
Supplement Article

Cross-Sectional Association Between Lifetime Use of Electronic Cigarettes With or Without Marijuana and Self-Reported Past 12-Month Respiratory Symptoms as well as Lifetime Respiratory Diseases in U.S. Adults

Zidian Xie PhD¹, Dongmei Li PhD^{1,✉}

¹Department of Clinical and Translational Research, University of Rochester Medical Center, Rochester, NY

Corresponding Author: Zidian Xie PhD, Department of Clinical and Translational Research, University of Rochester Medical Center, Saunders Research Building 1.303J, 265 Crittenden Boulevard CU 420708, Rochester, NY 14642-0708, USA. Telephone: +585-275-4398; E-mail: zidian_xie@urmc.rochester.edu

Abstract

Introduction: The use of electronic cigarettes (vaping), especially with marijuana, has become increasingly popular among adults.

Aims and Methods: The Population Assessment of Tobacco and Health study Wave 4 data on 33 606 adult participants who indicated ever using electronic cigarettes were included in the study. By controlling for confounding variables (such as age and smoking history), multivariable weighted logistic regression models were used to examine the cross-sectional association between lifetime e-cigarette use with or without marijuana and self-reported past 12-month respiratory symptoms as well as lifetime respiratory diseases.

Results: Compared to adults who never vaped, adults who had ever vaped with marijuana had a significantly higher association with self-reported past 12-month respiratory symptoms but not lifetime respiratory diseases. Compared to adults who had ever vaped without marijuana, adults who had ever vaped at least sometimes with marijuana had a significantly greater risk of having wheezing/whistling in the chest (adjusted odds ratio [aOR] = 1.21, 95% confidence interval [CI]: 1.01, 1.44), chest sounded wheezy during or after exercise (aOR = 1.59, 95% CI: 1.31, 1.93), and had a dry cough at night (aOR = 1.35, 95% CI: 1.16, 1.57), while adults who had ever vaped rarely with marijuana had a significantly greater risk of having wheezing/whistling in the chest (aOR = 1.31, 95% CI: 1.06, 1.61), chest sounded wheezy during or after exercise (aOR = 1.24, 95% CI: 1.01, 1.52), and had a dry cough at night (aOR = 1.24, 95% CI: 1.04, 1.47).

Conclusions: Lifetime e-cigarette use with marijuana is associated with self-reported past 12-month respiratory symptoms in adults.

Implications: The use of e-cigarettes with marijuana has become prevalent in recent years. Our cross-sectional study suggests that there may be respiratory health symptoms associated with ever vaping with marijuana that is independent of nicotine vaping, which should raise public awareness of potential health risks associated with the use of e-cigarettes with marijuana. Further longitudinal studies on the respiratory health effects of e-cigarette use with marijuana are warranted.

Introduction

Electronic cigarettes (e-cigarettes), considered as a harm-reduction alternative to cigarettes, have become increasingly popular, especially among youth, due to the availability of thousands of e-liquid flavors.¹ Compared to traditional cigarettes, e-cigarettes contain many potentially harmful ingredients, including propylene glycol (PG), vegetable glycerin (VG), flavor additives, aldehydes, metals, volatile organic compounds.² PG is known to be irritating to upper respiratory airways, which can form carcinogenic compounds when heated.^{3,4} The flavor chemicals (such as diacetyl and cinnamaldehyde) in e-liquid can cause inflammatory and oxidative stress responses in lung cells and monocytic cells.⁵⁻⁸

Extensive animal studies have shown that e-cigarettes could lead to oxidative stress and inflammatory responses in airways and lungs and also inhibit the immune response.^{5,9-13} By exposing to e-cigarette aerosol, mice had increased inflammatory responses and oxidative stress.⁵ With the exposure to PG/VG/nicotine, the mice had increased lung homogenate inflammatory cytokines, apoptosis of airway and alveolar cells, airspace enlargement, and other histological changes, which are the symptoms of chronic obstructive pulmonary disease (COPD).¹⁰ Exposure to e-cigarette aerosol induced two proinflammatory cytokine biomarkers (KC and TREM-1) in mice, which are associated with COPD and interstitial lung disease.¹¹ Consistent with the findings from animal studies, the associations of e-cigarette use (vaping) with respiratory diseases or symptoms in human have been reported. The use of e-cigarettes resulted in increased risks of chronic bronchitis in adolescents.¹⁴ Several studies identified an association between e-cigarette use in youth and the risk of respiratory symptoms/diseases.¹⁴⁻¹⁶ Several studies have shown a strong association between vaping and COPD after controlling for confounding variables (such as smoking history).¹⁷⁻²⁰ Together, the use of e-cigarettes is associated with respiratory symptoms/diseases.

