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Association Between Electronic Cigarette Use and Marijuana Use Among Adolescents and Young Adults
A Systematic Review and Meta-analysis

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➕ Supplemental content

IMPORTANCE Use of electronic cigarettes (often called *e-cigarettes*) has increased considerably among young people in the past 5 years. Use of e-cigarettes has been associated with higher rates of marijuana use, which is associated with several adverse health outcomes in youth.

OBJECTIVE To characterize and quantify the association between e-cigarette and marijuana use among youth using a meta-analysis.

DATA SOURCES PubMed, Embase, and Web of Science & ProQuest Dissertations and Theses were searched from inception to October 2018. A gray-literature search was also conducted on conference abstracts, government reports, and other sources.

STUDY SELECTION Included studies compared rates of marijuana use among youth aged 10 to 24 years who had used e-cigarettes vs those who had not used e-cigarettes. Two reviewers independently assessed studies for inclusion; disagreements were discussed with a third reviewer and resolved by consensus.

DATA EXTRACTION AND SYNTHESIS Data were extracted by 2 independent reviewers following Meta-analyses of Observational Studies in Epidemiology (MOOSE) reporting guidelines and pooled using a random-effects analysis. The Newcastle-Ottawa Scale was used to assess data quality and validity of individual studies.

MAIN OUTCOMES AND MEASURES Adjusted odds ratios (AORs) of self-reported past or current marijuana use by youth with vs without past or current e-cigarette use.

RESULTS Twenty-one of 835 initially identified studies (2.5%) met selection criteria. The meta-analysis included 3 longitudinal and 18 cross-sectional studies that included 128 227 participants. Odds of marijuana use were higher in youth who had an e-cigarette use history vs those who did not (AOR, 3.47 [95% CI, 2.63-4.59]; I^2, 94%). Odds of marijuana use were significantly increased in youth who used e-cigarettes in both longitudinal studies (3 studies; AOR, 2.43 [95% CI, 1.51-3.90]; I^2, 74%) and cross-sectional studies (18 studies; AOR, 3.70 [95% CI, 2.76-4.96]; I^2, 94%). Odds of using marijuana in youth with e-cigarette use were higher in adolescents aged 12 to 17 years (AOR, 4.29 [95% CI, 3.14-5.87]; I^2, 94%) than young adults aged 18 to 24 years (AOR, 2.30 [95% CI, 1.40-3.79]; I^2, 91%).

CONCLUSIONS AND RELEVANCE This meta-analysis found a significant increase in the odds of past or current and subsequent marijuana use in adolescents and young adults who used e-cigarettes. These findings highlight the importance of addressing the rapid increases in e-cigarette use among youths as a means to help limit marijuana use in this population.

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Use of electronic nicotine-delivery systems (ENDS), specifically electronic cigarettes (also known as *e-cigarettes*), among young people between the ages of 10 and 24 years has increased substantially in the past 5 years.[1] In fact, more than one-third of high school seniors in the United States report e-cigarette use in the past year.[2] While ENDS have been hypothesized to contain fewer harmful emissions than traditional cigarettes, research has shown that they are not without risk, and ENDS aerosols often contain high levels of nicotine, heavy metals, and carcinogens.[3,4] In addition, recent studies have shown a strong association between ENDS use and subsequent use of alcohol, marijuana, and other drugs.[5-7]

Most individuals with substance use disorders initiate substance use before the age of 18 years, and more than 95% do so before the age of 25 years.[8] Adolescents and young adults, whose brains are still developing, are more vulnerable than older adults to the addictive properties of nicotine, alcohol, marijuana, and other drugs.[9] While the current understanding of harmful long-term effects of nicotine use on the developing human brain, including decreased memorization and attention capacity, still mostly relies on preclinical trials,[10,11] the evidence of harmful long-term effects of adolescent marijuana use is more robust.[12] For instance, longitudinal studies have shown that marijuana use during adolescence is associated with reduced cognitive abilities, motivation, satisfaction with life, and life achievement, as well as significantly greater rates of mental health disorders, such as depression, anxiety, and schizophrenia.[13,14]

On the one hand, several governments around the world are moving forward with legislation aimed at containing rates of ENDS use among youth.[15] On the other hand, a strong global trend toward legalization and decriminalization of marijuana is increasing access to this substance.[16] The effects of these policies on rates of ENDS and marijuana use among youth remain controversial,[17] but the rapidly increasing prevalence of ENDS use in this population, and the possibility that this could lead to increases in comorbid substance use among youth, including marijuana use, is concerning.[6] More precise estimates of the risk of current or subsequent marijuana use in youth with ENDS use could inform development and implementation of public policies aiming to delay initiation and reduce rates of marijuana use among young people.

We conducted a systematic review of the literature and meta-analysis to characterize and quantify the association between ENDS and marijuana use among adolescents and young adults. We hypothesized that the odds of using marijuana would be significantly higher among youth with ENDS use (vs no use) and that this association would be stronger in adolescents vs young adults and youth with dual ENDS and cigarette use vs use of ENDS only.

Methods

Data Sources and Search Strategy

This meta-analysis is in accordance with proposed reporting set forth in Meta-Analysis and Systematic Review of Observa-

Key Points

Question Is electronic cigarette (e-cigarette) use associated with marijuana use in adolescents and young adults?

