Cardiovascular risk associated with the use of cannabis and cannabinoids: a systematic review and meta-analysis

Wilhelm Storck [1,2] Meyer Elbaz [3,4,5] Cécile Vindis [4,5] Amélia Déguilhem [6] Maryse Lapeyre-Mestre [5,7,8] Emilie Jouanjus [1,5,7]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/heartjnl-2024-325429).

For numbered affiliations see end of article.

Correspondence to
Dr Emilie Jouanjus;
emilie.jouanjus@univ-tlse3.fr

Received 16 November 2024
Accepted 28 March 2025

ABSTRACT

Background Awareness has recently risen about the potential associated risks to the cardiovascular health of cannabis users. The objective was to evaluate the possible association between major adverse cardiovascular events (MACE) and the use of cannabis or cannabinoids.

Methods Original pharmacoepidemiological studies providing risk estimates on cannabis-related MACE (ie, cardiovascular death, non-fatal acute coronary syndrome (ACS) including myocardial infarction (MI) or non-fatal stroke) published from 1 January 2016 to 31 January 2023 were included in the systematic review exploring PubMed, Web of Science and Scopus (last search: 20 September 2023). Design, duration, baseline characteristics, exposure, inclusion criteria, sample size, effect size and confusing factors, including exposure to psychoactive substances, were extracted. Study quality was assessed using the ROBINS-E (risk of bias in non-randomised studies—of exposures) tool. In the meta-analysis, adjusted effect estimates and their 95% CIs were pooled using a DerSimonian and Laird random effect model with inverse variance weighting based on the type of outcome (PROSPERO: CRD42023401401).

Results Overall, 24 articles were included from 3012 initial records, including 17 cross-sectional studies, 6 cohort studies and 1 case-control study. Exposure corresponded to the use of cannabis in all studies, with one focused on medical cannabis. The estimated risk ratio (RR) was 1.29 (95% CI 1.05 to 1.59) for ACS, 1.20 (1.13 to 1.26) for stroke and 2.10 (1.29 to 3.42) for cardiovascular death. As measured in two studies, no statistically significant association was found for the composite outcome combining ACS and stroke. The focused analysis restricted to cohort studies yielded comparable results to the primary model (RR=1.32, 1.01 to 1.73).

Conclusions This systematic review and meta-analysis uses an original approach centred on real-world data. The findings reveal positive associations between cannabis use and MACE. These findings should encourage investigating cannabis use in all patients presenting with serious cardiovascular disorders.

PROSPERO registration number CRD42023401401.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies reported on potential cannabis-related cardiovascular outcomes. However, knowledge gaps remained on the magnitude of the associated risk for the people who use cannabis, particularly in the actual context of profound changes in use prevalence and characteristics of users.

WHAT THIS STUDY ADDS

⇒ This systematic review and meta-analysis of real-world data outlines positive associations between cannabis use and major adverse cardiovascular events, with measured risk ratios of 1.20 (95% CI 1.13 to 1.26) for stroke, 1.29 (1.05 to 1.59) for acute coronary syndrome and 2.10 (1.29 to 3.42) for cardiovascular mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings outlined by this meta-analysis should enhance the general awareness of the potential of cannabis to cause cardiovascular harm. They call for the systematic investigation of cannabis use in all patients presenting with clinical pictures of serious cardiovascular disorders.

INTRODUCTION

The use of cannabis and cannabinoids has been rapidly growing worldwide over the past decade.[1] In Europe, despite being approved for medical purposes in a growing number of countries, recreational use remains largely illegal.[2] In France, for example, medical cannabis has been experimented on since 2021, while recreational cannabis is illegal and strictly regulated; nevertheless, its use is among the most prevalent in Europe, especially in the young.[3] By contrast, recreational cannabis was legalised in Germany in April 2024. Legalising the drug and expanding its medical use worldwide have likely contributed to profound changes in the general perception of cannabis and to the overall rise in cannabis consumption.[4] Consequently, users' profiles and consumption habits profoundly differ from those in the 2010s, especially as cannabis products show an increasing trend in potency, with rising concentrations of delta-9-tetrahydrocannabinol (THC). There is particular concern regarding users who initiated using illicit cannabis for medical reasons outside of the regulated medical system.[5] Studies have shown that patients diagnosed with cancer or psychiatric disorders may self-manage undesirable symptoms by using cannabis without informing their physician.[6 7]

► https://doi.org/10.1136/heartjnl-2025-326169

To cite: Storck W, Elbaz M, Vindis C, *et al*. *Heart* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/heartjnl-2024-325429

Amidst this increase, awareness has risen about the potential associated risks to users' health, especially cardiovascular.[8] We previously examined the evidence on the cardiovascular risk of cannabis-based products published until 2016.[9] This evidence was more substantial for ischaemic stroke, whereas few studies had investigated cardiac diseases, including myocardial infarction (MI), and almost none concerned other cardiovascular disorders. Although the pathophysiological pathways involved in these events are not entirely established, reversible vasospasm has been suggested as one mechanism associated with cannabis-related ischaemic events.[10] Experimental studies report cannabinoid-induced vasorelaxation in rats but also vasoconstriction in pathological conditions like hypertension or after administering high doses.[11 12] Cannabinoids have pleiotropic effects linked to various pharmacological targets besides the specific type 1 and type 2 cannabinoid receptors (CB1 and CB2).[13] THC and cannabidiol (CBD) are the primary active ingredients of cannabis: THC is a CB1 and CB2 partial agonist having a higher affinity for CB1, whereas CBD is described as a CB2 partial agonist, a CB1 negative allosteric modulator or as having no interaction at these receptors.[14 15] CB1 activation in the cardiovascular system has been associated with oxidative stress, tissue injury, cell death, proatherogenic, profibrotic, proinflammatory effects and vasodilation/vasoconstriction via the sympathetic nervous system.[8] THC-mediated sympathetic stimulation can cause tachycardia, increased oxygen cardiac demand and vasoconstriction, which can be transient and triggered by underlying pathological conditions, potentially leading to ischaemia in the heart, brain or periphery. CB2 activation, conversely, has been linked to anti-inflammatory effects and reduced oxidative stress and could have antiatherogenic and antifibrotic functions.

The combination of epidemiological factors and the pharmacological properties of cannabinoids raises further concerns about health risks associated with the use of cannabis and cannabinoids, especially the risk of cardiovascular disorders. To address these concerns, the present study aimed to evaluate the risk of major adverse cardiovascular events (MACE) related to cannabis use by analysing real-world pharmacoepidemiological data and conducting a systematic review and meta-analysis to quantify this risk.

MATERIAL AND METHODS

Study design

The study protocol has been registered in PROSPERO under registration number CRD42023401401 (online supplemental appendix e1). We conducted a systematic review and meta-analysis of the scientific evidence made available between 1 January 2016 and 31 January 2023 in accordance with the international methodological recommendations (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement from the Enhancing the QUAlity and Transparency Of Health Research Network guidelines) (online supplemental appendix e2).

Eligibility criteria were defined as follows based on the PICO approach:[16]

Population—Subjects from the general population likely to be exposed to cannabis or cannabinoids without restrictions on socio-demographic characteristics.

Intervention—Exposure to cannabis or cannabinoids.

Comparison—Subjects non-exposed to cannabis or cannabinoids.

