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Age of onset of cannabis use and substance use problems: A systematic review of prospective studies

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ABSTRACT

Background: The association between the age of cannabis use (CU) onset and substance use (SU) problems has been extensively studied, yet findings remain inconsistent.
Aims: This systematic review aimed to examine prospective studies on the association between age of CU onset and later SU problems, controlling for key individual, social, and SU-related risk factors.
Methods: PsycINFO, Web of Science and PubMed were searched for studies published between January 2000 and December 2024. Studies were included if they: 1) were prospective; 2) measured CU onset during adolescence; 3) measured CU or SU problems after CU onset, 4) examined whole plant or phytocannabinoids. Studies were excluded if they exclusively focused on high-risk samples. Risk of bias was assessed using the Risk of Bias in Non-randomised Studies-of Interventions tool. The review was registered with PROSPERO, number CRD42022332092.
Results: Sixteen studies met eligibility criteria. Earlier age of CU onset was associated with CU disorder (CUD) and CU negative consequences, with mixed findings for other SU problems (e.g., alcohol). CU frequency accounted for a significant portion of the risk for CU negative consequences, but the association with CUD remained independent of frequency. Only one study had low risk of bias, while seven had some concerns, and eight had a high or very high risk of bias.
Conclusions: Findings suggest that early age of CU onset is a specific risk factor in the development of CUD, but not other SU problems. Prevention approaches should aim to delay the onset and reduce the frequency of CU among youth to reduce risk of the development of CUD.

1. Introduction

Cannabis is one of the most commonly used substances, with 3 % to 17 % of adolescents aged 15–16 years worldwide actively using it (United Nations Office on Drugs and Crime, 2023). Some evidence suggests that cannabis use (CU) during adolescence increases the risk of developing substance use (SU) problems, such as SU disorders (SUD; Kaur et al., 2022). However, despite progress in understanding SUD etiology, the influence of CU age of onset on later SU problems has yielded mixed results across studies. It is not yet clear whether strong prospective evidence supports this association. Furthermore, it is unclear whether age of CU onset represents a unique risk factor or solely a risk marker, potentially co-occurring or interacting with other risk factors. One hypothesis suggests that early CU onset may directly contribute to later SU problems by altering brain functions, such as reward sensitivity (Levine, Clemenza, Rynn, & Lieberman, 2017). Alternatively, genetic and individual vulnerabilities (e.g., proneness to deviancy, mental health, personality traits, and familial predisposition

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to addiction) can serve as common liabilities, increasing the risk of both early age of onset and later SU problems (Iob et al., 2021; Van Leeuwen et al., 2011). In this context, early CU onset might reflect other risk factors, such as heritable vulnerability, adverse childhood experiences, or peer influence (Behrendt, 2017), rather than acting as an independent risk factor of later SU problems. While further research is needed to rigorously test these hypotheses and explore underlying mechanisms, it is essential to first conduct robust examinations of the relationship between CU onset and later SU problems to better distinguish between these alternative hypotheses. This is particularly important in light of cannabis legalization in the US, Canada, and other countries. This insight will help informing prevention, early intervention, and identifying risk factors during critical developmental periods (McGrath et al., 2023).

Investigating the unique effect of CU onset on later SU problems is challenging since numerous other variables have been identified as risk factors for both SU onset and SU problems (Connor et al., 2021; Trucco & Hartmann, 2021). These risk factors can be summarized into three groups, namely: (1) individual; (2) social environment; and (3) other SU-related factors. Individual risk factors include sex, temperament, and internalizing and externalizing disorders such as depression and conduct disorder (e.g., Bears Augustyn, Fulco, Agbeke, & Henry, 2022; Kaur et al., 2022; Rioux et al., 2015). For example, males generally report an earlier age of SU onset and higher rates of SUD (Agabio, Campesi, Pisanu, Gessa, & Franconi, 2016; Kozak et al., 2021). Furthermore, developmental trajectories of SU differ between males and females, with females undergoing a more rapid progression into SUD, compared to males (Kozak et al., 2021; Kuhn, 2015). Social environment risk factors including low socioeconomic status and family adversities have been associated SU problems (Hudson & Hudson, 2021; Rioux et al., 2018). Finally, SU-related factors including SU frequency and poly-SU have been linked to SUD and SU problems (Davis, Slutske, Martin, Agrawal, & Lynskey, 2019; Hudson & Hudson, 2021).

Recently, Kaur et al. (2022) conducted a scoping review exploring the mental health and addiction outcomes of adolescent CU onset. They found that earlier CU onset was associated with a higher risk of CU disorder (CUD) and negative CU consequences (e.g., concentration problems), while association with other SUD were mixed. While this review provides important insights into the association between age of CU onset and subsequent SUD, many studies included were cross-sectional and retrospective in nature, which are susceptible to recall bias and prevent establishing causal relationships (Wang & Cheng, 2020). Further, the review included studies that compared individuals with early CU onset to individuals who do not use cannabis, rather than those with later-age onset, making it difficult to separate the effects of any CU from those of age of CU onset. Moreover, Kaur et al. (2022) did not include a bias assessment, which is essential for evaluating the quality of existing studies. Finally, the study did not specifically examine the influence of key covariates, such as sex, on the association between age of CU onset and later SU problems.

1.1. Current study and objectives

There is a compelling need for a systematic review clarifying the prospective association between age of CU onset and later SU problems. In this article, SU problems are operationalized as a spectrum of adverse outcomes encompassing both clinically diagnosed SUD, as defined by diagnostic criteria such as those in the DSM, and broader SU negative consequences assessed using validated screening tools, such as the Cannabis Abuse Screening Test (CAST; Legleye, Karila, Beck, & Reynaud, 2007). These consequences include impairments in academic achievement, occupational performance, disruptions in family and interpersonal relationships, and involvement in legal or financial difficulties. Furthermore, SU problems are considered across a range of substances, including cannabis, alcohol, nicotine, and other substances (e.g., cocaine). This systematic review aimed to address the gap in the literature by determining whether early CU onset remains a reliable predictor of subsequent SU problems while controlling for individual, social, and other SU-related risk factors, and examining whether the association between age of CU onset and subsequent SU problems differs by sex.

2. Methods

The present systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines (Page et al., 2021) and was registered on the International Prospective Register of Systematic Reviews (PROSPERO number: CRD42022332092).

2.1. Eligibility criteria

Studies were included if they met the following criteria: 1) were prospective; 2) measured CU onset during adolescence; 3) measured CU or SU problems after CU onset; 4) examined whole plant or phytocannabinoids (i.e., Δ9-tetrahydrocannabinol or cannabidiol). Studies were excluded if they: 1) were cross-sectional, retrospective, case studies, clinical trials, case reports, or commentaries; 2) exclusively focused on high-risk samples (e.g., prenatal SU exposure); 3) focused on synthetic cannabis.

2.2. Information sources and search strategy

Searches were conducted on 3 databases: PsycINFO, Web of Science and PubMed. We limited our search to articles published from 2000 onwards, with the most recent search conducted on December 03, 2024, across all three databases. The keywords used for the search were: ("early onset" OR "early initiation" OR "age of onset" OR "age of initiation" OR "first use") and ("cannabis" OR "marijuana" OR "Marihuana" OR "hashish" OR "tetrahydrocannabinol" OR "cannabidiol") and ("use disorder" OR "dependence" OR "problematic substance use" OR "problem use" OR "problematic use" OR "addiction" OR "abuse") and ("prospective" OR "longitudinal" OR "followed-up" OR "follow-up" OR "cohort study" OR "cohort studies"). For an example of the results from this detailed search strategy, refer to Supplementary material 1.

2.3. Selection process

Search results were imported into Endnote. Seven authors independently conducted either the initial title and abstract screening (JH, NP, MD, CS, RA) and/or the subsequent full-text reviews (JH, NP, NCR, CH, MD), with each reference screened by at least two independent reviewers. In instances where discrepancies arose between two or more reviewers' assessments (Cohen's kappa = 0.60), a final decision was reached through consensus with additional input from an additional reviewer (generally NCR or NP).

2.4. Data collection process

Data were independently extracted by three reviewers (MD, NP, CH), with disagreements resolved by a third reviewer (NCR). Any data that were missing in the articles were obtained by contacting the corresponding author. Articles written in French, Spanish and German were reviewed by one of the authors fluent in those languages.