Findings In this systematic review and meta-analysis, the odds of past or current marijuana use among youth who used e-cigarettes were 3.5 times higher than for those who denied e-cigarette use; this association was significant in both cross-sectional and longitudinal studies. Studies conducted in adolescents aged 12 to 17 years (vs young adults aged 18 to 24 years) showed a stronger association between e-cigarette and marijuana use.

Meaning These findings suggest that clinical and regulatory approaches to managing e-cigarette use among youth amid the current trend of marijuana legalization should consider the significant association between e-cigarette and marijuana use.

tional Studies in Epidemiology (MOOSE)[18] and the Enhancing the Quality and Transparency of Health Research (EQUATOR) Reporting Guidelines.[19] PubMed, Embase, Web of Science, and ProQuest Dissertations & Theses databases were searched for potential studies. In addition, conference abstracts, proceedings, and reports from the past 10 years (2008-2018) from major substance use and tobacco prevention associations and conferences in the United States and international locations were searched for relevant sources. Finally, targeted searches of systematic reviews and summary reports on the health effects of e-cigarettes[3,20] were conducted, yielding 1 additional relevant review, which was searched for relevant studies.[21]

The database search strategy (eMethods in the Supplement) was developed in consultation with a medical reference librarian and was adapted from a recently published meta-analysis looking at the association between ENDS and tobacco cigarette use among adolescents.[22] When available, we used controlled vocabularies, such as medical subject headings (MeSH) on PubMed and Embase subject headings (Emtree) on Embase. Key terms included *ENDS*, *e-cigarette*, *vaping*, *marijuana*, *alcohol*, *prescription drug misuse*, *illicit drug use*, and *substance abuse*. We chose not to include any terms limiting participant age, language, type of substance used, study design, or year of publication in the search strategy, to minimize unintentional exclusions. Final PubMed, Embase, and Web of Science & ProQuest searches were conducted on October 8, 2018. Identified studies were imported and compiled using Covidence Software (Veritas Health Innovation).

Study Selection

To be included in this review, a study had to compare rates of marijuana use among youth with vs without a history of ENDS use. Studies could be cross-sectional or longitudinal, and the mean or median age of study participants needed to be between 10 and 24 years. The use of ENDS was defined as current (in the past month) and/or ever, and ENDS products with or without flavoring were included. Similarly, marijuana use was defined as current and/or ever use of marijuana products consumed by inhalation or ingestion. Studies were required to provide actual or calculable adjusted odds ratios of the association between ENDS use and co-occurring marijuana use

(in cross-sectional studies) or subsequent marijuana use (in longitudinal studies). In 1 case, provision of relevant unpublished data, which included adjusted odds ratios, allowed inclusion of the study.[23]

All titles and abstracts obtained through the literature search (835 studies) were reviewed independently by 2 of 3 coauthors (N.C., J.W.J., and/or R.S.) to determine suitability for full-text screening. All 3 reviewers have been trained in public health research methods. Each article selected for full-text screening was then screened individually by 2 of 3 coauthors (N.C., J.W.J., and/or R.S.) for ultimate inclusion in the review and meta-analysis. At each stage, any discrepancy between reviewers concerning inclusion suitability was resolved by discussion among the 3 reviewers until unanimous consensus was reached. Reasons for exclusion included participants older than 24 years, the absence of a participant group that did not use ENDS, and the measurement of marijuana vaping without mention of nicotine vaping in participants reporting use of e-cigarettes (eFigure 1 in the Supplement).

Data Extraction

Individual study data were extracted by a coauthor (J.W.J., R.S., or N.C.) and subsequently verified by a second coauthor. Data extracted for each study included study design and type; survey method; geographic location of study sample; sample size; age of study participants; ENDS use; marijuana use; comorbid cigarette, alcohol, and drug use; covariates accounted for in adjusted models; and adjusted odds ratios (AORs) with 95% CIs. If studies lacked clear indication of adjustment for confounders, study authors were contacted for clarification. Additionally, authors who did not report odds ratios were contacted if the results they did report suggested that a relevant measure of association, although not published, had likely been calculated. When 2 or more studies presented with an overlapping population, exposure (ENDS use), and outcome (marijuana use), the study with the largest sample size (or the most recent analysis, in the case of equal-sized samples) was retained.

Risk of Bias Assessment

Risk of bias was assessed using the Newcastle-Ottawa Scale for observational studies.[24] Studies were evaluated by 2 of 3 coauthors (N.C., J.W.J., and/or R.S.) and received a score of up to 6 points for cross-sectional studies and up to 9 points for longitudinal studies based on participant selection, study comparability, and assessment of the outcome of interest (marijuana use). Any disagreement was resolved by consensus between coauthors (N.C., J.W.J., and R.S.).

Statistical Analysis

The summary effect of ENDS use on marijuana use was calculated using a random-effects model. Several subgroup analyses based on clinically relevant factors were also conducted. Forest plots and measures of observed heterogeneity (I^2 statistic) were generated for all summary and subgroup analyses.