Outcome—Occurrence of MACE, defined by the three-point composite outcome: cardiovascular death, non-fatal MI or non-fatal stroke.[17] The primary outcome was to evaluate the risk of MACE associated with cannabis and cannabinoids based on real-life pharmacoepidemiological data. Four different subgroups of MACE were considered: acute coronary syndrome (ACS), stroke, composite outcome of ACS or stroke and cardiovascular mortality.

Study selection, data extraction and quality assessment

A search was performed on 20 September 2023 within PubMed, Web of Science and Scopus, following the search strategy detailed in online supplemental appendix e3.

Studies were independently selected by two investigators (WS and EJ) after title and abstract screening based on the defined inclusion and exclusion criteria. Each reviewer was blinded to the decision of the other, and any disagreement was resolved by discussion or by a third researcher (ML-M) in case of persisting disagreement. A cardiologist (ME) reviewed all included studies and clinically assessed the measured outcomes.

Studies were included when they contained original data with available risk estimates (relative risk RR, OR or HR). Case reports, systematic reviews, meta-analyses, in-vitro studies, animal studies, commentaries and editorials were excluded. Studies conducted specifically on subpopulations of disease patients (such as HIV positive cohorts) were excluded. Only studies written in the English language were included.

Data extraction aimed at collecting details on study design, duration, baseline characteristics, exposure levels and administration route when available, inclusion/exclusion criteria, sample size and effect size (HR, OR or RR) and the corresponding 95% CI, and any potential confounding factors including concomitant use of psychoactive substances. Two investigators (WS and EJ) were involved in carrying out data extraction and cross-checking the data. The online software Rayyan was used to manage the study selection process at all steps.[18]

The quality of each study was assessed using the ROBINS-E (risk of bias in non-randomised studies—of exposures) assessment tool, which provides a comprehensive and structured approach to assessing the risk of bias of non-randomised studies of exposure.[19] The latter risk is approached systematically in seven distinct domains, that is, (1) bias due to confounding (D1), (2) bias arising from measurement of the exposure (D2), (3) bias in selection of participants into the study (or into the analysis) (D3), (4) bias due to post-exposure interventions (D4), (5) bias due to missing data (D5), (6) bias arising from measurement of the outcome (D6) and (7) bias in selection of the reported result (D7). This assessment was carried out independently by two researchers (WS and EJ).

Statistical analysis

A descriptive analysis was performed to characterise the included studies. Participants' characteristics comprised the mean age, the proportion of males and the concomitant use of psychoactive substances. When these measures were unavailable in the original article, they were recalculated. When age was provided as a range, a weighted mean was calculated using the median for each age class.

The studies providing results in several outcomes were considered for each of the concerned outcomes in the quantitative analysis. Due to the rarity of the studied outcomes, all risk estimate measures were treated as equivalent for the meta-analysis. Pooled risk estimates were calculated using a DerSimonian and Laird random effects model with inverse variance weighting.[20] Adjusted estimate measures were incorporated into the statistical

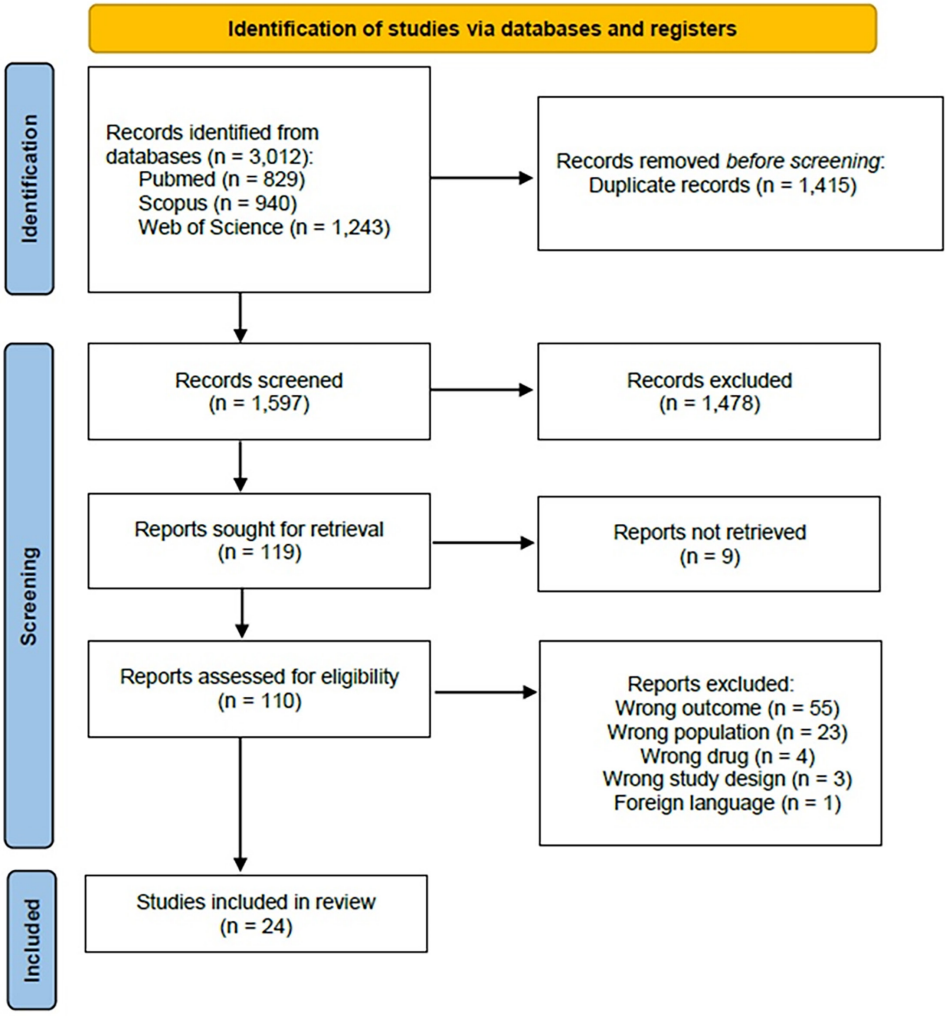

Figure 1 PRISMA flow diagram of the selection process and included studies. Diagram based on the PRISMA statement. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

model. The variance was calculated using the corresponding CI for each estimate measure. A subgroup analysis was performed according to the different outcome categories. Besides, sensitivity analyses were performed to evaluate the robustness of findings by excluding studies with a high risk of bias. The presence of between-study heterogeneity was assessed using the Cochran Q test and I^2 test. Heterogeneity was considered not important for I^2 values between 0% and 40%, moderate between 30% and 60%, substantial between 50% and 90% and considerable between 75% and 100%.[21] Publication bias was assessed both visually through the examination of a funnel plot and statistically by applying Egger's statistical test.[22] Statistical analyses were conducted in R statistical software, V.4.3.0 (R Project for Statistical Computing).

RESULTS

Literature search and inclusion process

The database query yielded 3012 records. After screening titles and abstracts, we identified 119 articles, 110 of which were deemed eligible for inclusion (figure 1). Ultimately, our systematic review included a total of 24 articles following the inclusion procedure.