2.5. Data items

This systematic review focuses on adolescents (Population) exposed to early CU (Exposure) and investigates its association with later SU problems (Outcome). The primary outcomes of interest include SU problems across various substances (e.g., cannabis, tobacco, alcohol, methamphetamine), assessed through either clinical diagnoses or self-

reported measures. Clinical diagnoses, such as CUD, were defined according to the DSM-III-R or DSM-IV criteria, depending on the study (detailed information on how each outcome was measured is provided in Table 1), and were treated as dichotomous measures (e.g., presence or absence of a CUD diagnosis). In addition, continuous measures (e.g., severity of CU negative consequences) were also included. These continuous measures, such as higher scores on self-reported questionnaires like the CAST, which assess problematic CU and its negative consequences (e.g., difficulties in fulfilling work or school obligations, social or interpersonal problems), are particularly informative. Not only are these tools frequently used as screening measures for problematic SU in general population and cohort studies, but they have also been shown to exhibit moderate to strong correlations with clinical diagnoses of disorders such as CUD (Richards, Schwebel, Sotelo, & Pearson, 2021). Therefore, considering both categorical and continuous outcomes when evaluating SU problems was deemed important to include as many relevant studies as possible and to provide a more comprehensive portrait of the evidence.

The main information extracted after full-text review included: 1) study design (e.g., duration of the study); 2) participant demographics and baseline characteristics (e.g., sample size, age at baseline, sex and/or gender distribution); 3) measures (e.g., whether age of CU onset was a continuous or categorical variable) and covariates; 4) type of first cannabis exposure (e.g., whole plant versus extract, if applicable); 5) any other reported cannabis-related information (e.g., quantity and/ or frequency of use); 6) SU outcomes.

2.6. Risk of bias

Following the PRISMA guidelines, two study authors (NP and NCR) independently conducted an evaluation of each study's risk of bias using the Risk of Bias in Non-randomised Studies-of Interventions tool (ROBINS-I, Sterne et al., 2016). The ROBINS-I helps to identify potential biases, including selection bias, measurement bias and biases arising from missing data. Additionally, the tool provides a classification of the risk of bias, categorizing it as low (i.e., low risk of bias), moderate (i.e., some concerns), serious (i.e., high risk of bias), or critical (i.e., very high risk of bias). It is worth noting that we deviated from the ROBINS-I guidelines on one aspect. While ROBINS-I asserts that controlling for a variable associated with the primary variable under investigation is a limitation in prospective studies, we considered that controlling for other SU during adolescence was a study strength, rather than a limitation. Discrepancies between the two authors on the ROBINS-I assessment for each study were discussed and resolved through consensus. The studies categorized with a low risk of bias or those with some concerns were considered the highest-rated studies.

3. Results

3.1. Study selection

Our initial search generated 955 potentially relevant articles. After removing duplicates, 544 articles remained for title and abstract screening. Following title and abstract screening, 80 articles remained for full-text review, with 16 studies included thereafter in the systematic review (see Table 1 for a comprehensive summary of all the studies' characteristics, covariates, and results, and see Supplementary material 2 for a summarized description of the studies). See Fig. 1 for the PRISMA flowchart for the present systematic review.

3.2. Risk of bias

The primary sources of bias identified were as follows: (1) Eight studies lacked control for key covariates, which could introduce confounding (Domain 1: Bias due to confounding); (2) Eight studies either failed to report or inadequately addressed missing data (Domain 5: Bias due to missing data); and (3) Three studies were subject to bias due to misclassification or measurement error, such as detection bias (Domain 3: Bias in classification of interventions). See Table 1 for the ROBINS-I risk of bias assessment for all studies. In summary, one study had low risk of bias, seven studies had some concerns, five studies had high risk of bias, and three studies had a very high risk of bias.

3.3. Age of onset of cannabis use

Age of onset of CU was examined across studies in two primary formats. Some studies analyzed age of onset of CU as a continuous variable (Behrendt et al., 2012; Ellickson, D'Amico, Collins, & Klein, 2005; Kirisci et al., 2013; Marmorstein, White, Loeber, & Stouthamer-Loeber, 2010; Rioux et al., 2018), while others categorized it as a discrete variable, either dichotomous or nominal. These categories defined early age of onset of CU using various age thresholds: $\leq$ 12 years old (Sittner, Hautala, & Walls, 2021), $\leq$ 13 years old (Griffin, Bang, & Botvin, 2010; Taylor et al., 2017), $\leq$ 14 years old (Behrendt, Wittchen, Höfler, Lieb, & Beesdo, 2009; Buu et al., 2014, 2015), $\leq$ 15 years old (Kandel & Chen, 2000; Pocuca et al., 2023; Scholes-Balog, Hemphill, Evans-Whipp, Toumbourou, & Patton, 2016; Windle & Windle, 2012), and $\leq$ 16 years old (Swift, Coffey, Carlin, Degenhardt, & Patton, 2008). See Table 1 for a detailed summary for each study.

3.4. Association between age of cannabis use onset and subsequent substance use problems

3.4.1. Cannabis use problems

Among the six studies examining cannabis use disorder (CUD) as an outcome, all found a significant association between early age of CU onset and CUD (Behrendt et al., 2009, 2012; Kirisci et al., 2013; Sittner et al., 2021; Swift et al., 2008; Windle & Windle, 2012). Across all studies, whether controlling for individual, social, or SU-related covariates (e.g., most studies controlled for CU frequency), the association between age of CU onset and CUD remained significant. No covariate (e.g., externalizing problems, parental SU) appeared to account for the association between age of CU onset and CUD. Behrendt et al. (2009, 2012) and Kirisci et al. (2013) demonstrated that later CU onset was associated with lower risk of developing CUD, with hazard ratios reported as low as 0.77 (e.g., Behrendt et al., 2012). Similarly, individuals with early CU onset had the highest likelihood of developing CUD (Sittner et al., 2021; Swift et al., 2008), with individuals with CU onset $<$ 16 years having a threefold higher risk of later CUD, than people who initiate CU after 16 years (Swift et al., 2008).

Five studies tested the relationship between early CU onset and subsequent negative CU consequences, encompassing missed school/work, legal issues (e.g., police detention), violence, antisocial behavior, delinquency, and attention or memory deficits. Initially, all studies reported that an earlier age of CU onset was associated with higher negative CU consequences, even after controlling for psychiatric and psychological covariates such as behavioral deviance and antisocial behavior (Ellickson et al., 2005; Kandel & Chen, 2000; Marmorstein et al., 2010; Pocuca et al., 2023; Scholes-Balog et al., 2016). Pocuca et al. (2023) also found that this association remained when controlling for individual (i.e., sex, prenatal alcohol exposure, living independently, currently studying, currently employed) and social (i.e., socioeconomic status, family composition, mother's age) covariates. However, when social anxiety was included as a covariate, Marmorstein et al. (2010) found that the association between age of CU onset and later negative CU consequences became non-significant (odds ratio (OR) = 0.88). The influence of controlling for CU frequency on the association between CU onset and subsequent negative CU consequences differed between the three studies that included this covariate. Namely, in Ellickson et al. (2005), a previously significant association between age of CU onset and later CU consequences (β = -0.015) became non-significant (β = 0.017) upon adding CU frequency in grade 10 as a covariate (β = 0.041). It is

Table 1
Summary of characteristics and results from studies included in the systematic review.

