Annals of Internal Medicine REVIEW

Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes

A Systematic Review

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Background: Marijuana use is increasing in the United States, and its effect on cardiovascular health is unknown.

Purpose: To review harms and benefits of marijuana use in relation to cardiovascular risk factors and clinical outcomes.

Data Sources: PubMed, MEDLINE, EMBASE, PsycINFO, and the Cochrane Library between 1 January 1975 and 30 September 2017.

Study Selection: Observational studies that were published in English, enrolled adults using any form of marijuana, and reported on vascular risk factors (hyperglycemia, diabetes, dyslipidemia, and obesity) or on outcomes (stroke, myocardial infarction, cardiovascular mortality, and all-cause mortality in cardiovascular cohorts).

Data Extraction: Study characteristics and quality were assessed by 4 reviewers independently; strength of evidence for each outcome was graded by consensus.

Data Synthesis: 13 and 11 studies examined associations between marijuana use and cardiovascular risk factors and clinical outcomes, respectively. Although 6 studies suggested a metabolic benefit from marijuana use, they were based on cross-sectional designs and were not supported by prospective studies. Evidence examining the effect of marijuana on diabetes, dyslipidemia, acute myocardial infarction, stroke, or cardiovascular and all-cause mortality was insufficient. Although the current literature includes several long-term prospective studies, they are limited by recall bias, inadequate exposure assessment, minimal marijuana exposure, and a predominance of low-risk cohorts.

Limitation: Poor- or moderate-quality data, inadequate assessment of marijuana exposure and minimal exposure in the populations studied, and variation in study design.

Conclusion: Evidence examining the effect of marijuana on cardiovascular risk factors and outcomes, including stroke and myocardial infarction, is insufficient.

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As more states legalize the sale and consumption of marijuana, the number of Americans using it continues to rise (1, 2). This increase in the use of marijuana highlights the need for a better understanding of its risks and benefits. One area of importance is its effect on cardiovascular disease, the number one cause of morbidity and mortality worldwide (3).

Marijuana may affect cardiovascular health in several ways. Like other psychoactive drugs, it may have hemodynamic effects that can precipitate events (4). The active ingredient in marijuana is Δ9-tetrahydrocannabinol (THC) (5), which is responsible for the psychoactive effects of marijuana through its interaction with cannabinoid receptors. These receptors are ubiquitous in the brain and its vasculature and present throughout the body, including the myocardium, coronary endothelium, and smooth muscle cells (6, 7). In vitro and animal studies have reported that THC can modulate cannabinoid receptors on human cardiomyocytes and vascular smooth muscles, resulting in ischemia (7, 8). In vitro studies also have demonstrated that THC influences the regulation of glucose and lipid metabolism, suggesting a possible effect on vascular risk factors (9, 10). At the cellular level, THC may cause inflammatory cytokine release, alteration in lipid metabolism (11, 12), and reactive oxygen species formation (13). These effects may potentiate the progression of vascular disease. Marijuana smoking, the predominant method of use, causes a 5-fold increase in the blood carboxyhemoglobin level and a 3-fold increment in the quantity of tar inhaled compared with tobacco (14). Studies on secondhand marijuana smoke have found endothelial dysfunction in rats after exposure (15).

Given the myriad ways in which marijuana might potentiate vascular disease, we conducted a systematic review to assess the effect of regular marijuana use on cardiovascular outcomes and their associated risk factors.

METHODS

The protocol was registered at PROSPERO (CRD42016051297) (16) at the start of our investigation. This review focuses on studies examining marijuana use and cardiovascular risk factors and outcomes; our protocol also includes searches and a review of hemodynamic changes associated with marijuana use that are not reported here.

See also:

Web-Only
Supplement

Data Sources and Searches

We searched several online databases (PubMed, MEDLINE, EMBASE, PsycINFO, and the Cochrane Library) for titles and abstracts between 1 January 1975 and 30 September 2017. We chose a 1975 start date because that was the year the Alaska Supreme Court ruled that the "Alaska constitution's right to privacy protects an adult's ability to use and possess a small amount of marijuana in the home for personal use" (17). We also conducted reference and author tracking to identify additional articles and searched ClinicalTrials.gov and the National Institutes of Health Research Portfolio (NIH RePORTER) for ongoing or completed studies not reported in the literature. For search terms and details, see Supplement 1 (available at Annals.org).

Study Selection

All titles and abstracts were independently screened by 2 reviewers (M.G. and D.R.). We included observational studies (cohort, case–control, cross-sectional) and interventional studies (randomized controlled trials, experimental studies) that enrolled participants older than 12 years and were published in English. The exposure criterion was any form of marijuana (plant or pharmaceutical). The main outcomes of interest were cardiovascular risk factors and outcomes. We excluded case reports, case series, review articles, editorials, and in vitro and animal studies. The same 2 investigators independently reviewed the full texts of selected articles to identify those that met our inclusion criteria. Disagreements regarding inclusion were resolved by a third reviewer (S.K.). Interrater reliability for the abstract selection process and the concurrent decision to include the article in the review was excellent (Cohen κ, 0.87). For the selection process, see Supplement 2 (available at Annals.org).

Data Extraction and Quality Assessment

For each included study, the reviewers collected information on study design (observational or experimental), the study population (for example, healthy volunteers, regular users, or hospitalized patients), age distribution, cannabis make-up (plant based or pharmaceutical), route of exposure (smoking, vaporizing, eating, or injecting), exposure duration, and funding source.