Characteristics of included studies

Table 1 depicts the included studies. They were of cross-sectional (n=17, 70.8%), cohort (n=6, 25.0%) and case-control (n=1, 4.2%) study designs. All assessed the potential association between recreational use of cannabis and MACE. 14 studies were based on the exploration of three databases: the National Inpatient Sample (NIS) (n=8 studies), the Behavioural Risk Factor Surveillance System (BRFSS) (n=4) and the National Health and Nutrition Examination Survey (NHANES) (n=2), with potential overlaps. The 24 studies involved a total of 432 245 972 patients.

The mean age across studies ranged from 19 to 59 years, as reported in 16 studies (table 1). The corresponding weighted average age was 38.4. Mean age calculation was not possible, unavailable or limited to cases for the remaining eight studies. Similarly, the calculation of male proportion was not possible or unavailable in five studies. Cannabis users were predominantly males (54–100%) in studies for which this data was available (n=14) and tended to be younger than non-users.

Risk of bias within studies

The risk of bias assessment retrieved a high rating for most studies (n=20, 83.3%), while the remaining four (16.7%) raised some concerns (figure 2). The most frequent causes of overall risk of

Table 1 Detailed overview of study characteristics

First author	Year	Study design (effect measure)	Data source	Population	Number of participants	Outcome measure	Exposure measure	Mean age (total, years)	Male (total, %)	Mean age (cannabis, years)	Male (cannabis, %,)
Chelikam	2022	Cross-sectional study (OR)	National Health and Nutrition Examination Survey (NHANES)	Age: 18 and above Period: 2013–2018	264 740	Stroke (undefined)	Self-reported "Have you ever, even once, used marijuana or hashish?"	NA	47.3	NA	NA
Defilippis	2018	Retrospective cohort study (HR)	YOUNG-MI registry, Brigham and Women's Hospital and Massachusetts General Hospital in Boston, Massachusetts, USA	Age: 50 and below Period: 2000–2016	2097	Cardiovascular (CV) mortality (acute myocardial infarction (AMI), heart failure, sudden cardiac death, ischaemic stroke, non-traumatic haemorrhagic stroke, immediate complications of a cardiovascular procedure, cardiovascular haemorrhage, pulmonary embolism or peripheral arterial disease)	Review of electronic medical records (self-reported or drug screening)	42.8	76.7	44	87.2
Desai	2017	Cross-sectional study (OR)	National Inpatient Sample (NIS)	Age: 11–70 Period: 2010–2014	2 451 933	AMI	ICD-9 codes	58.5	66.1	49.3 (among cases)	76.9 (among cases)
Desai	2020	Cross-sectional study (OR)	NIS	Age: 18–49 Period: 2007–2014	NA	Stroke (undefined) Acute ischaemic stroke	ICD-9 codes	NA	NA	NA	NA
Draz	2016	Cross-sectional study (OR)	Electronic medical records, cardiac care unit of the University Hospital in Egypt	Sex: male Age: 40 or less Period: August 2014–January 2015	85	AMI	Urine drug screening	34.3	100	34	100
Dutta	2021	Case-control study (OR)	Discharge data from 59 acute care hospitals in the greater Baltimore/ Washington DC (USA) area and direct referral from regional neurologists	Age: 15–49 Period: 1992–2008	1564	Ischaemic stroke	Self-reported	39.1	44.5	39 (control group)	48.7 (control group)
Falkstedt	2017	Retrospective cohort study (HR)	Swedish national survey of men conscripted into military service in 1969/1970	Sex: male Age: up to 60, all conscripted between the ages of 18 and 20 Period: 1971–2009	45 081	Stroke: all stroke including transient ischaemic attack (TIA)	Self-reported	NA	100	NA	NA
Hemachandra	2016	Cross-sectional study (IRR)	PATH Through Life Cohort: subjects randomly selected from the electoral roll of the Australian Capital Territory and Queanbeyan	Three cohorts: Age: 20–24, 40–44, 60–64 Period: 1999–2000, 2000–2001, 2001–2002	7455	Stroke (undefined), ministroke or TIA	Self-reported "Have you used marijuana/hash in the past 12 months?"	45.6	49.0	27.0	59.0
Jivanji	2020	Cross-sectional study (OR)	Behavioural Risk Factor Surveillance System (BRFSS)	Age: 18 and above Period: 2017	56 742	Cardiovascular disease (CVD) defined as myocardial infarction (MI), angina, chronic heart disease (CHD), stroke	Self-reported "During the past 30 days, on how many days did you use marijuana or cannabis?"	63% of the population was 65 or younger	44.7	Age <65 was more common in marijuana users (93.2% vs 77.1% in non-marijuana users).	63.1

Continued

Table 1 Continued

First author	Year	Study design (effect measure)	Data source	Population	Number of participants	Outcome measure	Exposure measure	Mean age (total, years)	Male (total, %)	Mean age (cannabis, years)	Male (cannabis, %,)
Kalla	2018	Cross-sectional study (OR)	NIS	Age: 18–55 Period: 2009–2010	20 815 612	Heart failure Cerebrovascular accident	ICD-9 codes	26.4	38.3	33.1	60
Karki	2022	Cross-sectional study (OR)	Electronic medical records, community hospital in Bronx, New York, USA	Age: 18–54 Period: 2012–2014	14 490	Acute coronary syndrome: unstable angina, ST-elevated MI (STEMI) and non-STEMI (NSTEMI)	Urine drug screening	46.7 (among cases)	62.5 (among cases)	45.3 (among cases)	61 (cases)
Ladha	2021	Cross-sectional study (OR)	BRFSS	Age: 18–44 Period: 2017–2018	33 173	MI	Self-reported	32.6	49.3	31.6	62.9
Ma	2021	Retrospective cohort study (HR)	National French hospital database (PMSI)	Age: 18 and above Period: 2010–2018	3 381 472	AMI: STEMI and NSTEMI	ICD-10 codes	59.2	21.2	37	74.5
Malhotra	2018	Cross-sectional study (OR)	NIS	Age: 15–54 Period: 2004–2011	118 659 619	Non-traumatic intracerebral haemorrhage	ICD-9 codes	NA	NA	NA	65.7 (cases)
Parekh	2020	Cross-sectional study (OR)	BRFSS	Age: 18–44 Period: 2006–2017	43 860	Stroke (undefined)	Self-reported	31.1	49.9	29.2	63.3
Patel	2020	Cross-sectional study (OR)	NIS	Age: 15–22 Period: 2010–2014	9 466 949	AMI	ICD-9 codes	19	25.2	NA	92.1 (cases)
Reis	2017	Prospective cohort study (HR)	Coronary Artery Risk Development in Young Adults (CARDIA) cohort	Age: 18–30 at baseline in 1985/1986 Period: 1985–2013	5113	CVD defined as CHD, MI, acute coronary syndrome (ACS), CHD death including fatal MI, stroke, TIA, hospitalisation for heart failure, intervention for peripheral arterial disease, death from cardiovascular causes	Self-reported	NA	NA	NA	NA
Rumalla_1	2016	Cross-sectional study (OR)	NIS	Age: 15–54 Period: 2004–2011	118 659 618	Aneurysmal subarachnoid haemorrhage	ICD-9 codes	36.1	41.0	40.4 (among cases)	53.3 (cases)
Rumalla_2	2016	Cross-sectional study (OR)	NIS	Age: 15–54 Period: 2004–2011	118 659 618	Acute ischaemic stroke	ICD-9 codes	46.1 (among cases)	55.6	43.7 (among cases)	67.4 (among cases)
San Luis	2020	Cross-sectional study (OR)	Medical records from the University of Mississippi Medical Center (UMMC)	Age: 18 and above Period: 2015–2017	9350	Ischaemic stroke	Urine drug screening	47.9	65.3	38	67.8
Shah	2021	Cross-sectional study (OR)	BRFSS	Age: 18 and above Period: 2016–2018	133 706	MI or coronary artery disease Stroke	Self-reported	43.5	43.8	33.2	57.5
Sun	2020	Retrospective cohort study (HR)	NHANES	Age: 20–59 Period: 2005–2014	14 818	CV mortality defined as death from heart disease or cerebrovascular disease	Self-reported	38.8	50.7	44.7 (among cases)	55.8
Vin-Raviv	2017	Cross-sectional study (OR)	NIS	Period: 2007–2011	39 448 981	-Heart failure -Cardiac disease (corresponding to ICD-9 codes of arrhythmias) -Ischaemic stroke -In-hospital mortality (all cause)	ICD-9 codes	53.2	42.0	34.0	62.2