Authors	Sample size and characteristics	Measurement times and ages	Measurements	Covariates and key analytical features	Results	Risk of bias
Behrendt et al., 2009 (Germany)	**N = 3021**	**W1:** 1995. Aged 14–24. **W2:** 1996/97[a] Aged 15–18 **Only for participants aged 14–17 years at W1.* **W3:** 1998/99[a]. Aged 16–19. **W4:** 2003/04[a]. Aged 21–34.	**Outcome:** Cannabis abuse and dependence assessed with DIA-X/M−CIDI section for medication and illicit SU. **Independent variable:** Age of onset measured with DIA-X/M−CIDI, with early onset defined < 14 years. Assessed at each timepoint. Minimum age of onset was retained in analyses when there were discrepancies between timepoints.	**Covariates:** frequency of Alcohol, nicotine, cannabis, and other illicit substance use prior to onset of CUD. **Analyses:** Cox regression. Analyses were stratified by age and sex	− Unadjusted: Early onset cannabis use was associated with elevated risk of cannabis abuse and cannabis dependence. − Analyses adjusted for alcohol, nicotine and other illicit substance use: No difference in results from unadjusted analyses.	Some concerns
Behrendt et al., 2012 (Germany)	**N = 3021** − 50 % 14–15 years − 49 % Women −60 % Middle Class *Same sample as that used in Behrendt et al. (2009) above.	**W1:** 1995. Aged 14–24. **W2:** 1996/97[a] Aged 15–18. **Only for participants aged 14–17 years at W1.* **W3:** 1998/99[a]. Aged 16–19. **W4:** 2003/04[a]. Aged 21–34.	**Outcome:** Cannabis use disorder assessed with DIA-X/M−CIDI section for medication and illicit SU. **Independent variable:** Age of CU onset (continuous).	**Covariates:** Age at onset of alcohol use and nicotine use; externalizing disorders; parental alcohol or illegal substance dependence **Analyses:** Cox regression	Younger age at CU onset was associated with a higher CUD-risk.	Some concerns
Buu et al., 2014 (USA)	**N = 160 female-male sibling pairs** − Sample was collected by way of the father's drunk driving conviction OR others' families by the same neighborhood − Consisting of a male target child and his female sibling nearest in age − 72.5 % families had at least one parent with AUD diagnosis	W1: Baseline assessment (ages 3–5) W2: 3y post baseline. (ages 6–8) W3: 6y post baseline (ages 9–11) W4: 9y post baseline (ages 12–14) W5: 12y post baseline (ages 15–17) W6: 15y post baseline (ages 18–20) W7: 18y post baseline (ages 21–23)	**Outcome:** Alcohol Use Disorder: diagnosis by doctoral level clinical psychologist using DIS (T6 & T7) and DISC (T3-T5) to assess for AUD (DSM-IV). Alcohol related problems such as losing friends and getting a ticket for drunk driving, assessed by the Drinking and Drug History Questionnaire (DDHQ; T3-T7). **Independent variable:** Early onset cannabis use (defined as ≤ 14y old) assessed with the Health and Daily Living Questionnaire (HDLQ). Assessed at each wave. Age of onset reported at the earliest wave was retained in case of discrepancies.	**Covariates:** Age; sex; frequency of cannabis use; alcohol (early onset (≤14 years), frequency, related-problems); nicotine (early onset (≤14 years), frequency, related-problems) **Analyses:** Kernel smoothing method was used to estimate the hazard function	Early-onset cannabis use was not significantly associated with alcohol problems or alcohol use disorder.	High risk of bias
Buu et al., 2015 (USA)	**N = 850** − 9th grade GPA 3.0 and below in 4 public high schools in an economically disadvantaged school district (high risk youth) − 50 % males − 80 % Black; 17 % White; 3 % Black/White	Duration of the study: roughly 8 years W1: Baseline (1994) (14 years old) W2: 1995 W3: 1996 W4: 1997 W5: 1999 W6: 2000 W7: 2001 W8: 2002	**Outcome:** Heavy drinking defined as the mean score of two items: (1) "Think back over the LAST TWO WEEKS. How many times have you had five or more drinks in a row?" [0 = none to 5 = ≥10]; and (2) "When you drink alcoholic beverages, how often do you drink enough to feel pretty high?" [0 = never to 4 = on nearly all of the occasions]. **Independent variables:** Early onset cannabis use (defined as ≤ 14 years), assessed via the question: "How old were you when you first used marijuana (grass, pot, weed)?", assessed at waves 1 to 3. First response for age of onset variable was used in the present study. Later-onset cannabis use (any cannabis use during the	**Covariates:** Age; sex; frequency of cannabis use; nicotine (early onset (≤13 years), frequency, quantity); alcohol (age of onset (≤13 years), heavy drinking) **Analyses:** Linear mixed effects regression	Adjusting for covariates, both early and later onset cannabis use were associated with increased heavy drinking compared to non-users.	High risk of bias

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Table 1 (*continued*)

Authors	Sample size and characteristics	Measurement times and ages	Measurements	Covariates and key analytical features	Results	Risk of bias
			study period) was also included in analyses.			
Ellickson et al., 2005 (USA)	**N = 2079** youth who reported using cannabis during at least one wave. 47 % female − 66 % White, 11 % African American, 13 % Hispanic, 5 % Asian, and 5 % other race or ethnicity. − Project ALERT	W1: 1984 (13 years[a]) W2: 1985 (14 years[a]) W3: 1986 (15 years[a]) W4: 1987 (16 years[a]) W4: 1989 (17 years[a])	**Outcome variable:** Negative CU consequences at 18 years (e.g., missed school/ work; did something they later felt sorry for; got into trouble/ arrested; trouble concentrating). **Independent variable:** Past-year cannabis use was assessed at each wave. Continuous variable coded as: 1 for ≤ initiation in grade seven; 2 = initiation in grade eight; 3 for initiation in grade nine; 4 for initiation in grade ten; and 6 for initiation between grades 11 and 12.	**Covariates:** Model 1: social influence; bonding; problem behavior; and demographic variables all assessed in grade 7 (i.e., gender; age; race; parental education; presence of an older sibling; number of schools attended; grade point average; parent/ peer interaction; school grade repetition; behavioral deviance and rebellious attitude; intact family; alcohol; cigarette and cannabis use frequency). Model 2: All covariates in Model 1 + CU frequency in grade 10. **Analyses:** Linear regression	− **Model 1:** Age of CU onset is negatively associated with CU consequences. − **Model 2:** Age of CU onset is not significantly associated with CU consequences.	Low risk of bias
Griffin et al., 2010 (USA)	**N = 621** − 47 % Male − 91 % White − Mostly middle class, two-parent families	W1: Baseline (1986) (7th grade/ mean age 13) W2: 1y post-baseline (1987) W3: 2y post-baseline (1988) W4: 3y post-baseline (1989) W5: 5y post-baseline (1991) W6: 12y post-baseline (1998) (54 % retention rate)	**Outcome:** Alcohol or drug-related problems in young adulthood (i.e., employment, relationship, legal issues, physical harm). **Independent variables:** Age of initiation derived from a question asking whether participants had ever smoked marijuana (yes or no) at each wave. This was converted to a dichotomous variable indicating CU onset prior to high school (no/yes).	**Covariates:** Alcohol (frequency & age of initiation); sex; income; marital status. **Analyses:** Generalized estimating equations (GEE) accounting for clustering of data within schools	Males who initiated CU prior to high school were more likely to experience occupational, relationship, or overall alcohol or drug-related harms in young adulthood. This association was not present for females.	High risk of bias
Kandel & Chen, 2000 (USA)	**N = 708** − 51 % Male − Adults who ever used cannabis at least 10 times − Enrolled in the New York State Follow-Up Cohort, recruited from New York State public high schools	W1: 1971 (15–16 years) W2: 1980 (24–25 years) W3: 1984 (28–29 years) W4: 1990 (34–35 years)	**Outcome:** Drug Use History: −Number of cannabis and drug related problems (1980–90; i.e., health, school and/or job-related, mental health, legal problems). −last year alcohol dependence (according to DSM-IV criteria; 1990) −Feeling addicted to drugs (by 1990) −Being treated for a drug problem (by 1990) **Independent variables:** Assessed at each wave among participants who had used cannabis ≥ 10 times. Used alongside chronicity of heavy use and persistence of use to derive 4 clusters: (1) early-heavy (mean onset ~ 15 years); (2) early-light (mean onset ~ 15 years); (3) mid-heavy (mean onset ~ 16 years); (4) late-light (mean onset ~ 20 years).	**Covariates:** None. **Analyses:** ANOVA	**Early-Heavy CU cluster:** − Significantly greater number of cannabis-related problems compared to early-light, late-light, and mid-heavy groups. − Significantly greater number of other drug-related problems compared to early-light, late-light, and mid-heavy groups. − Significantly more likely to have alcohol dependence compared to early-light and late-light groups. Did not significantly differ to the mid-heavy group. − Significantly more likely to feel addicted to drugs compared to early-light, late-light, and mid-heavy groups. − Significantly more likely to be treated for drug problems compared to other early-light, late-light, and mid-heavy groups. **Early-light cluster:** − Significantly lower number of cannabis-related problems compared to the mid-heavy cluster. Not significantly different from the late-light cluster. − Significantly lower number of other drug-related problems compared to mid-heavy cluster, but	Very high risk of bias

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Table 1 (*continued*)

