

REVIEW

ADDICTION

SSA

The relationship between cannabis and nicotine use: A systematic review and meta-analysis

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Abstract

Background and aims: Cannabis and nicotine (tobacco or e-cigarettes) use commonly co-occurs and understanding their relationship can help to inform public health strategies to prevent their harms. We conducted a systematic review and meta-analysis to estimate the association of cannabis use given prior nicotine use and vice versa.

Methods: PubMed, Embase, PsycINFO, Google Scholar and a hand-search were conducted in 2023 for longitudinal studies of the general population with no restrictions in settings (locations). Random-effects meta-analysis was conducted to estimate odds ratios between cannabis and nicotine use in both directions. The impact of unmeasured confounding was assessed using E-values.

Results: From 5387 identified records, we included 20 studies. Among cannabis-naïve youths, baseline use of any nicotine products was positively associated with initiation of any cannabis use at follow-up [odds ratio (OR) = 5.39, 95% confidence interval (CI) = 3.19, 9.11; adjusted OR (aOR) = 2.59, 95% CI = 2.01, 3.32]. In nicotine-naïve participants (youths + adults), baseline cannabis use was positively associated with the initiation of any nicotine use at follow-up (OR = 4.08, 95% CI = 2.05, 8.11; aOR = 2.94, 95% CI = 1.54, 5.61). There were no significant associations between baseline cannabis use and subsequent initiation of any nicotine (aOR = 3.29, 95% CI = 0.85, 12.76) or daily nicotine use (aOR = 2.63, 95% CI = 0.41, 16.95) among youths. The median E-values were 5.5 for nicotine exposure and cannabis use initiation and 4.1 for cannabis exposure and nicotine use initiation, indicating that substantial unmeasured confounding would need to have a strong association with both outcomes to fully explain away the cannabis and nicotine relationship.

Conclusion: Although the evidence for associations between cannabis use and tobacco use is mixed, a majority of studies to date have found that cannabis use is associated with prior nicotine use and vice versa.

KEYWORDS

Cannabis, E-values, longitudinal association, smoking, tobacco, unmeasured confounder

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INTRODUCTION

Policies to regulate medical and adult cannabis use have been liberalized in many jurisdictions [1]. This has renewed concerns about the 'gateway' hypothesis, according to which cannabis use may be a catalyst for subsequent illicit drug use [2]. There is also a concern that the initiation of tobacco smoking may increase the risk of using cannabis, given the common method of administration and the frequent co-use of these two substances among youth [3]. The mixing of cannabis and tobacco is also common, usually administered as blunts (cannabis in an emptied cigar) and spliffs (adding tobacco to cannabis joint) [4]. In Switzerland, four out of five students who used cannabis added tobacco to their cannabis and in Ontario, Canada 31.1% of adult cannabis consumers mixed tobacco into their cannabis [5, 6].

The use of cannabis and tobacco during adolescence and young adulthood is of particular concern, given the potential for increased adverse health outcomes, initiation of use and transition to heavy (frequent) use [7]. Initiation of cannabis and tobacco usually occurs during adolescence [8]. However, early adulthood is marked with an escalation in use (e.g. transition to daily use) and there is also a shift in increased initiation of use in young adults [9]. A comprehensive review by Agrawal *et al.* [10] examined the mechanisms for co-occurring use of cannabis and tobacco. The authors discussed various mechanisms that may link these substances, including the gateway (tobacco leading to cannabis use) and reverse gateway (cannabis leading to tobacco use) hypotheses, shared genetic factors, common environmental influences and common route of administration. Lemyre *et al.* [11] expanded upon the Agrawal and colleagues review and reported that motivations to use and perceptions of both substances are important factors influencing the relationship between cannabis and tobacco use.

In the United States, those who used both cigarettes and cannabis have typically smoked cigarettes first [12]. The Monitoring the Future (MTF) study, for example, found that adolescents were at increased risk of cannabis use if cigarette smoking was initiated before the 12th grade [12]. In another study that analysed 11 059 respondents from the Population Assessment of Tobacco and Health (PATH) study, adolescents who smoked cigarettes or used e-cigarettes in the past 30 days were more likely to have used cannabis in the past 30 days than peers who had not smoked cigarettes in the past 30 days [13].

A reversed trend has been found more recently. In the United States, analysis of cross-sectional surveys of 246 050 participants from the MTF study found that youth who had used cannabis first were more likely to start smoking cigarettes later [12]. Cannabis has increasingly become the first substance used in the sequence of adolescent drug use. As the prevalence of cigarette smoking has declined, the prevalence of cannabis use has remained relatively stable [12]. Changing regulatory policies over time, including the strengthened tobacco controls and relaxation of cannabis use through legalization, may contribute to this trend. This new sequence raises questions about the relationship between tobacco and cannabis use among young individuals.

The association between tobacco and cannabis use could be bidirectional. Such a relationship was reported by Doran *et al.* [14], who found that cigarette smoking was associated with an increased dosage and frequency of cannabis use and vice versa [14]. The cigarette and cannabis relationship may also apply to newer nicotine or tobacco products, including e-cigarettes; for ease of reference, in this paper our reference to 'nicotine' includes tobacco products and e-cigarettes. In 2019, a systematic review of 21 observational studies (18 cross-sectional and three longitudinal) by Chadi *et al.* [15] reported that the odds of cannabis use were more than three times higher in youth aged 12–17 years who reported e-cigarette use than those who did not [adjusted OR (aOR) = 3.47, 95% confidence interval (CI) = 2.63, 4.59]. However, the Chadi *et al.* review was limited to studies that specifically focused on e-cigarettes and did not consider other tobacco products. Additionally, most of the studies included in the review were cross-sectional, which limits the ability to draw conclusions regarding the temporal relationship between e-cigarette and cannabis use. The potential bidirectional link between cannabis and tobacco use emphasizes the need for a comprehensive understanding of their relationship.