Four investigators (D.R., M.G., S.K., and D.K.) independently rated study quality as low, moderate, or high risk of bias (ROB). We assessed ROB for outcomes in trials with the Cochrane Risk of Bias Tool (18), and for outcomes in observational studies with the Newcastle-Ottawa scale (19). Disagreements were resolved by consensus. Risk-of-bias tools and scoring are available in Supplement 3 (available at Annals.org).

Data Synthesis and Analysis

We performed a qualitative assessment and synthesis of evidence. Because of the heterogeneity of outcomes and lack of reporting of effect sizes, we did not pool any data. Through group discussion, we graded the overall strength of the evidence for each outcome as insufficient, low, moderate, or high on the basis of methods outlined by the Agency for Healthcare Research and Quality (20).

Role of the Funding Source

The NIH had no role in the design, analysis, interpretation of data, preparation or approval of the manuscript, or decision to submit the manuscript for publication.

RESULTS

Literature Search

Our search yielded 3006 abstracts, 1669 of which were selected for further evaluation. Among these, 140 were selected for full-text review. Another 7 articles were added via author and reference tracking. Of these 147 papers, 24 met our inclusion criteria (Figure).

Study Characteristics

The evidence included 9 prospective cohort studies, 3 retrospective cohort studies, 2 case–control studies, 2 interventional studies (1 experimental study and 1 randomized trial), 7 cross-sectional studies, and 1 case-crossover study. Thirteen studies assessed cardiovascular risk factors, and 11 examined cardiovascular diseases. Most studies (n = 16; 66.7%) did not report the chemical constitution (for example, THC vs. cannabidiol) of the marijuana used in the study. Among articles that specified the form of marijuana used, the plant-based form was predominant (n = 7). Among those that specified the route of exposure, smoking was predominant (n = 11), followed by oral use (n = 2). Eleven papers did not report the specific route or form of marijuana administration (such as edible or smoked). Tables 1 to 4 of Supplement 3 (available at Annals.org) detail the quality assessments for individual studies.

Cardiovascular Risk Factors

Metabolic Parameters: Lipid and Glucose Levels and Diabetes

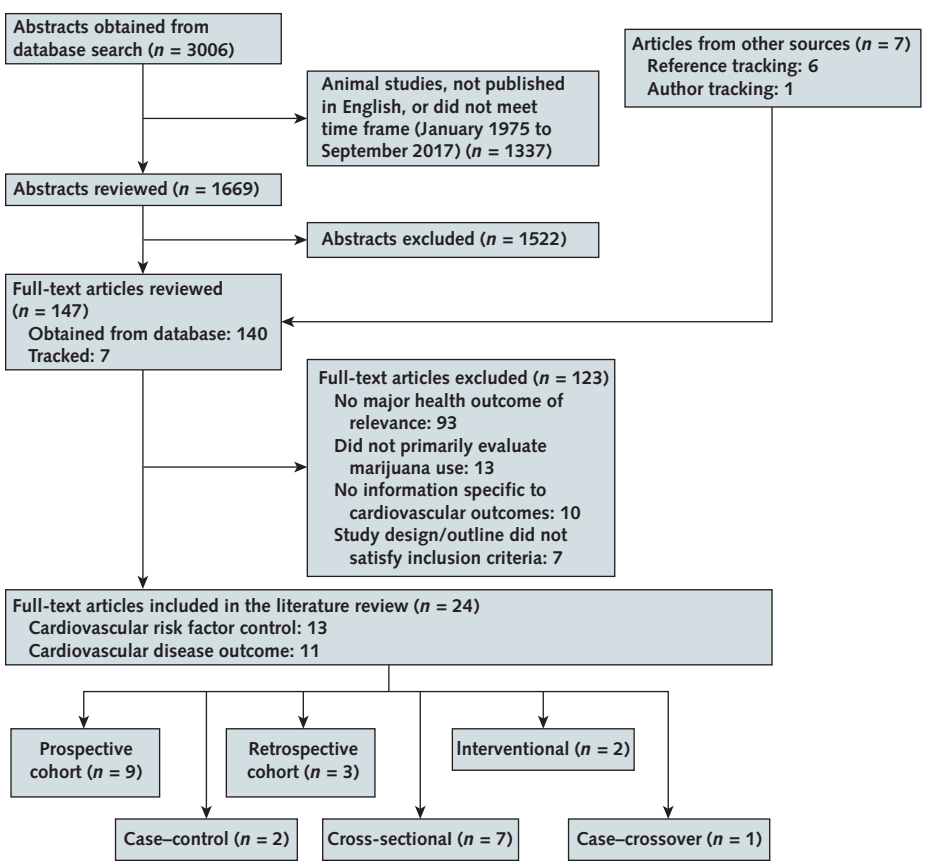
Eleven studies provided data on 1 or more metabolic parameter outcomes, including hyperglycemia, dyslipidemia, and diabetes (Appendix Table 1, available at Annals.org).

Five cross-sectional studies (3 low and 2 high ROB) examined the association between marijuana use and hyperglycemia, dyslipidemia, metabolic syndrome, or diabetes (21–25). Marijuana use was measured by self-report in all studies. Four studies were based on 3 different waves of the NHANES (National Health and Nutrition Examination Survey; 1988 to 1994, 2005 to 2010, and 2005 to 2012) (21–23, 25). Three of the 4 used multivariable analysis to examine the association between marijuana use and metabolic parameters after adjustment for baseline characteristics. All 3 studies reported that marijuana use had different favorable associations, including a lower prevalence of diabetes (22), lower glucose levels (25), or higher high-density lipoprotein cholesterol concentrations (21, 22, 25). The fourth NHANES study (2005 to 2012) used both regression models and an instrumental variable analysis to

examine associations (23). Marijuana use was associated with a beneficial metabolic effect in the regression model evaluation; no such effect was seen in the instrumental variable analysis. The final cross-sectional study was an exploratory analysis based on a small sample of 30 persons who were heavy marijuana users and 30 control participants matched for age, sex, ethnicity, and body mass index (BMI) (24). The authors identified no differences between groups in glucose tolerance or fasting glucose, total cholesterol, or triglyceride levels.

