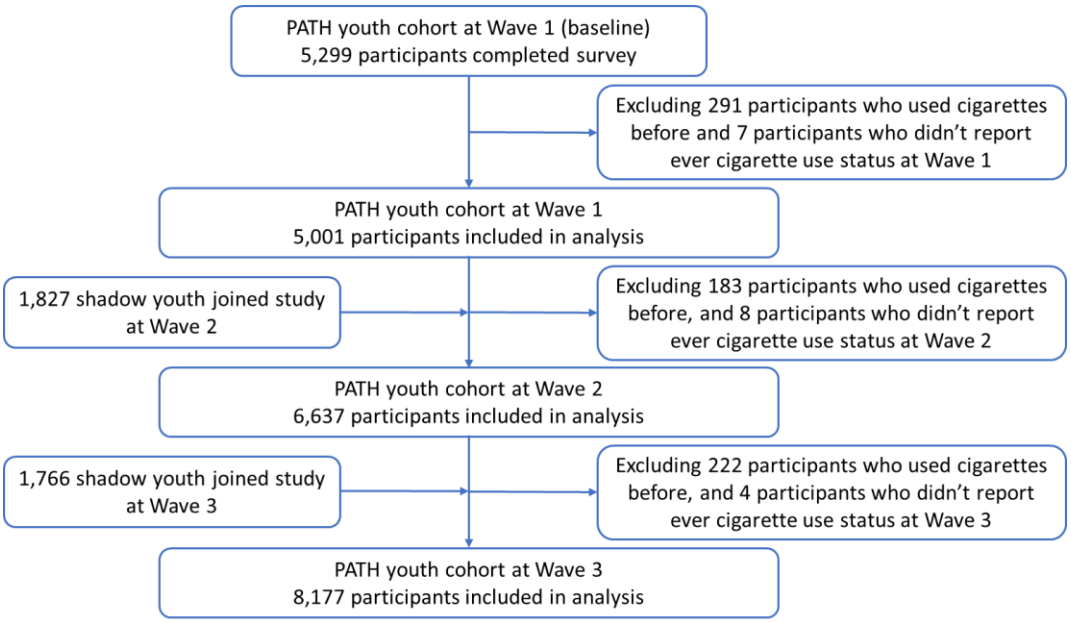

Table 2.1. Items for internalizing and externalizing mental health problems.

GAIN-SS Subscale [1]	Items
Internalizing mental health problems	Feeling very trapped, lonely, sad, blue, depressed, or hopeless about the future
	Sleep trouble - such as bad dreams, sleeping restlessly or falling asleep during the day
	Feeling very anxious, nervous, tense, scared, panicked or like something bad was going to happen
	Becoming very distressed and upset when something reminded you of the past
Externalizing mental health problems	Lied or conned to get things you wanted or to avoid having to do something
	Had a hard time paying attention at school, work, or home
	Had a hard time listening to instructions at school, work, or home
	Were a bully or threatened other people
	Started physical fights with other people
	Felt restless or the need to run around or climb on things
	Gave answers before the other person finished asking the question

[1] GAIN-SS: Global Appraisal of Individual Needs – Short Screener.

Table 2.2. Weighted descriptive statistics of covariates at baseline waves among adolescents (aged 12-17 years) who reported never having smoked cigarettes.

Baseline exposure and covariates	Wave 1 (n=5,001) n (%)	Wave 2 (n=6,637) n (%)	Wave 3 (n=8,177) n (%)
Interview status			
Youth (aged 12-17)	5001 (100)	4864 (73.3)	4711 (57.6)
Shadow youth (aged 9-11)	0 (0)	1773 (26.7)	3466 (42.4)
P30D e-cigarette use			
Yes	19 (0.4)	53 (0.9)	112 (1.5)
No	4949 (99.6)	6538 (99.1)	8033 (98.5)
Age group			
12-14	4388 (96.7)	5147 (77.0)	5175 (63.3)
15-17	168 (3.3)	1490 (23.0)	3002 (36.7)
Sex			
Male	2551 (50.8)	3365 (50.8)	4190 (51.1)
Female	2450 (49.2)	3253 (49.2)	3963 (48.9)
Race/ethnicity			
Non-Hispanic White	2334 (53.4)	2984 (52.5)	3624 (51.7)
Non-Hispanic Black	722 (14.4)	899 (13.9)	1087 (13.6)
Non-Hispanic Other	447 (9.2)	586 (9.7)	739 (10.1)
Hispanic	1498 (23.0)	1946 (23.9)	2402 (24.6)
Sexual orientation (ages 14+)			
Straight/Heterosexual	1455 (94.9)	2867 (92.3)	4145 (90.9)
Gay, lesbian, bisexual, or other	75 (5.1)	234 (7.7)	421 (9.1)
Parental education			
Less than high school	1009 (17.4)	1199 (16.4)	1511 (15.9)
High school graduate	907 (17.3)	1105 (17.0)	1392 (16.4)
Some college or associate degree	1024 (19.9)	1882 (30.3)	2519 (31.0)
Bachelor's degree or above	2032 (45.4)	1928 (36.6)	2583 (36.7)
P30D use of other tobacco products [1]			
Yes	19 (0.4)	32 (0.6)	56 (0.7)
No	4757 (99.6)	6461 (99.4)	8059 (99.3)
Past year internalizing problems			
Low	2558 (52.5)	3420 (52.6)	4023 (50.7)
Moderate	1432 (29.4)	1771 (27.7)	2205 (28.0)
High	856 (18.1)	1269 (19.7)	1704 (21.3)
Past year externalizing problems			
Low	1901 (39.8)	2776 (43.4)	3397 (43.2)
Moderate	1446 (30.7)	1738 (27.8)	2127 (27.8)
High	1368 (29.5)	1807 (28.8)	2249 (29.1)

[1] Other tobacco included cigars (traditional cigars, cigarillos, or filtered cigars), hookah, and smokeless tobacco (snus pouches, loose snus, moist snuff, dip, spit, or chewing tobacco)

Table 2.3. Weighted percentage of P30D cigarette smoking at each follow-up wave by covariates at its corresponding baseline wave among baseline never cigarette smokers.

	P30D Cigarette Smoking at Follow-up Waves		
	Wave 2 (n=5,001)	Wave 3 (n=6,637)	Wave 4 (n=8,177)
Baseline exposure and covariates	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**
Total	1.2 (0.9 – 1.6)	0.9 (0.7 – 1.2)	1.5 (1.2 – 1.8)
P30D e-cigarette use			
Yes	4.0 (0.5 - 27.7)	12.6 (5.1 - 27.6)	9.1 (4.9 - 16.4)
No	1.2 (0.9 - 1.6)	0.8 (0.6 - 1.2)	1.4 (1.1 - 1.7)
Age group			
12-14	1.1 (0.8 - 1.6)	0.7 (0.5 - 1.1)	0.9 (0.6 - 1.2)
15-17	1.9 (0.6 - 5.9)	1.7 (1.2 - 2.5)	2.6 (2.0 - 3.5)
Sex			
Male	0.8 (0.5 - 1.3)	0.6 (0.4 - 1.0)	1.7 (1.3 - 2.1)
Female	1.6 (1.1 - 2.2)	1.3 (0.9 - 1.8)	1.4 (1.0 - 1.9)
Race/ethnicity			
Non-Hispanic White	1.3 (0.9 - 2.0)	1.3 (0.9 - 1.8)	1.9 (1.4 - 2.5)
Non-Hispanic Black	0.5 (0.2 - 1.7)	0.3 (0.1 - 0.8)	0.8 (0.4 - 1.7)
Non-Hispanic Other	1.1 (0.4 - 3.2)	1.1 (0.4 - 2.9)	1.0 (0.5 - 1.8)
Hispanic	1.2 (0.7 - 2.0)	0.6 (0.3 - 1.1)	1.4 (1.0 - 2.0)
Sexual orientation (ages 14+)			
Straight/Heterosexual	1.7 (1.0 - 2.7)	1.0 (0.7 - 1.6)	2.0 (1.5 - 2.5)
Gay, lesbian, bisexual, or other	4.7 (1.6 - 12.9)	3.3 (1.5 - 7.1)	5.3 (3.4 - 8.3)
Parental education			
Less than high school	1.5 (0.8 - 2.8)	0.6 (0.3 - 1.5)	2.1 (1.4 - 3.0)
High school graduate	1.7 (0.9 - 3.0)	1.4 (1.7 - 2.8)	1.4 (0.9 - 2.2)
Some college or associate degree	1.9 (1.1 - 3.0)	0.8 (0.5 - 1.3)	1.8 (1.3 - 2.5)
Bachelor's degree or above	0.6 (0.3 - 1.0)	0.8 (0.5 - 1.4)	1.1 (0.7 - 1.7)
P30D use of other tobacco products [1]			
Yes	4.5 (0.5 - 30.8)	8.7 (2.2 - 29.0)	12.7 (6.1 - 24.8)
No	1.2 (0.9 - 1.6)	0.9 (0.7 - 1.2)	1.4 (1.2 - 1.8)
Past year internalizing problems			
Low	0.7 (0.4 - 1.2)	0.6 (0.4 - 1.0)	1.3 (0.9 - 1.8)
Moderate	1.5 (0.9 - 2.5)	1.2 (0.7 - 2.0)	1.1 (0.7 - 1.7)
High	1.8 (1.1 - 3.0)	1.4 (0.8 - 2.4)	2.6 (1.9 - 3.5)
Past year externalizing problems			
Low	0.4 (0.2 - 0.9)	0.6 (0.4 - 1.0)	1.1 (0.8 - 1.6)
Moderate	1.1 (0.6 - 2.0)	0.8 (0.4 - 1.6)	1.2 (0.8 - 1.9)
High	2.5 (1.7 - 3.6)	1.5 (0.9 - 2.4)	2.2 (1.6 - 2.9)

[1] Other tobacco included cigars (traditional cigars, cigarillos, or filtered cigars), hookah, and smokeless tobacco (snus pouches, loose snus, moist snuff, dip, spit, or chewing tobacco)

Table 2.4. Adjusted odds ratios (aORs) of P30D cigarette smoking at 12-month follow-up waves among adolescents (aged 12-17 years) who were never cigarette smokers at baseline waves.

Baseline exposure and covariates	Model 1 No interaction aOR (95% CI)	Model 2 With interaction aOR (95% CI)
P30D e-cigarette use		
Yes	3.90 (2.51 - 6.08)	1.93 (0.79 - 4.71)
No	1 [Reference]	1 [Reference]
Sex		
Male	1.24 (1.03 - 1.49)	1.19 (0.98 - 1.43)
Female	1 [Reference]	1 [Reference]
P30D e-cigarette use by Sex		
Yes by Male		3.18 (2.21 - 4.57)
No by Female		1 [Reference]
Age group		
12-14	1 [Reference]	1 [Reference]
15-17	1.80 (1.44 - 2.26)	1.81 (1.44 - 2.26)
Race/ethnicity		
Non-Hispanic White	1 [Reference]	1 [Reference]
Non-Hispanic Black	0.46 (0.30 - 0.70)	0.46 (0.30 - 0.70)
Non-Hispanic Other	0.66 (0.43 - 1.01)	0.66 (0.43 - 1.01)
Hispanic	0.66 (0.50 - 0.89)	0.66 (0.50 - 0.89)
Parental education		
Less than high school	1 [Reference]	1 [Reference]
High school graduate	0.92 (0.66 - 1.29)	0.92 (0.65 - 1.29)
Some college or associate degree	0.76 (0.55 - 1.05)	0.75 (0.54 - 1.04)
Bachelor's degree or above	0.50 (0.35 - 0.71)	0.50 (0.35 - 0.71)
P30D use of other tobacco products [1]		
Yes	3.22 (1.23 - 8.46)	3.45 (1.36 - 8.70)
No	1 [Reference]	1 [Reference]
Internalizing mental health problems		
Low	1 [Reference]	1 [Reference]
Moderate	1.33 (1.04 - 2.58)	1.33 (1.05 - 1.69)
High	1.90 (1.40 - 2.58)	1.93 (1.42 - 2.63)
Externalizing mental health problems		
Low	1 [Reference]	1 [Reference]
Moderate	1.40 (1.01 - 1.95)	1.41 (1.01 - 1.97)
High	2.11 (1.55 - 2.88)	2.09 (1.54 - 2.85)

[1] Other tobacco included cigars (traditional cigars, cigarillos, or filtered cigars), hookah, and smokeless tobacco (snus pouches, loose snus, moist snuff, dip, spit, or chewing tobacco)

Table 2.5. Adjusted odds ratios (aORs)[1] of P30D cigarette smoking at 12-month follow-up waves from subgroup analysis for adolescent boys and girls (aged 12-17 years).

	Boys P30D cigarette smoking aOR (95% CI)	Girls P30D cigarette smoking aOR (95% CI)
P30D e-cigarette use		
Yes	6.17 (2.43 - 15.68)	1.10 (0.14 - 8.33)
No	1 [Reference]	1 [Reference]

[1] Controlling for age, race/ethnicity, parental education, P30D other tobacco use, past-year internalizing mental health problems, and past-year externalizing mental health problems.

Table 2.6. Weighted percentage of ever cigarette smoking at each follow-up wave by covariates at its corresponding baseline wave among baseline never cigarette smokers.

Baseline exposure and covariates	Wave 2 (n=5001) % (95% CI)	Wave 3 (n=6637) % (95% CI)	Wave 4 (n=8177) % (95% CI)
P30D e-cigarette use			
Yes	12.8 (3.6 - 36.5)	25.6 (14.2 - 41.9)	18.9 (12.4 - 27.7)
No	2.8 (2.3 - 3.3)	2.7 (2.3 - 3.1)	3.2 (2.7 - 3.6)
Age group			
12-14	2.8 (2.3 - 3.4)	2.3 (2.0 - 2.8)	2.3 (1.9 - 2.8)
15-17	2.9 (1.2 - 7.0)	4.6 (3.6 - 5.9)	5.3 (4.4 - 6.3)
Sex			
Male	2.6 (1.9 - 3.5)	2.8 (2.2 - 3.5)	3.8 (3.2 - 4.4)
Female	3.1 (2.5 - 3.8)	3.0 (2.4 - 3.6)	3.0 (2.5 - 3.7)
Race/ethnicity			
Non-Hispanic White	3.1 (2.4 - 3.9)	3.7 (3.0 - 4.5)	3.9 (3.2 - 4.8)
Non-Hispanic Black	2.6 (1.5 - 4.4)	1.4 (0.8 - 2.6)	2.1 (1.3 - 3.3)
Non-Hispanic Other	1.6 (0.7 - 3.6)	2.7 (1.5 - 4.7)	2.5 (1.7 - 3.8)
Hispanic	2.8 (2.0 - 3.8)	2.3 (1.6 - 3.2)	3.3 (2.6 - 4.4)
Sexual orientation (ages 14+)			
Straight/Heterosexual	3.6 (2.7 - 4.8)	3.5 (2.8 - 4.4)	4.2 (3.6 - 5.0)
Gay, lesbian, bisexual, or other	10.8 (4.5 - 23.8)	9.4 (5.8 - 14.8)	9.8 (7.3 - 13.2)
Parental education			
Less than high school	4.1 (2.9 - 5.8)	2.6 (1.8 - 3.8)	4.1 (3.0 - 5.5)
High school graduate	3.3 (2.2 - 4.9)	4.2 (3.0 - 5.9)	3.7 (2.7 - 5.1)
Some college or associate degree	2.9 (2.0 - 4.1)	3.2 (2.5 - 4.1)	3.7 (3.1 - 4.6)
Bachelor's degree or above	2.1 (1.5 - 2.9)	2.1 (1.5 - 2.9)	2.7 (2.1 - 3.4)
P30D use of other tobacco products [1]			
Yes	4.5 (0.5 - 30.8)	8.7 (2.2 - 29.0)	21.9 (11.8 - 37.0)
No	2.8 (2.3 - 3.4)	2.8 (2.4 - 3.3)	3.2 (2.8 - 3.7)
Past year internalizing problems			
Low	1.4 (0.9 - 2.1)	1.8 (1.3 - 2.5)	2.6 (2.11 - 3.2)
Moderate	3.7 (2.8 - 5.0)	2.9 (2.1 - 4.0)	2.8 (2.0 - 4.0)
High	5.2 (4.0 - 6.8)	5.7 (4.3 - 7.4)	5.8 (4.8 - 7.1)
Past year externalizing problems			
Low	0.6 (0.3 - 1.2)	1.9 (1.4 - 2.6)	2.4 (1.8 - 3.1)
Moderate	3.1 (2.3 - 4.3)	2.5 (1.8 - 3.5)	3.2 (2.5 - 4.2)
High	5.8 (4.6 - 7.3)	4.6 (3.5 - 5.9)	5.0 (4.0 - 6.1)

[1] Other tobacco included cigars (traditional cigars, cigarillos, or filtered cigars), hookah, and smokeless tobacco (snus pouches, loose snus, moist snuff, dip, spit, or chewing tobacco)

Table 2.7. Adjusted odds ratios (aORs) of ever cigarette smoking at 12-month follow-up waves among adolescents (aged 12-17 years) who were never cigarette smokers at baseline waves.