A first subgroup analysis compared cross-sectional studies, limited to a strict determination of association without temporal ordering, to longitudinal studies, which could offer insights on temporal ordering of ENDS and marijuana use (and minimize the risk for reverse causation). A second subgroup analysis was conducted on studies divided by mean or median participant age (<18 years vs ≥18 years). This analysis was conducted in light of neurophysiologic differences between younger and older youths that have been shown to have a characteristic effect on risk-taking behaviors, impulse control, and susceptibility to substance use.[9,25] We chose to have a cut point at 18 years because this separated studies that were conducted on middle school or high school students (the younger group) from studies that were generally conducted on college students (the older group). A third subanalysis compared youths with and without co-occurring use of conventional cigarettes or other forms of tobacco, since youths with dual or polytobacco use may have different substance use risk profiles than youth with ENDS-only use.[5] A fourth subanalysis divided studies by publication year to account for the arrival of rechargeable, higher-technology, and often youth-friendly ENDS called *pod mods*, which became popular around 2015.[26] We chose 2017 as a divider between older and newer studies because many studies published in 2017 or beyond used study data collected after the arrival of pod mods–type ENDS. A regional subgroup analysis by continent was conducted (North America, Europe, and other continents), given differences in prevalence, regulation, and taxation of ENDS between different continents.[27] Finally, an Egger test was performed to assess the risk for publication bias and small study effects. All analyses were conducted using Stata computational software version 14.2 (StataCorp).

Results

Of 835 potentially relevant studies identified through the database search and 4 through the gray-literature search, 158 reports appeared potentially eligible after title and abstract screening. After exclusion of 137 studies through full-text screening, including 3 studies with overlapping data sets,[28-30] 21 studies were found to be eligible[5-7,23,31-47] and were included in the qualitative and quantitative syntheses. All studies were observational; there were 3 longitudinal studies[6,7,45] representing 14 364 participants and 18 cross-sectional studies[5,23,31-44,46,47] representing 113 863 participants in total. Summary characteristics of included studies are shown in **Table 1**.

Pooling of data from all studies (**Figure 1**) suggested that ENDS use is associated with an increased risk of marijuana use (AOR, 3.47 [95% CI, 2.63-4.59]; I^2, 94%). Subgroup analysis by study type (**Figure 2**) revealed significantly increased odds of marijuana use in both longitudinal (3 studies[6,7,45]; AOR, 2.43 [95% CI, 1.51-3.90]; I^2, 73.8%) and cross-sectional studies (18 studies[5,23,31-44,46,47]; AOR, 3.70 [95% CI, 2.76-4.96]; I^2, 94%).

Subgroup analyses by age (**Figure 3**) showed a stronger association between ENDS use and marijuana use in studies with participants with a mean or median age younger than 18 years (14 studies[5-7,23,32,34,36-41,46,47]; AOR, 4.29 [95% CI, 3.14-5.87]; I^2, 93.5%) vs studies with participants with a mean or median

Table 1. Summary Characteristics of Included Studies

Source	Region and Country	Study Design	Study Period	Population	School Grade or Age of Study Participants	Sample Size, No.	Exposure to Electronic Cigarettes	Marijuana Use Outcome
Audrain-McGovern et al,[7] 2018	California, United States	Prospective, longitudinal (baseline and 24-mo follow-up)	2013-2015	Students from 10 public high schools	Mean (SD), 14.6 (0.4) y	2668	Ever	Ever or past 30-d marijuana use
Azagba,[32] 2018	Canada	Cross-sectional	2014-2015	Secondary data analysis of the 2014-2015 Canadian Student Tobacco and Alcohol and Drugs Survey	Grades 9-12	23 429	Past 30 d, dual use	Past 30-d marijuana use
Bluestein,[33] 2017	United States	Retrospective, cross-sectional	2013-2014	Secondary data analysis of the Population Assessment of Tobacco and Health Study, wave 1	Range, 18-24 y	8954	Ever or past 30 d	Ever marijuana use
Camenga et al,[34] 2014	Connecticut and New York, United States	Cross-sectional	2010-2011	Secondary data analysis of a student survey conducted in 4 high schools	Grades 9-12	1556	Past 30 d	Past 30-d marijuana use
Cohn et al,[35] 2015	United States	Retrospective, cross-sectional	2013	Secondary data analysis from Legacy Young Adult Cohort, wave 4	Mean (SD), 20.9 (2.0) y	1609	Ever or past 30 d	Past 30-d marijuana use
Conway et al,[36] 2018	United States	Retrospective, cross-sectional	2013-2014	Secondary data analysis of Population Assessment of Tobacco and Health Study, wave 1	Range, 12-17 y	13 617	Ever	Ever marijuana use
Curran et al,[5] 2018	United States	Cross-sectional	2015	Secondary data analysis of the National Youth Risk Behavior Survey	Grades 9-12	15 624	Past 30 d, dual use	Ever or past 30-d marijuana use
Dai et al,[6] 2018	United States	Retrospective, longitudinal	2013-2015	Secondary data analysis of Population Assessment of Tobacco and Health Study, wave 1 and 2	Range, 12-17 y	10 364	Ever	Marijuana use 1-y follow-up
Dautzenberg et al,[37] 2015	France	Cross-sectional	2013	Secondary data analysis from 2013 Paris Sans Tabac surveys	Range, 12-19 y	2279	Ever	Ever marijuana use
Dunbar et al,[23] 2017	California, United States	Retrospective, cross-sectional	2014	Secondary data analysis from wave 7 of the CHOICE project cohort	Mean (SD), 17 (0.7) y	2488	Past year, dual use	Past-year marijuana use
Fotiou et al,[38] 2015	Greece	Cross-sectional	2014	2014 Health Behavior in School-aged Children study	Mean (SD), 15 (0) y	435	Ever	Ever marijuana use
Kong et al,[39] 2017	Russia	Cross-sectional	2015	Survey of high school students	Range, 15-18 y	716	Ever	Ever marijuana use
Kristjansson et al,[40] 2017	West Virginia, United States	Cross-sectional	2015	School survey conducted in 15 middle schools in 3 counties	Grades 6-8	5553	Ever	Ever marijuana use
McCabe et al,[31] 2017	United States	Cross-sectional	2014	Secondary data analysis of Monitoring the Future study	Grades 12[a]	7711	Past 30 d	Past 30-d marijuana use
Milicic and Leatherdale,[41] 2017	Ontario and Alberta, Canada	Prospective cross-sectional	2012-2015	Ongoing cohort study in schools (the COMPASS Study)	Grades 9-12	39 837	Past 30 d	Ever or past 30-d marijuana use
Saddleson et al,[42] 2015	New York, United States	Cross-sectional	2013	Internet survey from a convenience sample of students at 4 colleges and universities	Mean (SD), 19.0 (1.3) y	1292	Ever or past 30 d	Past-year marijuana use
Sutfin et al,[43] 2013	North Carolina, United States	Cross-sectional	2009	Survey of students from 8 colleges	Mean (SD), 20.5 (2.9) y	4444	Ever	Past 30-d marijuana use
Tavolacci et al,[44] 2016	France	Cross-sectional	2014-2015	Multicenter study on 2 major campuses	Mean (SD), 20.8 (3.6) y	1134	Ever or past 30 d	Past 30-d marijuana use
Unger et al,[45] 2016	California, United States	Retrospective, longitudinal	2014-2015	Secondary data analysis of longitudinal survey of Hispanic young adults	Mean (SD), 22.7 (0.4) y	1332	Past 30 d	Past 30-d marijuana use
White et al,[46] 2015	Australia and New Zealand	Cross-sectional	2014	Youth Insights survey of year 10 students	Range, 14-15 y	2855	Ever, dual use	Ever marijuana use
Williams and White,[47] 2018	Victoria, Australia	Cross-sectional	2014	Australian Secondary Students' Alcohol and Drug Survey	Range, 12-17 y	3158	Ever	Ever marijuana use