Our systematic review and meta-analysis follows the study by Chadi *et al.* and examines the relationship between cannabis and nicotine use. We systematically reviewed and meta-analysed findings from longitudinal studies that examined: (1) cannabis use following prior nicotine use and (2) nicotine use following prior cannabis use. By including a broader range of nicotine products and considering the bidirectional nature of the association, our review provides a more comprehensive understanding of the complex relationship between cannabis and nicotine use. This review seeks to inform policy, prevention and intervention strategies aimed at addressing the complex relationships between nicotine and cannabis use.

METHODS

Protocol

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline (see Supporting information, Supplement 1) and the protocol was registered on the international Prospective Register Of Systematic Review (PROSPERO) (CRD42023425963).

Eligibility

We included peer-reviewed longitudinal observational studies with quantitative data on the prospective relationships between cannabis and nicotine use. Studies were included if they examined the relationship between: (1) cannabis use at an earlier

time-point and nicotine use at a later time-point; or (2) nicotine use at an earlier time-point and cannabis use at a later time-point. Qualitative studies, case studies, conference abstracts, book reviews, reviews, commentaries and clinical trials were excluded.

We included studies that examined exposure to any cannabis use and reported the prospective association of initiating the use of tobacco products or e-cigarettes among baseline nicotine-naïve participants and vice versa. We also included studies reporting the bidirectional association of cannabis and nicotine use.

For cannabis use, we included any cannabis type with any level of use, i.e. any cannabis use, heavy cannabis use and cannabis use disorders. Nicotine use includes any use of combustible tobacco, smokeless tobacco, e-cigarettes and frequency of use (e.g. daily use). We reported on heavy cannabis use, cannabis use disorder and daily nicotine use due to the increased risk of adverse health outcomes with such patterns of use. For a study to be included, exposure to either cannabis or nicotine should be compared with no use at baseline.

Data source and search strategy

The search was conducted using PubMed (including MEDLINE), Embase, PsycINFO through EBSCOhost and a supplementary search on Google Scholar and secondary references of included studies. The search concept was Cannabis AND (Tobacco OR Nicotine) AND (Longitudinal OR Cohort study), with a variation of search terms (see Supporting information, Supplement 2). We searched English language-published studies from 2018 to 2023, as we aim to cover studies based on newer data in the past 5 years that included e-cigarettes, as a previous systematic review and meta-analysis has covered the association of e-cigarettes and cannabis use before 2018 [15].

Screening and data collection

Two authors (T.Y. and C.M.T.) screened the title, abstract and full text against the inclusion criteria, and one author (J.L.) double-checked the screening. Disagreements were resolved by discussion and by involving another author as necessary.

Data were extracted using a standardized data extraction form (Excel spreadsheet). Data on study characteristics (author, publication year, title), population, data related to cannabis and nicotine use (dose, frequency, type, initiation time, duration), proportions and effect sizes were extracted. Measures of effects were relative risks, odds ratios (ORs) and risk difference. The data extraction was conducted by one author (T.Y.) and double-checked by another author (C.M.T.). Disagreements related to the data extraction were resolved by discussion.

Quality assessment

The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) [16]. The NOS assesses the methodological quality of studies considering the robustness of participant selection, measurement of exposure, comparability based on design or analysis and outcome assessment.

Synthesis

Two sets of random-effects meta-analyses were conducted to estimate the longitudinal association between nicotine and cannabis use: the first estimating the odds of future cannabis initiation based on baseline nicotine use and the second estimating the odds of future nicotine use initiation based on baseline cannabis use. When a study has multiple observations for an exposure (e.g. cigarettes, cigars and combining cigarettes and cigars to estimate combustible tobacco) we utilized a multi-level meta-analysis approach, which appropriately adjusts for dependencies between outcomes. In the multi-level meta-analysis, these multiple observations of a single study are considered as nested to that study.

For nicotine, analyses were conducted for any nicotine use or by specific types of products used. If the studies provided specific data on various forms of tobacco/nicotine, we conducted separate meta-analyses for each form. If the studies did not differentiate between specific products, we conducted a meta-analysis by combining effect sizes across these forms. This approach provided an analysis of the relationship between different forms of nicotine use when such data are available.

The final analyses conducted were based on data as reported in the original studies from which the data were extracted. Subgroup analyses for baseline nicotine use to follow-up cannabis use were conducted by type of tobacco exposure [any combustible tobacco, cigarettes (specifically), e-cigarettes and any nicotine product] and level of cannabis use (any cannabis use, heavy cannabis use, cannabis use disorder). Subgroup analyses for baseline cannabis use to follow-up nicotine use were conducted for any cannabis use exposure at baseline by the level of nicotine use at follow-up (daily use or any use).

Sensitivity analyses

Sensitivity analyses were conducted to assess the robustness of our findings. These sensitivity analyses considered variations in population (youth or adult) and analysis of unmeasured confounding. We assessed if removing studies with adult participants had an impact in our findings.