Continued

Table 1 Continued

First author	Year	Study design (effect measure)	Data source	Population	Number of participants	Outcome measure	Exposure measure	Mean age (total, years)	Male (total, %)	Mean age (cannabis, years)	Male (cannabis, %,)
Zongo	2021	Retrospective cohort study (HR)	Ontario administrative health data	Age: 18 and above Period: 2017–2017 Other criteria: patients authorised to access cannabis for medical purposes	69 896	Primary outcome: ACS or stroke Secondary outcome: any CV event	Not measured: Patients authorised to use cannabis were presumed to be exposed	46.3	54.6	45.5	54.3

ICD, International Classification of Disease; IRR, incidence rate ratio; PATH, Personality and Total Health; PMSI, Programme de médicalisation des systèmes d'information.

bias were uncontrolled confounding factors (ROBINS-E risk of bias domain 1) and misclassification of exposure (domain 2). The risk of bias due to postexposure interventions (ROBINS-E Domain 4) was irrelevant to the selected studies, leading to a systematically low risk of bias in this domain.

Risk of bias across studies

No asymmetry was evidenced after visual inspection of the funnel plot (figure 3) and the Egger's test was not significant (p=0.0829) for funnel plot asymmetry, suggesting the absence of systematic bias towards the reporting or publication of studies with more favourable results.

Cannabis use and risk of cardiovascular diseases

Included studies evaluated stroke (n=14),[23–36] ACS (n=7),[26 37–42] cardiovascular mortality (n=3)[36 43 44] and the composite endpoint of ACS and stroke (n=2).[45 46] Two studies measured different outcomes, and their results were considered in each of the concerned outcomes.[26 36]

The measured ORs of ACS, stroke and cardiovascular mortality associated with cannabis use were 1.29 (95% CI 1.05 to 1.59), 1.20 (1.13 to 1.26) and 2.10 (1.29 to 3.42), respectively, and that of the composite ACS/stroke outcome, 1.04 (0.54 to 1.99) (figure 4). Heterogeneity between studies was substantial to considerable with I^2 values ranging from 79.2% to 89.3% across subgroups except cardiovascular mortality. The sensitivity analysis restricted to cohort studies yielded comparable results to the primary model (RR=1.32, 1.01 to 1.73) (figure 5). The limited number of studies did not allow us to perform other sensitivity analyses.

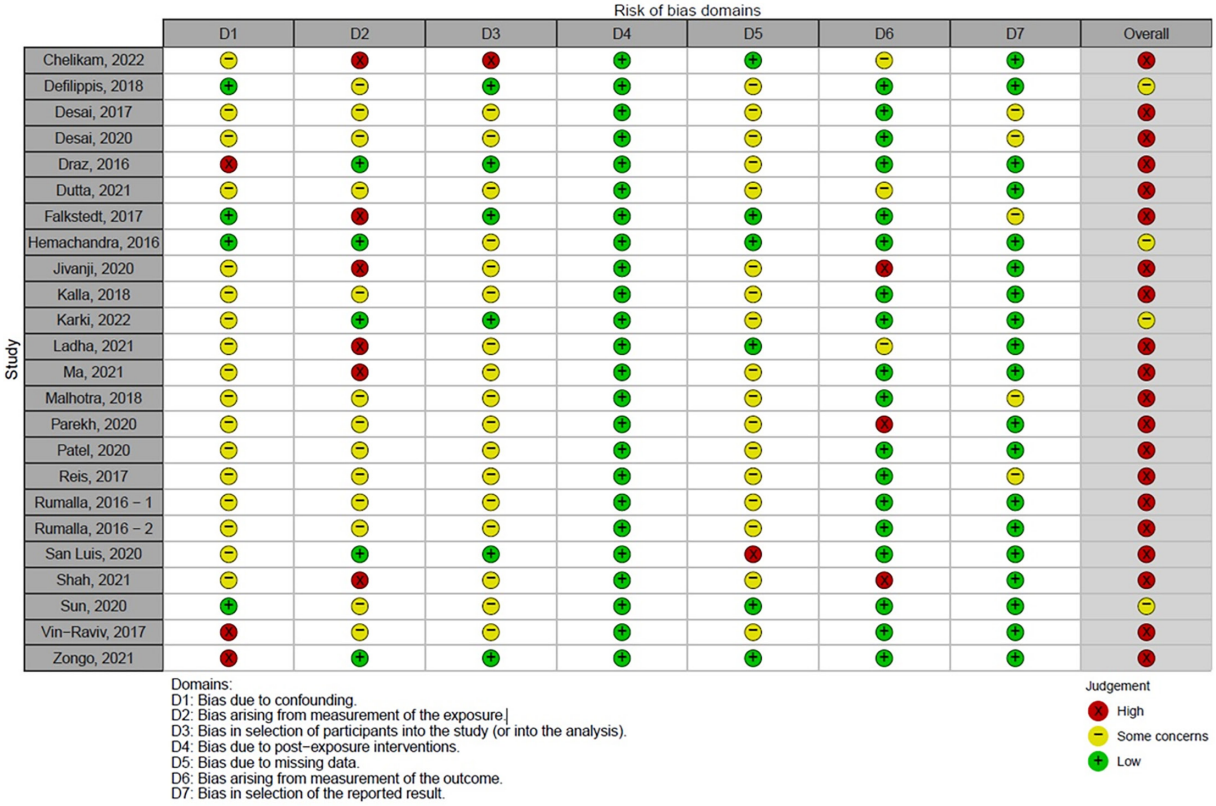

Figure 2 Assessment of the risk of bias in the studies included using the ROBINS-E tool. Judgement on risk of bias is rated 'high', 'some concerns' or 'low'. ROBINS-E, risk of bias in non-randomised studies—of exposures.