[a] Most students were aged 18 years and older.

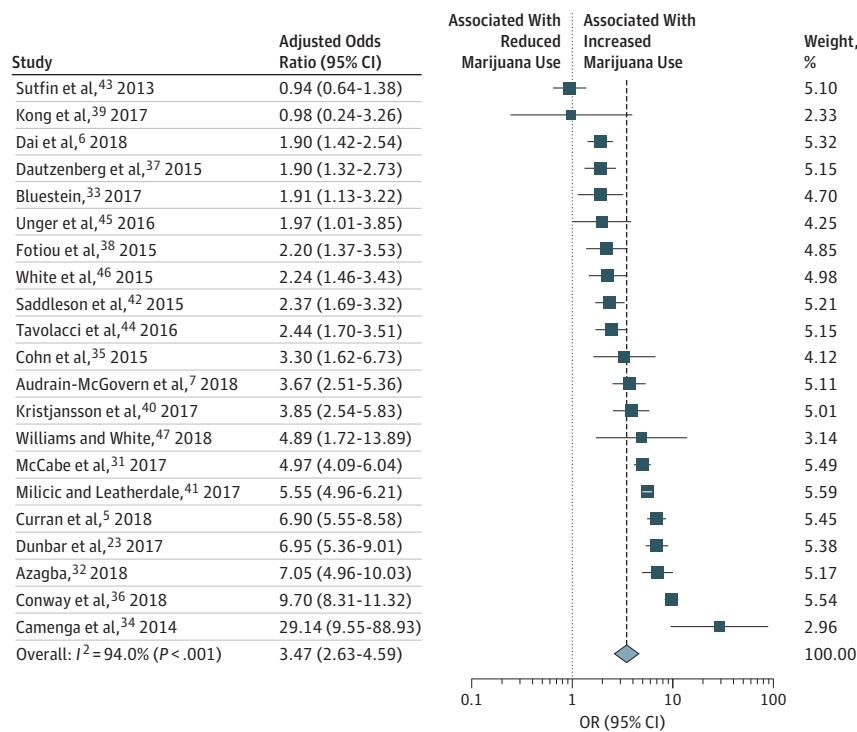Figure 1. Marijuana Use in Youth With e-Cigarette Use in Individual Studies

Study	Adjusted Odds Ratio (95% CI)	Associated With Reduced Marijuana Use	Associated With Increased Marijuana Use	Weight, %
Sutfin et al,[43] 2013	0.94 (0.64-1.38)			5.10
Kong et al,[39] 2017	0.98 (0.24-3.26)			2.33
Dai et al,[6] 2018	1.90 (1.42-2.54)			5.32
Dautzenberg et al,[37] 2015	1.90 (1.32-2.73)			5.15
Bluestein,[33] 2017	1.91 (1.13-3.22)			4.70
Unger et al,[45] 2016	1.97 (1.01-3.85)			4.25
Fotiou et al,[38] 2015	2.20 (1.37-3.53)			4.85
White et al,[46] 2015	2.24 (1.46-3.43)			4.98
Saddleson et al,[42] 2015	2.37 (1.69-3.32)			5.21
Tavolacci et al,[44] 2016	2.44 (1.70-3.51)			5.15
Cohn et al,[35] 2015	3.30 (1.62-6.73)			4.12
Audrain-McGovern et al,[7] 2018	3.67 (2.51-5.36)			5.11
Kristjansson et al,[40] 2017	3.85 (2.54-5.83)			5.01
Williams and White,[47] 2018	4.89 (1.72-13.89)			3.14
McCabe et al,[31] 2017	4.97 (4.09-6.04)			5.49
Milicic and Leatherdale,[41] 2017	5.55 (4.96-6.21)			5.59
Curran et al,[5] 2018	6.90 (5.55-8.58)			5.45
Dunbar et al,[23] 2017	6.95 (5.36-9.01)			5.38
Azagba,[32] 2018	7.05 (4.96-10.03)			5.17
Conway et al,[36] 2018	9.70 (8.31-11.32)			5.54
Camenga et al,[34] 2014	29.14 (9.55-88.93)			2.96
Overall: $I^2 = 94.0\%$ ($P < .001$)	3.47 (2.63-4.59)			100.00