We then assessed whether the studies considered important potential confounding variables that were identified during the review planning stage. These key variables were age, gender, education, peer

and parental substance use and use of substances other than cannabis and nicotine products. We then calculated E-values for point estimates and lower confidence levels for each of the included studies and our meta-analysis estimates [17].

E-values were computed from the odds ratios derived from each study. The interpretation of a substantial E-value depends upon its context relative to the outcome, exposure and the covariates considered and adjusted for in the estimation process [17]. In our study, the E-value represents the minimum strength of an association on a risk ratio scale that an unmeasured confounding variable would need to have, in association with both cannabis and nicotine use, to fully account for the observed association. A higher E-value means that an unmeasured confounder would need a very strong association to explain the cannabis and nicotine relationship. When a study presented both unadjusted and adjusted effect sizes, we prioritized the adjusted effect size for the E-value analysis.

E-value confidence intervals (E-value CI) were calculated to examine the level of uncertainties. The lower bound E-value CI represents the minimum strength of an association that the omitted confounding variable would need to have with the outcome and exposure variables to shift the confidence interval of the cannabis–nicotine association to include a risk ratio of 1. Coupled with the random-effects model, the E-value analysis provided a useful insight into unmeasured confounding, including the considerable differences in tobacco and cannabis policies within and across countries.

RESULTS

Study selection

Our search identified 5387 records, and 4242 unique titles and abstracts were screened. From these, 85 full-text articles were assessed against the eligibility criteria. In the final selection, 20 articles with sample size ranged from 434 to 33 374 participants were included in the narrative summary, with 18 articles (14 youths and four adults) contributing to the meta-analysis (Fig. 1).

Study characteristics

Most of the included articles ($n = 18$) were conducted in the United States [18–35], with two studies from the United Kingdom [36] and Germany [37]. Eighteen studies were on a nationally representative sample. The populations for all the studies were either community samples ($n = 12$) or college/high-school students ($n = 8$; Table 1).

Study quality

According to the NOS, the methodological quality of included studies was high in 65% ($n = 13$) and fair in 35% ($n = 7$).

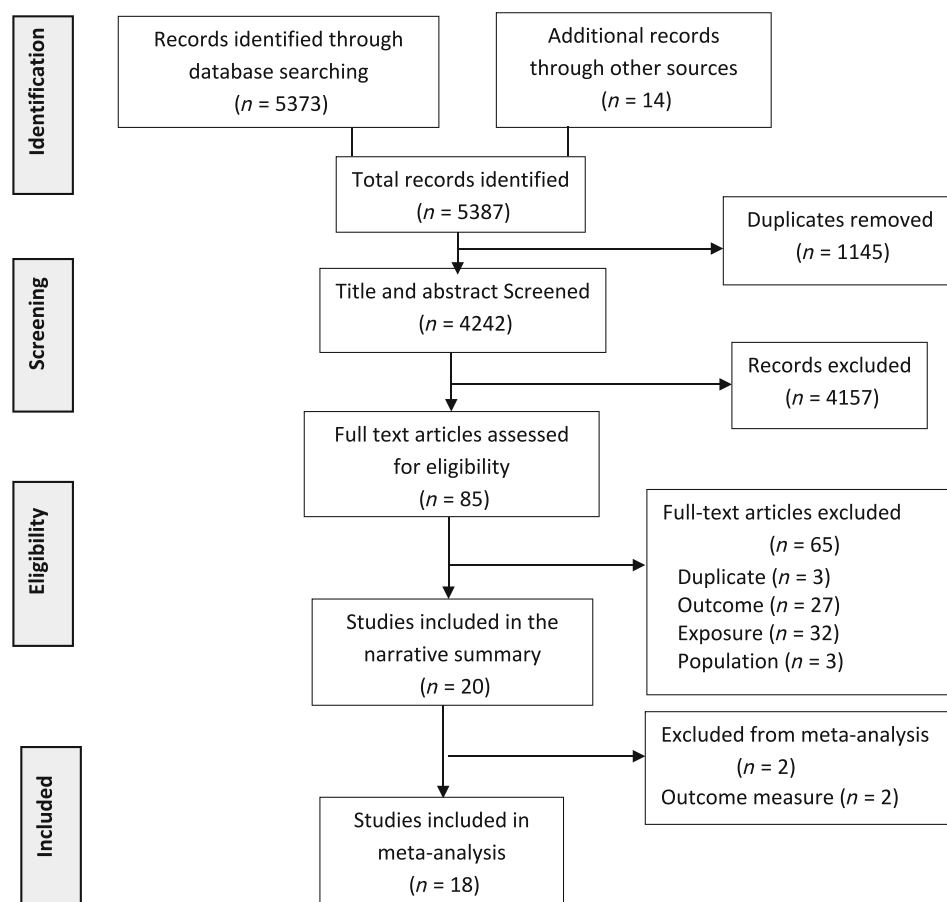


FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow-chart.

TABLE 1 Study characteristics.