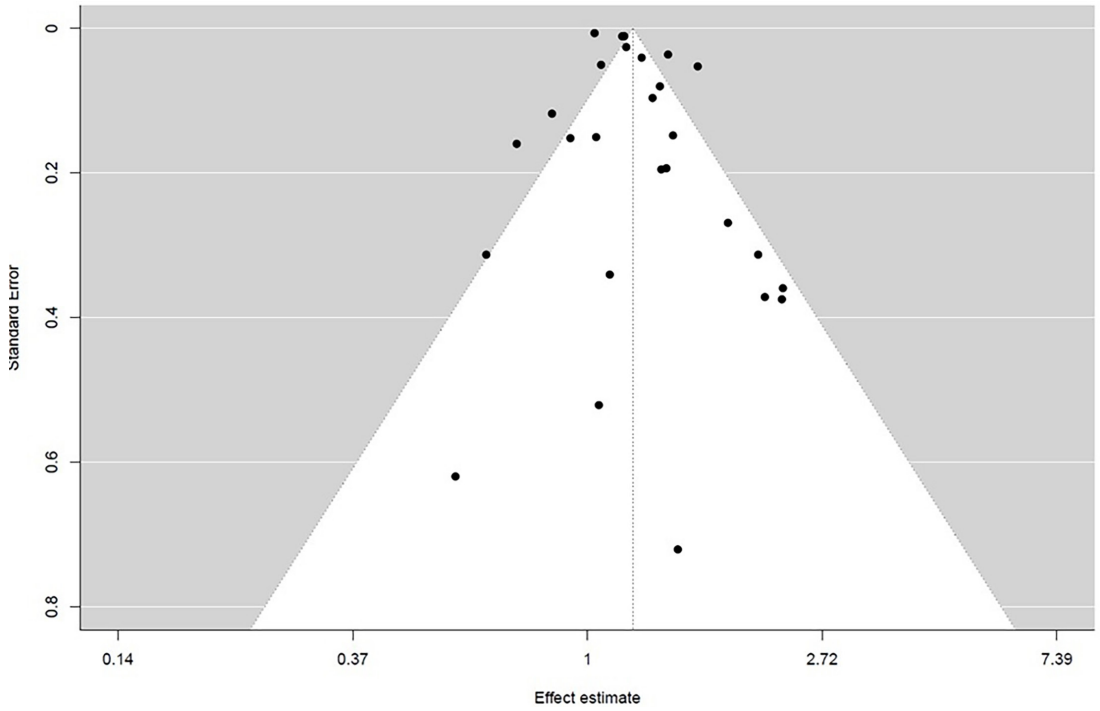

Figure 3 Funnel plot for cannabis use and MACE (major adverse cardiovascular events). The absence of asymmetry suggests the absence of publication bias (Egger's test: p=0.0829, non-significant).

DISCUSSION

Main findings

24 studies evaluated the occurrence of MACE in the context of exposure to cannabis, including one to medical cannabis and none to other cannabinoids. The quantitative analysis suggests a positive association between cannabis use and MACE. Findings from the sensitivity analysis restricted to cohort studies were consistent with the primary analysis. These results cohere

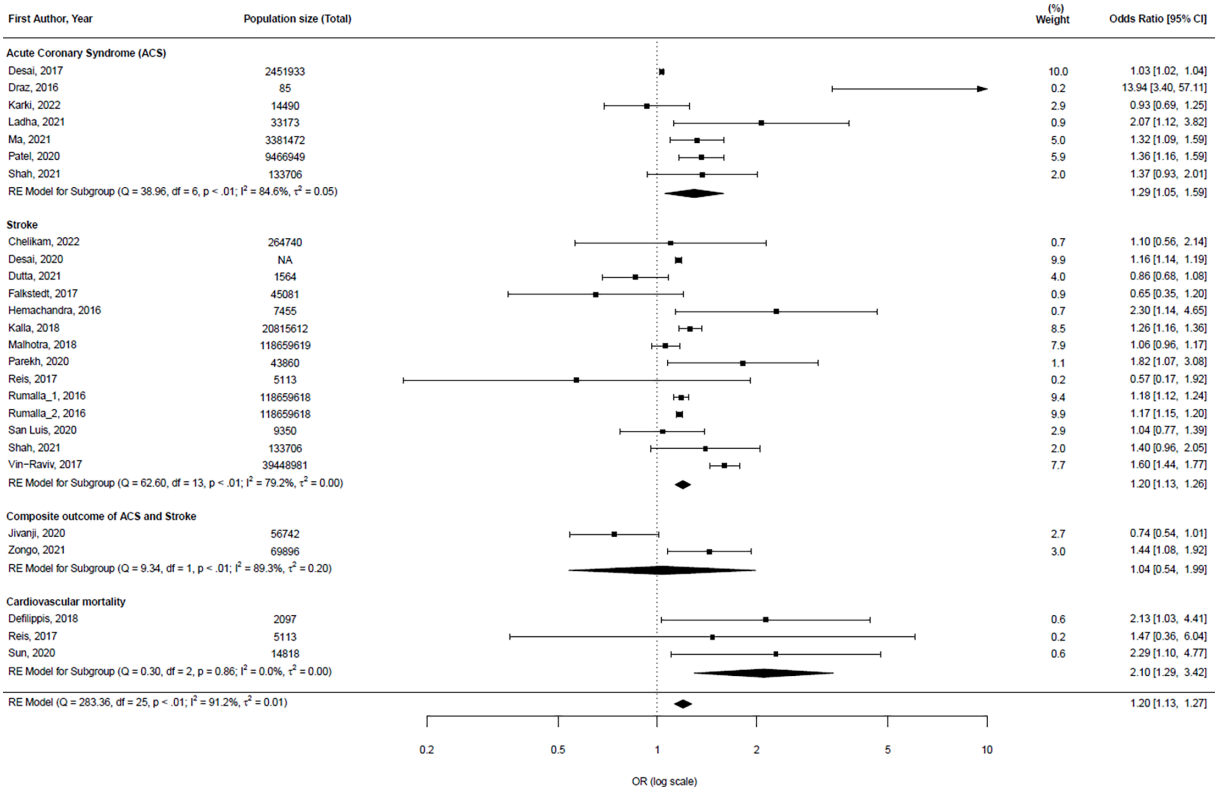

Figure 4 Forest plot of the association between cannabis use and MACE. NA: the population size is not available in this study conducted in the entire NIS database (containing around 8 million hospital stays each year). MACE, major adverse cardiovascular events; NIS, National Inpatient Sample.