As an alternative way to smoke marijuana, vaping e-cigarettes with marijuana has gained more popularity in recent years, especially among youth and young adults.²¹⁻²⁴ It has been reported that the use of marijuana was associated with respiratory symptoms (such as wheezing and cough) in adults.^{25,26} However, potential respiratory risks associated with co-use of marijuana with e-cigarettes remain unknown. Using the national study, the Population Assessment of Tobacco and Health (PATH) Study Wave 4 data collected from December 2016 to January 2018 on 33 822 adults in total, we investigated the cross-sectional association of adults who had ever vaped with or without marijuana (including marijuana concentrates/waxes, THC, or hash oils) and self-reported past 12-month respiratory symptoms (wheezing and dry cough) or lifetime respiratory diseases (COPD, bronchitis, emphysema, and other lung conditions) in US adults, respectively, and compared adults who vaped with marijuana with those who vaped without marijuana on these respiratory outcomes.

Methods

Study Participants

Launched in 2011, the PATH Study is a national, longitudinal cohort study on tobacco use behavior, attitudes, and beliefs, as well as tobacco-related health outcomes, which used a four-stage stratified area probability sample design.²⁷ To provide the evidence-based information for developing, implementing, and evaluating regulations about tobacco products, the PATH Study sampled over 150 000 mailing addresses in the United States, and conducted

the survey through audio computer-assisted self-interviewing and computer-assisted personal interviewing administered questionnaires, as well as paper data collection. The weights were assigned to each respondent to compensate for variable probabilities of selection, different nonresponse rates, possible deficiencies in the sample frame, and especially oversampling tobacco users, young adults aged 18–24 and African Americans.²⁷ The PATH Study Wave 4 data (December 2016 to January 2018) include 33 822 adults in total (aged 18 years and above).

Outcome Variables

Self-reported health outcomes related to respiratory symptoms/diseases were examined, including (1) wheezing or whistling in the chest (the survey question “Have you had wheezing or whistling in the chest in the past 12 months?”); (2) chest sounded wheezy during or after exercise (the survey question “In past 12 months, has your chest sounded wheezy during or after exercise?”); (3) a dry cough at night (the survey question “A dry cough is a cough without phlegm or mucus. In the past 12 months, have you had a dry cough at night?”); (4) COPD (the survey question “Has a doctor, nurse or other health professional ever told you that you had COPD?”); (5) bronchitis (the survey question “Has a doctor, nurse or other health professional ever told you that you had Chronic Bronchitis?”); (6) emphysema (the survey question “Has a doctor, nurse or other health professional ever told you that you had Emphysema?”); (7) other lung conditions (the survey question “Has a doctor, nurse or other health professional ever told you that you had some other lung or respiratory condition?”); (8) Any respiratory condition from (1) to (7). All outcome variables are categorical variables, with two levels, “yes” or “no.”

Covariates

The predictor variable is the status of ever vaping with marijuana (the survey questions “Have you ever used marijuana, including marijuana concentrates, marijuana waxes, THC, or hash oils in an electronic product such as an e-cigarette, vape, mod, personal vaporizer, e-hookah, or hookah pen?” and “When you have used an electronic nicotine product, how often were you using it to smoke marijuana, marijuana concentrates, marijuana waxes, THC, or hash oils?”) with four levels, including never vaped, ever vaped without marijuana, ever vaped with marijuana at least sometimes (include every time, most of the time or sometimes), and ever vaped rarely with marijuana. Covariates included in the statistical analysis are age, gender, ethnicity, race, education, body mass index (BMI),^{20,28} self-perception of mental health,²⁹ second-hand smoking exposure,³⁰ lived with a regular smoker who smoked inside your home during childhood, home policy about smoking, home policy about vaping, number of cigarettes smoked in the entire life, ever smoked marijuana from a hookah, how often tobacco in filtered cigars was replaced with marijuana, how often tobacco in cigarillos with or without tips was replaced with marijuana, how often tobacco in traditional cigar was replaced with marijuana, substance used weekly or more often (marijuana, hash, THC or grass, pot or weed), ever smoked part or all of a traditional cigar, cigarillo or filtered cigar with marijuana in it, cigarette smoking status (established smoker, experimental smoker, ex-smoker, and nonsmoker), any other tobacco use (including cigars, cigarillos, filtered cigars, traditional cigars, pipe tobacco, hookah, snus, and smokeless tobacco), ever told you that you had asthma. All covariates were categorical variables.