Baseline exposure and covariates	Model 1 No interaction aOR (95% CI)	Model 2 With interaction aOR (95% CI)
P30D e-cigarette use		
Yes	3.17 (1.45 - 6.94)	0.86 (0.12 - 6.43)
No	1 [Reference]	1 [Reference]
Sex		
Male	0.84 (0.62 - 1.14)	0.77 (0.56 - 1.04)
Female	1 [Reference]	1 [Reference]
P30D e-cigarette use by Sex		
Yes by Male		7.78 (5.01 - 12.08)
No by Female		1 [Reference]
Age group		
12-14	1 [Reference]	1 [Reference]
15-17	2.34 (1.63 - 3.36)	2.34 (1.63 - 3.35)
Race/ethnicity		
Non-Hispanic White	1 [Reference]	1 [Reference]
Non-Hispanic Black	0.31 (0.15 - 0.64)	0.30 (0.14 - 0.63)
Non-Hispanic Other	0.71 (0.38 - 1.32)	0.71 (0.38 - 1.32)
Hispanic	0.53 (0.34 - 0.84)	0.53 (0.33 - 0.83)
Parental education		
Less than high school	1 [Reference]	1 [Reference]
High school graduate	0.79 (0.47 - 1.34)	0.78 (0.47 - 1.32)
Some college or associate degree	0.79 (0.48 - 1.30)	0.77 (0.47 - 1.27)
Bachelor's degree or above	0.41 (0.24 - 0.69)	0.40 (0.24 - 0.67)
P30D use of other tobacco products [1]		
Yes	5.07 (1.48 - 17.42)	5.73 (1.75 - 18.73)
No	1 [Reference]	1 [Reference]
Internalizing mental health problems		
Low	1 [Reference]	1 [Reference]
Moderate	1.07 (0.65 - 1.75)	1.08 (0.66 - 1.77)
High	1.19 (0.73 - 1.94)	1.23 (0.75 - 2.02)
Externalizing mental health problems		
Low	1 [Reference]	1 [Reference]
Moderate	1.33 (0.84 - 2.11)	1.35 (0.85 - 2.16)
High	2.56 (1.64 - 4.00)	2.53 (1.63 - 3.92)

[1] Other tobacco included cigars (traditional cigars, cigarillos, or filtered cigars), hookah, and smokeless tobacco (snus pouches, loose snus, moist snuff, dip, spit, or chewing tobacco)

Table 2.8. Adjusted odds ratios (aORs)[1] from subgroup analysis for adolescent boys and girls (aged 12-17 years).

Baseline exposure and covariates	Boys ever cigarette smoking aOR (95% CI)	Girls ever cigarette smoking aOR (95% CI)
P30D e-cigarette use		
Yes	5.81 (3.34 - 10.13)	2.31 (0.98 - 5.41)
No	1 [Reference]	1 [Reference]

[1] Controlling for age, race/ethnicity, parental education, P30D other tobacco use, past-year internalizing mental health problems, and past-year externalizing mental health problems.

Table 2.9. E-cigarette dependence among P30D e-cigarette users for adolescent boys and girls (aged 12-17 years).

Baseline exposure and covariates	Wave 1 (n=29) n (mean/%)	Wave 2 (n=54) n (mean/%)	Wave 3 (n=97) n (mean/%)
Number of days using an e-cigarette in P30D (mean)			
Overall	29 (4.1)	54 (4.3)	97 (7.5)
Male	15 (5.0)	30 (5.6)	60 (8.4)
Female	14 (3.1)	24 (2.9)	37 (6.1)
E-cigarette dependence [1] (%)			
Low	27 (93.4)	52 (97.3)	82 (83.1)
High	2 (6.6)	2 (2.7)	15 (16.9)
E-cigarette dependence for boys (%)			
Low	13 (87)	28 (94.8)	49 (81.9)
High	2 (13)	2 (5.2)	11 (18.1)
E-cigarette dependence for girls (%)			
Low	14 (100)	24 (100)	33 (85.2)
High	0 (0)	0 (0)	4 (14.8)

[1] Nicotine dependence was dichotomized into low (used an e-cigarette for 1-19 days in P30D) and high (used an e-cigarette for 20-30 days).

Chapter 3: Study Two

Effect Modification of Mental Health Problems on the Association between E-Cigarette Use and Subsequent Marijuana Use among US Adolescents

Abstract

Introduction: E-cigarette use may be prospectively associated with subsequent marijuana use among U.S. adolescents. However, it remains unclear whether this association differs by individual mental health status. This longitudinal study examines effect modifications by mental health status, using the first four waves (2013-2017) of the Population Assessment of Tobacco and Health (PATH) Study.

Methods: The study population included adolescents (aged 12-17) who reported never using marijuana at baseline waves. Wave 1 to 3 were each considered as baseline for its 12-month follow-up wave. Generalized estimating equations were used to evaluate the effect modification of mental health problems on the associations between baseline past-30-day e-cigarette use and past-30-day marijuana use at 12-month follow-ups, controlling for individual characteristics and state recreational marijuana laws.

Results: Baseline e-cigarette use was significantly associated with marijuana use at 12-month follow-ups (aOR=5.92, 95% CI: 3.64–9.63). Adolescents with severe internalizing (IMH) or externalizing mental health (EMH) problems were significantly more likely to initiate marijuana use. However, current e-cigarette users who reported more severe IMH symptoms were less likely to initiate marijuana use (aOR=3.04, 95% CI: 1.20–7.74), compared with those who

reported less severe IMH problems (aOR=10.15, 95% CI: 4.72–21.81). There were no differences by severity of EMH problems.

Conclusions: Baseline e-cigarette use and endorsement of severe mental health problems were significantly associated with subsequent marijuana use among U.S. adolescents. Efforts to reduce youth vaping and improve youth mental health could help curb marijuana initiation. Tailored interventions may be warranted for e-cigarette-using adolescents with IMH conditions.

Introduction

In 2020, the prevalence of current e-cigarette use was 19.6% among high school students and 4.7% among middle school students in the United States.[1] The youth vaping epidemic could also heighten the use of other substances among young people.[2] For example, a growing body of longitudinal studies indicated that e-cigarette use was associated with subsequent marijuana initiation among adolescents.[3-6] A recent meta-analysis, which analyzed eighteen cross-sectional and three longitudinal studies, found that the pooled odds of marijuana use among adolescents who used e-cigarettes were 3.5 times the corresponding odds for non-e-cigarette adolescents (adjusted odds ratio [aOR]=3.47; 95% confidence interval [95% CI]=2.63–4.59).[7]

However, this overall association between e-cigarette use and subsequent marijuana initiation may mask important differences among vulnerable population subgroups, particularly those with mental health problems. Mental health problems are generally categorized into two broad categories: internalizing and externalizing problems.[8] Internalizing mental health (IMH) problems are characterized as inner-directed and consist of anxiety, depressive, and somatic symptoms; externalizing mental health (EMH) problems are outer-directed and feature symptoms that include emotional dysregulation, impulsivity, and oppositional behavior.[8 9] The evidence regarding the prospective association between IMH problems and substance use is still mixed.[10-15] Some studies suggest that adolescents with IMH problems are more likely to use substances to cope with stress/anxiety. In contrast, other studies suggest that these youth tend to be more socially isolated and may have less access to marijuana products, suggesting that IMH problems can be moderately protective against adolescent substance use.[10 14 16] The

literature on EMH disorders is much more consistent, with current evidence suggesting a strong and robust association between EMH problems and adolescent substance use.[10-13 17] Among e-cigarette-using adolescents, those who experience more severe mental health conditions may be more motivated to use substances in efforts to cope with their symptoms, which could increase their likelihood of transitioning from e-cigarette use to marijuana use. Consequently, exploring the patterns and associations of e-cigarette use and marijuana use among adolescents who endorse severe mental health conditions is warranted.

In addition to mental health, adolescent marijuana use may be influenced by geographic location and the state recreational marijuana laws. Very few studies examining the association between e-cigarette use and marijuana use accounted for the confounding effect of state recreational marijuana laws, which have been found to be associated with marijuana use, abuse, and dependence.[18-20] With an increasing number of U.S. states legalizing adult recreational marijuana use, which could lead to changes in perceptions about health risks of using marijuana products and product availability,[21 22] it is critically important to consider the policy impacts on adolescents' marijuana use behaviors. Population-based longitudinal studies that take into account the impact of policy environment are needed.

The objective of this longitudinal study was to investigate whether the prospective association between e-cigarette use and marijuana use differs by mental health status among U.S. adolescents, controlling for individual socio-demographic characteristics and state recreational marijuana laws. We hypothesized that among U.S. adolescents, more severe mental health problems at baseline would be associated with an elevated risk of initiating marijuana use at the follow-ups. Additionally, we hypothesized that the association between e-

cigarette use and subsequent marijuana use would differ by baseline levels of mental health problems. Specifically, we hypothesized that the association between baseline e-cigarette use and higher risk for initiating marijuana use at follow-ups would be stronger among those who endorsed more severe IMH or EMH problems.

Methods

Study Sample/Population

This study used the Wave 1 to Wave 4 youth cohort of the Population Assessment of Tobacco and Health (PATH) Study, an ongoing longitudinal study designed to examine tobacco and substance use among U.S. youth and adults. A multi-stage, stratified probability youth sample was selected to represent the noninstitutionalized population in the U.S.[23] The in-person data were collected from September 2013 to December 2014 (Wave 1), October 2014 to October 2015 (Wave 2), October 2015 to October 2016 (Wave 3), and December 2016 to January 2018 (Wave 4), respectively. The weighted response rates for the youth cohort were 78.4% (Wave 1), 87.3% (Wave 2), 83.3% (Wave 3), and 79.5% (Wave 4), respectively.[24] In the PATH data, multiple imputations were performed for demographic and tobacco use variables to handle the missing data bias.[23] Further details on study design, sampling, weighting, imputation, and data collection procedures are available in the PATH Study user guide.[24] The Georgia State University IRB exempted this study from review. This report follows the reporting guideline for cohort studies of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[25]

In this study, we followed a validated approach recommended by the PATH Study research team to treat each of the first three waves as a baseline for its corresponding 12-month follow-up wave, and stacked baseline covariates with marijuana use status at corresponding follow-up wave.[26 27] For instance, Wave 2 served as the 12-month follow-up of Wave 1 and the baseline for Wave 3. The corresponding all-wave weights for the youth cohort (aged 12-17) were used to produce nationally representative estimates.[24] The all-wave weights were restricted to Wave 1 respondents who completed all follow-up surveys or the shadow sample (aged 9-11) who completed at least one interview at follow-up waves while they were 12-17 years old.[24] The target population were youth who never used marijuana, and the study sample was composed of respondents who reported having never used marijuana at the baseline waves. Participants were asked at baseline, “Have you ever used marijuana, hash, THC, grass, pot or weed?” and “Have you ever smoked part or all of a cigar, cigarillo or filtered cigar with marijuana in it?”. Those who responded “No” to both questions were identified as never marijuana users at baseline. As illustrated in Appendix Figure 1, this study included 5,049 youth at Wave 1, 6,522 youth at Wave 2, and 7,888 youth at Wave 3.

Measures

The primary outcome was the self-reported past-30-day (P30D) use of marijuana at the 12-month follow-up waves among adolescents (aged 12-17) who had never used marijuana at baseline. At the 12-month follow-up surveys, those who reported using marijuana in the past 30 days were categorized as P30D marijuana users, and those who reported using marijuana were coded as ever marijuana users.

The exposures of interest were the P30D use of e-cigarettes and mental health problems at baseline. Respondents who reported using any e-cigarette products in the past 30 days at baseline were categorized as P30D users of e-cigarettes. Mental health problems were coded based on 4 internalizing and 7 externalizing problems measured in the PATH Study survey (Table 3.1). In this study, we followed a validated approach to sum up the scores for internalizing and externalizing problems, where the severity of mental health problems was categorized into three levels: low (0-1), moderate (2-3), and high (4 for internalizing problems or 4-7 for externalizing problems).[28 29]

State recreational marijuana law (legalized or not legalized) at the survey year, which was retrieved from the National Institutes of Health (NIH) Alcohol Policy Information System, was analyzed as a covariate.[30] Other baseline covariates were included to control for potential confounding effects: age (12-14 or 15-17), sex (male or female), race/ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, or Non-Hispanic Other), parental education (less than high school, high school graduate, some college or associate degree, and bachelor's degree or above), and dichotomous P30D use of combustible tobacco (cigarettes, traditional cigars, cigarillos, or filtered cigars). The question on sexual orientation was only available for participants aged 14 and above, so dichotomized sexual orientation (straight vs. other) was only used to estimate the bivariate association with outcomes but not included in the regression models.

Statistical Analysis

Data management and analyses were conducted using Stata 15 (College Station, TX. StataCorp). The youth cohort all-wave weights were applied to account for complex sample

design and produce representative estimates. The balanced repeated replication (BRR) approach with Fay's adjustment of 0.3 was used to compute statistical precision.[23 31] The weighted prevalence of P30D marijuana use at 12-month follow-up waves was estimated overall and stratified by exposure and covariates. Generalized estimating equations (GEE) with unstructured covariance were fitted to evaluate the associations between the outcomes (P30D marijuana use at follow-up) and exposure variables (P30D e-cigarette use, internalizing and externalizing problems), controlling for individual socio-demographic characteristics and state recreational marijuana laws. Additional GEE models were fitted to examine the potential effect modifications of internalizing and externalizing problems on the association between e-cigarette use and subsequent marijuana use by adding corresponding interaction terms (P30D e-cigarette use by Internalizing problems, P30D e-cigarette use by Externalizing problems). When a significant interaction was identified, subgroup analyses were conducted to present the associations between baseline e-cigarette use and subsequent marijuana use. Additionally, two sets of sensitivity analyses were conducted, by replacing the outcome with ever marijuana use and replacing 3-category internalizing and externalizing problems with continuous measures, respectively. All statistical tests were two-sided with the significance level set to 0.05.

Results

At Wave 1, 49.0% of respondents were female, 54.3% were Non-Hispanic White, 14.1% were Non-Hispanic Black, 9.3% were Non-Hispanic Other, and 22.3% were Hispanic. The sex and race/ethnicity proportions were consistent across three baseline waves. Detailed descriptive statistics of other covariates are available in Table 3.2.

As shown in Table 3.3, among baseline never marijuana users, the prevalence of P30D marijuana use was 2.3% (95% CI: 1.8%-2.9%) at Wave 2, 2.4% (95% CI: 2.0%-2.9%) at Wave 3, and 3.2% (95% CI: 2.9%-3.6%) at Wave 4, respectively. Among adolescents who reported P30D e-cigarette use at baseline waves, the prevalence of P30D marijuana use was 13.8% (95% CI: 4.3%-36.1%) at Wave 2, 9.7% (95% CI: 4.3%-20.2%) at Wave 3, and 26.3% (95% CI: 18.0%-36.7%) at Wave 4, respectively. By contrast, among adolescents who reported that they had not used e-cigarettes in the past 30 days, the prevalence of P30D marijuana use was 2.2% (95% CI: 1.8%-2.8%) at Wave 2, 2.4% (95% CI: 2.0%-2.8%) at Wave 3, and 2.9% (95% CI: 2.6%-3.2%) at Wave 4, respectively. In addition, at each baseline wave, the weighted prevalence of self-reported P30D marijuana use was higher among participants who endorsed severe IMH or EMH problems, were older, were sexual minorities, and lived in states legalizing recreational marijuana use.