Three prospective studies (1 low, 1 moderate, and 1 high ROB) examined the association of marijuana use with risk factors (26–28). Two were based on the CARDIA (Coronary Artery Risk Development in Young Adults) cohort study, which examined the development and determinants of clinical and subclinical cardiovascular disease and its risk factors (26, 28). The CARDIA study began in 1985 to 1986 with 5113 black and white men and women aged 18 to 30 years. It included comprehensive in-person baseline and outcome data (sociodemographic characteristics; fasting glucose levels; BMI; diet and physical activity; and use of tobacco, alcohol, and other substances) and several exposure assessments during a long follow-up. Questions pertaining to marijuana use lacked detail on the form used, and exposure was quantified differently in each study. The low-ROB CARDIA-based study reported no associations between marijuana use and changes in glucose, high-density lipoprotein cholesterol, or triglyceride levels among heavy users (>1800 days of use) compared with nonusers during 15 years of follow-up (26). The moderate-ROB CARDIA-based study examined the association between marijuana use and diabetes and prediabetes (28). Marijuana use was ascertained in year 7 of the prospective cohort, and exposure was very limited: The highest category of use was a lifetime frequency of more than 100 times. Incidence of diabetes and prediabetes assessed at 4 subsequent follow-up examinations over 18 years was based on laboratory assessment (oral glucose tolerance or glycosylated hemoglobin test). A greater risk for prediabetes (hazard ratio [HR], 1.39 [95% CI, 1.13 to 1.71]) was identified among participants who reported using marijuana 100 or more times during follow-up compared with nonusers. The final prospective study (high ROB) followed 18 000 Swedish men and women aged 18 to 84 years over 10 years but assessed marijuana exposure only once, at baseline (27). Measures of socioeconomic factors, diet, or other drug use at baseline were limited. No definite relationship was found between marijuana use and diabetes; CIs around the risk estimate were wide and compatible with either increased or decreased risk for diabetes with marijuana use (adjusted odds ratio, 0.94 [CI, 0.63 to 1.42]).

Figure. Evidence search and selection.



Two experimental studies (high ROB) examined the effect of cannabis-related compounds on metabolic factors (29, 30). Both had small sample sizes, and neither identified a measurable effect on metabolic parameters.

Obesity

The association between marijuana use and obesity was evaluated in 1 prospective study; 1 retrospective study; 1 randomized controlled trial; and 4 cross-sectional studies, 2 of which were based on NHANES (both low ROB) (21, 23). None of these studies found an association between marijuana use and BMI. Another cross-sectional study of 786 Inuit adults (moderate ROB) found that participants who used marijuana in the past year had a lower BMI than nonusers (odds ratio, 0.56 [CI, 0.37 to 0.84]). Although this study included important baseline characteristics, such as physical activity and dietary intake, the marijuana exposure assessment that divided the population into ever- and never-users was inadequate (31). Another study (high ROB) examined the charts of 297 women referred for weight management and found that marijuana use was associated with a lower BMI (R^2, 0.96; $P = 0.0173$). This trial was limited by lack of adjustment for baseline characteristics and biased sample selection (32).

One prospective cohort study (low ROB) found no association between marijuana use and changes in BMI (mean [±SE] adjusted BMI among nonusers, 28.9 ± 0.3 kg/m^2; mean [±SE] BMI among frequent users, 28.9 ± 0.3 kg/m^2) (26). In a longitudinal pre birth study (the Mater-University of Queensland Study of Pregnancy) in 7223 women and their offspring (high ROB), the children were administered health, sociodemographic, and lifestyle questionnaires at ages 14 and 21 years (33). Although BMI was measured at both ages, a retrospective assessment of marijuana use was conducted only at age 21. Daily cannabis users were less likely (odds ratio, 0.2 [CI, 0.1 to 0.4]) to have a BMI greater than 25 kg/m^2 than were never-users. This study was limited by inadequate baseline data on the children.

In a small double-blind placebo-controlled randomized trial (high ROB), the effect of 5 mg of dronabinol on BMI was assessed at 28 days in 13 of the 19 participants who completed follow-up (30). No statistically significant association was found between marijuana use and BMI.

Clinical Outcomes

Details of described studies are available in Appendix Table 2 (available at Annals.org).

Acute Myocardial Infarction

The MIOS (Determinants of Myocardial Infarction Onset Study) was a case-crossover study that examined marijuana use as a potential trigger for myocardial infarction (34). In this multicenter trial, 3882 patients with acute myocardial infarction were interviewed, on average within 4 days of their infarction, about their history, timing, and frequency of marijuana smoking. Marijuana use in the 1 hour immediately preceding the onset of myocardial infarction symptoms was then compared with its expected frequency on the basis of self-reported use during the previous year. Of the 3882 patients, 9 (0.2%) and 124 (3.2%) reported smoking marijuana within 1 hour of the onset of myocardial infarction symptoms and in the previous year, respectively. The myocardial infarction risk in the first hour after smoking was greater than that expected among users (relative risk, 4.8 [CI, 2.4 to 9.5]). That individuals served as their own control helped limit confounding from other behaviors that may be associated with marijuana use. The study, however, was assessed as moderate ROB, primarily because of recall bias.