Statistical Analysis

Weighted frequency distributions were conducted to examine the association between vaping with or without marijuana and covariates. Multivariable weighted logistic regression models were used to examine the association of adults who had ever vaped with or without marijuana and self-reported respiratory symptoms or diseases (such as wheezing, dry cough, and COPD) by comparing adults who ever vaped with marijuana rarely or at least sometimes to adults who ever vaped without marijuana or never vaped in respect of different respiratory symptoms or diseases (Supplementary Table 1). The covariates were included in multivariable weighted logistic regression models (Supplementary Table 2) if they significantly contributed to the model ($p < .05$) and showed no multicollinearity with other covariates based on the variance inflation factor values. The model fit was evaluated using the F -adjusted mean residual goodness-of-fit test.

Adjusted odds ratios (aORs) from multivariable weighted logistic regression models and their 95% confidence intervals (CIs) were used to quantify the cross-sectional association between adults who vaped with or without marijuana and self-reported respiratory symptoms/diseases. All analyses were conducted using PROC SURVEY procedure in SAS V9.4 (SAS Institute, Inc., Cary, NC) accounting for the complex sampling design. All tests were two sided with a significance level of 5%.

Results

Demographic Characteristics of Adults Who Had Ever Vaped With or Without Marijuana

Among the 33 822 adult participants in Wave 4 of the PATH Study, 33 602 (99.4%) had a valid answer (yes or no) to the question if they had ever used e-cigarettes. Among them, 20 411 (61%) adults never vaped and 13 191 (39%) adults ever vaped. Among adults who had ever vaped, 9485 (72%) adults vaped without marijuana and 3706 (28%) adults ever vaped with marijuana. Among adults who had ever vaped with marijuana, 1485 (40%) adults vaped rarely with marijuana and 2221 (60%) adults vaped at least sometimes with marijuana.

Compared to adults who never vaped, adults who had ever vaped with or without marijuana had a higher percentage of self-reported past 12-month respiratory symptoms or lifetime respiratory diseases (including wheezing, dry cough, COPD, asthma, bronchitis, and emphysema) (Supplementary Table 3). For example, there were 24.28% (95% CI: 23.25%, 25.35%) adults who had ever vaped at least sometimes with marijuana, 27.75% (95% CI: 26.03%, 29.57%) adults who had ever vaped rarely with marijuana and 23.28% (95% CI: 22.65%, 23.93%) adults who had ever vaped without marijuana had reported wheezing or whistling in the chest while only 12.92% (95% CI: 12.33%, 13.54%) adults who never vaped had reported wheezing or whistling in the chest. The majority of adults who had ever vaped with or without marijuana were young adults (aged 18–34). Most of the adults who had ever vaped with or without marijuana were male. There were similar percentage of adults who had ever vaped with or without marijuana or never vaped among different races. Adult participants who have graduate equivalency degree had a higher percentage of ever vaping with or without marijuana than never vaped while adults who have a Bachelor's degree or above had a lower probability. Adults who had lower BMI levels (underweight or normal) had a higher percentage of ever vaping with

marijuana than those with higher BMI levels (overweight or obese). With the worsening of mental health, the percentage of vaping with or without marijuana increased. As expected, with the home policy allowing smoking and vaping at home, the percentage of adults who had ever vaped with or without marijuana was high. With more cigarettes smoked, the percentage of adults who had ever vaped with or without marijuana increased. Adults participants who had ever vaped with or without marijuana had a higher percentage of using traditional combustible cigarettes or any other tobacco products than those who never vaped. With more frequently used marijuana either with or without other tobacco products (such as cigars and cigarillos), the percentage of adults who had ever vaped with marijuana was higher.