Table 3.4 presents the adjusted associations between baseline P30D e-cigarette use and P30D marijuana use at the 12-month follow-up waves, controlling for individual socio-demographic characteristics and state recreational marijuana laws. As shown in Model 1, P30D e-cigarette use at baseline was significantly associated with P30D marijuana use in the follow-up wave (aOR=5.92, 95% CI: 3.64–9.63). In addition, high severity IMH problems (aOR=1.50, 95% CI: 1.05–2.14) and EMH problems (aOR=1.62, 95% CI: 1.28–2.04) were significantly associated with P30D marijuana use in follow-up waves, controlling for other covariates. Additionally, older age and using combustible tobacco were also significantly associated with elevated odds of P30D marijuana use in follow-up waves, while being Non-Hispanic other and having parents with a bachelor's degree or above were associated with reduced odds of P30D

marijuana use in follow-up waves. Model 2 shows that the interaction between P30D e-cigarette use and IMH problems, noted as “P30D e-cigarette use by Internalizing problems”, was statistically significant for high vs. low severity. In addition, Model 3 shows that the interaction term for EMH problems, noted as “P30D e-cigarette use by Externalizing problems”, was not significant.

Table 3.5 presents the subgroup analysis results stratified by IMH problems, controlling for other individual characteristics and state recreational marijuana law. Among adolescents with high severity IMH problems, the adjusted OR between baseline P30D e-cigarette use and P30D marijuana use at 12-month follow-up waves was 3.04 (95% CI: 1.20–7.72); while among adolescents with low severity IMH problems, the corresponding adjusted OR was 10.15 (95% CI: 4.72–21.81).

To examine the sensitivity of our findings, we first examined ever marijuana use at the 12-month follow-up as the outcome, and then replaced categorical mental health problems with continuous measures. The results are presented in Table 3.6-3.9. Consistent with Table 3.3, results in Table 3.6 show that, in each follow-up wave, ever marijuana use was higher among adolescents who reported baseline P30D e-cigarette use, compared with those who did not. In addition, Table 3.7 shows consistent results regarding the adjusted associations and interactions. Furthermore, the adjusted ORs between ever marijuana use at follow-up waves and baseline P30D e-cigarette use were 6.44 (95% CI: 3.51-11.81) and 1.80 (95% CI: 0.89-3.60) for adolescents with low and high severity IMH problems, respectively (Table 3.8). Table 3.9 presents the sensitivity analysis results using continuous IMH and EMH problems, which

showed that the associations and effect modifications were consistent with categorical or continuous exposures.

Discussion

Although the longitudinal association between e-cigarette use and subsequent marijuana initiation has been documented in several previous studies,[3-7] the potential effect modification by mental health conditions has not previously been documented to our knowledge. This study revealed that although baseline P30D e-cigarette use was associated with higher likelihood of subsequent P30D marijuana use at 12-month follow-up waves regardless of mental health status, the strength of the association differed based on the severity of baseline IMH problems. Sensitivity analyses showed that this effect modification was robust to different exposure and outcome measures.

Consistent with the findings of the previous literature,[32-34] our study found that adolescents who reported more severe externalizing mental health problems were significantly more likely to use marijuana, after controlling for e-cigarette use and other covariates. Despite the current mixed evidence prospective association between IMH problems and substance use,[10-15] our findings showed that adolescents endorsing more severe internalizing mental health problems were significantly more likely to use marijuana. In addition, the magnitudes of associations indicated that EMH problems were a stronger predictor of subsequent P30D marijuana use at 12-month follow-ups, compared with IMH problems. The findings suggest that mental health interventions (e.g., school counseling and advising from primary care providers) may help prevent the onset of early marijuana use among vulnerable adolescents.

One of the unique contributions of our study was the revelation of the interaction between IMH problems and e-cigarette use in predicting subsequent marijuana use. We initially hypothesized that among adolescents who used e-cigarettes, those who endorsed more severe mental health problems, regardless of internalizing or externalizing symptoms, would be more likely to transition to marijuana use. Contradictory to our hypothesis, the results showed that current e-cigarette users who reported more severe IMH symptoms were less likely to initiate marijuana use, compared with those who reported less severe IMH problems. In addition, effect modification by EMH problems was not significant. Several potential reasons may explain the attenuation of the modifying effect of IMH problems on the association between e-cigarette use and marijuana use. First, compared with adolescents with low level of IMH problems, adolescents with more severe IMH problems were more likely to suffer from anxiety, depressive, and somatic symptoms,[8] which could lead to social withdrawal that limited their interactions with their peers who engage in substance use.[10 14] The reduction in the likelihood of interacting with peers engaging in substance use likely reduced their access to marijuana products, consequently, weakening the association between e-cigarette use and subsequent marijuana use. Second, given the ubiquitous marketing and availability of e-cigarettes,[35 36] many of which are discreet and stealth in their designs, and difficult to be detected by parents and teachers, these products may be the easiest and most accessible substance for adolescents, particularly for those with severe IMH problems,[1 37] who would use e-cigarettes to deal with anxiety, stress and depression.[38] If adolescents endorsing more severe IMH problems found that e-cigarettes were able to help them deal with their anxiety, stress and depression, once they started using e-cigarettes, they may be less likely to resort to other substances at a

later time, including marijuana, as such, attenuating the association between e-cigarette use and transition to marijuana use.

Previous studies, however, indicated that adolescents characterized by high levels of internalizing symptoms may experience elevated risks of marijuana use onset in late youth or early adulthood, when their social context became more supportive of marijuana use.[14 39] Given the positive prospective association between IMH and subsequent marijuana use, once initiated, marijuana could escalate to a regular way to manage stress for those endorsing more severe IMH problems. Future studies are needed to investigate how the associations would vary across different developmental stages, particularly among those with more severe IMH problems. Additionally, early interventions may be warranted to help younger adolescents effectively manage their distress without turning to substance use.

Our study also found that older age and using combustible tobacco were significantly associated with elevated odds of P30D marijuana use in follow-up waves, consistent with the findings from previous studies.[3-6] In addition to controlling for socio-demographic characteristics and smoking status, our study also distinguished the effect of state recreational marijuana laws, a factor that has not been adequately considered in previous studies. Our results showed state laws that legalized recreational marijuana use for adults were positively associated with marijuana use among adolescents, however, this association is only significant at p=0.1 (aOR=1.29, 95% CI: 0.94-1.78). Growing evidence suggested that legalizing recreational marijuana use for adults could substantially affect the knowledge, risk perceptions, and use behaviors of marijuana among adolescents.[20 40] With more U.S. states legalizing recreational marijuana for adults,[41] it may be prudent to limit youth access to marijuana products and

prevent further decline in perceived risks associated with marijuana use among youth and young adults.[42]

Limitations

This study is subject to several limitations. First, self-reported use of marijuana and tobacco products may introduce recall bias and social desirability bias.[43] Previous studies found that the prevalence of e-cigarette use in the PATH survey was smaller compared with those reported in other surveys, this implies that if these biases existed, they would bias our results towards zero. As such, our results would be a conservative estimate. Second, although this study established a temporal association between e-cigarette use and marijuana use, it did not necessarily imply a causal relationship. Third, due to the restrictions imposed by sample weights, which only applied to the younger adolescent (aged 12-17) cohort, this study was not able to analyze older adolescents and young adults. Furthermore, future study may also need to consider controlling for other risk factors, including genetic vulnerability, psychosocial experiences, and/or general environmental influences.[44]

Conclusions

Results suggest that efforts to prevent adolescent marijuana initiation need to incorporate measures addressing the youth vaping epidemic. Tailored interventions may also be needed for vulnerable population groups characterized by severe internalizing and externalizing mental health conditions. In addition, among adolescents who use e-cigarettes, youth with high severity IMH problems may be less likely to transition to marijuana use. Efforts to prevent substance use might need to target different motivations for substance use among

youth experiencing different types and severity of mental health symptomatology. More research is needed to clarify mechanistic pathways connecting e-cigarette use to later marijuana use.

References

1. Wang TW, Neff LJ, Park-Lee E, et al. E-cigarette use among middle and high school students—United States, 2020. *Morbidity and Mortality Weekly Report* 2020;69(37):1310.
2. King BA, Jones CM, Baldwin GT, et al. The EVALI and youth vaping epidemics—implications for public health. *New England Journal of Medicine* 2020;382(8):689-91.
3. Audrain-McGovern J, Stone MD, Barrington-Trimis J, et al. Adolescent e-cigarette, hookah, and conventional cigarette use and subsequent marijuana use. *Pediatrics* 2018;142(3):e20173616.
4. Park E, Livingston JA, Wang W, et al. Adolescent E-cigarette use trajectories and subsequent alcohol and marijuana use. *Addictive Behaviors* 2020;103:106213.
5. Dai H, Catley D, Richter KP, et al. Electronic cigarettes and future marijuana use: a longitudinal study. *Pediatrics* 2018;141(5):e20173787.
6. Evans-Polce RJ, Veliz PT, Boyd CJ, et al. E-Cigarette and Cigarette Use Among US Adolescents: Longitudinal Associations With Marijuana Use and Perceptions. *American Journal of Preventive Medicine* 2020
7. Chadi N, Schroeder R, Jensen JW, et al. Association between electronic cigarette use and marijuana use among adolescents and young adults: a systematic review and meta-analysis. *Jama Pediatrics* 2019;173(10):e192574-e74.
8. Achenbach TM, Ivanova MY, Rescorla LA, et al. Internalizing/externalizing problems: Review and recommendations for clinical and research applications. *Journal of the American Academy of Child & Adolescent Psychiatry* 2016;55(8):647-56.
9. Brown BB, Prinstein MJ. Encyclopedia of adolescence: Academic Press 2011.
10. Scalco MD, Colder CR, Hawk Jr LW, et al. Internalizing and externalizing problem behavior and early adolescent substance use: A test of a latent variable interaction and conditional indirect effects. *Psychology of Addictive Behaviors* 2014;28(3):828.
11. Colder CR, Frndak S, Lengua LJ, et al. Internalizing and externalizing problem behavior: A test of a latent variable interaction predicting a two-part growth model of adolescent substance use. *Journal of abnormal child psychology* 2018;46(2):319-30.
12. Miettunen J, Murray G, Jones P, et al. Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. *Psychological medicine* 2014;44(8):1727-38.
13. Pedersen MU, Thomsen KR, Heradstveit O, et al. Externalizing behavior problems are related to substance use in adolescents across six samples from Nordic countries. *European child & adolescent psychiatry* 2018;27(12):1551-61.
14. Colder CR, Scalco M, Trucco EM, et al. Prospective associations of internalizing and externalizing problems and their co-occurrence with early adolescent substance use. *Journal of abnormal child psychology* 2013;41(4):667-77.
15. Dev MSRC. A dynamic cascade model of the development of substance-use onset. *Monogr Soc Res Child Dev* 2009;74(3)
16. Kassel JD. Substance abuse and emotion: American Psychological Association 2010.
17. Audrain-McGovern J, Rodriguez D, Testa S, et al. Adolescent E-Cigarette Onset and Escalation: Associations With Internalizing and Externalizing Symptoms. *Journal of Adolescent Health* 2020

18. Cerdá M, Wall M, Keyes KM, et al. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug and alcohol dependence* 2012;120(1-3):22-27.
19. Cerdá M, Wall M, Feng T, et al. Association of state recreational marijuana laws with adolescent marijuana use. *JAMA pediatrics* 2017;171(2):142-49.
20. Cerdá M, Mauro C, Hamilton A, et al. Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA psychiatry* 2020;77(2):165-71.
21. Miech R, Johnston L, O'Malley PM. Prevalence and attitudes regarding marijuana use among adolescents over the past decade. *Pediatrics* 2017;140(6):e20170982.
22. Ammerman S, Ryan S, Adelman WP, et al. The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics* 2015;135(3):e769-e85.
23. Hyland A, Ambrose BK, Conway KP, et al. Design and methods of the Population Assessment of Tobacco and Health (PATH) Study. *Tobacco control* 2017;26(4):371-78.
24. Health USDo, Abuse HSNIoHNIoD, Health USDo, et al. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files: Inter-university Consortium for Political and Social Research [distributor], 2020.
25. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Annals of internal medicine* 2007;147(8):573-77.
26. Kasza KA, Edwards KC, Tang Z, et al. Correlates of tobacco product initiation among youth and adults in the USA: findings from the PATH Study Waves 1–3 (2013–2016). *Tobacco Control* 2020;29(Suppl 3):s191-s202.
27. Edwards KC, Kasza KA, Tang Z, et al. Correlates of tobacco product reuptake and relapse among youth and adults in the USA: findings from the PATH Study Waves 1–3 (2013–2016). *Tobacco Control* 2020;29(Suppl 3):s216-s26.
28. Conway KP, Green VR, Kasza KA, et al. Co-occurrence of tobacco product use, substance use, and mental health problems among youth: findings from wave 1 (2013–2014) of the population assessment of tobacco and health (PATH) study. *Addictive behaviors* 2018;76:208-17.
29. Duan Z, Wang Y, Huang J. Sex Difference in the Association between Electronic Cigarette Use and Subsequent Cigarette Smoking among US Adolescents: Findings from the PATH Study Waves 1–4. *International Journal of Environmental Research and Public Health* 2021;18(4):1695.
30. NIH Alcohol Policy Information System. CANNABIS POLICY TOPICS - Recreational Use of Cannabis: Volume 1 [Available from: https://alcoholpolicy.niaaa.nih.gov/cannabis-policy-topics/recreational-use-of-cannabis-volume-1/104 accessed June 17 2020.
31. Judkins DR. Fay's method for variance estimation. *Journal of Official Statistics* 1990;6(3):223-39.
32. Esmaeelzadeh S, Moraros J, Thorpe L, et al. Examining the association and directionality between mental health disorders and substance use among adolescents and young adults in the US and Canada—a systematic review and meta-analysis. *Journal of clinical medicine* 2018;7(12):543.

33. Groenman AP, Janssen TW, Oosterlaan J. Childhood psychiatric disorders as risk factor for subsequent substance abuse: a meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry* 2017;56(7):556-69.
34. Becker TD, Arnold MK, Ro V, et al. Systematic review of electronic cigarette use (vaping) and mental health comorbidity among adolescents and young adults. *Nicotine and Tobacco Research* 2021;23(3):415-25.
35. Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tobacco control* 2019;28(2):146-51.
36. Marynak K, Gentzke A, Wang TW, et al. Exposure to electronic cigarette advertising among middle and high school students—United States, 2014–2016. *Morbidity and Mortality Weekly Report* 2018;67(10):294.
37. Miech R, Johnston L, O'Malley P, et al. Monitoring the future national survey results on drug use, 1975-2018: volume I, secondary school students, 2019.
38. Green VR, Conway KP, Silveira ML, et al. Mental health problems and onset of tobacco use among 12-to 24-year-olds in the PATH study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2018;57(12):944-54. e4.
39. Sung M, Erkanli A, Angold A, et al. Effects of age at first substance use and psychiatric comorbidity on the development of substance use disorders. *Drug and alcohol dependence* 2004;75(3):287-99.
40. Mason WA, Hanson K, Fleming CB, et al. Washington State recreational marijuana legalization: Parent and adolescent perceptions, knowledge, and discussions in a sample of low-income families. *Substance use & misuse* 2015;50(5):541-45.
41. National Conference of State Legislatures. State Medical Marijuana Laws 2021 [Available from: https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx accessed Feb 2 2021.
42. Johnston LD, Miech RA, O'Malley PM, et al. Monitoring the Future national survey results on drug use 1975-2020: Overview, key findings on adolescent drug use.: Ann Arbor: Institute for Social Research, University of Michigan. , 2021.
43. Coughlin SS. Recall bias in epidemiologic studies. *Journal of clinical epidemiology* 1990;43(1):87-91.
44. NIDA. Common Comorbidities with Substance Use Disorders Research Report, Part 1: The Connection Between Substance Use Disorders and Mental Illness 2021 [Available from: https://www.drugabuse.gov/publications/research-reports/common-comorbidities-substance-use-disorders/part-1-connection-between-substance-use-disorders-mental-illness accessed April 30 2021.

Figure 3.1. Flowchart for participants included in final analysis.