Authors	Sample size and characteristics	Measurement times and ages	Measurements	Covariates and key analytical features	Results	Risk of bias
					greater number of problems compared to the late-light cluster. – Significantly less likely to have alcohol dependence compared to mid-heavy group. Did not significantly different from the late-light group. – Significantly less likely to feel addicted to drugs compared to mid-heavy group. Did not significantly different from the late-light group. – Significantly more likely to be treated for drug problems compared to the late-light group. Did not significantly different from the mid-heavy group. **Mid-heavy CU cluster:** – Significantly greater number of cannabis and other drug-related problems, compared to the late-light cluster. – Significantly more likely to be dependent on alcohol, feel addicted to drugs, and be treated for a drug problem, compared to the late-light cluster.	
Kirisci et al., 2013 (USA)	**N = 339** – 75 % Male – 71 % White; 29 % Black – Participants had to have at least one experience with both alcohol and cannabis following baseline. – Combination of participants who did and did not have a father with a substance use disorder	Duration: 10 years roughly T1: Baseline (10-12y) T2: 0-2y post-baseline (when 12y) T3: 2-4y post-baseline T4: 5-7y post-baseline T5:8-10y post-baseline	**Outcome:** CUD/AUD: Assessed at each wave using the Kiddie-Schedule for affective Disorders and Schizophrenia (K-SADS) between ages 10 to 16 and the structured Clinical Interview (DSM-III-R) from 16 to 22 years. **Independent variables:** Age of CU onset: Lifetime Drug Use History survey collected at each follow-up evaluation.	**Covariates:** Sex; Transmissible Liability Index (quantifies the component of SUD liability correlating across generations); age of alcohol use onset. **Analyses:** Multiple logistic regression (including mediation analyses).	– Age at the time of first CU predicts CUD. – Age at the time of first cannabis use mediates the association between the Transmissible Liability Index and CUD. – Age at the time of first cannabis use predicts AUD and mediates the association between the Transmissible Liability Index and AUD.	High risk of bias
Marmorstein et al., 2010 (USA)	**N = 503** – All male sample – 56 % African American (rest were predominantly Caucasian) – Pittsburgh Youth Study	Duration: 12 years W1: Baseline (6.2 years) Roughly 17 Waves (12 years post-baseline)	**Outcome:** Age at first substance use problem. Assessed at age 20 using the Diagnostic Interview Schedule (DIS). **Independent variables:** Age at first cannabis use assessed via interviews* *It is not clear at what timepoint this information was obtained	**Covariates:** Age; generalized anxiety (model 1 only); social anxiety (model 2 only); delinquency; time since cannabis use onset. **Analyses:** Survival analyses.	– Model 1: Younger age at first cannabis use was associated with greater risk for cannabis use problems the following year. – Model 2: Younger age at first cannabis use was not significantly associated with later cannabis use problems after controlling for social anxiety.	Very high risk of bias
Pocuca et al., 2023 (Canada)	**N = 794** – 56 % female – Youth from the Québec Longitudinal Study of Child Development (stratified random sample of youth born between 1997 and 1998) who reported lifetime cannabis use by age 21.	W1: 12 years (2010) W2: 13 years (2012) W3: 15 years (2013) W4: 17 years (2015) W5: 21 years (2019)	**Outcome:** Problem cannabis use assessed at 21 years using the Cannabis Abuse Screening Test. **Independent variables:** Early onset cannabis use (≤15 years), assessed at 12, 13, and 15 years. Any use reported at any of these timepoints was considered early onset.	**Covariates:** Sex assigned at birth; prenatal alcohol exposure (reported at age 5 months by mother); socioeconomic status (at age 5 months); family composition (i.e., intact yes/ no; at age 12); mother's age; independent living (at age 21); currently studying (at age 21); employed (at age 21). **Analyses:** Multivariate linear regressions.	– Model 1: Youth with early onset cannabis use (≤15 years) had greater cannabis use frequency and cannabis use problems at 21 years, compared to youth with later adolescent-onset cannabis use (16–18 years). – Model 2: Youth with early onset cannabis use (≤15 years) had greater cannabis use frequency and cannabis use problems at 21 years, compared to youth with adult-onset cannabis use (≥19 years).	Some concerns

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Table 1 (*continued*)

Authors	Sample size and characteristics	Measurement times and ages	Measurements	Covariates and key analytical features	Results	Risk of bias
Rioux et al., 2018 (Canada)	**N = 1030** – Boys with low socioeconomic status (SES) – Montreal Longitudinal and Experimental Study	W1: 6 years (1984) W2: 12 years (1990) W3: 13 years (1991) W4: 14 years (1992) W5: 15 years (1993) W6: 16 years (1994) W7: 17 years (1995) W8: 20 years (1998) W9: 28 years (2006)	**Outcome:** Drug abuse symptoms. Measured by a scale adapted from Problem Severity scale of the Personal Experience Screening Questionnaire. **Independent variable:** Past 6-month cannabis use assessed from 13 to 17 years. Age of onset derived from the first time the respondent reported using cannabis.	**Covariates:** Paternal alcohol use problems; family adversity at 6 years; academic achievement at 12 years; verbal IQ at 13 years; impulsivity at 13 years; deviant friends at 13 years; delinquency at 12 years; parental supervision at 12 years; substance use frequency at 17 years (cigarette, alcohol, marijuana); high school graduation; delinquency at 20 years. **Analyses:** Logistic regressions.	– No covariates: Likelihood of drug abuse symptoms at 28 years were reduced by 31 % for each year of delayed CU onset. – Controlling for early common risk factors: No change in the association between age of CU onset and drug abuse symptoms (results as per the above). – Controlling for substance use frequency at 17 years: No significant association between age of CU onset and drug abuse symptoms at 28 years. – Controlling for early adulthood risk factors: No significant association between age of CU onset and drug abuse symptoms at 28 years. – Controlling only for cannabis and alcohol use frequency at 17 years (i.e., covariates significantly associated with drug abuse problems at 28 years): CU onset by 13 years and CU onset by 14 years were associated with increased odds of drug abuse symptoms at 28 years. – Age of CU onset was indirectly associated with drug abuse at 28 years via its association with CU at 17 years and other drug use frequency at 17 years.	Some concerns
Scholes-Balog et al., 2016 (Australia)	**N = 852** – 53 % Female – Australian cohort from the International Youth Development Study (IYDS).	W1: 2003 (Mean age = 11.94 years) W2: 2004 (12.95 years) W3: 2006 (15.15 years) W4: 2007 (15.99 years) W5: 2008 (17.00 years) W6: 2010 (19.3 years) W7: 2012 (21.05 years)	**Outcomes:** Assessed during the final wave. Alcohol use problems (assessed using the AUDIT); past year cannabis/alcohol harms ["In the past 12 months, how often has your use caused you to get into arguments with your family?"]; past year other illicit drug use ["In the past year (12 months), on how many occasions (if any) have you used [illicit drug]?"] **Independent variable:** Early onset CU (≤15 years) derived from a latent class growth analysis using the following item assessed at each timepoint: "In the past year (12 months), on how many occasions (if any) have you used marijuana (pot, weed, grass)?" Each wave of data collection was based on an Australian adaptation of the Communities That Care youth survey.	**Covariates:** Sex; parent education; school grades at 12 years; antisocial behavior at 12 years; maximum frequency of alcohol, cigarette, and other illicit drug use at ages 12–19 years. **Analyses:** ANCOVA comparing the early onset CU group, abstinent group, and late onset occasional CU group (i.e., onset ≤ 17 years).	– Past year cannabis harms: The early onset group had significantly greater CU harms. – Alcohol use problems: The three CU groups did not significantly differ from each other. – Past year alcohol harms: The early onset group had significantly greater alcohol harms. – Past year other illicit drug use: The early onset CU group did not significantly differ to the abstinent and late-onset occasional group.	Some concerns
Sittner et al., 2021 (USA/ Canada)	**N = 735** – 57 % Female (W9) – 28 % did not graduate high school (W9)	W1: 2002/03 W2: 2003/04 W3: 2004/05 W4: 2005/06	**Outcome:** Lifetime and past 12-month alcohol and cannabis use disorder at W9. Assessed using the	**Covariates:** Sex. **Analyses:** Chi-square test comparing the substance use profiles derived from	– Lifetime alcohol use disorder: No significant difference between the four groups.	Very high risk of bias

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Table 1 (*continued*)