Stroke

Two prospective studies examined the effect of marijuana exposure on stroke and transient ischemic attack (35, 36). One study (moderate ROB), based on CARDIA, reported that marijuana was not associated with stroke (adjusted HR, 0.65 [CI, 0.16 to 2.66]; $P = 0.76$); however, the exposure was minimal (median lifetime of 0.51 marijuana-years or 50 times) and the population was young and healthy (35). Another study (high ROB) enrolled 49 321 Swedish men conscripted into compulsory military service between the ages of 18 and 20 years. They were followed until age 59 to assess the initial occurrence of stroke. No association between cannabis use and stroke (HR, 0.93 [CI, 0.34 to 2.57]) was identified, but the study was limited by potential misclassification of the exposure, given that it was not reassessed over 25 years of follow-up and adjustment for baseline characteristics was inadequate (36).

A third study (high ROB) using a case–control design compared patients (aged 18 to 55 years) admitted to the hospital for stroke or transient ischemic attack with other, matched hospitalized patients. It found no association between stroke and plant-based marijuana use (adjusted odds ratio, 1.59 [CI, 0.71 to 3.70]); however, the study was limited because it measured use with urine toxicology screens, and although all case participants were screened, it is unclear why the control participants underwent screening. The urine drug screen may have misclassified exposure, because results may remain positive for up to 10 weeks (37).

Cardiovascular Mortality and All-Cause Mortality

Two prospective cohort studies (both high ROB) involving myocardial infarction survivors enrolled in MIOS between 1989 and 1996 examined the association between marijuana use and mortality (38, 39). Marijuana use in the year before the first myocardial infarction was self-reported at baseline and was not evaluated again. Cause of death was assessed by physician review of death certificates. In the study that followed patients for a median of 3.8 years, baseline use of marijuana once weekly or more (HR, 4.2 [CI, 1.2 to 14.3]) and less than once weekly (HR, 2.5 [CI, 0.9 to

7.3]) was associated with an increased risk for cardiovascular mortality compared with nonuse. This study also found an association between marijuana use and an increased risk for all-cause mortality (HR, 3.0 [CI, 1.3 to 7.0]; $P = 0.009$) (38). In the other MIOS-based study, which followed patients for a median of 12.7 years, any marijuana use was associated with an increased risk for all-cause mortality compared with nonuse, although the finding was not statistically significant (HR, 1.29 [CI, 0.81 to 2.05]; $P = 0.28$) (39).

Another investigation (moderate ROB) used CARDIA data to examine the association between cumulative lifetime marijuana use and cardiovascular mortality (35). This study measured exposure several times and had robust assessment of baseline characteristics and outcomes. It found no association between marijuana use (cumulative ≥5 years and recent) and cardiovascular mortality (adjusted HR, 0.95 [CI, 0.2 to 4.59]). The study also included a composite outcome of cardiovascular mortality, stroke, and coronary heart disease and, again, found no association between 5 or more years of marijuana use and this combined outcome (adjusted HR, 0.72 [CI, 0.35 to 1.50]). However, median cumulative marijuana exposure in the cohort was minimal (0.51 marijuana-years over 26 years). Further, although participants were followed for 26 years, the median age at recruitment was 18 to 30 years. Because of these factors, the study probably was underpowered to assess the association between marijuana use and cardiovascular disease. Finally, a retrospective cohort study (high ROB) linking NHANES to the National Center for Health Statistics survey found that users were at higher risk than nonusers for "hypertension-related" mortality. However, the marijuana exposure assessment was flawed, the outcome definition unclear, and the adjustment for baseline differences inadequate (40).

Other Cardiovascular Outcomes

Four studies examined the association between marijuana use and various outcomes, including peripheral arterial disease (41), irregular heartbeat (42), multifocal intracranial stenosis (43), and aneurysmal subarachnoid hemorrhage (44). All 4 studies were rated as high ROB, primarily because their marijuana exposure assessments and adjustments for baseline risk factors were inadequate.

Ongoing Studies

We found no relevant ongoing or completed studies at ClinicalTrials.gov (**Supplement 1**). Our search of NIH RePORTER revealed a prospective cohort study funded by the NIH in 2017 called Impact of Marijuana on Adherence, Risk Factor Control and Cardiovascular Outcomes (45). This project is evaluating the association between smoking marijuana in the past 30 days and the composite outcome of acute myocardial infarction, stroke, and revascularization in elderly patients with coronary artery disease.

DISCUSSION

Evidence that marijuana use either increases or decreases most cardiovascular risk factors is insufficient, as is evidence regarding any association between marijuana use and adverse cardiovascular outcomes (**Table**). The current available literature is limited by a preponderance of cross-sectional study designs. Although the literature includes several long-term prospective studies, they are limited by recall bias, a lack of robust longitudinal assessment of marijuana use, participants with infrequent marijuana use, and the relative youth of some of the cohorts.

A MEDLINE search revealed a recent systematic review (46) of marijuana harms that identified 2 studies (rated as high ROB in the review) on the relationship between marijuana use and cardiovascular events (34, 39). We included both articles in our systematic review and assessed 1 of them differently, assigning its ROB as moderate rather than high (34). The strength of this study lies in the minimization of confounding. Marijuana users also engage in other behaviors that are associated with poor outcomes. The use of a case-crossover design in the study of marijuana compares each participant to him- or herself and eliminates this problem. The study was limited by recall bias related to the marijuana use assessment; otherwise, it was well-designed.