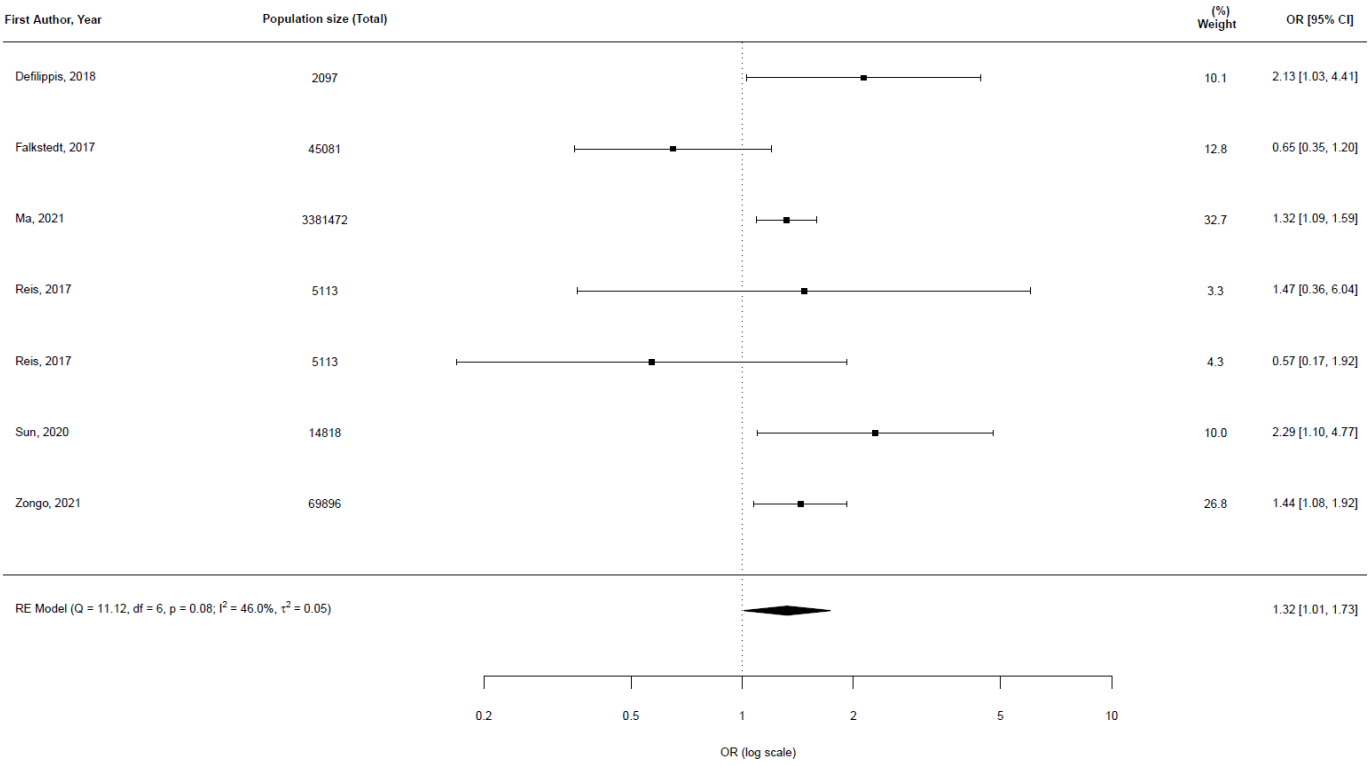

Figure 5 Forest plot of the association between cannabis use and MACE, including studies with a cohort design only. MACE, major adverse cardiovascular events.

with other studies published outside of the time window of the present meta-analysis, including those from various cohorts in France or in the USA, respectively, showing an independent association between cannabis and in-hospital MACE,[47 48] or between daily cannabis use and MI, stroke and the composite of coronary heart disease, MI and stroke.[49] The only study on medical cannabis among those included in the meta-analysis also highlighted such a positive association.[45]

Cerebrovascular disorders

The studies centred on the assessment of stroke provide divergent results, whether suggesting or not a significant association between cannabis use and stroke. First, no association was found between cannabis use in young adulthood and early stroke (HR: 1.59, 0.59 to 4.28) in a study among a cohort of 50 000 men included during the compulsory military service in Sweden.[35] In a case-control study among US adults younger than 50, the odds for stroke were found to be similar in subjects ever exposed to cannabis than in those never exposed.[34] In both studies, estimation of exposure is likely biased since use of cannabis was measured at inclusion with no follow-up data in the first study; and the inclusion of single use over the lifetime in the second. No association was found in another cohort of US subjects included between the ages of 18 and 30 and followed up more than 25 years in the Coronary Artery Risk Development in Young Adults cohort (OR=0.57, 0.17 to 1.93).[36] Age when cerebrovascular accidents occurred is not provided. Interestingly, no significant association was emphasised in the focused analysis on recent cannabis use, possibly due to a lack of power. Similar conclusions were provided from two additional studies among adults over 18 despite an overall adjustment on relevant covariables.[31–33] In contrast, several studies within large cohorts found a higher risk of stroke in cannabis users, persistently significant after adjustment on relevant cardiovascular risk factors.[23–25 28] Among those based on the exploration of the NIS, the largest database of US inpatients, the study by Vin-Raviv *et al* included all hospitalised patients (OR=1.60, 1.44 to 1.77), whereas in those by Kalla *et al*, Desai *et al*, Parekh *et al* and Rumalla *et al*, only patients under the age of 55 were included. In the latter study, ischaemic stroke was significantly associated with use of cannabis, with a marked increase in the 25–34 age range.[28] The exploration of the PATH through life study cohort in Australia outlined that elevated stroke/transient ischaemic attack was specific to participants who used cannabis at least weekly (IRR=4.7, 2.1–10.7). Similarly, a higher proportion of stroke was emphasised only among subjects aged 18–74 who used cannabis frequently.

Cardiac disorders

Seven studies investigated the potential implication of cannabis in the occurrence of ACS, including five focused on acute MI, which demonstrated an independent association with the use of cannabis after adjustment for tobacco smoking and abuse of cocaine and amphetamine.[37–41] In the study by Desai *et al* exploring the NIS database by millions of participants, the measured association was barely significant (OR=1.03, 1.02 to 1.05, p<0.001), raising the question of the clinical significance of statistically significant results.[41] Three of the other four studies were also conducted on large electronic health databases,[38–40] including that by Patel *et al*, which specifically explored this association in a younger population aged 15–22 (OR=1.36, 1.16 to 1.59). Similar results were found in a study examining the BRFSS: higher odds of acute MI were observed in patients who used cannabis more than once a week (OR=2.31, 1.18 to 4.50) but not in less frequent users (OR=1.48, 0.52 to 4.21).[38] Surprisingly, the third study, which explored the French administrative hospital discharge database, concluded that among illicit drugs, cannabis was a predictor for MI, unlike cocaine and opioids.[40] The authors hypothesise that their results lacked

power due to the lower prevalence of cocaine and opioids than cannabis use in France. The non-significant association between the use of cocaine and MI may also illustrate the limitation of hospital databases to accurately measure exposure to illicit drugs. The fifth study highlighted a positive association within a small cohort of 85 men younger than 40.[37] Considering the low number of included patients, caution is required to interpret the high OR value (OR=13.9, 3.4 to 57.1). Finally, one study specifically investigated the association between cannabis use and ACS in nearly 15 000 patients aged 18–54 and found no significant association in the overall sample but a higher risk in the subgroup of patients aged 18–36 (OR=5.24, IC 95% 1.85 to 16.94).[42]

Cardiovascular mortality

Cannabis use significantly increased all-cause mortality and cardiovascular mortality in a cohort of patients diagnosed with MI before the age of 50, after adjustment for age, cardiovascular risk factors including tobacco smoking and other health conditions.[44] These findings are consistent with results from studies included in our previous review in which cannabis was statistically associated with increased middle-term but not long-term mortality in subjects with a history of acute MI.[50 51] These were further supported by a more recent study exploring data from the NHANES which revealed a significant association between cannabis use and death from cardiovascular causes (HR=2.29, 1.10 to 4.78).[43] No significant association was found for all-cause mortality (HR=1.14, 0.81 to 1.59).