Authors	Sample size and characteristics	Measurement times and ages	Measurements	Covariates and key analytical features	Results	Risk of bias
	− 43 % Employed full-time (W9) − Indigenous adolescents from eight reserves/ reservations in the US and Canada	W5: 2006/07 W6: 2007/08 W7: 2008/09 W8: 2009/10 W9: 2017/18 (24 to 29 years)	Diagnostic Interview Schedule for Children-Revised (DISC-R) in W1–W8, and using the World Mental Health Survey Initiative version of the World Health Organization Composite International Diagnostic Interview (CIDI) in wave 9. **Independent variables:** Age of onset. Alcohol and CU frequency assessed at 5 timepoints across adolescence. Items used to inform group-based trajectory modelling which resulted in an early-onset combined alcohol and CU profile (onset ≤ 12 years).	group-based trajectory modelling (i.e., non-use; mid-onset alcohol-only; mid-onset combined alcohol and cannabis; early-onset combined).	− Past year alcohol use disorder: Adolescents belonging to the non-use alcohol and CU profile across adolescence had a significantly lower prevalence of lifetime AUD than the other three profiles. − Lifetime cannabis use disorder: No significant difference between the four groups. − Past year cannabis use disorder: Youth in the early-onset combined adolescent alcohol and CU profile had the highest rate of lifetime CU disorder compared to the other profiles.	
Swift et al., 2008 (Australia)	**N = 1943** − Two randomly-selected classes from a state-wide sample (Victoria) of 44 catholic and independent private schools. One class entered the study at W1, while the second class entered the study at W2. −Female: 54 % −School in a metropolitan area: 74 %	W1: 1992 (Mean age = 14.9 years). First entry. W2: 1993 (Mean age = 15.5 years). Second entry. W3: 1993 (Mean age = 15.9 years). W4: 1994 (Mean age = 16.4 years). W5: 1994 (Mean age = 16.8 years). W6: 1995 (Mean age = 17.4 years). W7: 1998 (Mean age = 20.7 years). W8: 2001/03 (Mean age = 24.1 years).	**Outcome:** Cannabis dependance at W8 (according to DSM-IV criteria). Assessed using the computerized CIDI. **Independent variables:** Early CU onset defined as first use between W1-W6 (<16 years). Derived from measure of past 6-month cannabis use assessed at each wave.	**Covariates:** Sex; parental divorce/ separation by W6; parental regular smoking (at least one). **Analyses:** Logistic regression analyses comparing early CU onset to later CU onset (i.e., W4-W6). Restricted to participants who completed W8. Multiple imputation used to handle 13 missing observations.	Early CU onset associated with higher CU dependence at W8, compared to later CU onset.	High risk of bias
Taylor et al., 2017 (UK)	**N = 5315** − Participants required to have completed three or more measures of CU across the study period. − Avon Longitudinal Study of Parents and Children (ALSPAC).	W1: 2004–2006 (13 years) W2: (14 years) W3: (15 years) W4: (16 years) W5: (17 years) W6: (18 years) W7: 2012/13 (median age = 20.11)	**Outcomes:** Problem alcohol use (i.e., score of ≥ 16 on the Alcohol Use Disorders Identification Test). Nicotine dependence (Fagerström test). **Independent variables:** Early-onset (<13 years) occasional CU and regular CU (onset ≤ 15 years) trajectories derived from a longitudinal latent class analysis of CU assessed from W1 to W6 (i.e., non-use, occasional (<weekly), frequent (≥weekly) use). Comparison classes include non-use and late-onset-occasional use.	**Covariates:** Adjusted Model 1: Sex; household income; housing tenure (mortgaged/owned, rented, subsidized rented); home overcrowding (>1 person in room); sibling order; maternal education. Adjusted Model 2: Model 1 covariates in addition to: maternal CU when participant aged 9 years; maternal alcohol use, binge drinking, and cigarette use when participant aged 12 years. Adjusted Model 3: Model 1 and 2 covariates in addition to: Child conduct problems at age 11 years. Adjusted Model 4: Model 1, 2, and 3 covariates in addition to: Participant smoking and drinking at 12 years, 10 months **Analyses:** Logistic regression (unadjusted model and four models adjusting for covariates).	**Early-onset (<13 years) occasional:** −Significantly more likely to have harmful alcohol consumption at W7 compared to non-use trajectory in all 5 models. − Significantly more likely to have harmful alcohol consumption at W7 compared to late-onset occasional trajectory in adjusted model 3. Other models were non-significant. − Significantly less likely to have harmful alcohol consumption at W7 compared to regular CU trajectory in adjusted model 1. Other models were non-significant. − Significantly more likely to have nicotine dependence at W7 compared to non-use trajectory in the unadjusted model. Other models were non-significant. − Not significantly different from the late-onset occasional and regular CU trajectories on nicotine dependence, in any of the models.	Some concerns

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Table 1 (*continued*)

Authors	Sample size and characteristics	Measurement times and ages	Measurements	Covariates and key analytical features	Results	Risk of bias
					Regular CU (onset ≤ 15 years): −Significantly more likely to have harmful alcohol consumption at W7 compared to non-use trajectory in unadjusted model. No significant difference in adjusted model 4. −Not significantly different from the late-onset occasional trajectory on harmful alcohol use at W7, in any of the models. −Significantly more likely to have nicotine dependence at W7 compared to non-use trajectory in all 5 models. −Significantly more likely to have nicotine dependence at W7 compared to late-onset occasional trajectory in all 5 models.	
Windle et Windle, 2012 (USA)	**N = 671** − Roughly 50 % female − 98 % White − Recruited from three public high schools − Lives Across Time (LAT) study.	W1: 1988 (mean age = 15.54, SD = 0.66) W2: 1988/89[a] W3: 1989/90[a] W4: 1990/91[a]* W5: 1996/97[a] (mean age = 23.5 years). W6: ~2001/02[a] (mean age 28.7) *W1 to W4 were conducted at 6-month intervals.	**Outcome:** Alcohol, cannabis, and cocaine-use disorders in young adulthood, assessed by the World Health Organization Composite International Diagnostic Interview (WHO-CIDI). Young adult tobacco dependence, assessed by the 10-item Tobacco Dependence Screener. **Independent variables:** Early CU onset (≤15 years) assessed at W2.	**Covariates:** Sex; early onset alcohol, cigarette and cocaine/crack use; police contact; property damage; stealing; starting fights; truancy and running away from home. **Analyses:** Structural Equation Models.	Early onset CU was significantly associated with CU disorder symptoms and tobacco dependence symptoms, but not alcohol or cocaine-use disorders.	Some concerns

Notes [a] Estimated year (not provided by the cited study or another paper describing the parent study).

noteworthy that in this study, the beta coefficients are very small relative to those reported in other studies. Similarly, the significant association found in Kandel and Chen (2000) was limited to a cluster consisting of people with early age of CU onset who continued to use CU heavily (all members exhibited near-daily use), rather than those with early age of CU onset who used cannabis less frequently (with 44 % exhibiting near-daily use). In contrast, Scholes-Balog et al. (2016) did not find that including CU frequency influenced the association between early CU onset and later negative CU consequences. However, the authors highlighted that their sample reported very low CU frequency, with the majority being abstinent, thus advising careful interpretation of the result regarding this covariate.

3.4.2. *Alcohol use problems*

Six studies examined the association between early age of CU onset and alcohol use disorder (AUD). One study reported that people with later age of CU onset exhibited a significant reduced risk of AUD (OR = 0.89; Kirisci et al., 2013). Another study reported a significantly increased risk of problem AU for people with both early (OR = 5.03) and late (OR = 2.59) age of CU onset, compared to people with no CU (Taylor et al., 2017). However, individuals with early age of CU onset did not differ significantly from those with late-onset CU. In contrast, the remaining four studies failed to find a significant association between age of CU onset and later problem AU (Buu et al., 2014; Kandel & Chen, 2000; Sittner et al., 2021; Windle & Windle, 2012). One potential explanation for the mixed results may be due to differences between studies in included covariates, particularly SU-related factors. This is supported by Taylor et al. (2017), who found that although individuals with early CU onset were significantly more likely to have problem AU compared to those with late-onset CU (OR = 2.48), this difference ceased to be significant when controlling for tobacco and alcohol use (AU) in early adolescence (see Table 1 for details on covariates and various models). Furthermore, while CU frequency did not change the association in Taylor et al. (2017), it seemed to be more strongly linked to AUD ($\beta = 0.59$) than CU onset age in Buu et al. (2014). Similarly, Kandel and Chen (2000) found that the cluster of individuals who heavily use CU, regardless of age of CU onset, had the highest risk of developing later problem AU.

One study examined the association between age of CU onset and heavy AU (Buu, Dabrowska, Heinze, Hsieh, & Zimmerman, 2015). Namely, Buu et al. (2015) found that any CU, regardless of onset timing (early: $\beta = 0.22$ or late: $\beta = 0.18$), was associated with increased heavy drinking, controlling for individual, social, and SU-related covariates. The authors also found that higher levels of CU frequency were associated with subsequent increased involvement in heavy drinking ($\beta = 0.27$).

Two studies investigated the relationship between early age of CU onset and negative AU consequences, such as drunk driving, going to work while drunk, or legal problems due to alcohol. One study found a significant association between early age of CU onset and later negative alcohol consequences (Scholes-Balog et al., 2016), whereas the other did not (Buu et al., 2014). While both studies controlled for individual, social, and SU-related covariates, Buu et al. (2014) identified CU frequency as a significant covariate contributing to negative AU