Although some cross-sectional studies in this review suggested that marijuana has metabolic benefits (21, 22, 25, 31–33), those with more robust analytic designs found no evidence of benefit (23), and other prospective studies found potentially harmful effects (28). These findings are of particular interest. Many articles in the lay press have suggested to the public that marijuana use has cardiovascular benefits, reduces blood pressure, stabilizes blood sugar levels, or improves cholesterol profiles (47, 48). Our review found insufficient evidence to support these claims. Given public opinion that marijuana is safe or even beneficial, the insufficiency of the literature is concerning (49). An active research agenda in this area is needed to provide the public with accurate information. Finally, despite the popular belief that marijuana use causes "the munchies" (50), we found no evidence that it is associated with weight gain or obesity.

An important consideration in our understanding of marijuana effects relates to the standards of evidence necessary to identify harms. Using experimental trials to study marijuana harms is unethical; only observational studies are feasible, despite their inherent biases. Further, the greatest clinical uncertainty concerns older patients at higher risk for cardiovascular disease (such as those with hypertension and diabetes) who use marijuana regularly over long periods. Therefore, the best possible study to assess the effect of marijuana use on cardiovascular outcomes would be a prospective cohort study among higher-risk participants, with several exposure assessments during follow-up and a robust evaluation of baseline characteristics and outcomes. The best evidence currently available, in contrast, is from the MIOS and CARDIA cohorts, although

Table. Strength of Evidence Between Marijuana and Each Risk Factor and Outcome

Outcome	Study Type	Strength of Evidence	Comments/Limitations
Blood glucose level	1 prospective cohort study, 1 RCT, 1 experimental study, and 5 cross-sectional studies	Insufficient	1 well-designed prospective study found marijuana had no effect on blood glucose levels. Experimental studies limited by small sample size and cross-sectional studies (with variable rigor in analysis) reported mixed findings.
Hypertension	1 cross-sectional study	Insufficient	Limited data from NHANES.
Diabetes	2 prospective cohort studies and 1 cross-sectional study	Insufficient	Most of these studies were limited by minimal exposure to marijuana and single-exposure assessments over long follow-up periods.
TC level	1 prospective cohort study, 1 RCT, and 3 cross-sectional studies	Insufficient	1 well-designed, prospective study found no effect on TC levels. Poorly designed RCTs and cross-sectional studies (variable rigor in analysis) reported mixed findings.
LDL-C level	3 cross-sectional studies	Insufficient	Limited data with variable study quality and mixed findings.
TG level	1 prospective cohort study, 1 RCT, and 5 cross-sectional studies	Insufficient	1 well-designed, prospective study found no effect on TG levels. Poorly designed RCTs and cross-sectional studies (with variable rigor in analysis) reported mixed findings.
HDL-C level	1 prospective cohort study,1 RCT, and 6 cross-sectional studies	Insufficient	1 well-designed prospective study with low bias found no effect on HDL-C levels. 1 RCT limited by small, unjustified sample size and the cross-sectional studies (with variable rigor in analysis) reported mixed findings.
Obesity (BMI)	1 prospective cohort study, 1 retrospective cohort study, 1 trial, and 4 cross-sectional studies	Low	1 well-designed prospective study and 2 low-ROB cross-sectional studies found no link to obesity. All available data suggested that marijuana use had no association with BMI or that marijuana use was associated with lower BMI. The studies that suggested marijuana use was associated with lower BMI were limited by cross-sectional study designs.
Myocardial infarction	1 case-crossover study	Insufficient	Potential confounding from recall bias but an otherwise well-designed study.
Stroke	2 prospective cohort studies and 1 case–control study	Insufficient	Minimal exposure to marijuana and single-exposure assessments over long follow-ups; some cohorts were young and healthy (underpowered).
Cardiovascular mortality	2 prospective cohort studies and 1 retrospective study	Insufficient	1 prospective study was limited by recall bias and inadequate exposure assessment, and the second was flawed because it was probably underpowered to assess events; the retrospective study had several methodological flaws, including an inadequate exposure assessment.
All-cause mortality	1 prospective cohort study	Insufficient	Flawed exposure assessment (subject to recall bias).
Cardiovascular disease	1 prospective cohort study	Insufficient	Minimal exposure to marijuana, and cohorts were young and healthy (underpowered).
Peripheral vascular disease	1 case–control study	Insufficient	Inadequate adjustment for confounders and several other methodological flaws.
Arrhythmia	1 cross-sectional study	Insufficient	Inadequate adjustment for confounders and several other methodological flaws.
Multifocal intracranial stenosis	1 cross-sectional study	Insufficient	Inadequate adjustment for confounders and several other methodological flaws.
Intracranial hemorrhage	1 cross-sectional study	Insufficient	Inadequate adjustment for confounders and several other methodological flaws.

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NHANES = National Health and Nutrition Examination Survey; RCT = randomized controlled trial; ROB = risk of bias; TC = total cholesterol; TG = triglyceride.

both have serious flaws (26, 28, 34, 35). Whereas MIOS assessed marijuana exposure only once and was limited by recall bias, CARDIA made several assessments of marijuana exposure, but the overall exposure in the cohort was minimal and the cohort was young and likely underpowered to assess the outcomes of stroke and cardiovascular mortality.