OR (95% CI)

Figure 2. Marijuana Use in Youth With e-Cigarette Use by Study Design in Individual Studies

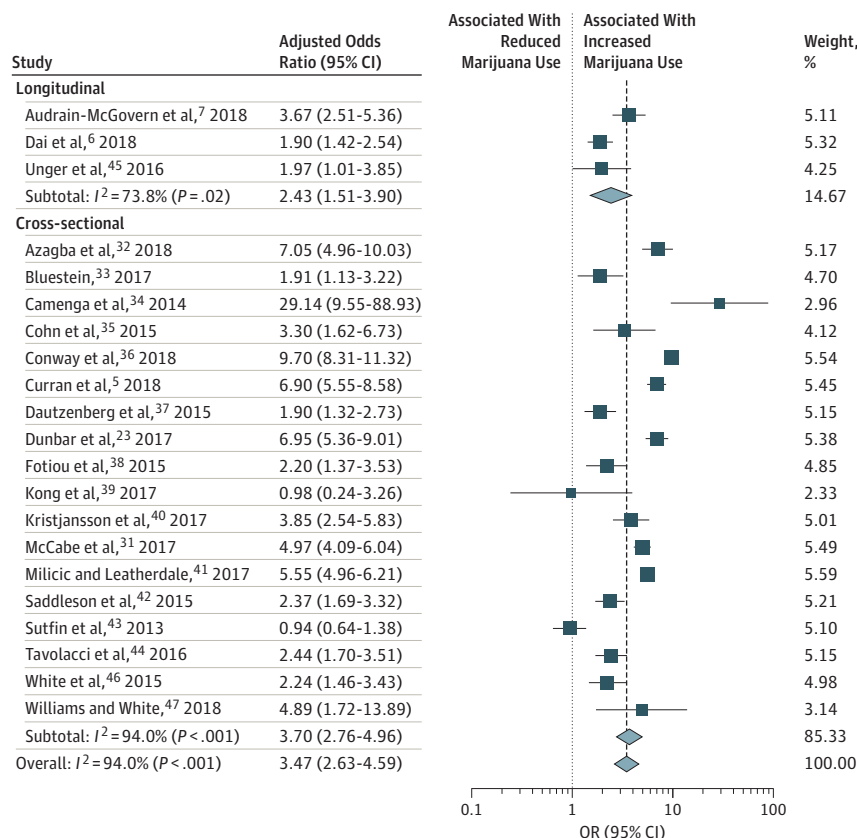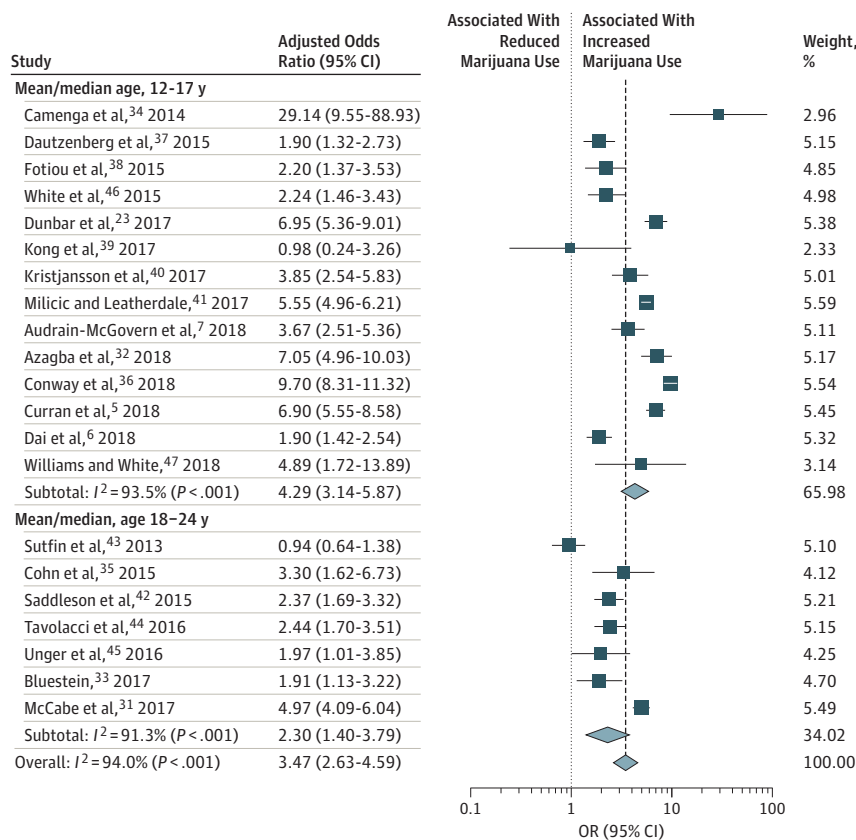| Study	Adjusted Odds Ratio (95% CI)	Associated With Reduced Marijuana Use	Associated With Increased Marijuana Use	Weight, %
Longitudinal				
Audrain-McGovern et al,[7] 2018	3.67 (2.51-5.36)			5.11
Dai et al,[6] 2018	1.90 (1.42-2.54)			5.32
Unger et al,[45] 2016	1.97 (1.01-3.85)			4.25
Subtotal: $I^2 = 73.8\%$ ($P = .02$)	2.43 (1.51-3.90)			14.67
Cross-sectional				
Azagba et al,[32] 2018	7.05 (4.96-10.03)			5.17
Bluestein,[33] 2017	1.91 (1.13-3.22)			4.70
Camenga et al,[34] 2014	29.14 (9.55-88.93)			2.96
Cohn et al,[35] 2015	3.30 (1.62-6.73)			4.12
Conway et al,[36] 2018	9.70 (8.31-11.32)			5.54
Curran et al,[5] 2018	6.90 (5.55-8.58)			5.45
Dautzenberg et al,[37] 2015	1.90 (1.32-2.73)			5.15
Dunbar et al,[23] 2017	6.95 (5.36-9.01)			5.38
Fotiou et al,[38] 2015	2.20 (1.37-3.53)			4.85
Kong et al,[39] 2017	0.98 (0.24-3.26)			2.33
Kristjansson et al,[40] 2017	3.85 (2.54-5.83)			5.01
McCabe et al,[31] 2017	4.97 (4.09-6.04)			5.49
Milicic and Leatherdale,[41] 2017	5.55 (4.96-6.21)			5.59
Saddleson et al,[42] 2015	2.37 (1.69-3.32)			5.21
Sutfin et al,[43] 2013	0.94 (0.64-1.38)			5.10
Tavolacci et al,[44] 2016	2.44 (1.70-3.51)			5.15
White et al,[46] 2015	2.24 (1.46-3.43)			4.98
Williams and White,[47] 2018	4.89 (1.72-13.89)			3.14
Subtotal: $I^2 = 94.0\%$ ($P < .001$)	3.70 (2.76-4.96)			85.33
Overall: $I^2 = 94.0\%$ ($P < .001$)	3.47 (2.63-4.59)			100.00