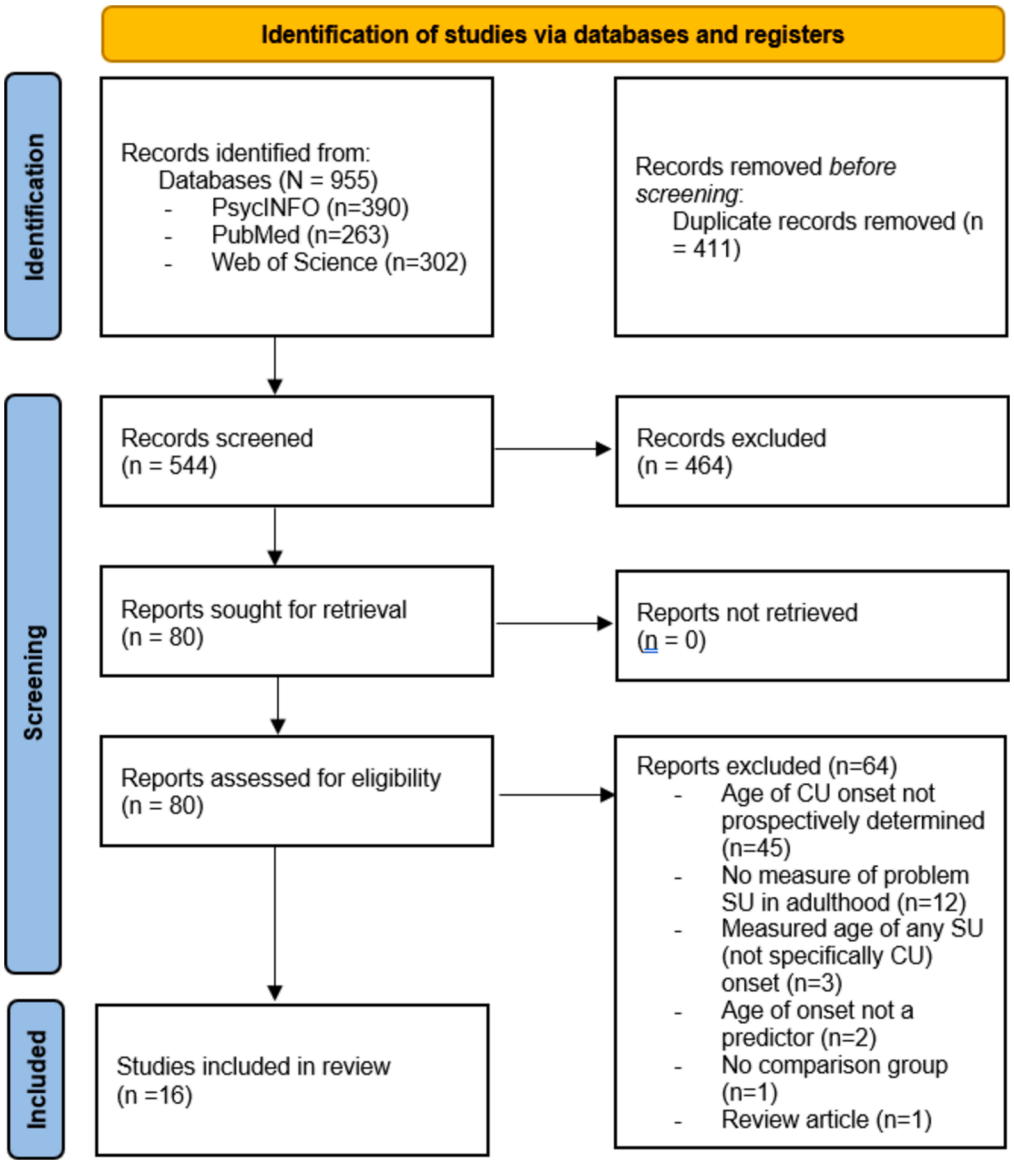

Fig. 1. PRISMA Flowchart illustrating the identification and screening process of articles.

consequences ($\beta = 0.55$).

3.4.3. Nicotine use problems

Two studies investigated the relationship between age of CU onset and NU problems, both finding a significant association with NU dependence (Taylor et al., 2017; Windle & Windle, 2012). Notably, both studies controlled for individual and SU-related covariates, with Taylor et al. (2017) additionally controlling for social covariates. The association between age of CU onset and later NU problems does not appear to be influenced by such covariates. Nonetheless, it is worth mentioning that Taylor et al. (2017) showed that people with both early CU onset (<13 years) who reported occasional CU (i.e., less than once per week) and individuals with regular CU (i.e., once a week or more; <15 years) had a higher prevalence of NU dependence (OR = 12.1 and OR = 37.2, respectively). However, there is no significant difference between early CU onset and late CU onset for later NU dependence.

3.4.4. Other illicit substance use problems

Two studies examined the association between early age of CU onset and other SU problems. In the sole study investigating the association between early age of CU onset and later cocaine use disorder, Windle and Windle (2012) found no significant association between these variables. In contrast, Kandel and Chen (2000), who investigated problems with drugs other than cannabis (e.g., cocaine, heroin, psychedelics), found early age of CU onset was significantly associated with later problems, but solely among people who used cannabis heavily.

3.4.5. Composite measures of substance use problems

The remaining two studies by Griffin et al. (2010) and Rioux et al. (2018) examined later SU problems broadly (i.e., without focusing on a specific substance). That is, Griffin et al. (2010) assessed negative SU consequences by encompassing adverse outcomes from either AU or CU, while Rioux et al. (2018) focused on negative SU consequences excluding AU and NU. Both studies controlled for individual, social, and SU-related covariates. Griffin et al. (2010) identified a significant association between early CU and AU onset, and subsequent SU-related occupational ($\beta = 0.105$), relationship ($\beta = 0.188$), and legal problems ($\beta = 0.138$) during adulthood. Rioux et al. (2018) showed that young people with early CU onset (< 15 years) had a higher risk of developing negative SU consequences (OR for onset by 14 years = 1.97 and for onset by 13 years = 3.44). Further, Rioux et al. (2018) found that the likelihood of negative SU consequences was higher among people with

frequent CU (>20 times in the last year), compared to their peers (72 % vs. 40 %; respectively).

3.5. Sex differences

While 11 studies included sex as a covariate, only five reported sex differences in CU rates and onset, and only one reported sex differences in the association between age of CU onset and later SU problems (Buu et al., 2014, 2015; Griffin et al., 2010; Kandel & Chen, 2000; Sittner et al., 2021). While some studies reported no sex differences in CU onset (Buu et al., 2015; Griffin et al., 2010), two studies found that females initiated CU earlier than males, but as adolescence progressed, CU among males equalled or surpassed those among females (Buu et al., 2014; Sittner et al., 2021). In contrast, Kandel and Chen (2000) found males initiated CU earlier than females, but only among the heavy use cluster. The only study reporting sex differences in the association between age of CU onset and later SU problems found risk of negative CU and AU consequences was 2-to-3 times higher in young adult males, compared to young adult females with early CU onset (Griffin et al., 2010).

4. Discussion

We identified 16 peer-reviewed prospective studies examining the association of age of CU onset and later SU problems. Overall, the findings consistently identified an association between early CU onset and CUD, despite variations in the covariates that were controlled for in these studies (Behrendt et al., 2009, 2012; Kirisci et al., 2013; Sittner et al., 2021; Swift et al., 2008; Windle & Windle, 2012). These covariates included externalizing behaviors, conduct disorders, parental SU, early onset of alcohol and nicotine use, and SU frequency. These results suggest that early CU onset may act as a risk factor for the development of CUD, rather than merely serving as a risk marker related to other underlying factors. In contrast, the associations between age of CU onset and CU negative consequences or other SU problems were mixed, potentially due to variations between studies in controlling for key covariates. One important covariate influencing the relationship between age of CU onset and SU problems across various substances was CU frequency. For instance, many of the studies that controlled for CU frequency in the association between age of CU onset and later SU problems, either failed to find a significant association (Buu et al., 2014; Ellickson et al., 2005; Kandel & Chen, 2000), or found a significantly weaker association (Rioux et al., 2018). Furthermore, one study found that age of CU onset was linked to negative SU consequences only among individuals with high CU frequency (Kandel & Chen, 2000). In sum, it appears that SU consequences, such as academic or occupational difficulties and legal issues (e.g., police detention), may be more strongly associated with CU frequency rather than age of CU onset. This finding aligns with previous research, which has demonstrated associations between CU frequency and academic challenges and unemployment (see Castellanos-Ryan, Morin, Rioux, London-Nadeau, & Leblond, 2022 for a review).

AU frequency may also play a significant role in the association between age of CU onset and later SU problems, particularly AUD. Namely, while Kirisci et al. (2013) identified a significant association between age of CU onset and later AUD, they did not account for adolescent AU frequency, contrary to most studies that did not find a significant association (Buu et al., 2014; Kandel & Chen, 2000; Sittner et al., 2021). It is important to note that CU during adolescence often co-occurs with the use of other substances, which plays a significant role in the development of SU problems. For instance, the early age of onset and the frequency of AU during adolescence have been identified as strong predictors of later AUD (Callinan, Livingston, Dietze, Gmel, & Room, 2022; Raninen et al., 2024). Therefore, controlling for AU is essential when examining the relationship between the age of CU onset and later AUD. Given the well-established co-occurrence of CU and AU during adolescence (Yurasek, Aston, & Metrik, 2017), the observed association between the age of CU onset and AUD may be partially explained by the lack of control for AU frequency in previous studies.

Both Buu et al. (2015) and Taylor et al. (2017) observed that both early and later age of CU onset were associated with heavy drinking and NU, respectively. The results of Buu et al., 2015 suggest that any form of CU, regardless of onset timing and CU frequency is linked to a higher likelihood of heavy drinking. However, the results of Taylor et al. (2017) point to a significant effect of early-onset occasional and regular CU on later NU dependence. The relationship between age of CU onset and NU dependence may partly be attributed to the common practice of combining cannabis with tobacco. Specifically, smoking cannabis joints with tobacco significantly influences the initiation of daily cigarette use among young adults (Becker, Schaub, Gmel, & Haug, 2015).