Association between Adults Who Had Ever Vaped with or Without Marijuana and Self-Reported Respiratory Symptoms/Diseases

To examine the association between adults who had ever vaped with or without marijuana and self-reported respiratory symptoms/diseases, the adjusted ORs based on multivariable weighted logistic regression models were calculated (Table 1). The aORs of respiratory symptoms/diseases for covariates controlled for in each model were present in Supplementary Table 2. For example, adults with asthma had significantly higher aOR for the reported respiratory symptoms/diseases than adults without asthma. Compared to adults who never vaped, adults who had ever vaped with marijuana at least sometimes or rarely showed significantly higher aOR for self-reported wheezing/whistling in the chest, with aOR = 1.25 (95% CI: 1.03, 1.51), aOR = 1.35 (95% CI: 1.11, 1.65), respectively (Table 1). Similarly, adults who had ever vaped with marijuana at least sometimes or rarely had significantly higher aORs for self-reported chest sounded wheezy during or after exercise than adults who never vaped, with aOR = 1.72 (95% CI: 1.42, 2.09), aOR = 1.34 (95% CI: 1.09, 1.65), respectively. The odds for adults who had ever vaped with marijuana at least sometimes or rarely were significantly higher than adults who never vaped, with aOR = 1.33 (95% CI: 1.14, 1.55) and aOR = 1.22 (95% CI: 1.03, 1.44), respectively.

For self-reported COPD, adults who had ever vaped with marijuana at least sometimes or rarely showed higher but not significantly aORs than adults who never vaped, with aOR = 1.17 (95% CI: 0.76, 1.80) and aOR = 1.40 (95% CI: 0.91, 2.16). For self-reported bronchitis, emphysema, and other lung conditions, compared to adults who never vaped, while adults who had ever vaped with marijuana at least sometimes or rarely did not show significantly higher aORs except that adults who had ever vaped with marijuana rarely and self-reported emphysema (aOR = 2.97, 95% CI: 1.60, 5.50). The odds of any self-reported respiratory conditions for adults who had ever vaped with marijuana at least sometimes or rarely were significantly higher than adults who never vaped, with aOR = 1.36 (95% CI: 1.16, 1.60), aOR = 1.25 (95% CI: 1.05, 1.50), respectively.

The Involvement of Marijuana on the Association of Adults Who Had Ever Vaped with Self-Reported Respiratory Symptoms/Diseases

To examine if ever marijuana use in e-cigarettes have any association with respiratory symptoms/diseases, we compared adults who had ever vaped with marijuana to adults who had ever vaped without marijuana. As shown in Table 1, compared to adults who had ever vaped without marijuana, adults who had ever vaped with marijuana

Table 1. Association between ever vaping with or without marijuana and self-reported respiratory symptoms/diseases

| Respiratory diseases/ symptoms (unweighted sample size) | Adjusted odds ratios(95% CIs) | | | | |
|--|--|--|--|---|---|
| | Ever vaped with marijuana (at least sometimes) versus never vaped | Ever vaped with marijuana (rarely) versus never vaped | Ever vaped without marijuana versus never vaped | Ever vaped with marijuana (at least sometimes) versus ever vaped without marijuana | Ever vaped with marijuana (rarely) versus ever vaped without marijuana |
| Past 12-month respiratory symptoms | | | | | |
| Wheezing or whistling in the chest (N = 5860) ^a | 1.25 (1.03, 1.51) | 1.35 (1.11, 1.65) | 1.04 (0.92, 1.16) | 1.21 (1.01, 1.44) | 1.31 (1.06, 1.61) |
| Chest sounded wheezy during or after exercise (N =4462) ^b | 1.72 (1.42, 2.09) | 1.34 (1.09, 1.65) | 1.08 (0.94, 1.25) | 1.59 (1.31, 1.93) | 1.24 (1.01, 1.52) |
| A dry cough at night (N = 7119) ^c | 1.33 (1.14, 1.55) | 1.22 (1.03, 1.44) | 0.98 (0.89, 1.08) | 1.35 (1.16, 1.57) | 1.24 (1.04, 1.47) |
| Lifetime respiratory diseases | | | | | |
| Chronic obstructive pulmonary disease (N = 1054) ^d | 1.17 (0.76, 1.80) | 1.40 (0.91, 2.16) | 1.27 (0.99, 1.62) | 0.92 (0.62, 1.37) | 1.11 (0.70, 1.75) |
| Bronchitis (N = 884) ^e | 1.17 (0.83, 1.65) | 0.99 (0.64, 1.53) | 1.19 (0.93, 1.51) | 0.99 (0.69, 1.41) | 0.83 (0.55, 1.27) |
| Emphysema (N = 390) ^f | 1.34 (0.65, 2.77) | 2.97 (1.60, 5.50) | 1.35 (1.01, 1.80) | 0.99 (0.50, 1.98) | 2.21 (1.12, 4.35) |
| Other lung conditions (N = 681) ^g | 1.36 (0.81, 2.27) | 1.75 (1.00, 3.05) | 1.02 (0.81, 1.28) | 1.33 (0.79, 2.23) | 1.72 (0.97, 3.05) |
| Any respiratory condition (N = 11 011)^h | 1.36 (1.16, 1.60) | 1.25 (1.05, 1.50) | 0.95 (0.86, 1.04) | 1.43 (1.24, 1.66) | 1.32 (1.09, 1.60) |