OR (95% CI)

Figure 3. Marijuana Use in Youth With e-Cigarette Use by Mean/Median Participant Age in Individual Studies

age 18 years and older (7 studies[31,33,35,42-45]; AOR, 2.30 [95% CI, 1.40-3.79]; I^2, 91%). Subgroup analysis by single use of ENDS vs dual use of both ENDS and cigarettes or other tobacco products (eFigure 2 in the Supplement) revealed a stronger association between ENDS and marijuana use in studies with youths with dual use (4 studies[5,23,32,46]; AOR, 5.39 [95% CI, 3.53-8.24]; I^2, 87.6%) than in studies with youths with single use (17 studies[6,7,31,33-47]; AOR, 3.10 [95% CI, 2.22-4.34]; I^2, 94.6%).

The pooled AOR for the association between ENDS use and marijuana use was higher for North American studies (15 studies[5-7,23,31-36,40-43,45]; AOR, 4.03 [95% CI, 2.97-5.49]) than for European studies (4 studies[37-39,44]; AOR, 2.12 [95% CI, 1.70-2.65]). There were only 2 non-European, non-North American studies (from Australia and New Zealand; 2 studies[46,47]; AOR, 2.84 [95% CI, 1.41-5.76]), and they had a pooled AOR with a 95% CI that overlaps with the 95% CIs of the pooled AOR for the North American and European studies.

Studies published in 2017 or later (12 studies[5-7,23,31-33,36,39-41,47]; AOR, 4.57 [95% CI, 3.47-6.03]) revealed a stronger association between ENDS use and marijuana use than studies that were published before 2017 (9 studies[34,35,37,38,42-46]; AOR, 2.39 [95% CI, 1.67-3.40]). Measures of association and risk of bias for each of the 21 selected studies are shown in Table 2. Quality ratings ranged from 3 to 5 points (of 6 points) for cross-sectional studies and 6 to 8 points (of 9 points) for longitudinal studies. The Egger test was nonsignificant, suggesting that a small study effect was unlikely.

Discussion

This study revealed that ENDS use was significantly associated with marijuana use in a large sample of adolescents and young adults pooled from 21 independent observational studies. While most included articles were cross-sectional, 3 longitudinal studies were included, and these suggested a temporal association between ENDS use and subsequent marijuana use. Subgroup analyses revealed that the association was stronger in youths who were younger and who combined ENDS and cigarette or tobacco use. The analyses also revealed regional and temporal variations: North American studies and studies published since 2017 showed stronger associations between ENDS use and marijuana use than European studies and studies published before 2017 did.