Study; location	Setting; data source; survey year; sample	Exposure	Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Result key
Cannabis use exposure at baseline > nicotine use outcome at follow-up						
Azagba (2020); USA (National)	Community; PATH 2013; follow-up: 2 years; n = 11 792 Youth (age 12–17)	Ever use of any cannabis type	Past year smoking wave 2	5.11 (2.91–8.95)	–	+
			Past year smoking wave 3	2.72 (1.09–6.81)	–	+
			Past month smoking wave 2	6.14 (2.89–13.03)	–	+
			Past-month smoking wave 3	2.33 (1.06–5.11)	–	+
Cohn (2018); USA (national)	Community; Truth Initiative Young Adult Cohort 2011; follow-up: 4 years; n = 2217 Young adults (age 18–34)	Ever use of any cannabis type	Past 30 days smoking of large cigars (a)	2.35 (1.01–5.04)	0.29 (0.06–1.46)	NS
			Past 30 days smoking of small cigars (a)	5.22 (2.51–10.83)	2.79 (1.12–6.95)	+
Ross (2020); USA (subnational)	University students; ACE study 2010; follow-up: 8 years; n = 2189 Students (mean age = 18.6)	Past month use of any cannabis type	Small cigars smoking (a)	–	1.60 (1.01–2.50)	+
			Large cigars smoking (a)	–	1.20 (0.80–1.80)	NS
Mayer (2020); USA (subnational)	High-school students; H&H and YASS 2013; follow-up: 2 years; n = 2973 Students	Ever use of non-blunt cannabis	Ever use of combustible tobacco (initiation)	–	2.38 (1.41–4.00)	+
		Ever use of blunt cannabis		–	1.98 (1.30–3.01)	+
Nguyen (2019); USA (national)	High-school students; Add Health 1994; follow-up: 14 years; n = 2928 Students	Past month use of cannabis	Daily cigarette smoking in the past 30 days, males	1.13 (0.73–1.76)	–	NS
			Daily cigarette smoking in the past 30 days, females	1.71 (1.13–2.59)	–	+
Weinberger (2020); USA (national)	Community; PATH 2013; follow-up: 1 year; n = 26 341 Adults (age 18+)	Past year use of any cannabis type	Current cigarette smoking (past year daily or non-daily)	6.77 (5.50–8.33)	6.18 (4.85–7.87)	+
			Current non-daily cigarette smoking (past year)	7.01 (5.06–9.85)	5.50 (4.02–7.55)	+
			Current daily cigarette smoking (past year)	6.56 (5.08–8.47)	6.70 (4.75–9.46)	+
Weinberger (2018); USA (national)	Community; NESARC 2001; follow-up: 4 years; n = 20 077 Adults (age 18+)	Past year use of any cannabis type	Current non-daily cigarette smoking	4.45 (3.97–5.00)	1.86 (1.59–2.16)	+
			Current daily cigarette smoking	2.90 (2.10–4.00)	1.00 (0.61–1.65)	NS
Weinberger (2021)a; USA (national)	Community; PATH 2013; follow-up: 1 year; n = 13 651 Youth (age 12–17)	Past month use of any cannabis type	Past 30 days cigarette smoking	8.70 (5.40–14.00)	5.70 (3.60–9.10)	+
			Past 30 days e-cigarette use	6.80 (4.50–10.10)	4.50 (2.90–6.90)	+
			Past 30 days cigarette + e-cigarette use	12.50 (6.50–24.40)	7.60 (4.00–14.30)	+
			Past 30 days exclusive cigarette smoking	6.30 (3.60–10.90)	4.40 (2.50–7.70)	+

(Continues)

TABLE 1 (Continued)

Study; location	Setting; data source; survey year; sample	Exposure	Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Result key
			Past 30 days exclusive e-cigarette use	4.40 (2.40–7.90)	3.10 (1.70–5.70)	+
Wong (2020); USA (national)	Community; PATH 2013; follow-up: 3 years; n = 14 426 Adults (age 18+)	Past month use of any cannabis type	E-cigarette use	–	2.23 (1.58–3.14)	+
Nicotine use exposure at baseline > cannabis use outcome at follow-up						
Audrain-McGovern (2018); USA (local)	High-school; 2013; follow-up: 2 years; n = 2668 Students	Cigarette ever use	Cannabis ever use (initiation)	5.98 (3.99–8.98)	4.30 (2.79–6.63)	+
		E-cigarette ever use		4.74 (3.58–6.27)	3.63 (2.69–4.94)	+
		Hookah ever use		4.89 (3.49–6.86)	3.55 (2.49–5.08)	+
		Any ever use		5.26 (4.16–6.65)	4.00 (3.12–5.14)	+
Bentivegna (2021); USA (national)	Community; PATH 2013; follow-up: 3 years; n = 7551 Youth (age 12–17)	E-cigarette ever use	Cannabis use past 12 months	–	2.30 (1.72–3.07)	+
Ross (2020); USA (subnational)*	College/University; ACE 2010; follow-up: 7 years; n = 2189 Students (mean age 18.8)	Small cigar ever use	Cannabis ever use (initiation)	–	1.40 (1.10–1.80)	+
		Large cigar ever use		–	1.30 (1.10–1.80)	+
		Cigarette past month use		–	1.90 (1.30–2.90)	+
		E-cigarette past month use		–	1.80 (0.90–3.30)	NS
		Hookah past month use		–	2.20 (1.70–2.90)	+
		Smokeless tobacco past month		–	0.80 (0.50–1.20)	NS
Dai (2018); USA (national)	Community; PATH 2013; follow-up: 1 year; n = 10 364 Youth (age 12–17)	E-cigarette ever use	Cannabis use past 12 months	4.37 (3.55–5.39)	1.90 (1.40–2.50)	+
		E-cigarette ever use	Cannabis heavy use past 12 months (weekly+)	3.41 (2.42–4.81)	1.30 (0.80–2.10)	NS
		Cigarette ever use	Cannabis use past 12 months	4.39 (3.62–5.34)	2.00 (1.50–2.70)	+
		Cigarette ever use	Cannabis heavy use past 12 months (weekly+)	4.41 (3.27–5.95)	2.10 (1.40–3.20)	+
Duan (2022); USA (national)	Community; PATH 2013; follow-up: 4 years; n = 7888 Youth (age 12–17)	E-cigarette past month use versus No use	Cannabis use past 30 days	–	4.81 (2.93–7.90)	+
		Combustible tobacco past month		–	2.23 (1.08–4.64)	+
Evans-Polce (2020); USA (national)	High school; MTF 2014; follow-up: 1 year; n = 434 Students (age 19)	E-cigarette past month use at age 18	Cannabis use past 12 months	4.50 (1.70–11.93)	3.22 (1.03–10.10)	+
Pampati (2018); USA (national)	High-school; Add Health 1994; follow-up: n = 1775; Students	Cigarette use before age 12	Cannabis use past 12 months	–	2.04 (1.23–3.37)	+
		E-cigarette past month use	Cannabis use past 12 months	–	4.63 (1.98–10.80)	+