^aThe covariates controlled for the adjusted ORs: asthma, age, if Hispanic, race, BMI, self-perception of mental health, cigarette smoking status, lived with a regular smoker who smoked inside home (during childhood), home policy about vaping, ever smoked marijuana from a hookah, any other tobacco use, substance (marijuana, hash, THC or grass, pot or weed) used weekly or more often.

^bThe covariates controlled for the adjusted ORs: asthma, if Hispanic, race, education, BMI, self-perception of mental health, cigarette smoking status, home policy about vaping, ever smoked marijuana from a hookah, any other tobacco use, substance (marijuana, hash, THC or grass, pot or weed) used weekly or more often.

^cThe covariates controlled for the adjusted ORs: asthma, age, if Hispanic, race, BMI, self-perception of mental health, cigarette smoking status, lived with a regular smoker who smoked inside home (during childhood), home policy about vaping, any other tobacco use, second-hand smoking, substance (marijuana, hash, THC or grass, pot or weed) used weekly or more often.

^dThe covariates controlled for the adjusted ORs: asthma, age, if Hispanic, race, education, cigarette smoking status, lived with a regular smoker who smoked inside home (during childhood), home policy about smoking.

^eThe covariates controlled for the adjusted ORs: asthma, age, gender, education, BMI, self-perception of mental health, cigarette smoking status, lived with a regular smoker who smoked inside home (during childhood), ever smoked marijuana from a hookah, ever smoked part or all of (a traditional cigar, cigarillo, or filtered cigar) with marijuana in it.

^fThe covariates controlled for the adjusted ORs: asthma, age, race, education, BMI, self-perception of mental health, cigarette smoking status, lived with a regular smoker who smoked inside home (during childhood), ever smoked part or all of (a traditional cigar, cigarillo, or filtered cigar) with marijuana in it.

^gThe covariates controlled for the adjusted ORs: asthma, age, gender, race, self-perception of mental health, cigarette smoking status, lived with a regular smoker who smoked inside home (during childhood), home policy about smoking, ever smoked part or all of (a traditional cigar, cigarillo, or filtered cigar) with marijuana in it.

^hThe covariates controlled for the adjusted ORs: asthma, age, if Hispanic, education, BMI, self-perception of mental health, cigarette smoking status, lived with a regular smoker who smoked inside home (during childhood), home policy about vaping, ever smoked marijuana from a hookah, any other tobacco use, second-hand smoking, substance (marijuana, hash, THC or grass, pot or weed) used weekly or more often, ever smoked part or all of (a traditional cigar, cigarillo, or filtered cigar) with marijuana in it.

Bold values denote statistical significance at the $p < .05$ level.

at least sometimes or rarely had significantly higher aORs for several self-reported respiratory symptoms, for example, aOR = 1.21 (95% CI: 1.01, 1.44) and aOR = 1.31 (95% CI: 1.06, 1.61), respectively, for wheezing or whistling in the chest, aOR = 1.59 (95% CI: 1.31, 1.93) and aOR = 1.24 (95% CI: 1.01, 1.52), respectively, for chest sounded wheezy during or after exercise, aOR = 1.35 (95% CI: 1.16, 1.57) and aOR = 1.24 (95% CI: 1.04, 1.47), respectively, for having a dry cough at night. As to self-reported respiratory diseases, the odds of adults who vaped with marijuana were not significantly different from adults who vaped without marijuana except that adults who had ever vaped with marijuana rarely had significantly higher aORs (aOR = 2.21, 95% CI: 1.12, 4.35) for emphysema. For any respiratory condition, adults who had ever vaped with marijuana at

least sometimes or rarely had significantly higher aORs than adults who had ever vaped without marijuana, with aOR = 1.43 (95% CI: 1.24, 1.66) and aOR = 1.32 (95% CI: 1.09, 1.60), respectively.