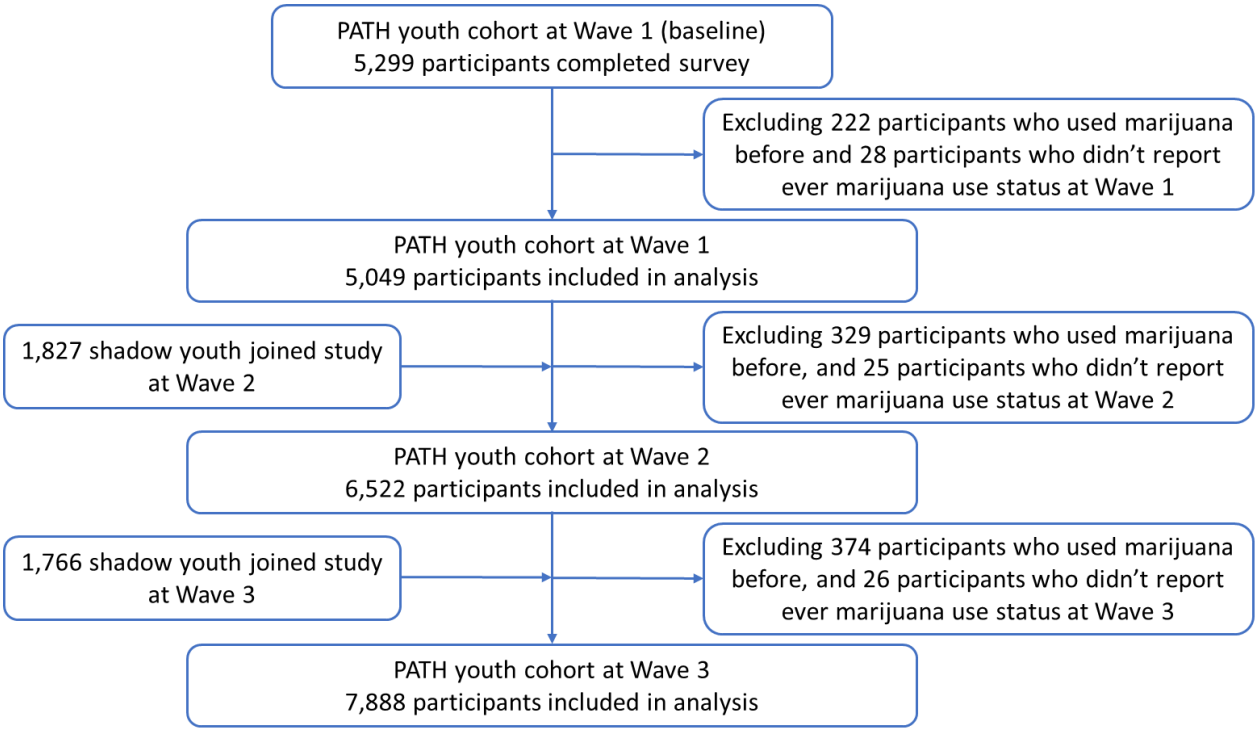

Table 3.1. Items for internalizing and externalizing mental health problems.

GAIN-SS Subscale[a]	Items
Internalizing mental health problems	Feeling very trapped, lonely, sad, blue, depressed, or hopeless about the future.
	Sleep trouble - such as bad dreams, sleeping restlessly or falling asleep during the day.
	Feeling very anxious, nervous, tense, scared, panicked or like something bad was going to happen.
	Becoming very distressed and upset when something reminded you of the past.
Externalizing mental health problems	Lied or conned to get things you wanted or to avoid having to do something.
	Had a hard time paying attention at school, work, or home.
	Had a hard time listening to instructions at school, work, or home.
	Were a bully or threatened other people.
	Started physical fights with other people.
	Felt restless or the need to run around or climb on things.
	Gave answers before the other person finished asking the question.

[a]GAIN-SS: Global Appraisal of Individual Needs – Short Screener.

Table 3.2. Weighted descriptive statistics of covariates at baseline waves among adolescents (aged 12-17 years) who reported never having used marijuana.

	Wave 1 n = 5,049		Wave 2 n = 6,522		Wave 3 n = 7,888	
Baseline exposure and covariates	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
P30D e-cigarette use						
Yes	0.6	0.4 - 0.9	0.9	0.6 - 1.2	1.4	1.1 - 1.7
No	99.4	99.1 - 99.6	99.1	98.8 - 99.4	98.6	98.3 - 98.9
Internalizing problems						
Low	52.3	50.6 - 53.9	53.1	51.7 - 54.5	51.3	49.9 - 52.7
Moderate	29.3	28.0 - 30.7	27.8	26.7 - 29.0	28.2	27.1 - 29.3
High	18.4	17.2 - 19.7	19.1	18.1 - 20.1	20.5	19.4 - 21.6
Externalizing problems						
Low	39.6	37.9 - 41.3	44.0	42.7 - 45.3	43.9	42.7 - 45.2
Moderate	30.7	29.2 - 32.2	27.9	26.8 - 29.1	27.6	26.6 - 28.7
High	29.7	28.4 - 31.1	28.1	26.9 - 29.4	28.4	27.3 - 29.6
Age group						
12-14	96.7	96.0 - 97.3	77.8	77.1 - 78.5	65.0	64.3 - 65.6
15-17	3.3	2.7 - 4.0	22.2	21.5 - 22.9	35.0	34.4 - 35.7
Sex						
Male	51.0	50.5 - 51.5	51.0	50.4 - 51.5	51.0	50.4 - 51.5
Female	49.0	48.5 - 49.5	49.0	48.5 - 49.6	49.0	48.5 - 49.6
Race/ethnicity						
Non-Hispanic White	54.3	53.8 - 54.9	53.7	53.0 - 54.3	52.8	52.1 - 53.5
Non-Hispanic Black	14.1	13.6 - 14.5	13.3	12.8 - 13.8	12.9	12.5 - 13.3
Non-Hispanic Other	9.3	8.9 - 9.6	9.8	9.4 - 10.3	10.3	9.9 - 10.8
Hispanic	22.3	21.9 - 22.7	23.2	22.7 - 23.7	24.0	23.4 - 24.5
Sexual orientation (ages 14+)						
Straight/Heterosexual	95.0	93.7 - 96.1	92.5	91.4 - 93.4	91.3	90.4 - 92.0
Gay, Lesbian, Bisexual or Other	5.0	3.9 - 6.3	7.5	6.6 - 8.6	8.7	8.0 - 9.6
P30D combustible tobacco use[a]						
Yes	0.6	0.4 - 0.9	0.6	0.4 - 0.9	0.7	0.5 - 1.0
No	99.4	99.1 - 99.6	99.4	99.1 - 99.6	99.3	99.0 - 99.5
Parental education						
Less than high school	17.4	16.0 - 18.9	16.5	15.2 - 17.9	15.7	14.5 - 16.9
High school graduate	17.5	16.2 - 19.0	16.8	15.8 - 18.0	16.3	15.2 - 17.4
Some college or associate degree	20.1	18.8 - 21.5	30.3	28.7 - 32.0	31.3	29.7 - 32.9
Bachelor's degree or above	45.0	42.6 - 47.3	36.3	34.0 - 38.8	36.8	34.7 - 38.9
State recreational marijuana law						
Legalized	6.2	3.5 - 10.8	6.2	3.5 - 10.6	18.8	15.0 - 23.3
Not legalized	93.8	89.2 - 96.5	93.8	89.4 - 96.5	81.2	76.7 - 85.0

[a]Combustible tobacco included cigarette, cigar, cigarillo, and filtered cigar.
P30D, past-30-day.

Table 3.3. Weighted percentage of P30D marijuana use at each follow-up wave by covariates at its corresponding baseline wave among baseline never marijuana users.

	Wave 1		Wave 2		Wave 3	
Baseline exposure and covariates	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
Overall P30D marijuana use at follow-up waves	2.3	1.8 - 2.9	2.4	2.0 - 2.9	3.2	2.9 - 3.6
P30D e-cigarette use						
Yes	13.8	4.3 - 36.1	9.7	4.3 - 20.2	26.3	18.0 - 36.7
No	2.2	1.8 - 2.8	2.4	2.0 - 2.8	2.9	2.6 - 3.2
Internalizing mental health problems						
Low	1.3	0.9 - 1.9	1.9	1.5 - 2.5	2.7	2.2 - 3.2
Moderate	2.4	1.7 - 3.4	2.3	1.7 - 3.1	3.1	2.4 - 4.0
High	5.1	3.7 - 7.1	4.2	3.1 - 5.7	4.9	4.0 - 6.0
Externalizing mental health problems						
Low	1.1	0.7 - 1.8	1.9	1.4 - 2.6	2.3	1.8 - 2.8
Moderate	2.1	1.4 - 3.0	1.9	1.3 - 2.7	3.3	2.6 - 4.2
High	4.4	3.3 - 5.9	3.7	2.9 - 4.7	4.7	3.9 - 5.7
Age group						
12-14	2.3	1.8 - 2.9	2.0	1.6 - 2.5	2.4	2.0 - 2.8
15-17	2.4	0.8 - 6.8	3.9	3.0 - 5.2	4.8	4.0 - 5.6
Sex						
Male	1.8	1.3 - 2.6	2.4	1.9 - 3.0	3.0	2.5 - 3.7
Female	2.8	2.1 - 3.6	2.5	1.9 - 3.2	3.4	2.8 - 4.0
Race/ethnicity						
Non-Hispanic White	2.4	1.8 - 3.2	2.6	2.0 - 3.3	3.7	3.1 - 4.3
Non-Hispanic Black	3.5	2.1 - 5.8	1.8	1.1 - 3.1	3.2	2.2 - 4.8
Non-Hispanic Other	0.8	0.3 - 2.6	2.3	1.2 - 4.1	1.2	0.6 - 2.1
Hispanic	1.9	1.2 - 2.8	2.4	1.8 - 3.3	3.2	2.6 - 4.1
Sexual orientation (ages 14+)						
Straight/Heterosexual	3.4	2.6 - 4.5	3.5	2.8 - 4.2	4.3	3.7 - 5.0
Gay, Lesbian, Bisexual or Other	7.9	2.9 - 19.9	5.6	2.6 - 11.4	6.1	4.1 - 8.9
P30D combustible tobacco use[a]						
Yes	12.9	4.5 - 31.7	14.8	6.8 - 29.4	18.9	10.8 - 31.0
No	2.3	1.8 - 2.9	2.4	2.0 - 2.8	3.1	2.7 - 3.4
Parental education						
Less than high school	4.2	3.2 - 5.7	2.1	1.3 - 3.2	3.9	3.0 - 4.9
High school graduate	2.1	1.2 - 3.5	2.3	1.4 - 3.6	3.2	2.3 - 4.5
Some college or associate degree	2.0	1.3 - 3.0	3.4	2.5 - 4.5	3.5	2.9 - 4.3
Bachelor's degree or above	1.8	1.2 - 2.7	1.9	1.3 - 2.7	2.6	2.1 - 3.3
State recreational marijuana law						
Legalized	3.4	1.6 - 7.3	2.9	1.3 - 6.4	3.4	2.6 - 4.4
Not legalized	2.2	1.8 - 2.8	2.4	2.0 - 2.9	3.2	2.6 - 4.4

[a]Combustible tobacco included cigarette, cigar, cigarillo, and filtered cigar.
P30D, past-30-day.

Table 3.4. Adjusted odds ratios (aORs) of P30D marijuana use at 12-month follow-up waves among adolescents (aged 12-17 years) who were never marijuana users at baseline waves.

	Model 1 No interaction		Model 2 IMH interaction		Model 3 EMH interaction	
Baseline exposure and covariates	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
P30D e-cigarette use						
Yes	**5.92**	**3.64 - 9.63**	**11.74**	**5.7 - 24.19**	**10.63**	**4.18 - 27.01**
No	Ref.		Ref.		Ref.	
Internalizing problems						
Low	Ref.		Ref.		Ref.	
Moderate	1.08	0.81 - 1.44	1.11	0.83 - 1.5	1.08	0.81 - 1.44
High	**1.50**	**1.11 - 2.03**	**1.65**	**1.22 - 2.22**	**1.51**	**1.12 - 2.04**
Externalizing problems						
Low or moderate	Ref.		Ref.		Ref.	
Moderate	1.25	0.95 - 1.66	1.25	0.94 - 1.66	1.31	0.98 - 1.75
High	**1.79**	**1.36 - 2.35**	**1.78**	**1.35 - 2.34**	**1.84**	**1.37 - 2.45**
P30D e-cigarette use by IMH problems						
Yes by High			**0.23**	**0.07 - 0.70**		
Yes by Moderate			0.59	0.16 - 2.18		
No by Low			Ref.			
P30D e-cigarette use by EMH problems						
Yes by High					0.52	0.16 - 1.66
Yes by Moderate					0.33	0.06 - 1.92
No by Low					Ref.	
Age group						
12-14	Ref.		Ref.		Ref.	
15-17	**1.80**	**1.45 - 2.25**	**1.80**	**1.45 - 2.24**	**1.82**	**1.46 - 2.26**
Sex						
Male	0.91	0.73 - 1.13	0.91	0.73 - 1.13	0.91	0.73 - 1.13
Female	Ref.		Ref.		Ref.	
Race/ethnicity						
Non-Hispanic White	Ref.		Ref.		Ref.	
Non-Hispanic Black	1.04	0.71 - 1.51	1.04	0.72 - 1.51	1.04	0.72 - 1.51
Non-Hispanic Other	**0.51**	**0.33 - 0.78**	**0.51**	**0.33 - 0.78**	**0.51**	**0.33 - 0.78**
Hispanic	0.86	0.66 - 1.11	0.84	0.65 - 1.09	0.85	0.66 - 1.1
P30D combustible tobacco use[a]						
Yes	**2.68**	**1.39 - 5.18**	**2.67**	**1.39 - 5.11**	**2.62**	**1.32 - 5.18**
No	Ref.		Ref.		Ref.	
Parental education						
Less than high school	Ref.		Ref.		Ref.	
High school graduate	0.71	0.49 - 1.04	0.72	0.49 - 1.05	0.71	0.49 - 1.04
Some college or associate degree	0.82	0.64 - 1.04	0.81	0.63 - 1.03	0.82	0.64 - 1.04

Bachelor's degree or above	**0.61**	**0.44 - 0.84**	**0.61**	**0.44 - 0.83**	**0.61**	**0.44 - 0.84**
State recreational marijuana law						
Legalized	1.29	0.94 - 1.78	1.32	0.96 - 1.82	1.30	0.95 - 1.79
Not legalized	Ref.		Ref.		Ref.	

Note: Boldface indicates statistical significance ($p<0.05$).

[a]Combustible tobacco included cigarette, cigar, cigarillo, and filtered cigar.

P30D, past-30-day.

IMH, Internalizing mental health.

EMH, Externalizing mental health.

Table 3.5. Adjusted odds ratios (aORs) of P30D marijuana use at 12-month follow-up waves from subgroup analysis for adolescents (aged 12-17 years) with low and high severity internalizing mental health problems.

	P30D marijuana use for low internalizing problems		P30D marijuana use for high internalizing problems	
Baseline exposure	**aOR[a]**	**95% CI**	**aOR[a]**	**95% CI**
P30D E-cigarette use				
Yes	**10.15**	**4.72 - 21.81**	**3.04**	**1.20 - 7.72**
No	Ref.		Ref.	

Note: Boldface indicates statistical significance (p<0.05).

[a]Controlling for wave, sex, age, race/ethnicity, parental education, past-year externalizing mental health problems, P30D combustible tobacco use, state-level marijuana legalization status at baseline.

P30D, past-30-day.

Table 3.6. Weighted percentage of ever marijuana use at each follow-up wave by covariates at its corresponding baseline wave among baseline never marijuana users.