TABLE 1 (Continued)

Study; location	Setting; data source; survey year; sample	Exposure	Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Result key
Pokhrel (2020); USA (local)	University; 2017; follow-up: 1 year; <i>n</i> = 1162 (mean age 20.8)	Cigarette past month use		–	5.93 (1.79–19.70)	+
		Both e-cigarette and cigarette past month use		–	13.40 (5.37–33.30)	+
Seidel (2022); Germany (subnational)	School; 2017; follow-up: 1.5 year; <i>n</i> = 3040 Youth (age 13–18)	E-cigarette ever use versus no use	Cannabis use past 18 months (b)	9.75 (7.13–13.34)	1.83 (1.48–2.25)	+
		Cigarette ever use		–	1.71 (1.39–2.10)	+
Staff (2022); UK (national)	Community; MCS at age 14; follow-up: at age 17; <i>n</i> = 10 251 Youth	E-cigarette ever use	Cannabis ever use (initiation)	–	2.75 (1.82–4.15)	+
		Cigarette ever use		–	3.68 (2.40–5.63)	+
		E-cigarette ever use	Cannabis use past 12 months	–	2.46 (1.48–4.08)	+
		Cigarette ever use		–	1.93 (1.03–3.60)	+
Sun (2022); USA (national)	Community; PATH 2017; follow-up: 1 year; <i>n</i> = 9828 Youth (age 12–17)	E-cigarette ever use versus no use	Cannabis use past 12 months	–	3.40 (2.59–4.46)	+
		E-cigarette past year use		–	3.56 (2.70–4.71)	+
		E-cigarette past month use		–	2.84 (1.82–4.44)	+
		E-cigarette ever use	Cannabis use past 30 days	–	3.66 (2.47–5.42)	+
		E-cigarette past year		–	3.96 (2.59–6.04)	+
		E-cigarette past month		–	3.46 (1.92–6.26)	+
Weinberger (2021)b; USA (national)	Community; NESARC 2001; follow-up; <i>n</i> = 33 374 Adult	Cigarette ever use versus no use	Cannabis use disorder	2.60 (2.29–2.96)	1.62 (1.35–1.94)	+
Wong (2020); USA (national)	Community; PATH 2013; follow-up: 3 years; <i>n</i> = 10 762 Adult (age 18+)	E-cigarette past month use versus no use	Cannabis ever use (initiation)	–	2.08 (1.11–3.90)	+

Abbreviations: ACE = Assessment of the College Experience; Add Health = National Longitudinal Study of Adolescent to Adult Health; (a) incidence rate ratio; blunt = cannabis in an emptied cigar; (b) relative risk; H&H = Happiness & Health Study; NESARC = National Epidemiologic Survey on Alcohol and Related Conditions; NS = not significant; PATH = Population Assessment of Tobacco and Health; result key: + positive association; YASS = Yale Adolescent Survey Study.

of studies. The most common shortfall was that all studies used self-reported outcomes (see Supporting information, Supplement 3).

Cannabis use at follow-up, given baseline nicotine use

Thirteen studies provided data on nicotine use exposure at baseline and subsequent initiation of cannabis use at follow-up. However, one study [20] was excluded, as the estimates were in incidence rate ratio (IRR), as opposed to OR in other included studies. This study, by Ross *et al.* [20], examined the incidence of cannabis use among college students who had used nicotine products at baseline (i.e. cigars,

cigarettes, e-cigarettes, hookah and smokeless tobacco). After adjusting for sex and other substance use, Ross and colleagues found a positive and significant longitudinal association between baseline cigar, cigarettes and hookah use and subsequent initiation of cannabis use, but not for e-cigarettes and smokeless tobacco (see Table 1).

Studies with unadjusted estimates reported significant and positive associations between the initiation of cannabis use at follow-up among baseline cannabis-naïve nicotine users. For example, a US study among 10 364 youths (aged 12–17 years) reported that past year initiation of cannabis use was four times higher in those who reported ever use of e-cigarettes at baseline (unadjusted OR = 4.4, 95% CI = 3.5, 5.4) [21]. Another US study among 2668 high-school students also reported that initiation of cannabis use was more than

five times higher among those who were exposed to any nicotine products (including cigarettes, e-cigarettes and hookah) at baseline (OR = 5.26, 95% CI = 4.16, 6.65) [18]. Moreover, the incidence of cannabis use disorder was more than twofold in a community sample of adults who reported ever use of cigarettes at baseline (OR = 2.60, 95% CI = 2.29, 2.96) [26].