Our systematic review also highlights other important evidence gaps. First, most studies failed to capture current and lifetime marijuana use adequately. More robust exposure assessment tools are necessary to allow evaluation of the acute and long-term health effects of marijuana (51). Second, almost a quarter of the studies failed to report the specific route of cannabis use and the chemical constitution of the cannabis examined. The number of marijuana users, as well as the variety of routes (for example, vaping, dabbing, ingesting, topical application), is increasing; therefore, collection of data regarding use must be more standardized, because the various forms may differ in toxic effects. In particular, high-quality safety data on the effects of edible marijuana on the cardiovascular system are lacking. The effects of THC persist in the body longer after oral administration than inhalation. Prospective studies examining the effects of edible marijuana on other cardiovascular events, such as acute myocardial infarction

and stroke, are necessary, especially because use of edible forms is increasing among older adults, who are at higher risk for cardiovascular disease (52).

Our study has several limitations that deserve comment. We excluded articles not published in English; thus, we may have overlooked relevant studies. The diverse representation of outcomes across studies, variation in study design, and frequent lack of effect size reporting precluded a meta-analysis. In addition, most studies inadequately assessed marijuana exposure. Finally, most studies in this review were rated as high ROB, so their results should be interpreted with caution.

In summary, although several studies suggested a metabolic benefit from marijuana use, they were based on cross-sectional designs and not supported by prospective studies. Evidence examining the effect of marijuana on diabetes, hyperlipidemia, acute myocardial infarction, stroke, and cardiovascular mortality was insufficient. Adequately powered prospective studies are needed to determine the effect of chronic marijuana use on cardiovascular health.

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Appendix Table 1. Studies That Examined Exposure to MJ and CVD

Study, Year (Reference) Design	Study Population	Sample Size, *n*	Age, *y*	Cannabis Form/Route of Exposure	MJ Exposure Assessment*	Outcome Examined	Follow-up	Findings†	Risk of Bias	Funding Source
Danielsson et al, 2016 (27) Prospective cohort	Stockholm Public Health Cohort	17 833	18–84	Plant/smoke	Users categorized as never-/ever-users; 14.3% were ever-users	Diabetes (plasma glucose)	8 y	No association between MJ use and diabetes (OR, 0.94 [95% CI, 0.63-1.42])	High	Research Council for Health
Rajavashisth et al, 2012 (22) Cross-sectional	Participants from NHANES III (1988–1994)		20–59	Plant/smoke or edible	Participants categorized as light current users (≤4 d/mo) or heavy current users (≥5 d/mo); 36.7% and 8.8% reported past and current MJ use, respectively	1. Diabetes (plasma glucose, HbA_{1c}) 2. Dyslipidemia (HDL-C, LDL-C, TC, TG) 3. HTN	NA	Past users, current light and current heavy MJ users had lower prevalence of diabetes than non-MJ users ($P < 0.001$) All MJ users had higher prevalence of HDL-C >40 mg/dL, TC <240 mg/dL, and TG <200 mg/dL ($P < 0.0001$), and current MJ users had higher prevalence of LDL-C <160 mg/dL ($P < 0.05$) No significant association between MJ use and HTN	Low	Multiple grants CDU, NIH
Bancks et al, 2015 (28) Prospective cohort	Adults without diabetes from CARDIA study	3151 at year 7, 3034 at year 25	18–30	NS/NS	Users were asked about number of days of use in prior 30 d and lifetime use (i.e., 1–2, 3–9, 10–99, or ≥100 times)	1. Diabetes (HbA_{1c}, serum glucose) 2. Glucose intolerance (OGTT)	18 y	No association between MJ use and diabetes Current MJ users (OR, 1.65 [CI, 1.15-2.38]) and lifetime users (OR, 1.49 [CI, 1.06-2.11]) had higher odds of impaired fasting glucose than nonusers Current MJ users (≥100 times) had elevated risk for prediabetes (HR, 1.39 [CI, 1.13-1.71]) than nonusers	Moderate	NIH, NHLBI
Permutt et al,1976 (29) Experimental study	Long-term MJ users	10	23–31	Plant/smoke	Participants who smoked MJ or placebo cigarette underwent a 5-h GTT	Plasma glucose levels	5-h OGTT assessed	No significant difference between peak BG, time of peak BG, low BG, total insulin secreted, peak insulin secreted, and time of peak insulin secretion	High	NIH, NIDA, NIAAA
Vidot et al, 2014 (25) Cross-sectional	Adults without diabetes selected from NHANES (2005–2010)	8478	20–59	NS/NS	Users categorized as past and current MJ users (≥1 d in the past 30 d)	1. FBG 2. Dyslipidemia (HDLC, TG) 3. Metabolic syndrome	NA	Past and current MJ users had lower mean FBG than never-users ($P = 0.03$) Among men, past and current MJ users had higher mean HDL-C than never-users ($P < 0.001$) Among male current MJ users, prevalence of elevated waist circumference was significantly lower than that of never-users ($P < 0.0001$) Past (OR, 0.61 [CI, 0.40-0.91]) and current (OR, 0.49 [CI, 0.25-0.97]) MJ users less likely than never-users to have metabolic syndrome	High	NIH/NIDA, NIH/NIMHD
Thompson and Hay, 2015 (23) Cross-sectional	Participants from NHANES (2005–2012)	6281	20–59	NS/NS	Users categorized as past and current MJ users (≥1 d in the past 30 d)	1. FBG 2. Dyslipidemia (HDLC, TG) 3. Obesity (BMI)	NA	Although simple regression analyses demonstrated current MJ use was associated with lower BMI, instrumental variable analysis demonstrated no significant relationship between current MJ use and any metabolic parameters, including FBG, TG, HDL-C, and BMI	Low	None