This systematic review has several strengths including the use of a comprehensive search strategy and inclusion of diverse SU outcomes. This approach allowed a broad exploration of the association between early onset CU and subsequent negative SU consequences beyond just CU. The presents study also included a thorough assessment of the risk of bias for each study, providing valuable insights into the validity and reliability of the results of included studies. Nonetheless, this systematic review has some limitations. First, only a few studies explored the link between age of CU onset and SU problems other than cannabis and alcohol (e.g., nicotine, cocaine) and thus, these associations should be approached with caution. One limitation of this systematic review is its reliance on a relatively small number of studies, 50 % of which had a high or very-high risk of bias, according to the ROBINS-I assessment. These findings highlight the need for additional, methodologically-robust longitudinal studies. Other limitations are primarily related to the considerable heterogeneity observed among the included studies, particularly at a methodological level. These studies differ with regards to: (1) definition of age of CU onset; (2) sample size; (3) control variables; and (4) how later SU problems were assessed. These discrepancies pose a challenge when attempting to compare study findings. Another limitation is the inadequate reporting of missing data in the reviewed studies. Only five studies provided details regarding the extent of missing data and the strategies employed to address them. According to the ROBINS-I, the reporting the amount of missing data and how it was handled is crucial, as both the presence of missing data and the techniques used to handle it can introduce biases (Newman, 2014; Sterne et al., 2016). Future research should endeavour to explicitly detail their approach to handling missing data. Finally, only five out of the 16 included studies explicitly reported findings based on sex differences and only one study compared the association between age of CU onset and subsequent SU problems in males and females. The mixed results regarding sex differences may be attributed to variations in study designs, related to sample size, measurement tools, and controlled covariates. Considering the well-established findings of sex differences in SU problems, this limitation should be addressed in future studies. Future research should also include additional CU variables, including potency and mode of consumption as these variables could be linked to CU problems and could significantly enhance the precision of measuring cannabis and cannabinoid exposure (Prince & Conner, 2019). In line with recent advancements in cannabis research, it is important to adopt a standardized measure, such as the “standard THC unit” (Freeman & Lorenzetti, 2020), across studies. This approach would enable more consistent quantification of CU, which is crucial given the role of CU frequency in the development of subsequent problems. However, it is important to acknowledge that the accurate assessment of cannabis potency will mostly be limited to countries where cannabis is legalized, which could pose some challenges for large-scale studies in countries with varying regulations.

5. Conclusion

Although comprehensive examinations are limited, the age of onset

of CU emerges as a potential risk factor for CU-specific problems, particularly CUD, where it remains significant even after controlling for key variables. The findings regarding CU negative consequences varied across studies, depending on the covariates analyzed (e.g., CU frequency, social anxiety). Nevertheless, CU onset may still be a contributing factor to these outcomes. Furthermore, it is noteworthy that the findings suggest that CU frequency plays an important role in increasing the risk of CU negative consequences and potentially other SU problems. These results highlight the importance of considering CU frequency as complementary factor to CU age of onset, especially when evaluating a broad spectrum of SU problems. Future studies should explore common liabilities to provide a more comprehensive understanding of the relationship between the age of CU onset and later SU problems. While the absence of a consistent age of onset in included studies makes it challenging to recommend a guideline for a safe age limit for cannabis consumption, findings support that prevention approaches should aim to delay CU onset as longs as possible, particularly considering the strong association with future CUD. Furthermore, our recommendation for future research emphasizes the need to account for significant confounding factors, including CU frequency.

CRediT authorship contribution statement

Jad Hamaoui: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Nina Pocuca:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Mikaela Ditoma:** Writing – original draft, Methodology, Investigation, Data curation. **Camille Héguy:** Writing – original draft, Investigation, Data curation. **Cléa Simard:** Investigation, Data curation. **Raphael Aubin:** Investigation, Data curation. **Anastasia Lucic:** Investigation, Data curation. **Natalie Castellanos-Ryan:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2025.108259.

Data availability

No data was used for the research described in the article.

References

Agabio, R., Campesi, I., Pisanu, C., Gessa, G. L., & Franconi, F. (2016). Sex differences in substance use disorders: Focus on side effects. *Addiction Biology, 21*(5), 1030–1042. https://doi.org/10.1111/adb.12395

Behrendt, S. (2017). The role of age in the onset and further development of cannabis use disorders. *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment, 138–150*. https://doi.org/10.1016/B978-0-12-800756-3.00016-8

Bears Augustyn, M., Fulco, C. J., Agbeke, D., & Henry, K. L. (2022). The joint development of externalizing and internalizing behaviors in black and Hispanic youth and the link to late adolescent substance use. *Development and Psychopathology, 34*(3), 1144–1162. https://doi.org/10.1017/S0954579420001881

Becker, J., Schaub, M. P., Gmel, G., & Haug, S. (2015). Cannabis use and other predictors of the onset of daily cigarette use in young men: What matters most? Results from a longitudinal study Health behavior, health promotion and society. *BMC Public Health, 15*(1), 1–10. https://doi.org/10.1186/s12889-015-2194-3

Behrendt, S., Beesdo-Baum, K., Höfler, M., Perkonigg, A., Bühringer, G., Lieb, R., & Wittchen, H. U. (2012). The relevance of age at first alcohol and nicotine use for initiation of cannabis use and progression to cannabis use disorders. *Drug and Alcohol Dependence, 123*(1–3), 48–56. https://doi.org/10.1016/j.drugalcdep.2011.10.013

Behrendt, S., Wittchen, H. U., Höfler, M., Lieb, R., & Beesdo, K. (2009). Transitions from first substance use to substance use disorders in adolescence: Is early onset associated with a rapid escalation? *Drug and Alcohol Dependence, 99*(1–3), 68–78. https://doi.org/10.1016/j.drugalcdep.2008.06.014

Buu, A., Dabrowska, A., Heinze, J. E., Hsieh, H.-F., & Zimmerman, M. A. (2015). Gender differences in the developmental trajectories of multiple substance use and the effect of nicotine and marijuana use on heavy drinking in a high-risk sample. *Addictive Behaviors, 50*, 6–12. https://doi.org/10.1016/j.addbeh.2015.06.015

Buu, A., Dabrowska, A., Mygrants, M., Puttler, L. I., Jester, J. M., & Zucker, R. A. (2014). Gender differences in the developmental risk of onset of alcohol, nicotine, and marijuana use and the effects of nicotine and marijuana use on alcohol outcomes. *Journal of Studies on Alcohol and Drugs, 75*(5), 850–858. https://doi.org/10.15288/jsad.2014.75.850

Callinan, S., Livingston, M., Dietze, P., Gmel, G., & Room, R. (2022). Age-based differences in quantity and frequency of consumption when screening for harmful alcohol use. *Addiction, 117*(9), 2431–2437. https://doi.org/10.1111/add.15904

Castellanos-Ryan, N., Morin, É., Rioux, C., London-Nadeau, K., & Leblond, M. (2022). Academic, socioeconomic and interpersonal consequences of cannabis use: A narrative review. *Drugs: Education, Prevention and Policy, 29*(3), 199–217. https://doi.org/10.1080/09687637.2021.1906846

Connor, J. P., Stjepanović, D., Le Foll, B., Hoch, E., Budney, A. J., & Hall, W. D. (2021). Cannabis use and cannabis use disorder. *Nature Reviews Disease Primers, 7*(1), 1–24. https://doi.org/10.1038/s41572-021-00247-4

Davis, C. N., Slutske, W. S., Martin, N. G., Agrawal, A., & Lynskey, M. T. (2019). Identifying subtypes of cannabis users based on simultaneous polysubstance use. *Drug and alcohol dependence, 205*, Article 107696. https://doi.org/10.1016/j.drugalcdep.2019.107696

Ellickson, P. L., D'Amico, E. J., Collins, R. L., & Klein, D. J. (2005). Marijuana use and later problems: When frequency of recent use explains age of initiation effects (and when it does not). *Substance Use and Misuse, 40*(3), 343–359. https://doi.org/10.1081/JA-200049356

Freeman, T. P., & Lorenzetti, V. (2020). 'Standard THC units': A proposal to standardize dose across all cannabis products and methods of administration. *Addiction, 115*(7), 1207–1216. https://doi.org/10.1111/add.14842

Griffin, K. W., Bang, H., & Botvin, G. J. (2010). Age of alcohol and marijuana use onset predicts weekly substance use and related psychosocial problems during young adulthood. *Journal of Substance Use, 15*(3), 174–183. https://doi.org/10.3109/14659890903013109