Of the 12 studies included in the meta-analysis of nicotine exposure and subsequent cannabis use, nine studies adjusted for at least three of the six key variables (age, sex, education, other substance use, peer and parental substance use). Studies that adjusted their estimates for these key variables generally reported significant and positive associations with the initiation of cannabis use at follow-up among baseline cannabis-naïve nicotine users. For example, a UK study showed that participants who ever used cigarettes at baseline were more than threefold more likely to initiate subsequent cannabis use (aOR = 3.7, 95% CI = 2.4, 5.6) [36]. However, one study reported no significant association between baseline e-cigarette exposure and subsequent heavy cannabis use (aOR = 1.3, 95% CI = 0.8, 2.1) [21].

The random-effects meta-analyses found a positive and statistically significant longitudinal association between nicotine use

and subsequent initiation of cannabis use. Individuals who were cannabis-naïve at baseline but used e-cigarettes (aOR = 2.72, 95% CI = 2.06, 3.61), combustible tobacco (aOR = 2.58, 95% CI = 1.75, 3.81), cigarettes (aOR = 2.51, 95% CI = 1.74, 3.62) or any of these products (aOR = 2.59, 95% CI = 2.01, 3.32) were more than twofold more likely to initiate cannabis use after adjusting for important variables such as age and sex (Table 2).

Nicotine use at follow-up, given baseline cannabis use

Nine studies provided data on cannabis use at baseline and the initiation of nicotine use at follow-up. Two studies were not included in the meta-analysis as their effect size measure was in IRR, as opposed to the OR in the included studies. These two articles specifically examined the IRR of smoking cigars (large or small cigars) among baseline cannabis users. Both studies found a positive association between baseline cannabis use and the initiation of small cigar smoking. Cohn and colleagues [34] reported that the odds of initiating small cigar smoking in young adults who ever used cannabis at baseline was more than twofold higher than in those who never used cannabis (adjusted

TABLE 2 Random-effects meta-analysis results on longitudinal studies of subsequent cannabis use following nicotine use at baseline and studies of subsequent nicotine use following cannabis use at baseline.

	Unadjusted estimate				Adjusted estimate			
	n	OR (95% CI)	Q	I ²	n	aOR (95% CI)	Q	I ²
Analyses of nicotine use > cannabis use*								
Exposure: combustible tobacco								
Any cannabis use	3	4.87 (1.89, 12.55)	0.31	0.00%	8	2.58 (1.75, 3.81)	5.76	0.00%
Heavy cannabis use	1	4.41 (3.27, 5.95)	NA	NA	1	2.10 (1.40, 3.20)	NA	NA
Cannabis use disorder	1	2.60 (2.29, 2.96)	NA	NA	1	1.62 (1.35, 1.94)	NA	NA
Exposure: cigarette								
Any cannabis use	2	4.85 (2.92, 8.09)	0.31	0.00%	6	2.51 (1.74, 3.62)	5.03	4.49%
Heavy cannabis use	1	4.41 (3.27, 5.95)	NA	NA	1	2.10 (1.40, 3.20)	NA	NA
Cannabis use disorder	1	2.60 (2.29, 2.96)	NA	NA	1	1.62 (1.35, 1.94)	NA	NA
Exposure: e-cigarette								
Any cannabis use	4	5.53 (3.68, 8.33)	2.76	5.05%	9	2.72 (2.06, 3.61)	5.38	0.00%
Heavy cannabis use	1	3.41 (2.42, 4.81)	NA	NA	1	1.30 (0.80, 2.10)	NA	NA
Cannabis use disorder	0	–	–	–	0	–	–	–
Exposure: any nicotine								
Any cannabis use	5	5.39 (3.19, 9.11)	3.07	0.00%	16	2.59 (2.01, 3.32)	10.42	0.00%
Heavy cannabis use	2	3.92 (2.24, 6.87)	0.19	0.00%	2	1.68 (0.87, 3.26)	0.50	0.00%
Cannabis use disorder	1	2.60 (2.29, 2.96)	NA	NA	1	1.62 (1.35, 1.94)	NA	NA
Analyses of cannabis > nicotine use								
Exposure: any cannabis use								
Nicotine daily use	4	2.95 (0.69, 12.59)	10.47	70.59%	2	2.63 (0.41, 16.95)	8.40	88.09%
Nicotine any use (youth + adult)	9	4.08 (2.05, 8.11)	18.41	59.48%	8	2.94 (1.54, 5.61)	15.60	54.59%
Nicotine any use (youth only)	6	3.48 (0.94, 12.87)	14.39	64.36%	4	3.29 (0.85, 12.76)	3.31	11.12%

Note: See Supporting information, Supplement 3 for forest plots for each of the meta-analyses; OR = odds ratios; aOR = adjusted odds ratios; 95% CI = 95% confidence intervals; Q = Cochran's Q; I² = I-squared; NA = not applicable; *all studies are on youth except for cannabis use disorder.

IRR = 2.8, 95% CI = 1.1, 6.9). Similarly, Ross and colleagues [20] reported that past-month use of cannabis at baseline was positively associated with the initiation of subsequent smoking of small cigars among students (adjusted IRR = 1.6, 95% CI = 1.0, 2.5). Both studies found no significant association between baseline cannabis use and subsequent large cigar smoking.