	Wave 1		Wave 2		Wave 3	
Baseline exposure and covariates	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
Overall ever marijuana use at follow-up waves	5.9	5.3 - 6.6	5.7	5.0 - 6.3	7.7	7.1 - 8.3
P30D e-cigarette use						
Yes	24.4	10.5 - 47.0	19.9	12.5 - 30.3	41.1	31.7 - 51.2
No	5.8	5.2 - 6.5	5.5	4.9 - 6.2	7.2	6.6 - 7.8
Internalizing mental health problems						
Low	3.9	3.2 - 4.8	3.9	3.3 - 4.6	5.9	5.2 - 6.8
Moderate	6.0	4.9 - 7.4	6.2	5.1 - 7.6	7.9	6.6 - 9.3
High	11.8	9.6 - 14.3	10.0	8.2 - 12.1	12.2	10.8 - 13.8
Externalizing mental health problems						
Low	3.1	2.4 - 4.1	3.3	2.7 - 4.2	5.1	4.4 - 6.0
Moderate	5.4	4.3 - 6.7	5.4	4.2 - 6.8	8.1	6.8 - 9.5
High	10.9	9.3 - 12.7	9.6	8.2 - 11.3	11.7	10.5 - 13.0
Age group						
12-14	5.8	5.2 - 6.6	4.7	4.1 - 5.4	5.6	5.0 - 6.2
15-17	8.1	4.5 - 14.1	9.1	7.6 - 10.8	11.6	10.4 - 12.9
Sex						
Male	5.5	4.7 - 6.5	5.9	5.1 - 6.9	7.2	6.4 - 8.0
Female	6.3	5.4 - 7.4	5.4	4.6 - 6.3	8.2	7.3 - 9.2
Race/ethnicity						
Non-Hispanic White	5.6	4.8 - 6.6	6.0	5.1 - 7.1	8.0	7.1 - 9.0
Non-Hispanic Black	7.8	5.5 - 10.9	4.8	3.4 - 6.8	8.5	6.8 - 10.5
Non-Hispanic Other	2.7	1.5 - 4.9	4.3	2.5 - 7.2	5.3	4.0 - 7.1
Hispanic	6.8	5.7 - 8.3	5.8	4.8 - 7.0	8.0	6.8 - 9.4
Sexual orientation (ages 14+)						
Straight/Heterosexual	8.4	7.1 - 10.1	8.0	7.0 - 9.1	10.1	9.1 - 11.3
Gay, Lesbian, Bisexual or Other	18.8	9.4 - 33.9	14.6	9.7 - 21.3	16.7	13.1 - 21.0
P30D combustible tobacco use[a]						
Yes	32.8	19.1 - 50.2	28.1	15.8 - 44.8	39.0	26.6 - 53.1
No	5.9	5.2 - 6.6	5.5	4.8 - 6.2	7.4	6.9 - 8.0
Parental education						
Less than high school	8.6	7.0 - 10.5	5.1	3.9 - 6.6	8.7	7.4 - 10.2
High school graduate	7.4	5.6 - 9.6	6.6	5.1 - 8.6	7.3	6.0 - 8.9
Some college or associate degree	5.7	4.5 - 7.2	7.2	6.0 - 8.7	8.8	7.8 - 10.0
Bachelor's degree or above	4.4	3.5 - 5.5	4.4	3.4 - 5.7	6.6	5.6 - 7.7
State recreational marijuana law						
Legalized	9.1	5.6 - 14.4	5.4	3.2 - 8.9	8.2	7.0 - 9.6
Not legalized	5.7	5.1 - 6.4	5.7	5.0 - 6.4	7.6	6.9 - 8.2

[a]Combustible tobacco included cigarette, cigar, cigarillo, and filtered cigar.

P30D, past-30-day.

Table 3.7. Adjusted odds ratios (aORs) of ever marijuana use at 12-month follow-up waves among adolescents (aged 12-17 years) who were never marijuana users at baseline waves.

	Model 1 No interaction		Model 2 IMH interaction		Model 3 EMH interaction	
Baseline exposure and covariates	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
P30D e-cigarette use						
Yes	**3.84**	**2.51 - 5.86**	**6.98**	**4.01 - 12.15**	**6.01**	**2.74 - 13.18**
No	Ref.		Ref.		Ref.	
Internalizing problems						
Low	Ref.		Ref.		Ref.	
Moderate	1.13	0.95 - 1.34	1.13	0.95 - 1.35	1.13	0.95 - 1.34
High	**1.51**	**1.23 - 1.85**	**1.58**	**1.29 - 1.94**	**1.51**	**1.23 - 1.85**
Externalizing problems						
Low	Ref.		Ref.		Ref.	
Moderate	**1.60**	**1.27 - 2.01**	**1.60**	**1.27 - 2.01**	**1.63**	**1.29 - 2.04**
High	**2.43**	**1.98 - 2.97**	**2.43**	**1.98 - 2.97**	**2.46**	**2.00 - 3.03**
P30D e-cigarette use by IMH problems						
Yes by High			**0.24**	**0.11 - 0.54**		
Yes by Moderate			0.86	0.35 - 2.10		
No by Low			Ref.			
P30D e-cigarette use by EMH problems						
Yes by High					0.57	0.21 - 1.53
Yes by Moderate					0.51	0.14 - 1.84
No by Low					Ref.	
Age group						
12-14	Ref.		Ref.		Ref.	
15-17	**1.93**	**1.66 - 2.24**	**1.93**	**1.66 - 2.24**	**1.93**	**1.66 - 2.25**
Sex						
Male	0.99	0.86 - 1.14	0.99	0.86 - 1.13	0.99	0.86 - 1.14
Female	Ref.		Ref.		Ref.	
Race/ethnicity						
Non-Hispanic White	Ref.		Ref.		Ref.	
Non-Hispanic Black	1.07	0.85 - 1.36	1.07	0.85 - 1.35	1.07	0.85 - 1.36
Non-Hispanic Other	**0.66**	**0.51 - 0.85**	**0.66**	**0.51 - 0.85**	**0.66**	**0.51 - 0.85**
Hispanic	1.01	0.85 - 1.19	1.00	0.85 - 1.18	1.01	0.85 - 1.19
P30D combustible tobacco use[a]						
Yes	**3.41**	**1.87 - 6.19**	**3.43**	**1.95 - 6.01**	**3.35**	**1.84 - 6.09**
No	Ref.		Ref.		Ref.	
Parental education						
Less than high school	Ref.		Ref.		Ref.	
High school graduate	0.89	0.71 - 1.10	0.89	0.72 - 1.11	0.89	0.71 - 1.10
Some college or associate degree	0.90	0.74 - 1.09	0.89	0.74 - 1.08	0.90	0.74 - 1.09

Bachelor's degree or above	**0.67**	**0.55 - 0.81**	**0.67**	**0.55 - 0.81**	**0.67**	**0.55 - 0.81**
State recreational marijuana law						
Legalized	1.19	0.95 - 1.50	1.20	0.96 - 1.51	1.20	0.95 - 1.51
Not legalized	Ref.		Ref.		Ref.	

Note: Boldface indicates statistical significance (p<0.05).

[a]Combustible tobacco included cigarette, cigar, cigarillo, and filtered cigar.

P30D, past-30-day.

IMH, Internalizing mental health.

EMH, Externalizing mental health.

Table 3.8. Adjusted odds ratios (aORs) of ever marijuana use at 12-month follow-up waves from subgroup analysis for adolescents (aged 12-17 years) with low and high severity internalizing mental health problems.

	Ever marijuana use for low internalizing problems		Ever marijuana use for high internalizing problems	
Baseline exposure and covariates	**aOR[a]**	**95% CI**	**aOR[a]**	**95% CI**
P30D E-cigarette use				
Yes	**6.44**	**3.51 - 11.81**	1.80	0.89 - 3.60
No	Ref.		Ref.	

Note: Boldface indicates statistical significance (p<0.05).

[a]Controlling for wave, sex, age, race/ethnicity, parental education, past-year externalizing mental health problems, P30D combustible tobacco use, state-level marijuana legalization status at baseline.

P30D, past-30-day.

Table 3.9. Adjusted odds ratios (aORs) of P30D marijuana use at 12-month follow-up waves among adolescents (aged 12-17 years) who were never marijuana users at baseline waves.

	Model 1 No interaction		Model 2 IMH interaction		Model 3 EMH interaction	
Baseline exposure and covariates	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
P30D e-cigarette use						
Yes	**5.85**	**3.61 - 9.48**	**16.15**	**7.90 - 33.01**	**8.25**	**3.30 - 20.61**
No	Ref.		Ref.		Ref.	
Internalizing problems	**1.08**	**1.01 - 1.17**	**1.11**	**1.03 - 1.20**	1.08	0.99 - 1.17
Externalizing problems	**1.15**	**1.08 - 1.23**	**1.15**	**1.08 - 1.23**	**1.16**	**1.09 - 1.24**
P30D e-cigarette use by IMH problems						
Yes by >0			**0.63**	**0.47 - 0.84**		
No by 0			Ref.			
P30D e-cigarette use by EMH problems						
Yes by >0					0.91	0.72 - 1.14
No by 0					Ref.	
Age group						
12-14	Ref.		Ref.		Ref.	
15-17	**1.83**	**1.47 - 2.27**	**1.81**	**1.45 - 2.25**	**1.82**	**1.46 - 2.27**
Sex						
Male	0.89	0.71 - 1.11	0.88	0.71 - 1.1	0.89	0.71 - 1.11
Female	Ref.		Ref.		Ref.	
Race/ethnicity						
Non-Hispanic White	Ref.		Ref.		Ref.	
Non-Hispanic Black	1.03	0.71 - 1.50	1.02	0.71 - 1.48	1.03	0.71 - 1.49
Non-Hispanic Other	**0.51**	**0.33 - 0.79**	**0.51**	**0.33 - 0.78**	**0.51**	**0.33 - 0.79**
Hispanic	0.86	0.67 - 1.12	0.85	0.66 - 1.09	0.86	0.67 - 1.11
P30D combustible tobacco use[a]						
Yes	**2.64**	**1.36 - 5.15**	**2.68**	**1.38 - 5.20**	**2.61**	**1.33 - 5.10**
No	Ref.		Ref.		Ref.	
Parental education						
Less than high school	Ref.		Ref.		Ref.	
High school graduate	0.71	0.48 - 1.04	0.71	0.49 - 1.04	0.71	0.48 - 1.04
Some college or associate degree	0.81	0.64 - 1.04	0.79	0.62 - 1.01	0.81	0.64 - 1.03
Bachelor's degree or above	**0.60**	**0.44 - 0.83**	**0.60**	**0.43 - 0.82**	**0.60**	**0.44 - 0.83**
State recreational marijuana law						
Legalized	1.29	0.94 - 1.78	1.32	0.96 - 1.81	1.29	0.94 - 1.78
Not legalized	Ref.		Ref.		Ref.	

Note: Boldface indicates statistical significance (p<0.05).

[a]Combustible tobacco included cigarette, cigar, cigarillo, and filtered cigar.

P30D, past-30-day.

IMH, Internalizing mental health.
EMH, Externalizing mental health.

Chapter 4: Study Three

Effect modification of recreational marijuana legalization on the association between e-cigarette use and future marijuana use among US adolescents

Abstract

Importance: More states in the US are legalizing recreational marijuana use for adults. However, no study examined how this policy may modify the association between e-cigarette use and subsequent marijuana use among adolescents.

Objective: To investigate whether the association between baseline past-30-day e-cigarette use and subsequent past-30-day marijuana use at 12-month follow-up differs by state recreational marijuana legalization status.

Design, Setting, Participants: This population-based cohort study analyzed data from Wave 1-4 of the Population Assessment of Tobacco and Health Study, a nationally representative longitudinal survey. Wave 1-3 each was considered as the baseline wave of its subsequent 12-month follow-up wave. Data were collected from 2013 through 2018 and analyzed in 2020. In-person interviews were conducted among a nationally representative sample of American youth (aged 12 to 17). The study sample included adolescents who reported never use of marijuana at the baseline waves, including 7,888 youth assessed up to 3 follow-up waves for a total of 19,459 observations.

Exposures: Self-reported binary past-30-day e-cigarette use at baseline waves.

Main Outcomes and Measures: Self-reported past-30-day marijuana use at 12-month follow-up among adolescents who never used marijuana at baseline.

Results: Among never marijuana users at baseline, baseline past-30-day e-cigarette use was significantly associated with past 30-day marijuana use at 12-month follow-up (aOR=5.92, 95% CI: 3.52–9.95; P<0.001). This association was stronger for adolescents in states that legalized adult recreational marijuana use (aOR=18.39, 95% CI: 4.25–79.68; P<0.001) than their counterparts in states without such laws (aOR=5.09, 95% CI: 2.86–9.07; P<0.001). Older age, more severe mental health problems, and combustible tobacco use at baseline were significantly associated with an increased likelihood of marijuana use at follow-up waves. The results were robust to a different outcome measure.

Conclusions and Relevance: Adolescent e-cigarette users have a higher risk of initiating marijuana use. Living in states that legalized recreational marijuana may further elevate this risk. Efforts to curb the youth vaping epidemic may have added benefits of reducing future marijuana use among adolescents. States that legalized adult recreational marijuana use may need additional policies to reduce the transition from e-cigarettes to marijuana.

Introduction

Marijuana is the most widely used psychoactive substance among US youth, with 21.1% of 12th graders, 16.6% of 10th graders, and 6.5% of 8th graders reporting using marijuana in the past 30 days in 2020.[1] Although marijuana remains a Schedule I drug at the federal level,[2] more states are legalizing recreational marijuana use for adults aged 21 years and older in recent years.[3] In 2019, Illinois became the 11th state legalizing marijuana for recreational use, together with Alaska, California, Colorado, Maine, Massachusetts, Michigan, Nevada, Oregon, Vermont, Washington, and the District of Columbia.[4] In 2020, four more states, Arizona, Montana, New Jersey, and South Dakota, approved legalizing recreational marijuana use for adults, with enactment pending until future dates.[5] Previous studies have demonstrated that marijuana policies were associated with marijuana use, abuse, and dependence.[6-8] Legalizing recreational marijuana use for adults may have unintended consequences for adolescents, including diminished harm perceptions and increasing accessibility.[9-12] For example, the proportion of 12th-graders perceiving regular marijuana use as harmful has declined substantially from approximately 80% in the 1990s to about 30% in 2020,[13] though marijuana use may lead to various long-term adverse health effects among adolescents.[14-17]

E-cigarettes are gaining popularity among US youth. In 2020, 19.6% of high school students and 4.7% of middle school students reported e-cigarette use in the past 30 days.[18] Many e-cigarette devices can be customized by users to deliver liquid THC (tetrahydrocannabinol, the psychoactive ingredient in marijuana) or hash oil.[19] A growing body of literature indicates a putative prospective association between initial e-cigarette use and subsequent marijuana vaping and other forms of marijuana use among adolescents.[20-24] A recent meta-analysis revealed that the pooled odds of marijuana use among adolescent e-cigarette users were 3.5 times the corresponding odds among

non-e-cigarette users (adjusted odds ratio [aOR]=3.47; 95% confidence interval [95% CI]=2.63–4.59).[25]

State recreational marijuana laws have been demonstrated to be associated with marijuana use and other drug abuse among adolescents.[6-8] However, little is known about whether legalizing recreational marijuana use would interact with other risk factors of marijuana use and further elevate the likelihood of marijuana initiation among adolescents, particularly with regard to the interaction between state recreational marijuana law and e-cigarette use among adolescents. In this study, we hypothesized that adolescent e-cigarette users living in states that legalized recreational marijuana use for adults would be more likely to initiate marijuana use compared to their counterparts living in states where recreational marijuana use was not legalized.

In addition to e-cigarette use, existing evidence showed that adolescents with mental health disorders were more likely to use nicotine and other substance, leading to substance addiction.[26-28] For example, youth with internalizing mental health problems were more likely to suffer from depression and anxiety, and therefore more likely to use tobacco/marijuana to help cope with these symptoms.[29 30] Youth with externalizing mental health problems, however, tend to have more issues related to behavioral conducts, and thus were more likely to use tobacco/marijuana as a way to rebel against health behaviors considered to be “normal” or “acceptable”.[31] Despite their documented importance, few previous studies examining the association between e-cigarette use and subsequent marijuana use accounted for the potential confounding effects of individual mental health conditions.

This study aims to fill these research gaps by examining the potential effect modification of recreational marijuana legalization on the association between e-cigarette use and subsequent marijuana use among US adolescents, controlling for various confounders, such as mental health

condition and use of combustible tobacco products, which were not previously accounted for. Specifically, we used the youth cohort from of the Population Assessment of Tobacco and Health (PATH) Study to investigate whether the magnitude of the prospective association between e-cigarette use at baseline and marijuana use at follow-up vary dependent on state recreational marijuana legalization status, controlling for individual socio-demographic characteristics, use of combustible tobacco products, and mental health conditions.

Methods

Data and study design

Data used for this study were compiled from Wave 1-4 youth cohort of the PATH Study (2013-2018), a household-based, nationally representative, longitudinal study.[32] A multistage, stratified probability sample was selected to represent the noninstitutionalized youth population in the US. Youth aged 12-17 years old and shadow youth aged 9-11 were selected before data collection, and shadow youth would be interviewed when they aged up to 12 years old. Detailed sampling methods and study design of the PATH Study were available on its website.[32 33] This study followed a validated approach used by the PATH study data management and research team that stacked covariates in the baseline wave with marijuana use status at its corresponding follow-up wave,[28 34 35] where Wave 1-3 each was considered as the baseline wave of its subsequent 12-month follow-up wave. For instance, Wave 2 was both the follow-up wave of Wave 1 and the baseline wave for Wave 3.