Interestingly, an analysis conducted in 2024 from the UK Biobank population emphasised a sex difference regarding cardiovascular mortality related to heavy cannabis use, with a significantly higher risk for women unlike men.[52]

Strengths and limitations

The main strength of our study lies in its methodology, which aligns with international recommendations. To our knowledge, this is the first meta-analysis examining the potential association of cannabis use and MACE, performed from observational data and applying the highest-quality methodological standards. This approach better reflects the real-world scenario of cannabis use and the corresponding associated risks. Our study has several limitations. First, cannabis exposure was poorly reported in the included studies, which prevented our meta-analysis from assessing it. Second, a significant portion of included studies was at moderate to high risk of bias, primarily due to a lack of information regarding missing data. Concerns were also raised about the risk of misclassification of exposure, particularly in studies from medical databases, which have a low sensitivity for non-medical drug use. Studies that relied on patient surveys faced substantial bias regarding exposure and outcome misclassification when patients assessed these data themselves. Furthermore, most included studies (n=19) were cross-sectional, a design providing a poor level of evidence unable to establish the causal link between outcome and exposure. Third, several of the included studies used the same data source, sometimes overlapping in the period, with the risk of including the same patients. Fourth, our data collection was limited to between 1 January 2016 and 31 January 2023. Therefore, our results provide a fully comprehensive report of the recent situation towards the cardiovascular health of cannabis users. It is worth noting that our research team previously conducted a review that encompassed data until 2016.[9] Considering the current situation and recent trends in cannabis use, the need to specifically address these recent developments was critical.

Further research is warranted to address the methodological limitations of pharmacoepidemiological studies on cannabis-related adverse events. In particular, observational studies with an accurate measure of cannabis exposure are lacking.

CONCLUSION

This exhaustive analysis of published data on the potential association between cannabis use and the occurrence of MACE provides new insights from real-world data. Focusing on the most recent available data aimed at providing an accurate perspective of the current situation, given the recent evolutions in the modalities of cannabis use and profiles of cannabis users. Focusing on MACE enhanced the relevance of interpretation since it is based on cardiovascular disorders with similar pathophysiological characteristics. Our findings are consistent with those from previous reviews, which outlined a positive association between cannabis use and cardiovascular disorders.[53] The increased awareness of this potential risk among cannabis users should encourage investigating such use in all patients presenting with serious cardiovascular disorders.

Author affiliations
[1]CERPOP, University of Toulouse, Inserm, Toulouse, Occitanie, France
[2]Pharmacovigilance Center, Department of Hypertension, Vascular Disease and Clinical Pharmacology, Strasbourg Regional University Hospital, Strasbourg, Grand Est, France
[3]Department of Cardiology, Toulouse University Hospital, Toulouse, Occitanie, France
[4]Center for Clinical Investigation (CIC) 1436 Inserm, Toulouse University Hospital, Toulouse, Occitanie, France
[5]University of Toulouse, Toulouse, Occitanie, France
[6]Paris-Saclay University, Gif-sur-Yvette, Île-de-France, France
[7]Addictovigilance Center, Department of Clinical Pharmacology, Toulouse University Hospital, Toulouse, Occitanie, France
[8]PEPSS team (Pharmacology Population, cohortS, biobankS), CIC Inserm 1436, University of Toulouse, Toulouse, Occitanie, France

Contributors All authors made substantial contributions to the present study: EJ: conception of the work; acquisition, interpretation of data; manuscript drafting and critical manuscript revision for important intellectual content; final approval. WS: acquisition, analysis, interpretation of data; manuscript drafting and critical manuscript revision for important intellectual content; final approval. ME: interpretation of data; critical manuscript revision for important intellectual content; final approval. CV: critical manuscript revision for important intellectual content; final approval. AD: critical manuscript revision for important intellectual content; final approval. ML-M: conception of the work; interpretation of data; critical manuscript revision for important intellectual content; final approval. All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Guarantor: EJ.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data explored in this systematic review and meta-analysis have been extracted from publicly available databases. Although the authors will not share the data directly, any interested researcher may apply the search strategy developed for this analysis, available in the online supplemental appendix.

ORCID iDs
Wilhelm Storck http://orcid.org/0009-0003-2178-4895
Meyer Elbaz http://orcid.org/0000-0002-3520-7883
Cécile Vindis http://orcid.org/0000-0003-2421-1155
Amélia Déguilhem http://orcid.org/0000-0003-0619-8401
Maryse Lapeyre-Mestre http://orcid.org/0000-0002-5494-5873
Emilie Jouanjus http://orcid.org/0000-0002-3510-2475