The seven studies that were meta-analysed provided the pooled longitudinal association between baseline cannabis use and subsequent nicotine initiation. Four of the seven studies of cannabis exposure and subsequent nicotine use initiation had adjusted for at least three of the key variables. Two studies were not adjusted for any of the key variables.

In nicotine-naïve youths, baseline cannabis use was not significantly associated with subsequent initiation of any nicotine use at follow-up (OR = 3.48, 95% CI = 0.94, 12.87; aOR = 3.29, 95% CI = 0.85, 12.76), and daily nicotine use (OR = 2.95, 95% CI = 0.69, 12.59; aOR = 2.63, 95% CI = 0.41, 16.95). However, the association was significant when studies with adult participants added (OR = 4.08, 95% CI = 2.045, 8.11; aOR = 2.94, 95% CI = 1.54, 5.61) (Table 2).

Publication bias

The funnel plots for the estimates with sufficient data points showed no substantial asymmetry in visual inspection (Supporting information, Supplement 5). The regression test also indicated that there is no evidence of publication bias (the *P*-value for *Z*-score is greater than 0.09 for all estimates). Trim-and-fill assessment (Supporting information, Supplement 5) showed that a small number of potential studies (two or three studies) were missed on the left-hand side of some of the funnel plots, and findings were unlikely to be affected by publication bias.

Sensitivity analysis

In nicotine-naïve participants, baseline cannabis use was no longer positively associated with subsequent initiation of any tobacco use at follow-up after the three studies with adult participants were removed (OR = 3.48, 95% CI = 0.94, 12.87; aOR = 3.29, 95% CI = 0.85, 12.76) (Table 2).

The median point estimate *E*-value (*E*-value) and lower confidence interval *E*-value (CI *E*-value) for the nicotine exposure and subsequent cannabis use initiation in the studies were 5.5 and 2.9, respectively. This indicates that unmeasured confounders would need to be associated with both nicotine exposure and the risk of initiating cannabis use by a risk ratio of at least 5.5 to fully account for the observed longitudinal associations in half the studies. The median *E*-value and CI *E*-value for cannabis exposure and subsequent initiation of nicotine use in the included studies were 4.1 and 2.4, respectively. This indicates that unmeasured confounders would need to be associated with both cannabis exposure and the risk of initiating

nicotine use by at least a 4.1 risk ratio to fully explain the observed longitudinal associations in half the studies.

E-values of the meta-analysis estimates for the incidence of any cannabis use, given baseline exposure of combustible tobacco (*E*-value = 4.6, CI *E*-value = 2.9), cigarettes (*E*-value = 4.6, CI *E*-value = 2.9), e-cigarettes (*E*-value = 4.8, CI *E*-value = 3.3) and any nicotine products (*E*-value = 4.6, CI *E*-value = 3.4) are relatively higher. This indicates that unmeasured confounders need a strong association (risk ratio > 4.5) with both cannabis and nicotine use to fully account for our estimates. Thus, our estimates are unlikely to be biased by unmeasured confounders. The *E*-value for any nicotine use initiation among those who used cannabis at baseline was 5.3, CI *E*-value 2.4. This indicates that unmeasured confounders must be associated with a risk ratio of 5.3 to fully explain our findings (Supporting information, Supplement 4).

DISCUSSION

Among studies that examined nicotine use at baseline and cannabis use at follow-up there were mixed findings, but more studies reported a significant positive association for any cannabis use. The meta-analyses showed that baseline exposure to nicotine products was positively associated with the later initiation of cannabis use. Findings of nicotine use on associations with heavy cannabis use or cannabis use disorders were limited and mixed, probably because of the low prevalence of these patterns in the general population.

Among studies that examined the use of cannabis first, a positive association was observed with later nicotine use among general youth and adult participants (youth + adult), but not for youth only participants and daily nicotine use. This may imply the increased shift in initiation of nicotine use from adolescents to early adulthood [9], highlighting the need for prevention in harm reduction strategies in early adulthood. However, our evidence is limited by the small number of included studies for daily nicotine use outcome. Overall, many studies have appropriately adjusted for a range of potential confounding variables and *E*-value analyses showed reasonably high values, implying that significant associations reported are unlikely to be wholly explained by potential confounder variables.

Our findings showed a bidirectional prospective association between any nicotine and any cannabis use in youth and adult participants, but not for youth only participants. Even though it is not statistically significant, the bidirectional association in youth only participants is still high (aOR = 3.9). Previous studies reported that liberalization of cannabis policies has not affected tobacco use in the population [38, 39]. However, there have been debates and concerns that people might shift from tobacco to cannabis use. A recent age-period-cohort analysis of tobacco and cannabis use in the Australian population identified a consistent decrease in tobacco use and an increasing trend in cannabis use with or without tobacco [40]. This is a particularly important public health issue, given that more jurisdictions are liberalizing cannabis for adult use.

The bidirectional association between cannabis and tobacco use is of concern as it may lead to increased use of both substances and polydrug use. For instance, a previous study reported higher rates of cannabis use disorder among people who smoked cigarettes with an increased trend among those who smoked but not every day [41]. This is also reflected in our finding that exposure to any cannabis use was associated with an increased incidence of any nicotine use. The positive association between cannabis use and non-daily nicotine use is also noteworthy, as non-daily tobacco users tend to identify themselves as 'non-smokers' [42] and may be less likely to seek help. Public health policies should adopt comprehensive strategies that address both substances concurrently. These strategies should encompass prevention, intervention and harm reduction. For instance, cannabis users who also smoked tobacco have an increased risk of cannabis-related adverse health outcomes [43], and should be warned not to mix cannabis and tobacco and their increased risk of initiating other drugs, including nicotine.