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Appendix Table 1–Continued

Study, Year (Reference) Design	Study Population	Sample Size, *n*	Age, *y*	Cannabis Form/Route of Exposure	MJ Exposure Assessment*	Outcome Examined	Follow-up	Findings†	Risk of Bias	Funding Source
Ngueta et al, 2015 (31) Cross-sectional	Adults without diabetes	786	18–74	NS/NS	Participants grouped as users if they reported use in past 12 mo and as nonusers if they reported no use during same period	1. FBG 2. Dyslipidemia (HDL-C, LDL-C, TG, TC) 3. Obesity (BMI)	NA	No association between MJ use and FBG (P = 0.76), TC (P = 0.29), LDL-C (P = 0.08), HDL-C (P = 0.50), or TG (P = 0.13) MJ use was associated with lower prevalence of obesity (OR, 0.56 [CI, 0.37-0.84]) after adjustment for other factors	Moderate	Nunavik Regional Board of Health and Social Services
Reichenbach et al, 2015 (30) Randomized controlled trial	Patients with normal results on stress testing	19	18–75	Synthetic/ oral	NA	1. FBG 2. Dyslipidemia (HDL-C, TG, TC) 3. Obesity (BMI)	4 wk	Dronabinol exposure had no significant change in BG (P = 0.84), TC (P = 0.84), HDL-C (P = 0.28), TG (P = 0.44), or BMI (P = 0.63) before and after treatment compared with placebo group	High	American College of Gastroenterology
Muniyappa et al, 2013 (24) Cross-sectional	Case patients are healthy MJ users	30 case patients, 30 control participants	21–28	Plant/smoke	Case patients were adults who smoked (self-reported) 4 d/wk for at least 6 mo	1. FBG 2. Dyslipidemia (HDL-C, LDL-C, TG, TC)	NA	MJ smokers (median 6 joints/day) had no significant difference in FBG, insulin, TC, LDL-C, or TG compared with control participants MJ users had lower plasma HDL-C levels (40 ± 14 mg/dL) than control participants (55 ± 13 mg/dL) (P = 0.02)	High	NIDDK, NIH, NIDA
Penner et al, 2013 (21) Cross-sectional	Adults without diabetes (NHANES, 2005–2010)	4657	20–59	NS/smoke	Participants grouped as past users, current users (≥1 d in the past 30 d), and never-users	1. FBG 2. HbA_{1c} 3. Dyslipidemia (HDL-C, TG) 4. BMI	NA	Current MJ users had a higher HDL-C level (1.63 mg/dL [CI, 0.23-3.04]) than never-users No association with FBG, HbA_{1c}, TG, or BMI	Low	None
Hayatbakhsh et al, 2010 (33) Retrospective cohort	Young adults from the MUSP cohort	2566	18.2–23.1 (mean, 20.4)	NS/NS	Exposure assessed once (at age 21 y) Usage graded as never, not in the past month, once or so, every few days, and every day	Obesity (BMI)	7 y	Regular MJ users were less likely to have BMI ≥25 (OR, 0.5 [CI, 0.3–0.8]; P < 0.01), and daily users were the least likely to have BMI ≥25 (OR, 0.2 [CI, 0.1–0.4]; P < 0.001)	High	National Health and Medical Research Council (Australia)
Rodondi et al, 2006 (26) Prospective cohort	Young adults from CARDIA study	3617	18–30	NS/smoke	Exposure assessed several times Users asked about number of days of use and lifetime exposure	1. Glucose 2. Dyslipidemia (HDL-C, TG, TC) 3. Obesity (BMI)	Follow-up of 15 y	MJ use (average 10 d/mo) had no association with BG, TG, TC, HDL-C, or BMI	Low	NIH, Swiss National Foundation
Warren et al, 2005 (32) Cross-sectional	Female participants referred for weight management	297	16–79 (mean, 40.6 ± 1.64)	NS/NS	No information provided on exposure assessment	Obesity (BMI)	NA	Participants who used MJ in the past year had lower BMI (R^2 = 0.96; P = 0.0173), no adjustment for confounders	High	None

BG = blood glucose; BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults; CDU = Charles R. Drew University; FBG = fasting blood glucose; GTT = glucose tolerance test; HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; HTN = hypertension; LDL-C = low-density lipoprotein cholesterol; MJ = marijuana; MUSP = Mater-University of Queensland Study of Pregnancy; NA = not applicable; NHANES = National Health and Nutrition Examination Survey; NHLBI = National Heart, Lung, and Blood Institute; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIDA = National Institute on Drug Abuse; NIDDK = National Institute on Diabetes and Digestive and Kidney Diseases; NIH = National Institutes of Health; NIMHD = National Institute on Minority Health and Health Disparities; NS = not specified; OGTT = oral glucose tolerance test; OR = odds ratio; TC = total cholesterol; TG = triglycerides.

* Cumulative lifetime exposure listed if presented in study.

† Reported findings are adjusted for baseline factors unless otherwise indicated.