The target population of this study was youth respondents who reported never having used marijuana at baseline waves. To produce nationally representative estimates, we followed the recommended approach by the PATH Study team to apply the youth cohort all-wave weights to the

study sample. The all-wave weights were restricted to Wave 1 respondents and shadow youth who completed interviews of all waves while they were 12-17 years old.[36] Therefore, only never marijuana users at baseline waves with all-wave weights were included in this study, resulting in 7,888 youth assessed up to 3 follow-up waves for a total of 19,459 observations (Figure 4.1). Since only secondary data analyses of the de-identified PATH data were conducted, this study was exempt from ethical review by the Georgia State University (GSU) Institutional Review Board (IRB).

Measures

The primary outcome was self-reported binary past-30-day (P30D) marijuana use at 12-month follow-up waves. At the follow-up waves, study participants (never marijuana users at baseline waves) who reported having "used marijuana, hash, THC, grass, pot or weed" or having "smoked part or all of a cigar, cigarillo, or filtered cigar with marijuana in it" in the past 30 days at the survey time were coded as P30D marijuana users. The primary exposure variable was baseline P30D e-cigarette use. Participants who reported using any e-cigarette products in the past 30 days at baseline waves were coded as baseline P30D e-cigarette users. Recreational marijuana legalization status (adult recreational marijuana use legalized or not) at the time of survey administration, the putative effect modifier, was compiled from the NIH Alcohol Policy Information System.[37] State identifiers provided in the PATH Study Restricted-Use Files were used to link state marijuana laws with individual respondents.

Other covariates in this study included survey year, age (12-14 or 15-17), sex (male or female), race/ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, or Non-Hispanic Other), parental education (less than high school, high school graduate, some college or associate degree, and bachelor's degree or above), P30D use of combustible tobacco products (cigarettes, traditional cigars,

cigarillos, or filtered cigars), and internalizing and externalizing mental health status. The PATH youth survey incorporated four items measuring internalizing mental health conditions and seven items measuring externalizing mental health conditions (Table 4.1). In this study, we followed a validated approach to sum up the scores and categorize the severity of mental health problems to low (0-1), moderate (2-3), and high (4 for internalizing problems or 4-7 for externalizing problems).[28 31]

Data analysis

All data management and analyses were conducted using Stata 15 (StataCorp LLC. College Station, TX). The youth cohort all-wave weights were applied to account for the complex sample design and produce nationally representative estimates. The weighted prevalence of P30D marijuana use at each follow-up wave was estimated overall and by covariates at its corresponding baseline wave. Generalized estimating equation (GEE) with unstructured covariance was fitted to evaluate the prospective association between baseline e-cigarette use and subsequent marijuana use, controlling for individual characteristics and state recreational marijuana legalization status.[38] A second GEE model was fitted to examine the potential effect modification of recreational marijuana laws on the association between baseline e-cigarette use and marijuana use at follow-up waves. Subgroup analyses were then conducted to compare the magnitudes of this association for respondents living in states with/without adult recreational marijuana use legalization. Additionally, sensitivity analyses were conducted based on the same set of analyses described above in which the outcome measures were replaced with ever marijuana use during the follow-up period. All statistical analyses were two-sided with the significance level α=0.05.

Results

At Wave 1, 49.0% of respondents were female, 54.3% were Non-Hispanic White, 14.1% were Non-Hispanic Black, 9.3% were Non-Hispanic Other, and 22.3% were Hispanic. The sex and race/ethnicity proportions were consistent across three baseline waves. Detailed descriptive statistics of other demographic characteristics, tobacco use status, and mental health problems were presented in Table 4.2.

Table 4.3 shows the weighted percentages of P30D marijuana use at each follow-up wave by covariates at its corresponding baseline wave. Among adolescents who never used marijuana and reported P30D e-cigarette use at baseline wave, the percentage of P30D marijuana use was 13.8% (95% CI: 4.3%-36.1%) at Wave 2, 9.7% (95% CI: 4.3%-20.2%) at Wave 3, and 26.3% (95% CI: 18.0%-36.7%) at Wave 4, respectively. By contrast, among adolescents who never used marijuana and did not report P30D e-cigarette use at the baseline waves, the percentage of P30D marijuana use was 2.2% (95% CI: 1.8%-2.8%) at Wave 2, 2.4% (95% CI: 2.0%-2.8%) at Wave 3, and 2.9% (95% CI: 2.6%-3.2%) at Wave 4, respectively. In addition, the weighted percentages of self-reported P30D marijuana use at follow-up waves were higher among adolescents who were older, used combustible tobacco products, and experienced more severe internalizing or externalizing mental health problems.

Table 4.4 shows the adjusted associations between P30D marijuana use at follow-up waves and baseline characteristics among adolescents who reported never having used marijuana at baseline waves. Adolescents who reported P30D e-cigarette use at baseline waves were significantly more likely to report P30D marijuana use at follow-up waves (aOR=5.92, 95% CI: 3.52–9.95, $p<0.001$), after adjusting for individual characteristics and state recreational marijuana laws (Model 1). Older age, using combustible tobacco, and high severity of internalizing or externalizing mental health

problems at baseline waves were significantly associated with elevated odds of P30D marijuana use at follow-up waves, with other characteristics being constant. In addition, being Non-Hispanic Other and having parents with a bachelor's degree or above were associated with reduced odds of P30D marijuana use at follow-up waves. Notably, the interaction term, denoted as "P30D e-cigarette use by state recreational marijuana laws", was statistically significant from the null value (Model 2). This result indicated that the association between baseline e-cigarette use and subsequent marijuana use was significantly different between adolescents living in states that legalized recreational marijuana use and those in states that did not legalize recreational marijuana use.

Results of subgroup analysis stratified by state recreational marijuana law were presented in Table 4.5. Among adolescents living in states that legalized recreational marijuana use for adults, the adjusted OR between baseline P30D e-cigarette use and P30D marijuana use at follow-up waves was 18.39 (95% CI: 4.25–79.68, P<0.001), controlling for individual characteristics. In contrast, among adolescents living in states that did not legalize recreational marijuana use, the corresponding adjusted OR was 5.09 (95% CI: 2.86–9.07, P<0.001).

Sensitivity analyses were conducted by replacing the P30D outcome measure with ever marijuana use during the 12-month follow-up period. Consistent with the results in Table 4.3, results presented in Table 4.6 showed that at each follow-up wave, the weighted prevalence of ever marijuana use was higher among adolescents who reported baseline P30D e-cigarette use, compared with those who did not. In addition, results in Table 4.7 were consistent with those in Table 4.4 regarding the significance of the interaction term between e-cigarette use and state recreational marijuana legalization. Furthermore, the results of subgroup analyses in Table 4.8 consistently indicated that the association between baseline P30D e-cigarette use and ever marijuana use at

follow-up waves was stronger among adolescents living in states that legalized recreational marijuana use (aOR=15.93, 95% CI: 4.51–56.26, P<0.001), compared with those living in states that did not legalize recreational marijuana use (aOR=3.24, 95% CI: 2.02–5.22, P<0.001).

Discussion

Although many states have legalized recreational marijuana use for adults, the potential impact of marijuana legalization on adolescent marijuana initiation in the context of the youth vaping epidemic has received minimal research attention.[39] This study provided important evidence of the interaction of e-cigarette use and state marijuana legalization on adolescent marijuana initiation using the PATH data collected from 2013 to 2018, a period when substantial changes occurred in both the e-cigarette marketplace and the marijuana policy landscape.[40 41] Consistent with previous studies, we observed a positive prospective association between baseline e-cigarette use and subsequent marijuana use among adolescents.[20-25] In addition, our study showed a positive, albeit insignificant, association between recreational marijuana legalization and the onset of marijuana use at 12-month follow-up (aOR=1.29, 95% CI: 0.97-1.72, P=0.075). Previous studies indicated that legalizing recreational marijuana use for adults could substantially affect youth's knowledge, risk perceptions, and use behaviors of marijuana.[8 42] The decriminalization, legalization, and marketing of marijuana products might lower the perceived risk and increase the social acceptability of marijuana use,[43 44] and increase access to marijuana products among adolescents.[7 45 46] The insignificant result in our study may be partially due to the small sample size of adolescent marijuana users and the relatively short follow-up period.

Importantly, our analyses showed that adolescent e-cigarette users living in states with recreational marijuana laws were much more likely (aOR=18.39, 95% CI: 4.25–79.68, P<0.001) to use marijuana at follow-up than their counterparts living in states without such laws (aOR=5.09, 95% CI: 2.86–9.07, P<0.001), indicating that state recreational marijuana legalization significantly elevated the risk of marijuana initiation among adolescent e-cigarette users. For adolescents who had never used marijuana and who lived in states that legalized recreational marijuana use for adults, e-cigarette use significantly increased their risk of subsequent marijuana initiation. The revelation of the interaction between recreational marijuana legalization and e-cigarette use on the onset of marijuana use is one of the most important contributions of this study. These results suggest that in states that have legalized recreational marijuana use for adults, implementing policies aiming to reduce youth vaping could have added benefit of reducing future marijuana use among youth and young adults. Efforts to reduce youth marijuana use would benefit from a concerted approach that incorporates measures to reduce youth e-cigarette use.

In addition, we found a positive association between baseline mental health problems and the onset of marijuana use at follow-up. This finding is consistent with what was reported in previous studies, which showed that high severity of externalizing mental health problems was a robust predictor of adolescent substance use.[47-51] We also found a positive association between high severity of internalizing mental health problems and marijuana use. The evidence on the impact of internalizing mental health problems on substance use has been mixed so far.[47-49 51] One potential explanation is that while adolescents with internalizing mental health problems are more likely to use marijuana to cope with anxiety/depression, they also tend to be more socially isolated and less likely to get marijuana from peers or use marijuana with peers.[47] Our results suggest early screening for

mental health problems combined with targeted mental health interventions (e.g., preventive efforts through primary care providers, or targeted school counseling for adolescents with externalizing mental health problems) may help reduce marijuana initiation among adolescents.[52 53]

Other baseline factors that also increased the risk of marijuana use at follow-up waves include age and combustible tobacco use status. Specifically, we found older adolescents were more likely to use marijuana at 12-month follow-up, a finding consistent with what's reported by previous studies.[20 22] Older adolescents likely have more sources to access marijuana products, thus more likely to use them compared to their younger counterparts.[1 54] In addition, our study found that adolescents who used combustible tobacco products at baseline waves were more likely to use marijuana at follow-up waves, also consistent with previous findings.[20 22 23] This result indicated that youth tobacco users were at elevated risk of using substances in the future. These results suggest that efforts to reduce youth marijuana use may need to include interventions and health campaigns targeted at youth tobacco users.

This study is subject to several limitations. First, self-reported use of marijuana and tobacco products may introduce recall bias and social desirability bias.[55] Second, this study was not a randomized controlled trial and could not establish a causal relationship. However, this study controlled for a wide range of potential confounders, including individual-level socio-demographic characteristics, use of combustible tobacco products, mental health status, and state-level marijuana laws, and established a temporal association between e-cigarette use and subsequent marijuana use. Furthermore, due to data availability, mediation analyses were not allowed to examine whether the risk perceptions and availability of marijuana products may contribute to the differential patterns from e-cigarette use to marijuana use between adolescents living in states where recreational

marijuana use was legalized vs. not legalized. Future quantitative and qualitative studies are needed to explore the mechanisms of recreational marijuana legalization's impact on marijuana use among adolescent e-cigarette users in the context of the youth vaping epidemic.

Conclusions

Our study revealed the effect modification of recreational marijuana legalization on the association between baseline e-cigarette use and subsequent marijuana initiation. Our results suggest that adolescent e-cigarette users who live in states that legalized recreational marijuana use for adults are at higher risk of initiating marijuana use. The study findings highlight the importance of the interaction of the youth vaping epidemic and state marijuana laws in shaping youth use of marijuana. These findings suggest that efforts to reduce youth marijuana use in states that have legalized recreational marijuana use for adults may need to incorporate stronger and targeted actions to reduce youth e-cigarette use, which include tailored youth vaping interventions, health education campaigns communicating the risks of tobacco and marijuana use, and targeted actions focusing on vulnerable population groups, such as adolescents with severe mental health problems.

Reference

1. Johnston LD, Miech RA, O'Malley PM, et al. Monitoring the Future national survey results on drug use 1975-2020: Overview, key findings on adolescent drug use. *Institute for Social Research* 2021
2. United States Drug Enforcement Administration. Drug Scheduling [Available from: https://www.dea.gov/drug-scheduling accessed Jan 11 2021.
3. Yu B, Chen X, Chen X, et al. Marijuana legalization and historical trends in marijuana use among US residents aged 12–25: results from the 1979–2016 National Survey on drug use and health. *BMC public health* 2020;20(1):156.
4. Stracqualursi V. Illinois becomes the 11th state to legalize recreational marijuana. *CNN, Politics section* 2019;25
5. Dezenski L. Montana, Arizona, New Jersey, South Dakota and Mississippi approve marijuana ballot measures, CNN projects. *CNN* 2020 December 7, 2020.
6. Cerdá M, Wall M, Keyes KM, et al. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug and alcohol dependence* 2012;120(1-3):22-27.
7. Cerdá M, Wall M, Feng T, et al. Association of state recreational marijuana laws with adolescent marijuana use. *JAMA pediatrics* 2017;171(2):142-49.
8. Cerdá M, Mauro C, Hamilton A, et al. Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA psychiatry* 2020;77(2):165-71.
9. Borodovsky JT, Lee DC, Crosier BS, et al. US cannabis legalization and use of vaping and edible products among youth. *Drug and alcohol dependence* 2017;177:299-306.
10. Hall W, Weier M. Has marijuana legalization increased marijuana use among US youth? *Jama Pediatrics* 2017;171(2):116-18.
11. Ladegard K, Thurstone C, Rylander M. Marijuana legalization and youth. *Pediatrics* 2020;145(Supplement 2):S165-S74.
12. Wang GS, Davies SD, Halmo LS, et al. Impact of marijuana legalization in Colorado on adolescent emergency and urgent care visits. *Journal of Adolescent Health* 2018;63(2):239-41.
13. Johnston LD, Miech RA, O'Malley PM, et al. Monitoring the Future national survey results on drug use 1975-2020: Overview, key findings on adolescent drug use.: Ann Arbor: Institute for Social Research, University of Michigan. , 2021.
14. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences* 2012;109(40):E2657-E64.
15. Bagot KS, Milin R, Kaminer Y. Adolescent initiation of cannabis use and early-onset psychosis. *Substance Abuse* 2015;36(4):524-33.
16. Bechtold J, Simpson T, White HR, et al. Chronic adolescent marijuana use as a risk factor for physical and mental health problems in young adult men. *Psychology of Addictive Behaviors* 2015;29(3):552.
17. Guttmannova K, Kosterman R, White HR, et al. The association between regular marijuana use and adult mental health outcomes. *Drug and alcohol dependence* 2017;179:109-16.
18. Wang TW, Neff LJ, Park-Lee E, et al. E-cigarette use among middle and high school students—United States, 2020. *Morbidity and Mortality Weekly Report* 2020;69(37):1310.