Hudson, A., & Hudson, P. (2021). Risk factors for cannabis-related mental health harms in older adults: A review. *Clinical Gerontologist, 44*(1), 3–15. https://doi.org/10.1080/07317115.2020.1808134

Iob, E., Schoeler, T., Cecil, C. M., Walton, E., McQuillin, A., & Pingault, J. B. (2021). Identifying risk factors involved in the common versus specific liabilities to substance use: A genetically informed approach. *Addiction Biology, 26*(3), Article e12944. https://doi.org/10.1111/adb.12944

Kandel, D. B., & Chen, K. (2000). Types of marijuana users by longitudinal course. *Journal of Studies on Alcohol, 61*(3), 367–378. https://doi.org/10.15288/jsa.2000.61.367

Kaur, N., Bastien, G., Gagnon, L., Graham, J., Mongeau-Pérusse, V., Bakouni, H., Morissette, F., Theriault, C., Fischer, B., & Jutras-Aswad, D. (2022). Variations of cannabis-related adverse mental health and addiction outcomes across adolescence and adulthood: A scoping review. *Frontiers in Psychiatry, 13*(October), 1–13. https://doi.org/10.3389/fpsyt.2022.973988

Kirisci, L., Tarter, R., Ridenour, T., Zhai, Z. W., Fishbein, D., Reynolds, M., & Vanyukov, M. (2013). Age of alcohol and cannabis use onset mediates the association of transmissible risk in childhood and development of alcohol and cannabis disorders: Evidence for common liability. *Experimental and Clinical Psychopharmacology, 21*(1), 38–45. https://doi.org/10.1037/a0030742

Kozak, K. H., Smith, P., Lowe, D. J. E., Weinberger, A. H., Cooper, Z. D., Rabin, R. A., & George, T. P. (2021). A systematic review and meta-analysis of sex differences in cannabis use disorder amongst people with comorbid mental illness. *American Journal of Drug and Alcohol Abuse, 47*(5), 535–547. https://doi.org/10.1080/00952990.2021.1946071

Kuhn, C. (2015). Emergence of sex differences in the development of substance use and abuse during adolescence. *Pharmacology & Therapeutics, 153*, 55–78. https://doi.org/10.1016/j.pharmthera.2015.06.003

Legleye, S., Karila, L., Beck, F., & Reynaud, M. (2007). Validation of the CAST, a general population cannabis abuse screening test. *Journal of Substance Use, 12*(4), 233–242. https://doi.org/10.1080/14659890701476532

Levine, A., Clemenza, K., Rynn, M., & Lieberman, J. (2017). Evidence for the risks and consequences of adolescent cannabis exposure. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*(3), 214–225. https://doi.org/10.1016/j.jaac.2016.12.014

Marmorstein, N. R., White, H. R., Loeber, R., & Stouthamer-Loeber, M. (2010). Anxiety as a predictor of age at first use of substances and progression to substance use problems among boys. *Journal of Abnormal Child Psychology, 38*(2), 211–224. https://doi.org/10.1007/s10802-009-9360-y

McGrath, J. J., Al-Hamzawi, A., Alonso, J., Altwaijri, Y., Andrade, L. H., Bromet, E. J., Bruffaerts, R., de Almeida, J. M. C., Chardoul, S., Chiu, W. T., Degenhardt, L., Demler, O. V., Ferry, F., Gureje, O., Haro, J. M., Karam, E. G., Karam, G., Khaled, S. M., Kovess-Masfety, V., & Zaslavsky, A. M. (2023). Age of onset and cumulative risk of mental disorders: A cross-national analysis of population surveys from 29 countries. *The Lancet Psychiatry, 10*(9), 668–681. https://doi.org/10.1016/S2215-0366(23)00193-1

Newman, D. A. (2014). Missing data. *Organizational Research Methods, 17*(4), 372–411. https://doi.org/10.1177/1094428114548590

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., & Moher, D. (2021). Updating guidance for reporting systematic reviews: Development of the PRISMA 2020 statement. *Journal of Clinical Epidemiology, 134*, 103–112. https://doi.org/10.1016/j.jclinepi.2021.02.003

Pocuca, N., Chadi, N., Vergunst, F., Parent, S., Côté, S. M., Boivin, M., Tremblay, R. E., Séguin, J. R., & Castellanos-Ryan, N. (2023). Prospective Polysubstance use profiles among adolescents with early-onset cannabis use, and their association with cannabis outcomes in emerging adulthood. *International Journal of Mental Health and Addiction*. https://doi.org/10.1007/s11469-022-01005-7

Prince, M. A., & Conner, B. T. (2019). Examining links between cannabis potency and mental and physical health outcomes. *Behaviour Research and Therapy, 115*, 111–120. https://doi.org/10.1016/j.brat.2018.11.008

Richards, D. K., Schwebel, F. J., Sotelo, M., & Pearson, M. R. (2021). Self-reported symptoms of cannabis use disorder: Psychometric testing and validation. *Experimental and Clinical Psychopharmacology, 29*(2), 157. https://doi.org/10.1037/pha0000455

Rioux, C., Castellanos-Ryan, N., Parent, S., Vitaro, F., Tremblay, R. E., & Séguin, J. R. (2015). Differential susceptibility to environmental influences: Interactions between child temperament and parenting in adolescent alcohol use. *Development and Psychopathology, 28*(1), 265–275. https://doi.org/10.1017/S0954579415000437

Rioux, C., Castellanos-Ryan, N., Parent, S., Vitaro, F., Tremblay, R. E., & Séguin, J. R. (2018). Age of cannabis use onset and adult drug abuse symptoms: a prospective study of common risk factors and indirect effects. *Canadian Journal of Psychiatry, 63*(7), 457–464. https://doi.org/10.1177/0706743718760289

Scholes-Balog, K. E., Hemphill, S. A., Evans-Whipp, T. J., Toumbourou, J. W., & Patton, G. C. (2016). Developmental trajectories of adolescent cannabis use and their relationship to young adult social and behavioural adjustment: A longitudinal study of Australian youth. *Addictive Behaviors, 53*, 11–18. https://doi.org/10.1016/j.addbeh.2015.09.008

Sittner, K. J., Hautala, D. S., & Walls, M. L. (2021). Conjoint adolescent developmental trajectories of alcohol and marijuana use and early adult outcomes among North American Indigenous people. Addictive Behaviors, 114(December 2020). Doi: 10.1016/j.addbeh.2020.106758.

Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A. W., Churchill, R., Deeks, J. J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y. K., Pigott, T. D., & Higgins, J. P. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Online), 355*, 1–7. https://doi.org/10.1136/bmj.i4919

Swift, W., Coffey, C., Carlin, J. B., Degenhardt, L., & Patton, G. C. (2008). Adolescent cannabis users at 24 years: Trajectories to regular weekly use and dependence in young adulthood. *Addiction, 103*(8), 1361–1370. https://doi.org/10.1111/j.1360-0443.2008.02246.x

Taylor, M., Collin, S. M., Munafò, M. R., MacLeod, J., Hickman, M., & Heron, J. (2017). Patterns of cannabis use during adolescence and their association with harmful substance use behaviour: Findings from a UK birth cohort. *Journal of Epidemiology and Community Health, 71*(8), 764–770. https://doi.org/10.1136/jech-2016-208503

Trucco, E. M., & Hartmann, S. A. (2021). Understanding the etiology of adolescent substance use through developmental perspectives. *Child Development Perspectives, 15*(4), 257–264. https://doi.org/10.1111/cdep.12426

United Nations Office on Drugs and Crime. (2023). World Drug Report 2023. https://www.unodc.org/unodc/en/data-and-analysis/Exsum_wdr2023.html.

Van Leeuwen, A. P., Verhulst, F. C., Reijneveld, S. A., Vollebergh, W. A., Ormel, J., & Huizink, A. C. (2011). Can the gateway hypothesis, the common liability model and/or, the route of administration model predict initiation of cannabis use during adolescence? A survival analysis—the TRAILS study. *Journal of Adolescent Health, 48*(1), 73–78. https://doi.org/10.1016/j.jadohealth.2010.05.008

Wang, X., & Cheng, Z. (2020). Cross-sectional studies: Strengths, weaknesses, and recommendations. *Chest, 158*(1), S65–S71. https://doi.org/10.1016/j.chest.2020.03.012

Windle, M., & Windle, R. C. (2012). Early onset problem behaviors and alcohol, tobacco, and other substance use disorders in young adulthood. *Drug and Alcohol Dependence, 121*(1–2), 152–158. https://doi.org/10.1016/j.drugalcdep.2011.08.024

Yurasek, A. M., Aston, E. R., & Metrik, J. (2017). Co-use of alcohol and cannabis: A review. *Current Addiction Reports, 4*, 184–193. https://doi.org/10.1007/s40429-017-0149-8