The findings of increased concurrent and subsequent marijuana use in youths with ENDS use can be interpreted in the context of what is already known about the association between tobacco cigarette use and subsequent marijuana use. In fact, a systematic review of the literature published by Ramo and colleagues[48] in 2012 showed that tobacco use among youths is strongly and independently associated with current and subsequent use of marijuana. Among 24 longitudinal studies included in the review, 70% of associations between tobacco and subsequent marijuana use were statistically

Table 2. Measures of Association and Risk of Bias of Included Studies

| Source | Covariates | Newcastle-Ottawa Scale | | | | Adjusted Odds Ratio (95% CI) |
		Study Selection Subscore	Study Comparability Subscore	Outcomes Subscore	Quality Rating Summary Score	
Audrain-McGovern et al,[7] 2018	Age, sex, race/ethnicity, parental education, family history of combustible cigarette and drug use, peer combustible cigarette and marijuana use, Temperament and Character Inventory impulsivity subscale, and Center for Epidemiologic Studies Depression Scale	3	1	2	6	3.67 (2.51-5.36)
Azagba,[32] 2018	Sex, grade level, socioeconomic status, living area, and region of residence	2	1	0	3	7.05 (4.95-10.03)
Bluestein,[33] 2017	Sex, race, education level, household income, and the total number of tobacco products used	3	2	0	5	1.91 (1.13-3.22)
Camenga et al,[34] 2014	Sex, grade, and race	2	1	0	3	29.14 (9.54-88.92)
Cohn et al,[35] 2015	Age, sex, race/ethnicity, and educational attainment	2	1	0	3	3.30 (1.61-6.73)
Conway et al,[36] 2018	Age, sex, race/ethnicity, lifetime mental health (internalizing and externalizing) symptoms, and sensation seeking	3	1	0	4	9.70 (8.31-11.31)
Curran et al,[5] 2018	Age, sex, and race/ethnicity	2	2	0	4	6.90 (5.55-8.57)
Dai et al,[6] 2018	Sensation seeking, ever use of cigarettes, drinking, nonmedical use of prescription drugs and other illicit drugs, and demographic characteristics (sex, race and/or ethnicity, grade performance, parental education, and region)	4	2	2	8	1.90 (1.42-2.53)
Dautzenberg et al,[37] 2015	Age, smoking status of best friend, smoking status of sibling, ever smoked a cigarette, ever smoked shisha, smoking status, private school vs public, and parental message of prohibition	2	2	0	4	1.90 (1.32-2.72)
Dunbar et al,[23] 2017	Age, sex, mother's education level, nuclear family status, intervention group, and smokeless tobacco use	2	2	0	4	6.95 (5.36-9.01)
Fotiou et al,[38] 2015	Sex, life satisfaction, cigarette smoking, cannabis use, and presence of peers who smoke tobacco	2	2	0	4	2.20 (1.37-3.53)
Kong et al,[39] 2017	Age, sex, ethnicity, family structure, highest degree of mother and father, substance use, antisocial behaviors, stress coping scale, and school clustering	2	2	0	4	0.98 (0.24-3.26)
Kristjansson et al,[40] 2017	Age, sex, family structure, race, and each parent education	2	2	0	4	3.85 (2.54-5.84)
McCabe et al,[31] 2017	Age, sex, race/ethnicity, parental education, college plans, urbanicity, and geographical region	2	1	0	3	4.97 (4.09-6.04)
Milicic and Leatherdale,[41] 2017	Sex and school clustering	2	2	0	4	5.55 (4.96-6.20)
Saddleson et al,[42] 2015	Age, sex, race/ethnicity, institution, tobacco smoking, school ability, other tobacco use in the past 30 d, and beliefs about e-cigarette harm	1	2	0	3	2.37 (1.69-3.32)
Sutfin et al,[43] 2013	Sex, sensation seeking, current binge drinking, current marijuana use, lifetime illegal drug use, and e-cigarette harm perception	1	2	0	3	0.94 (0.64-1.38)
Tavolacci et al,[44] 2016	Age, university, student job holder, study grant holder, curriculum, and academic year	1	2	0	3	2.44 (1.70 -3.51)
Unger et al,[45] 2016	Age, sex, and other substance abuse	3	2	2	7	1.97 (1.01-3.85)
White et al,[46] 2015	Age, sex, school deprivation, income/allowance, smoking status, parental smoking behavior, close friends' smoking behavior, use of tobacco products other than cigarettes (eg, chewing tobacco and cigars) in the past 30 d, ever use of marijuana, and ever engagement in binge drinking	2	2	0	4	2.24 (1.46-3.43)
Williams and White,[47] 2018	Age, sex, socioeconomic status, school level clustering, and education sector	2	2	0	4	9.00 (1.72-13.89)

significant, with odds ratios ranging from 1.6 to 8.6 for the increased likelihood of using marijuana in those that had used tobacco (vs those who had not) during adolescence and early adulthood.[48]

The finding of increased marijuana use with ENDS use in younger vs older youths is consistent with developmental assumptions that a younger, less-developed brain is more vulnerable to substance use and addiction.[49] In fact, both

nicotine and marijuana directly affect neural pathways involved with pleasure and reward and may increase the brain's long-term sensitivity to other psychoactive substances and drug-seeking behaviors throughout adulthood.[50] While tobacco and nicotine products are considered legal in most parts of the world, nicotine use, especially during adolescence, should be discouraged because of risks of several negative long-term outcomes, including a chronic decrease in attention and memorization capacity.[10,51] Exposure to nonnicotine components contained in ENDS aerosols is also a concern. While the long-term health outcomes of using newer ENDS devices is not yet well understood, e-cigarette liquids contain several known toxins.[4] Chronic exposure accruing over a lifetime for individuals who initiate use early is a particular concern. It is well established that the younger the age at onset of substance use, the higher the likelihood of developing a substance use disorder later in life.[52,53] In this sense, these findings, which show a significant association between 2 psychoactive substances that have long-term deleterious effects on the brain, have important public health implications: addressing ENDS use and doing so early may be an effective way of delaying onset of marijuana use.