19. US Department of Health & Human Services. E-cigarette use among youth and young adults: a report of the Surgeon General. 2016
20. Audrain-McGovern J, Stone MD, Barrington-Trimis J, et al. Adolescent e-cigarette, hookah, and conventional cigarette use and subsequent marijuana use. *Pediatrics* 2018;142(3):e20173616.
21. Park E, Livingston JA, Wang W, et al. Adolescent E-cigarette use trajectories and subsequent alcohol and marijuana use. *Addictive Behaviors* 2020;103:106213.
22. Dai H, Catley D, Richter KP, et al. Electronic cigarettes and future marijuana use: a longitudinal study. *Pediatrics* 2018;141(5):e20173787.
23. Evans-Polce RJ, Veliz PT, Boyd CJ, et al. E-Cigarette and Cigarette Use Among US Adolescents: Longitudinal Associations With Marijuana Use and Perceptions. *American Journal of Preventive Medicine* 2020
24. Perrine CG, Pickens CM, Boehmer TK, et al. Characteristics of a multistate outbreak of lung injury associated with e-cigarette use, or vaping—United States, 2019. *Morbidity and Mortality Weekly Report* 2019;68(39):860.
25. Chadi N, Schroeder R, Jensen JW, et al. Association between electronic cigarette use and marijuana use among adolescents and young adults: a systematic review and meta-analysis. *Jama Pediatrics* 2019;173(10):e192574-e74.
26. Green VR, Conway KP, Silveira ML, et al. Mental health problems and onset of tobacco use among 12-to 24-year-olds in the PATH study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2018;57(12):944-54. e4.
27. Riehm KE, Young AS, Feder KA, et al. Mental health problems and initiation of e-cigarette and combustible cigarette use. *Pediatrics* 2019;144(1) doi: 10.1542/peds.2018-2935
28. Duan Z, Wang Y, Huang J. Sex Difference in the Association between Electronic Cigarette Use and Subsequent Cigarette Smoking among US Adolescents: Findings from the PATH Study Waves 1–4. *International Journal of Environmental Research and Public Health* 2021;18(4):1695.
29. Zahn–Waxler C, Klimes–Dougan B, Slattery MJ. Internalizing problems of childhood and adolescence: Prospects, pitfalls, and progress in understanding the development of anxiety and depression. *Development and psychopathology* 2000;12(3):443-66.
30. Groenman AP, Janssen TW, Oosterlaan J. Childhood psychiatric disorders as risk factor for subsequent substance abuse: a meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry* 2017;56(7):556-69.
31. Conway KP, Green VR, Kasza KA, et al. Co-occurrence of tobacco product use, substance use, and mental health problems among youth: findings from wave 1 (2013–2014) of the population assessment of tobacco and health (PATH) study. *Addictive behaviors* 2018;76:208-17.
32. United States Department of Health Human Services. National Institutes of Health. National Institute on Drug Abuse, United States Department of Health Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files. 2020.
33. Hyland A, Ambrose BK, Conway KP, et al. Design and methods of the Population Assessment of Tobacco and Health (PATH) Study. *Tobacco control* 2017;26(4):371-78.
34. Kasza KA, Edwards KC, Tang Z, et al. Correlates of tobacco product initiation among youth and adults in the USA: findings from the PATH Study Waves 1–3 (2013–2016). *Tobacco Control* 2020;29(Suppl 3):s191-s202.

35. Edwards KC, Kasza KA, Tang Z, et al. Correlates of tobacco product reuptake and relapse among youth and adults in the USA: findings from the PATH Study Waves 1–3 (2013–2016). *Tobacco Control* 2020;29(Suppl 3):s216-s26.
36. United States Department of Health & Human Services, National Institutes of Health National Institute on Drug Abuse, United States Department of Health Human Services, et al. Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted-Use Files: Inter-university Consortium for Political and Social Research [distributor], 2020.
37. NIH Alcohol Policy Information System. CANNABIS POLICY TOPICS - Recreational Use of Cannabis: Volume 1 [Available from: https://alcoholpolicy.niaaa.nih.gov/cannabis-policy-topics/recreational-use-of-cannabis-volume-1/104 accessed June 17 2020.
38. Hardin JW. Generalized estimating equations (GEE). *Encyclopedia of statistics in behavioral science* 2005
39. National Academies of Sciences E, Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. 2017
40. Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tobacco control* 2019;28(2):146-51.
41. King BA, Jones CM, Baldwin GT, et al. The EVALI and youth vaping epidemics—implications for public health. *New England Journal of Medicine* 2020;382(8):689-91.
42. Mason WA, Hanson K, Fleming CB, et al. Washington State recreational marijuana legalization: Parent and adolescent perceptions, knowledge, and discussions in a sample of low-income families. *Substance use & misuse* 2015;50(5):541-45.
43. Berg CJ, Stratton E, Schauer GL, et al. Perceived harm, addictiveness, and social acceptability of tobacco products and marijuana among young adults: marijuana, hookah, and electronic cigarettes win. *Substance use & misuse* 2015;50(1):79-89.
44. Miech RA, Johnston L, O'Malley PM, et al. Trends in use of marijuana and attitudes toward marijuana among youth before and after decriminalization: The case of California 2007–2013. *International Journal of Drug Policy* 2015;26(4):336-44.
45. Miech R, Johnston L, O'Malley PM. Prevalence and attitudes regarding marijuana use among adolescents over the past decade. *Pediatrics* 2017;140(6):e20170982.
46. Ammerman S, Ryan S, Adelman WP, et al. The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics* 2015;135(3):e769-e85.
47. Scalco MD, Colder CR, Hawk Jr LW, et al. Internalizing and externalizing problem behavior and early adolescent substance use: A test of a latent variable interaction and conditional indirect effects. *Psychology of Addictive Behaviors* 2014;28(3):828.
48. Colder CR, Frndak S, Lengua LJ, et al. Internalizing and externalizing problem behavior: A test of a latent variable interaction predicting a two-part growth model of adolescent substance use. *Journal of abnormal child psychology* 2018;46(2):319-30.
49. Miettunen J, Murray G, Jones P, et al. Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. *Psychological medicine* 2014;44(8):1727-38.
50. Pedersen MU, Thomsen KR, Heradstveit O, et al. Externalizing behavior problems are related to substance use in adolescents across six samples from Nordic countries. *European child & adolescent psychiatry* 2018;27(12):1551-61.

51. Audrain-McGovern J, Rodriguez D, Testa S, et al. Adolescent E-Cigarette Onset and Escalation: Associations With Internalizing and Externalizing Symptoms. *Journal of Adolescent Health* 2020
52. Flay BR. School-based smoking prevention programs with the promise of long-term effects. *Tobacco Induced Diseases* 2009;5(1):6. doi: 10.1186/1617-9625-5-6
53. Kulig JW. Tobacco, alcohol, and other drugs: the role of the pediatrician in prevention, identification, and management of substance abuse. *Pediatrics* 2005;115(3):816-21. doi: 10.1542/peds.2004-2841
54. King KA, Merianos AL, Vidourek RA. Characteristics of marijuana acquisition among a national sample of adolescent users. *American Journal of Health Education* 2016;47(3):126-35.
55. Coughlin SS. Recall bias in epidemiologic studies. *Journal of clinical epidemiology* 1990;43(1):87-91.

Figure 4.1. Flowchart for participants included in final analysis.

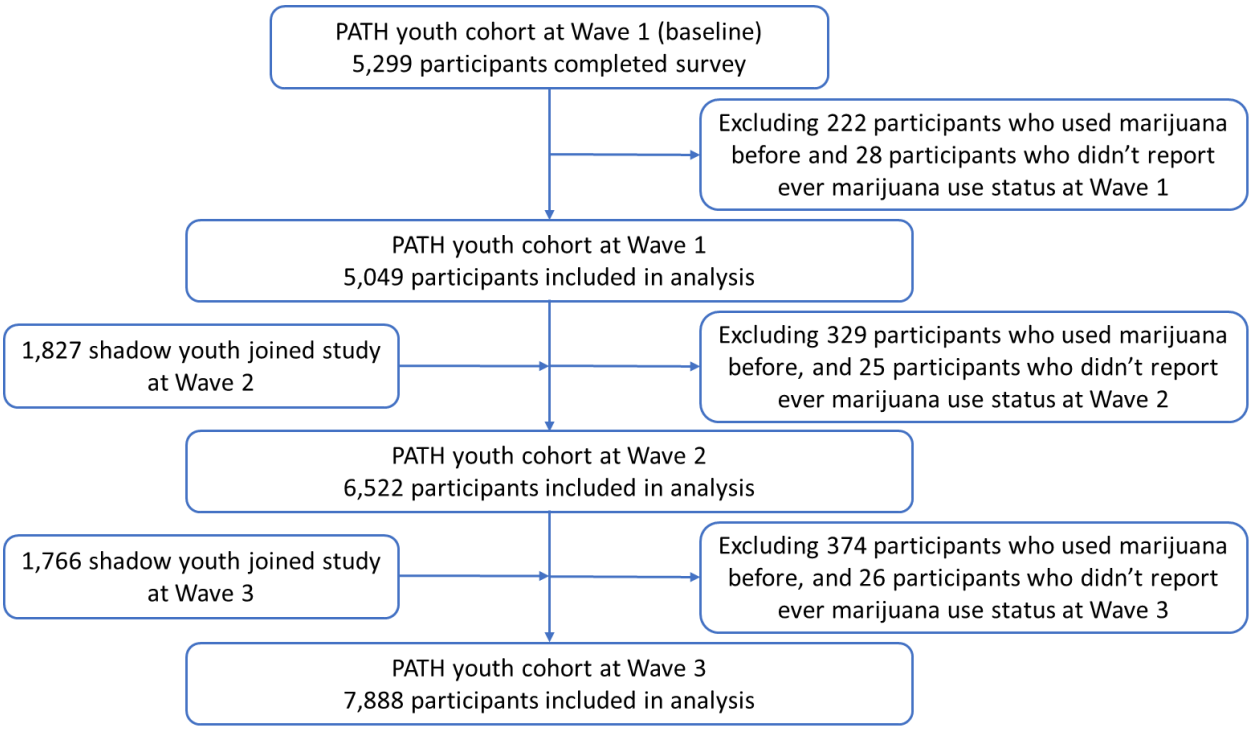

Table 4.1. Items for internalizing and externalizing mental health problems.

GAIN-SS Subscale	Items
Internalizing mental health problems	Feeling very trapped, lonely, sad, blue, depressed, or hopeless about the future
	Sleep trouble - such as bad dreams, sleeping restlessly or falling asleep during the day
	Feeling very anxious, nervous, tense, scared, panicked or like something bad was going to happen
	Becoming very distressed and upset when something reminded you of the past
Externalizing mental health problems	Lied or conned to get things you wanted or to avoid having to do something
	Had a hard time paying attention at school, work, or home
	Had a hard time listening to instructions at school, work, or home
	Were a bully or threatened other people
	Started physical fights with other people
	Felt restless or the need to run around or climb on things
	Gave answers before the other person finished asking the question

Abbreviations: GAIN-SS: Global Appraisal of Individual Needs – Short Screener.

Table 4.2. Weighted descriptive statistics of covariates at baseline waves among adolescents (aged 12-17 years) who reported never having used marijuana.

Baseline exposure and covariates	Wave 1 No. (%)	Wave 2 No. (%)	Wave 3 No. (%)
Total, No.	5049	6522	7888
P30D e-cigarette use			
Yes	29 (0.6)	55 (0.9)	103 (1.4)
No	4989 (99.4)	6425 (99.1)	7756 (98.6)
State recreational marijuana law			
Legalized	340 (6.2)	444 (6.2)	1607 (18.8)
Not legalized	4709 (93.8)	6708 (93.8)	6281 (81.2)
Age group			
12-14	4881 (96.7)	5116 (77.8)	5130 (65.0)
15-17	168 (3.3)	1406 (22.2)	2758 (35.0)
Sex			
Male	2580 (51.0)	3311 (51.0)	4032 (51.0)
Female	2469 (49.0)	3191 (49.0)	3832 (49.0)
Race/ethnicity			
Non-Hispanic White	2405 (54.3)	3011 (53.7)	3594 (52.8)
Non-Hispanic Black	715 (14.1)	845 (13.3)	994 (12.9)
Non-Hispanic Other	455 (9.3)	585 (9.8)	728 (10.3)
Hispanic	1474 (22.3)	1856 (23.2)	2251 (24.0)
Sexual orientation (ages 14+)			
Straight/Heterosexual	1459 (95.0)	2766 (92.5)	3877 (91.3)
Gay, Lesbian, Bisexual or Other	73 (5.0)	223 (7.5)	381 (8.7)
P30D combustible tobacco use[a]			
Yes	30 (0.6)	42 (0.6)	53 (0.7)
No	4840 (99.4)	6454 (99.4)	7805 (99.3)
Internalizing mental health problems			
Low	2574 (52.3)	3400 (53.1)	3928 (51.3)
Moderate	1447 (29.3)	1757 (27.8)	2152 (28.2)
High	879 (18.4)	1207 (19.1)	1585 (20.5)
Externalizing mental health problems			
Low	1917 (39.6)	2762 (44.0)	3335 (43.9)
Moderate	1460 (30.7)	1715 (27.9)	2041 (27.6)
High	1392 (29.7)	1738 (28.1)	2137 (28.4)
Parental education			
Less than high school	1017 (17.4)	1169 (16.5)	1430 (15.7)
High school graduate	928 (17.5)	1071 (16.8)	1344 (16.3)
Some college or associate degree	1045 (20.1)	1852 (30.3)	2451 (31.3)
Bachelor's degree or above	2033 (45.0)	1898 (36.3)	2498 (36.8)

Abbreviations: P30D, past-30-day.

[a]Combustible tobacco included cigarettes, traditional cigar, cigarillo, or filtered cigar.

Table 4.3. Weighted percentage of P30D marijuana use at each follow-up wave by covariates at its corresponding baseline wave among baseline never marijuana users.

Baseline exposure and covariates	Wave 2 % (95% CI)	Wave 3 % (95% CI)	Wave 4 % (95% CI)
Overall P30D marijuana use	2.3 (1.8 - 2.9)	2.4 (2.0 - 2.9)	3.2 (2.9 - 3.6)
P30D e-cigarette use			
Yes	13.8 (4.3 - 36.1)	9.7 (4.3 - 20.2)	26.3 (18.0 - 36.7)
No	2.2 (1.8 - 2.8)	2.4 (2.0 - 2.8)	2.9 (2.6 - 3.2)
State recreational marijuana law			
Legalized	3.4 (1.6 - 7.3)	2.9 (1.3 - 6.4)	3.4 (2.6 - 4.4)
Not legalized	2.2 (1.8 - 2.8)	2.4 (2.0 - 2.9)	3.2 (2.6 - 4.4)
Age group			
12-14	2.3 (1.8 - 2.9)	2.0 (1.6 - 2.5)	2.4 (2.0 - 2.8)
15-17	2.4 (0.8 - 6.8)	3.9 (3.0 - 5.2)	4.8 (4.0 - 5.6)
Sex			
Male	1.8 (1.3 - 2.6)	2.4 (1.9 - 3.0)	3.0 (2.5 - 3.7)
Female	2.8 (2.1 - 3.6)	2.5 (1.9 - 3.2)	3.4 (2.8 - 4.0)
Race/ethnicity			
Non-Hispanic White	2.4 (1.8 - 3.2)	2.6 (2.0 - 3.3)	3.7 (3.1 - 4.3)
Non-Hispanic Black	3.5 (2.1 - 5.8)	1.8 (1.1 - 3.1)	3.2 (2.2 - 4.8)
Non-Hispanic Other	0.8 (0.3 - 2.6)	2.3 (1.2 - 4.1)	1.2 (0.6 - 2.1)
Hispanic	1.9 (1.2 - 2.8)	2.4 (1.8 - 3.3)	3.2 (2.6 - 4.1)
Sexual orientation (ages 14+)			
Straight/Heterosexual	3.4 (2.6 - 4.5)	3.5 (2.8 - 4.2)	4.3 (3.7 - 5.0)
Gay, Lesbian, Bisexual or Other	7.9 (2.9 - 19.9)	5.6 (2.6 - 11.4)	6.1 (4.1 - 8.9)
P30D combustible tobacco use[a]			
Yes	12.9 (4.5 - 31.7)	14.8 (6.8 - 29.4)	18.9 (10.8 - 31.0)
No	2.3 (1.8 - 2.9)	2.4 (2.0 - 2.8)	3.1 (2.7 - 3.4)
Internalizing mental health problems			
Low	1.3 (0.9 - 1.9)	1.9 (1.5 - 2.5)	2.7 (2.2 - 3.2)
Moderate	2.4 (1.7 - 3.4)	2.3 (1.7 - 3.1)	3.1 (2.4 - 4.0)
High	5.1 (3.7 - 7.1)	4.2 (3.1 - 5.7)	4.9 (4.0 - 6.0)
Externalizing mental health problems			
Low	1.1 (0.7 - 1.8)	1.9 (1.4 - 2.6)	2.3 (1.8 - 2.8)
Moderate	2.1 (1.4 - 3.0)	1.9 (1.3 - 2.7)	3.3 (2.6 - 4.2)
High	4.4 (3.3 - 5.9)	3.7 (2.9 - 4.7)	4.7 (3.9 - 5.7)
Parental education			
Less than high school	4.2 (3.2 - 5.7)	2.1 (1.3 - 3.2)	3.9 (3.0 - 4.9)
High school graduate	2.1 (1.2 - 3.5)	2.3 (1.4 - 3.6)	3.2 (2.3 - 4.5)
Some college or associate degree	2.0 (1.3 - 3.0)	3.4 (2.5 - 4.5)	3.5 (2.9 - 4.3)
Bachelor's degree or above	1.8 (1.2 - 2.7)	1.9 (1.3 - 2.7)	2.6 (2.1 - 3.3)

Abbreviations: CI, confidence interval; P30D, past-30-day.

[a]Combustible tobacco included cigarettes, traditional cigar, cigarillo, or filtered cigar.