REFERENCES

1 Connor JP, Stjepanović D, Le Foll B, *et al*. Cannabis use and cannabis use disorder. *Nat Rev Dis Primer* 2021;7:16.
2 Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America. *Eur J Intern Med* 2018;49:2–6.
3 European Monitoring Centre for Drugs and Drug Addiction (EU body or agency). European drug report 2024: Cannabis, the current situation in Europe. LU:Publications Office of the European Union; 2024. Available: https://www.euda.europa.eu/publications/european-drug-report/2024/cannabis_en
4 Incze MA, Kelley AT, Singer PM. Heterogeneous State Cannabis Policies: Potential Implications for Patients and Health Care Professionals. *JAMA* 2021;326:2363–4.
5 Schlag AK, Baldwin DS, Barnes M, *et al*. Medical cannabis in the UK: From principle to practice. *J Psychopharmacol* 2020;34:931–7.
6 Vinette B, Côté J, El-Akhras A, *et al*. Routes of administration, reasons for use, and approved indications of medical cannabis in oncology: a scoping review. *BMC Cancer* 2022;22:319.
7 Wieckiewicz G, Stokłosa I, Stokłosa M, *et al*. Cannabidiol (CBD) in the Self-Treatment of Depression-Exploratory Study and a New Phenomenon of Concern for Psychiatrists. *Front Psychiatry* 2022;13:837946.
8 Pacher P, Steffens S, Haskó G, *et al*. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol* 2018;15:151–66.
9 Jouanjus E, Raymond V, Lapeyre-Mestre M, *et al*. What is the Current Knowledge About the Cardiovascular Risk for Users of Cannabis-Based Products? A Systematic Review. *Curr Atheroscler Rep* 2017;19:26.
10 Wolff V, Jouanjus E. Strokes are possible complications of cannabinoids use. *Epilepsy Behav* 2017;70:355–63.
11 O'Sullivan SE, Randall MD, Gardiner SM. The in vitro and in vivo cardiovascular effects of Delta9-tetrahydrocannabinol in rats made hypertensive by chronic inhibition of nitric-oxide synthase. *J Pharmacol Exp Ther* 2007;321:663–72.
12 Tamaki C, Nawa H, Takatori S, *et al*. Anandamide induces endothelium-dependent vasoconstriction and CGRPergic nerve-mediated vasodilatation in the rat mesenteric vascular bed. *J Pharmacol Sci* 2012;118:496–505.
13 Marzo V, Bisogno T, Petrocellis L. Endocannabinoids: new targets for drug development. *Curr Pharm Des* 2000;6:1361–80.
14 McPartland JM, Duncan M, Di Marzo V, *et al*. Are cannabidiol and Δ(9) -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. *Br J Pharmacol* 2015;172:737–53.
15 Paronis CA, Nikas SP, Shukla VG, *et al*. Δ(9)-Tetrahydrocannabinol acts as a partial agonist/antagonist in mice. *Behav Pharmacol* 2012;23:802–5.
16 da Costa Santos CM, de Mattos Pimenta CA, Nobre MRC. The PICO strategy for the research question construction and evidence search. *Rev Lat Am Enfermagem* 2007;15:508–11.
17 Bosco E, Hsueh L, McConeghy KW, *et al*. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. *BMC Med Res Methodol* 2021;21:241.
18 Ouzzani M, Hammady H, Fedorowicz Z, *et al*. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
19 Higgins JPT, Morgan RL, Rooney AA, *et al*. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). *Environ Int* 2024;186:108602.
20 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
21 Higgins JPT, Thomas J, Chandler J, eds. *Cochrane handbook for systematic reviews of interventions version 6.3*.Available: https://training.cochrane.org/handbook
22 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
23 Hemachandra D, McKetin R, Cherbuin N, *et al*. Heavy cannabis users at elevated risk of stroke: evidence from a general population survey. *Aust N Z J Public Health* 2016;40:226–30.
24 Parekh T, Pemmasani S, Desai R. Marijuana Use Among Young Adults (18-44 Years of Age) and Risk of Stroke: A Behavioral Risk Factor Surveillance System Survey Analysis. *Stroke* 2020;51:308–10.
25 Vin-Raviv N, Akinyemiju T, Meng QR, *et al*. Marijuana use and inpatient outcomes among hospitalized patients: analysis of the nationwide inpatient sample database. *Cancer Med* 2017;6:320–9.
26 Shah S, Patel S, Paulraj S, *et al*. Association of Marijuana Use and Cardiovascular Disease: A Behavioral Risk Factor Surveillance System Data Analysis of 133,706 US Adults. *Am J Med* 2021;134:614–20.
27 Kalla A, Krishnamoorthy PM, Gopalakrishnan A, *et al*. Cannabis use predicts risks of heart failure and cerebrovascular accidents: results from the National Inpatient Sample. *J Cardiovasc Med (Hagerstown)* 2018;19:480–4.
28 Rumalla K, Reddy AY, Mittal MK. Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. *J Neurol Sci* 2016;364:191–6.
29 Rumalla K, Reddy AY, Mittal MK. Association of Recreational Marijuana Use with Aneurysmal Subarachnoid Hemorrhage. *J Stroke Cerebrovasc Dis* 2016;25:452–60.
30 Desai R, Singh S, Patel K, *et al*. Stroke in young cannabis users (18-49 years): National trends in hospitalizations and outcomes. *Int J Stroke* 2020;15:535–9.
31 Chelikam N, Mohammad Z, Tavrawala K, *et al*. Prevalence of Cerebrovascular Accidents Among the US Population With Substance Use Disorders: A Nationwide Study. *Cureus* 2022;14:e31826.
32 Malhotra K, Rumalla K, Mittal MK. Association and Clinical Outcomes of Marijuana in Patients with Intracerebral Hemorrhage. *J Stroke Cerebrovasc Dis* 2018;27:3479–86.
33 San Luis CV, O'Hana S. Nobleza C, Shekhar S, *et al*. Association between recent cannabinoid use and acute ischemic stroke. *Neur Clin Pract* 2020;10:333–9.
34 Dutta T, Ryan KA, Thompson O, *et al*. Marijuana Use and the Risk of Early Ischemic Stroke: The Stroke Prevention in Young Adults Study. *Stroke* 2021;52:3184–90.
35 Falkstedt D, Wolff V, Allebeck P, *et al*. Cannabis, Tobacco, Alcohol Use, and the Risk of Early Stroke: A Population-Based Cohort Study of 45 000 Swedish Men. *Stroke* 2017;48:265–70.
36 Reis JP, Auer R, Bancks MP, *et al*. Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Public Health* 2017;107:601–6.
37 Draz EI, Oreby MM, Elsheikh EA, *et al*. Marijuana use in acute coronary syndromes. *Am J Drug Alcohol Abuse* 2017;43:576–82.
38 Ladha KS, Mistry N, Wijeysundera DN, *et al*. Recent cannabis use and myocardial infarction in young adults: a cross-sectional study. *Can Med Assoc J* 2022;194:E464–72.
39 Patel RS, Manocha P, Patel J, *et al*. Cannabis Use Is an Independent Predictor for Acute Myocardial Infarction Related Hospitalization in Younger Population. *J Adolesc Health* 2020;66:79–85.
40 Ma I, Genet T, Clementy N, *et al*. Outcomes in patients with acute myocardial infarction and history of illicit drug use: a French nationwide analysis. *Eur Heart J Acute Cardiovasc Care* 2021;10:1027–37.
41 Desai R, Patel U, Sharma S, *et al*. Recreational Marijuana Use and Acute Myocardial Infarction: Insights from Nationwide Inpatient Sample in the United States. *Cureus* 2017;9:e1816.
42 Karki N, Sapkota B, Magar SR, *et al*. Relationship Between Marijuana Use and Hospitalization for Acute Coronary Syndrome. *Cureus* 2022.
43 Sun Y, Liu B, Wallace RB, *et al*. Association of Cannabis Use With All-Cause and Cause-Specific Mortality Among Younger- and Middle-Aged U.S. Adults. *Am J Prev Med* 2020;59:873–9.
44 DeFilippis EM, Singh A, Divakaran S, *et al*. Cocaine and Marijuana Use Among Young Adults With Myocardial Infarction. *J Am Coll Cardiol* 2018;71:2540–51.
45 Zongo A, Lee C, Dyck JRB, *et al*. Medical cannabis authorization and the risk of cardiovascular events: a longitudinal cohort study. *BMC Cardiovasc Disord* 2021;21:426:426:.
46 Jivanji D, Mangosing M, Mahoney SP, *et al*. Association Between Marijuana Use and Cardiovascular Disease in US Adults. *Cureus* 2020;12:e11868.
47 Dillinger J-G, Pezel T, Fauvel C, *et al*. Prevalence of psychoactive drug use in patients hospitalized for acute cardiac events: Rationale and design of the ADDICT-ICCU trial, from the Emergency and Acute Cardiovascular Care Working Group and the National College of Cardiologists in Training of the French Society of Cardiology. *Arch Cardiovasc Dis* 2022;115:514–20.
48 Pezel T, Dillinger J-G, Trimaille A, *et al*. Prevalence and impact of recreational drug use in patients with acute cardiovascular events. *Heart* 2023;109:1608–16.
49 Jeffers AM, Glantz S, Byers AL, *et al*. Association of Cannabis Use With Cardiovascular Outcomes Among US Adults. *J Am Heart Assoc* 2024;13:e030178.
50 Frost L, Mostofsky E, Rosenbloom JI, *et al*. Marijuana use and long-term mortality among survivors of acute myocardial infarction. *Am Heart J* 2013;165:170–5.
51 Mukamal KJ, Maclure M, Muller JE, *et al*. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *Am Heart J* 2008;155:465–70.
52 Vallée A. Heavy Lifetime Cannabis Use and Mortality by Sex. *JAMA Netw Open* 2024;7:e2415227.
53 Chandy M, Jimenez-Tellez N, Wu JC. The relationship between cannabis and cardiovascular disease: clearing the haze. *Nat Rev Cardiol* 2025.