Discussion

In this study, we investigated the cross-sectional association between adults who had ever vaped with or without marijuana and self-reported past 12-month respiratory symptoms or lifetime respiratory diseases in adults using the nationally representative PATH Study Wave 4 data. Compared to adults who never vaped, adult participants who had ever vaped without marijuana did not show significantly higher aORs for self-reported

respiratory symptoms (wheezing), which is consistent with one previous cross-sectional study.²⁷ Our results showed that there was a marginally significant association with COPD for adults who had ever vaped without marijuana, which is consistent with a cross-sectional study,¹⁸ as well as a longitudinal study.²⁰ Similarly, compared to adults who never vaped, adults who had ever vaped with marijuana showed a significantly higher association with self-reported respiratory symptoms (wheezing and dry cough).

In this study, we showed that compared to adults who had ever vaped without marijuana, adults who had ever vaped with marijuana (at least sometimes or rarely) showed significantly higher adjusted odds for self-reported respiratory symptoms (such as wheezing and dry cough), suggesting that marijuana in e-liquid could have a higher association with the respiratory symptoms than vaping alone. However, we did not observe a significant difference in the associations with respiratory symptoms between adults who had ever vaped at least sometimes with marijuana and adults who had ever vaped rarely with marijuana. In addition, the aORs for self-reported respiratory diseases (such as COPD, chronic bronchitis, and emphysema) were not significantly different between adults who had ever vaped with and without marijuana. It is possible that marijuana does not have obvious effects on chronic respiratory diseases, or their effects are not significant due to the short-term use of marijuana in e-cigarettes, or the relatively small sample size (Supplementary Table S1). Consistent with previous studies,^{18,31,32} we observed the significant positive associations between combustible cigarette smoking and respiratory symptoms/diseases such as wheezing, wheezy chest, dry cough, COPD, and Bronchitis (Supplementary Table S2). Other tobacco uses, such as cigars, pipe tobacco, hookah, snus, and smokeless tobacco, were tested in the models. They were only included in the final models for self-reported respiratory symptoms. In addition, we explored possible moderating effects between the vaping marijuana variable and other covariates (such as age, gender, and race), and did not identify significant moderating effects.

While it is important to understand the health effects of marijuana use, the association of marijuana use and respiratory symptoms or diseases reported in other studies remains contradictory.^{33,34} While several studies reported that the marijuana use alone did have observed respiratory symptoms,^{35–37} one study showed that the use of marijuana and tobacco together had increased risk of respiratory symptoms and COPD than tobacco alone, indicative of an combined effect.³⁸ Here, we observed a similar combined association with respiratory symptoms for the co-use of marijuana and e-cigarettes together.

There are several limitations in our study. First, the respiratory symptoms or diseases reported in the PATH Study are self-reported, which are subject to recall error. Second, in this study, we showed the cross-sectional association of lifetime vaping with marijuana with self-reported past 12-month respiratory symptoms, which cannot establish the causal effect. Considering the health effects of the exposure to e-cigarette and marijuana is a slow process, which makes it reasonable to examine the health effects of the lifetime exposure of e-cigarette and marijuana. However, some other potential environmental factors (such as air pollution) could be involved during this long period, which might influence our conclusion. Further study using the data on vaping with marijuana and respiratory symptoms collected from the same period is required. Third, due to the unavailability from the dataset, our analysis might miss some important confounding variables, such as the amount of marijuana used and smoking marijuana, which might introduce biases into our results. Due to the limitation of sample size, we have to reduce the levels for some important variables, such as vaped with marijuana at least

sometimes (including every time, most of the time, or sometimes). In addition, the relatively small sample size as shown in Supplementary Table 1 might underestimate the potential association between ever vaping with marijuana and self-reported respiratory symptoms/diseases. Finally, considering the short history of e-cigarettes in the market, especially the short history of ever vaping with marijuana, the long-term association of vaping with marijuana with potential respiratory symptoms could be underestimated.

Our study is the first study to explore the potential cross-sectional association between ever vaping with marijuana and self-reported past 12-month respiratory symptoms or lifetime respiratory diseases. Our findings of the combined association of vaping marijuana in e-cigarettes with respiratory symptoms provide further support on the potential health effects of co-use of multiple substances.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

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Authors' Contributions

Z.X. and D.L. conceived, designed the study, analyzed the data, wrote, and edited the manuscript.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the FDA.

Declaration of Interests

None reported.

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