Table 4.4. Adjusted odds ratios (aORs) of P30D marijuana use at 12-month follow-up waves among adolescents (aged 12-17 years) who were never marijuana users at baseline waves.

	Model 1 - No interaction		Model 2 - Interaction	
Baseline exposure and covariates	**aOR (95% CI)**	**P value**	**aOR (95% CI)**	**P value**
P30D e-cigarette use				
Yes	5.92 (3.52 - 9.95)	<0.001	5.06 (2.86 - 8.95)	<0.001
No	Reference		Reference	
State recreational marijuana law				
Legalized	1.29 (0.97 - 1.72)	0.075	1.22 (0.91 - 1.64)	0.191
Not legalized	Reference		Reference	
P30D e-cigarette use by state recreational marijuana law[a]				
Yes by Legalized			3.94 (1.01 - 15.47)	0.049
No by Not legalized			Reference	
Age group				
12-14	Reference		Reference	
15-17	1.80 (1.44 - 2.26)	<0.001	1.81 (1.44 - 2.26)	<0.001
Sex				
Male	0.91 (0.74 - 1.12)	0.379	0.91 (0.74 - 1.12)	0.391
Female	Reference		Reference	
Race/ethnicity				
Non-Hispanic White	Reference		Reference	
Non-Hispanic Black	1.04 (0.76 - 1.42)	0.810	1.04 (0.76 - 1.42)	0.822
Non-Hispanic Other	0.51 (0.33 - 0.79)	0.003	0.51 (0.33 - 0.80)	0.003
Hispanic	0.86 (0.65 - 1.13)	0.270	0.86 (0.65 - 1.13)	0.273
Parental education				
Less than high school	Reference		Reference	
High school graduate	0.71 (0.51 - 1.01)	0.052	0.70 (0.50 - 0.99)	0.046
Some college or associate degree	0.82 (0.60 - 1.12)	0.207	0.82 (0.60 - 1.12)	0.205
Bachelor's degree or above	0.61 (0.44 - 0.85)	0.004	0.61 (0.43 - 0.85)	0.003
P30D combustible tobacco use[b]				
Yes	2.68 (1.36 - 5.29)	0.005	2.79 (1.41 - 5.49)	0.003
No	Reference		Reference	
Internalizing mental health problems				
Low	Reference		Reference	
Moderate	1.08 (0.81 - 1.43)	0.602	1.07 (0.81 - 1.42)	0.636
High	1.50 (1.10 - 2.05)	0.011	1.49 (1.09 - 2.04)	0.013
Externalizing mental health problems				
Low	Reference		Reference	
Moderate	1.25 (0.94 - 1.68)	0.130	1.25 (0.94 - 1.68)	0.129
High	1.79 (1.30 - 2.45)	<0.001	1.79 (1.31 - 2.46)	<0.001

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; P30D, past-30-day.

[a]Interaction term of P30D e-cigarette use and state recreational marijuana law.

[b]Combustible tobacco included cigarettes, traditional cigar, cigarillo, or filtered cigar.

Table 4.5. Adjusted odds ratios (aORs) of P30D marijuana use at 12-month follow-up waves from subgroup analysis for adolescents (aged 12-17 years) living in states legalizing or not legalizing recreational marijuana use.

	P30D marijuana use in states legalizing recreational marijuana use		P30D marijuana use in states not legalizing recreational marijuana use	
Baseline exposure	**aOR[a] (95% CI)**	**P value**	**aOR[a] (95% CI)**	**P value**
P30D e-cigarette use				
Yes	18.39 (4.25 - 79.68)	<0.001	5.09 (2.86 - 9.07)	<0.001
No	Reference		Reference	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; P30D, past-30-day.
[a]Controlling for P30D combustible tobacco use, sex, age, race/ethnicity, parental education, past-year internalizing mental health problems, past-year externalizing mental health problems.

Table 4.6. Weighted percentage of ever marijuana use at each follow-up wave by covariates at its corresponding baseline wave among baseline never marijuana users.

Baseline exposure and covariates	Wave 2 % (95% CI)	Wave 3 % (95% CI)	Wave 4 % (95% CI)
Overall ever marijuana use	5.9 (5.3 - 6.6)	5.7 (5.0 - 6.3)	7.7 (7.1 - 8.3)
P30D e-cigarette use			
Yes	24.4 (10.5 - 47.0)	19.9 (12.5 - 30.3)	41.1 (31.7 - 51.2)
No	5.8 (5.2 - 6.5)	5.5 (4.9 - 6.2)	7.2 (6.6 - 7.8)
State recreational marijuana law			
Legalized	9.1 (5.6 - 14.4)	5.4 (3.2 - 8.9)	8.2 (7.0 - 9.6)
Not legalized	5.7 (5.1 - 6.4)	5.7 (5.0 - 6.4)	7.6 (6.9 - 8.2)
Age group			
12-14	5.8 (5.2 - 6.6)	4.7 (4.1 - 5.4)	5.6 (5.0 - 6.2)
15-17	8.1 (4.5 - 14.1)	9.1 (7.6 - 10.8)	11.6 (10.4 - 12.9)
Sex			
Male	5.5 (4.7 - 6.5)	5.9 (5.1 - 6.9)	7.2 (6.4 - 8.0)
Female	6.3 (5.4 - 7.4)	5.4 (4.6 - 6.3)	8.2 (7.3 - 9.2)
Race/ethnicity			
Non-Hispanic White	5.6 (4.8 - 6.6)	6.0 (5.1 - 7.1)	8.0 (7.1 - 9.0)
Non-Hispanic Black	7.8 (5.5 - 10.9)	4.8 (3.4 - 6.8)	8.5 (6.8 - 10.5)
Non-Hispanic Other	2.7 (1.5 - 4.9)	4.3 (2.5 - 7.2)	5.3 (4.0 - 7.1)
Hispanic	6.8 (5.7 - 8.3)	5.8 (4.8 - 7.0)	8.0 (6.8 - 9.4)
Sexual orientation (ages 14+)			
Straight/Heterosexual	8.4 (7.1 - 10.1)	8 (7.0 - 9.1)	10.1 (9.1 - 11.3)
Gay, Lesbian, Bisexual or Other	18.8 (9.4 - 33.9)	14.6 (9.7 - 21.3)	16.7 (13.1 - 21.0)
P30D combustible tobacco use[a]			
Yes	32.8 (19.1 - 50.2)	28.1 (15.8 - 44.8)	39 (26.6 - 53.1)
No	5.9 (5.2 - 6.6)	5.5 (4.8 - 6.2)	7.4 (6.9 - 8.0)
Internalizing mental health problems			
Low	3.9 (3.2 - 4.8)	3.9 (3.3 - 4.6)	5.9 (5.2 - 6.8)
Moderate	6.0 (4.9 - 7.4)	6.2 (5.1 - 7.6)	7.9 (6.6 - 9.3)
High	11.8 (9.6 - 14.3)	10 (8.2 - 12.1)	12.2 (10.8 - 13.8)
Externalizing mental health problems			
Low	3.1 (2.4 - 4.1)	3.3 (2.7 - 4.2)	5.1 (4.4 - 6.0)
Moderate	5.4 (4.3 - 6.7)	5.4 (4.2 - 6.8)	8.1 (6.8 - 9.5)
High	10.9 (9.3 - 12.7)	9.6 (8.2 - 11.3)	11.7 (10.5 - 13.0)
Parental education			
Less than high school	8.6 (7.0 - 10.5)	5.1 (3.9 - 6.6)	8.7 (7.4 - 10.2)
High school graduate	7.4 (5.6 - 9.6)	6.6 (5.1 - 8.6)	7.3 (6.0 - 8.9)
Some college or associate degree	5.7 (4.5 - 7.2)	7.2 (6.0 - 8.7)	8.8 (7.8 - 10.0)
Bachelor's degree or above	4.4 (3.5 - 5.5)	4.4 (3.4 - 5.7)	6.6 (5.6 - 7.7)

Abbreviations: CI, confidence interval; P30D, past-30-day.

[a]Combustible tobacco included cigarettes, traditional cigar, cigarillo, or filtered cigar.

Table 4.7. Adjusted odds ratios (aORs) of ever marijuana use at 12-month follow-up waves among adolescents (aged 12-17 years) who were never marijuana users at baseline waves.

	Model 1 - No interaction		Model 2 - Interaction	
Baseline exposure and covariates	**aOR (95% CI)**	**P value**	**aOR (95% CI)**	**P value**
P30D e-cigarette use				
Yes	3.83 (2.47 - 5.95)	<0.001	3.27 (2.03 - 5.26)	<0.001
No	Reference		Reference	
State recreational marijuana law				
Legalized	1.19 (0.99 - 1.44)	0.067	1.15 (0.95 - 1.40)	0.160
Not legalized	Reference		Reference	
P30D e-cigarette use by state recreational marijuana law[a]				
Yes by Legalized			5.34 (1.26 - 22.65)	0.023
No by Not legalized			Reference	
Age group				
12-14	Reference		Reference	
15-17	1.93 (1.66 - 2.24)	<0.001	1.93 (1.66 - 2.24)	<0.001
Sex				
Male	0.99 (0.87 - 1.13)	0.896	0.99 (0.87 - 1.14)	0.911
Female	Reference		Reference	
Race/ethnicity				
Non-Hispanic White	Reference		Reference	
Non-Hispanic Black	1.07 (0.88 - 1.31)	0.501	1.07 (0.88 - 1.3)	0.514
Non-Hispanic Other	0.66 (0.51 - 0.85)	0.001	0.66 (0.51 - 0.85)	0.001
Hispanic	1.01 (0.85 - 1.19)	0.929	1.01 (0.85 - 1.19)	0.945
Parental education				
Less than high school	Reference		Reference	
High school graduate	0.89 (0.71 - 1.10)	0.278	0.88 (0.71 - 1.1)	0.257
Some college or associate degree	0.90 (0.73 - 1.10)	0.305	0.9 (0.73 - 1.1)	0.298
Bachelor's degree or above	1.49 (0.54 - 0.83)	<0.001	0.67 (0.54 - 0.83)	<0.001
P30D combustible tobacco use[b]				
Yes	3.40 (1.98 - 5.85)	<0.001	3.5 (2.04 - 6.01)	<0.001
No	Reference		Reference	
Internalizing mental health problems				
Low	Reference		Reference	
Moderate	1.13 (0.94 - 1.35)	0.201	1.12 (0.94 - 1.34)	0.214
High	1.51 (1.23 - 1.84)	<0.001	1.5 (1.23 - 1.83)	<0.001
Externalizing mental health problems				
Low	Reference		Reference	
Moderate	1.6 (1.32 - 1.94)	<0.001	1.6 (1.32 - 1.94)	<0.001
High	2.43 (1.98 - 2.97)	<0.001	2.43 (1.99 - 2.98)	<0.001

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; P30D, past-30-day.

[a]Interaction term of P30D e-cigarette use and state recreational marijuana law.

[b]Combustible tobacco included cigarettes, traditional cigar, cigarillo, or filtered cigar.

Table 4.8. Adjusted odds ratios (aORs) of ever marijuana use at 12-month follow-up waves from subgroup analysis for adolescents (aged 12-17 years) living in states legalizing or not legalizing recreational marijuana use.

	Ever marijuana use in states legalizing recreational marijuana use		Ever marijuana use in states not legalizing recreational marijuana use	
Baseline exposure	**aOR[a] (95% CI)**	**P value**	**aOR[a] (95% CI)**	**P value**
P30D e-cigarette use				
Yes	15.90 (34.51 - 56.26)	<0.001	3.24 (2.02 - 5.22)	<0.001
No	Reference		Reference	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; P30D, past-30-day.
[a]Controlling for P30D combustible tobacco use, sex, age, race/ethnicity, parental education, past-year internalizing mental health problems, past-year externalizing mental health problems.

Chapter 5: Summary and Conclusions

A growing body of evidence suggests that baseline e-cigarette use may be prospectively associated with subsequent cigarette and marijuana use among US adolescents. However, it remains unclear whether these longitudinal associations may differ by individual characteristics and state-level policies. This dissertation aims to address these important research gaps using the most recent nationally representative longitudinal survey. Specifically, Study One examines the effect modification of biological sex on the association between baseline e-cigarette use and subsequent cigarette use among never cigarette users at baseline waves. Study Two examines the effect modification of mental health types and conditions (internalizing vs. externalizing mental health problems) on the association between e-cigarette use and subsequent marijuana use among adolescents who reported never having used marijuana at baseline waves. Study Three examines the effect modification of state recreational marijuana laws on the association between baseline e-cigarette use and subsequent marijuana use among US adolescents who reported never using marijuana at baseline waves.

Study One found that among baseline never cigarette smokers, past-30-day e-cigarette use at baseline waves was significantly associated with past-30-day cigarette smoking at follow-up waves (aOR=3.90, 95% CI: 2.51–6.08). This association was significantly stronger for boys (aOR=6.17, 95% CI: 2.43–15.68) than for girls (aOR=1.10, 95% CI: 0.14–8.33). Additionally, using other tobacco products, older age, and having severe externalizing mental health problems at baseline were significantly associated with an increased likelihood of cigarette smoking at follow-up. Findings of Study One highlighted the important sex differences in the longitudinal association between initial e-cigarette use and subsequent cigarette smoking among US adolescents. Sex-specific tobacco control

interventions may be warranted to reduce youth tobacco use. In addition, targeted tobacco control interventions, focusing on youth with severe mental health conditions, are warranted. Finally, continued efforts are needed to monitor tobacco and cigarette transitions among youth, particularly among vulnerable and high-risk youth subpopulations.

Study Two found that baseline e-cigarette use was significantly associated with marijuana use at 12-month follow-ups (aOR=5.92, 95% CI: 3.64–9.63). Adolescents with severe internalizing (IMH) or externalizing mental health (EMH) problems were significantly more likely to initiate marijuana use. However, current e-cigarette users who reported more severe IMH symptoms were less likely to initiate marijuana use (aOR=3.04, 95% CI: 1.20–7.74), compared with those who report less severe IMH problems (aOR=10.15, 95% CI: 4.72–21.81). The difference in the estimated associations by the severity of EMH problems was not statistically significant. The study results suggest that tailored interventions are needed for vulnerable population groups characterized by severe internalizing and externalizing mental health conditions. In addition, among adolescents who use e-cigarettes, youth with high severity IMH problems may be less likely to transition to marijuana use. This result suggests that intervention efforts need to target different motivations of substance use, particularly among adolescents with internalizing problems. More research is needed to clarify the potential drivers of this important mechanistic pathway connecting e-cigarette to later marijuana use.

Study Three found that among never marijuana users at baseline, past 30-day marijuana use at 12-month follow-up was significantly associated with baseline past-30-day e-cigarette use (aOR=5.92, 95% CI: 3.52–9.95; P<0.001). This association was stronger for adolescents in states that legalized adult recreational marijuana use (aOR=18.39, 95% CI: 4.25–79.68; P<0.001) than their counterparts in states without such laws (aOR=5.09, 95% CI: 2.86–9.07; P<0.001). Older age, severe

mental health problems, and combustible tobacco use at baseline were significantly associated with an increased likelihood of marijuana use at follow-up waves. The results were robust to different outcome measures. The results revealed the effect modification of recreational marijuana legalization on the association between baseline e-cigarette use and subsequent marijuana initiation. Our results suggest that adolescent e-cigarette users who live in states that legalized recreational marijuana use for adults are at higher risk of initiating marijuana use. Our findings highlight the importance of the interaction of current youth vaping epidemic and state marijuana laws in shaping youth use of marijuana. These findings suggest that efforts to reduce youth marijuana use in states that have legalized recreational marijuana use for adults may need to incorporate stronger and targeted actions to reduce youth e-cigarette use, which include tailored youth vaping interventions, health education campaigns communicating the risks of tobacco and marijuana use, and targeted actions focusing on vulnerable population groups, such as adolescents with severe mental health problems.

The findings of this dissertation indicated that compared with adolescents who reported not using e-cigarettes, the youth e-cigarette users may have an elevated likelihood of initiating future cigarette smoking and marijuana use. Preventive efforts to curb youth cigarette and marijuana initiation may benefit from efforts to reduce youth vaping. Given the interactive effects of the youth vaping and individual demographics and state policies, tailored tobacco and substance control interventions are warranted for e-cigarette using adolescents. In addition, targeted intervention efforts may be warranted to reduce youth tobacco and substance use, particularly among the vulnerable population groups characterized by low socioeconomic status and severe mental health problems. Finally, continued efforts are needed to monitor tobacco and cigarette transitions among youth, particularly among vulnerable and high-risk youth subpopulations.

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