The 3 longitudinal studies included in this review suggest that ENDS use typically predates use of marijuana. While the number of longitudinal studies included in the meta-analysis was small, this finding yields high clinical relevance. In fact, recent surveys and epidemiological studies have shown that ENDS are often the first psychoactive substance used by youths, and based on epidemiological evidence, many of these youth would have been assessed as having never used nicotine or other substances.[54] The use of ENDS may sensitize the reward and pleasure center of the brain and increase the odds of using other forms of nicotine and other psychoactive substances.[5] While it is possible that youths who are substance naive and initiate substance use through ENDS would have gravitated toward other substances with the passage of time, the possibility of delaying onset of substance use by reducing use of ENDS in youths could have important benefits—notably by decreasing the burden of substance use on a population level.[55]

We found a stronger association between ENDS and marijuana use in youths with dual use of ENDS and other forms of tobacco than in youths with use of ENDS only. While ENDS were initially designed to help adults with chronic cigarette smoking habits quit smoking or use a less harmful alternative form of nicotine delivery, a recent systematic review of the literature has highlighted that, when used by adolescents, ENDS are associated with a significant increase in the odds of using cigarettes and other forms of tobacco.[22] This association is both cross-sectional and longitudinal, whereby youth with ENDS-only use have an increased risk of using traditional cigarettes in the future.[56] The concurrent use of several nicotine or tobacco products has not only been associated with higher rates of substance use and substance use disorders,[57] poly-tobacco use has also been associated with increased risk of high-risk substance use behaviors in youth.[58] While co-occurring mental health disorders are common and may be a factor,[31] the effect of nicotine in individuals who are suscep-

tible and have a still-developing brain should not be dismissed, and prevention and intervention efforts in youths should consider ENDS in the broader context of nicotine and tobacco use.

The subgroup analysis by region suggested that the association between ENDS use and marijuana use may be stronger in North American vs European countries. Marijuana use is much more common in North America, while cigarette use is more prevalent in most European countries[59]; this discordant epidemiology may be the basis of this finding, whereas youths in Europe may be less inclined to use marijuana whether they have used ENDS or not. In addition, large variations in public policies, laws surrounding sales (including legal age of purchase of ENDS and tobacco products), and taxation practices in North America and Europe may also contribute.[15] Neither the European Union nor the US federal government has placed an excise tax on ENDS, although constituent member states can and do tax it at varying levels. While this falls beyond the scope of this review, it is likely that certain jurisdictions have already put in place successful protective policies and practices to limit the outcomes of ENDS use in youths. With further research, promising regional initiatives could be identified and replicated.

Finally, we conducted a subgroup analysis for studies published before 2017 vs in 2017 or later. The time separation with this method is imperfect, since most studies published in 2017 or later still used data that was collected before 2017, and there was some overlap in data collection dates between the 2 subgroups. However, more recent studies had a higher pooled AOR than older studies, which could be a reflection of the rapidly evolving landscape of ENDS products.[60] In North America, the rise of companies manufacturing small, high-technology types of ENDS with refillable cartridges (pod mods) could have contributed to increases in rates of use of ENDS with high levels of nicotine.[26] Given the susceptibility of the adolescent brain to psychoactive substances, such as nicotine, which may increase vulnerability to other substances as well, this shift in ENDS products over time may have played a role in the stronger association between ENDS and marijuana use found in more recent studies. Altogether, efforts to contain ENDS use should be mindful of rapidly changing products, which may have different effects on youths.

Limitations

This study had several limitations. First, all of the included studies were observational and adjusted for different sets of confounders. This could have led to overinflated odds ratios in the case of underadjusted models and could have contributed to the high level of heterogeneity seen between studies. Second, most included studies were cross-sectional and did not provide information about the temporal association between nicotine exposure through ENDS use and subsequent changes in marijuana use, although the 95% CIs for the AORs of the cross-sectional and longitudinal subgroups were overlapping. Conducting a new meta-analysis of longitudinal studies would be a useful next step, once a greater number of such studies become available. Third, to increase the number of included studies, we considered any use of

marijuana, be it ever, in the past year, or currently or daily, to be a marijuana-positive outcome. This again could have contributed to the high level of heterogeneity found in this study and renders the clinical implications of the findings more difficult to interpret (ie, daily vs monthly use of marijuana use does not carry the same level of risk in youths). Fourth, although there were several studies from Europe and North America, no studies from Asia met criteria for inclusion in this meta-analysis, which limits the generalizability of the findings. Finally, there was a high level of heterogeneity between included studies (I^2, 94% for the pooled AOR). Nonetheless, owing to the observational design of the studies included in the meta-analysis, and since many of the studies used large, nationally representative samples or cohorts, we considered the risk of publication bias to be of lesser concern than if this meta-analysis had included primarily experimental studies.

Conclusions

To our knowledge, this study is the first meta-analysis to summarize the evidence to date about the association between ENDS use and marijuana use among youths. We found a significant increase in the odds of using marijuana in youths who had used ENDS in both cross-sectional and longitudinal studies. This study suggests that, in addition to potential harms of using ENDS alone and an increased risk of using other forms of nicotine or tobacco, ENDS use is significantly associated with use of at least 1 other addictive psychoactive substance: marijuana. These findings should be taken into account in the design of public policies aiming to restrict access to ENDS for minors. This study also opens the door to other similar meta-analyses looking at the association between ENDS use and use of alcohol or other drugs.

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