Several mechanisms can explain the bidirectional association between cannabis and tobacco use [10, 44]. Environmental and psychosocial factors such as peer influence, social norms and availability probably play an important role [10, 45]. Both cannabis and tobacco smoking share a common route of administration that facilitates use and serves as a behavioural cue. Genetic predisposition may also account for a significant share of the association, because there is some evidence that the genetic system involved in cannabis and tobacco use has an overlap [10]. This complex potential mechanism demands public health policies to develop comprehensive strategies addressing both substances, considering environmental, psychosocial and genetic factors. Future research to more clearly understand the causal relationship between cannabis and nicotine use needs to have comprehensive measures of all these factors.

Limitations

There are several key limitations of this systematic review that need to be taken into consideration for the interpretation of findings. There was a small number of studies that specifically examined heavy cannabis use and cannabis use disorder. While there was a reasonable amount of research available on any cannabis use, the scarcity of studies addressing these more problematic patterns of cannabis consumption restricts our ability to draw conclusions about harmful use. Any cannabis use could include those who may have only tried it once or twice, which would be of less concern from a public health perspective. Regular or heavy cannabis use and cannabis use disorder are of particular concern due to their potential for harm, especially in youth. Therefore, future studies that focus upon the development of addiction indicated by heavier cannabis use or cannabis use disorder are warranted. This can be the same for tobacco or e-cigarette use; ever-use could include those who have had only one puff in a lifetime. Some individuals who use e-cigarettes do not use nicotine [46], and it is unclear if some respondents in the included studies may have reported ever-use of e-cigarettes, even if no nicotine was present.

While our review offers a comprehensive insight into the relationship between nicotine and cannabis, we were unable to account for additional pathways. For example, our review does not provide data on scenarios where youth may have started with e-cigarettes then transitioned to smoking cigarettes, and subsequently initiated cannabis use.

Most of the included studies were conducted in the United States, raising questions regarding the generalizability of the findings to other regions and cultural contexts. There may be greater cannabis accessibility in the United States due to the legalization of recreational cannabis use in many states. Further research from more diverse geographical locations is needed to understand whether the observed associations are consistent across different populations with different cultural norms. In addition, the included studies are self-reported and subjected to response bias due to stigma and social desirability effects. For example, participants may identify themselves as non-smokers while they are co-using cannabis and smoked tobacco.

While some studies adjusted for a range of potential confounding variables, variations in the control for these factors across different studies may impact the comparability of results. The policy difference in cannabis and tobacco regulation within and across countries may affect the accessibility and patterns of use for cannabis and tobacco. We did not consider this policy difference in the eligibility criteria and analysis of the current review. Future study is warranted to investigate the potential influence of such policy difference in cannabis and tobacco use. Genetic predispositions to addiction could influence the observed associations between tobacco and cannabis use, so future studies that include genetic data could add to our understanding of their relationship. Specifically, Mendelian randomization (MR) studies, can test where a genetic variant strongly associated with an exposure (e.g. cannabis use) may predict an outcome (e.g. tobacco use). A previous MR study that estimated bidirectional causal effects between nicotine and cannabis found that most tests did not reveal causal associations [47], but there was some suggestive evidence that smoking increased cannabis initiation. However, updated data and investigations are warranted, as social and population trends around smoking and cannabis have been evolving in recent years.

CONCLUSIONS

In summary, this systematic review and meta-analysis of associations between cannabis and tobacco found mixed evidence, but more studies found a link between any cannabis and any tobacco use in both directions. Our analysis suggests that these associations are unlikely to be solely explained by confounding factors. It was not clear if the use of one drug causes the use of the other, or if the timing and sequence of their use may be affected by population trends. The evidence for youth use on the development of addiction, as indicated by daily tobacco use, heavy cannabis use or cannabis use disorders, was limited. The common use of both cannabis and tobacco supports public health and prevention strategies to discourage the uptake of both drugs by youth regardless of their sequence of initiation.

AUTHOR CONTRIBUTIONS

Tesfa Mekonen Yimer: Conceptualization (equal); data curation (equal); formal analysis (lead); investigation (equal); methodology (equal); project administration (equal); resources (equal); validation (equal); visualization (equal); writing—original draft (lead); writing—review and editing (equal).

Caitlin McClure-Thomas: Data curation (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); validation (lead); writing—original draft (equal); writing—review and editing (equal). **Daniel Stjepanovic:** Data curation (equal); investigation (equal); methodology (equal); supervision (equal); validation (equal); writing—original draft (equal); writing—review and editing (equal). **Jack Wilson:** Investigation (equal); methodology (equal); validation (equal); writing—review and editing (equal). **Gary Chung Kai Chan:** Investigation (equal); methodology (equal); supervision (equal); validation (equal); writing—review and editing (equal). **Wayne Denis Hall:** Conceptualization (lead); investigation (equal); methodology (equal); supervision (equal); writing—review and editing (equal). **Janni Leung:** Conceptualization (lead); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); supervision (equal); validation (equal); visualization (equal); writing—original draft (lead); writing—review and editing (equal).

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DECLARATION OF INTERESTS

None to declare.

DATA AVAILABILITY STATEMENT

The data is available from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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