Appendix Table 2. Studies That Examined Exposure to MJ and CVD

Study, Year (Reference) Design	Study Population	Sample Size, *n*	Age, *y*	Cannabis Form/Route of Exposure	MJ Exposure Assessment*	Follow-up	Findings†	Risk of Bias	Funding Source
Cardiovascular and all-cause mortality									
Yankey et al, 2017 (40) Retrospective	Participants from NHANES	1213	Mean: 37.7 ± 11.2	Plant/smoke	Assessed once at baseline	20 y	MJ users had higher risk for HTN-related mortality (AHR, 3.42 [95% CI, 1.2-9.79]) vs. nonusers but no increase in risk for heart disease mortality (AHR, 1.09 [CI, 0.63–1.88])	High	None
Reis et al, 2017 (35) Prospective cohort	MJ users from CARDIA study	5113	18-30	NS/smoke	Cumulative lifetime exposure was 0.51 MJ-years	26.9 y	≥5 MJ-years (HR, 0.95 [CI, 0.2-4.59]) and recent MJ use (HR, 1.2 [CI, 0.23-6.16]) had no association with CVD mortality In addition, ≥5 years' MJ use had no association with composite outcome of stroke, CVD mortality, and CAD (AHR, 0.72 [CI, 0.35-1.50])	Moderate	NHLBI, NIA
Frost et al, 2013 (39) Prospective cohort	Patients hospitalized with AMI (MIOS)	2097	Mean: 43.7 ± 8.2 (users) and 52 ± 7.7 (nonusers)	NS/NS	Exposure assessed only once. 5.2% of population reported MJ use in the year preceding MI	18 y	No association between any MJ use and all-cause mortality (HR, 1.29 [CI, 0.81–2.05]; $P = 0.28$)	High	NIH, Harvard Medical School Scholars in Medicine Office
Mukamal et al, 2008 (38) Prospective cohort	Patients hospitalized with AMI	1913	Mean: 42.6 ± 8.8 (users) and 62.0 ± 12.3 (nonusers)	NS/NS	Users classified as less than weekly and weekly or more. 2.7% of participants reported MJ use in the year preceding MI	3.8 y	Exposure to any form of MJ was associated with a nonsignificant increased CVD mortality rate (HR, 1.9 [CI, 0.6−6.3]) among patients vs. nonusers MJ use was associated with increased risk for all-cause mortality (HR, 3.0 [CI, 1.3-7.0]; $P = 0.009$)	High	NHLBI, NIAAA, AHA
AMI									
Mittleman et al, 2001 (34) Case-crossover	Patients hospitalized with AMI	3882	Mean: 43.7 ± 8 (users) and 62.0 ± 12.5 (nonusers)	Plant/smoke	Frequency over the past year and most recent use of MJ assessed to estimate exposure within 1 h prior to MI onset, 3.2% of participants reported MJ use in the year preceding MI	Median: 4 d	First hour after smoking MJ associated with higher risk for AMI onset (RR, 4.8 [CI, 2.4-9.5]; $P < 0.001$) Association lost in the second hour (RR, 1.7 [CI, 0.6-5.1]; $P = 0.34$)	Moderate	NHLBI, AHA
Stroke/TIA									
Falksted et al, 2017 (36) Prospective cohort	Healthy MJ users	49 321	18-59	NS/NS	Collected once at baseline Exposure status quantified never, 1–10 times, 11–50 times, and >50 times	39 y	Overall, no association between MJ use and stroke (HR, 0.93 [CI, 0.34-2.57]) In addition, MJ use >50 times had no association with ischemic stroke (HR, 1.47 [CI, 0.83-2.56]) after adjustment for tobacco use	High	The Research Council for Health, Working Life and Welfare

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Appendix Table 2–Continued

Study, Year (Reference) Design	Study Population	Sample Size, *n*	Age, *y*	Cannabis Form/Route of Exposure	MJ Exposure Assessment*	Follow-up	Findings†	Risk of Bias	Funding Source
Reis et al, 2017 (35) Prospective cohort	Healthy MJ users from CARDIA study	5113	18-30 at baseline	NS/smoke	Cumulative lifetime exposure was 0.51 MJ-years	26.9 y	MJ use had no association with ischemic stroke/TIA (AHR, 0.65 [CI, 0.16-2.66]; $P = 0.76$) after adjustment for baseline factors	Moderate	NHLBI, NIA
Barber et al, 2013 (37) Case–control	Case patients: patients hospitalized for ischemic stroke/TIA	218 case patients and 160 control participants	18-55	Plant/NS	Urine drug screens used to verify exposure	NA	Cannabis use had no association with ischemic stroke/TIA (OR, 1.59 [CI, 0.71-3.70])	High	The Auckland District Health Board A+ Trust provided funding for drug screens
Cerebrovascular mortality									
Yankey et al, 2017 (40) Retrospective	Participants from NHANES linked to NCHS	1213	Mean: 37.7 ± 11.2	Plant/smoke	Assessed once at baseline, and one-time users counted as exposed during follow-up	20 y	MJ use was not significantly associated with cerebrovascular mortality (IRR, 1.32 [CI, 0.54–3.43])	High	None
Irregular pulse/arrhythmia									
Khiabani et al, 2008 (42) Cross-sectional	Drivers with suspected DUIs	502 case patients and 125 control participants	Mean: 26 (case patients) and 32.5 (control participants)	NS/NS	Exposure status determined from database Frequency, duration, lifetime exposure not measured	NA	THC-positive drivers had a higher mean pulse rate and irregular pulse rate, but no ECGs were recorded to identify the nature of the irregular pulse	High	The Norwegian Institute of Public Health
PVD									
Bérard et al, 2013 (41) Case–control	Nondiabetic patients with PAD	113 case patient and 241 control participants	Mean: 39 ± 7.8 (case patients) and 33.1 ± 6 (control participants)	NS/smoke	Exposure status determined via questionnaire and urine testing Frequency, duration, lifetime exposure not measured	NA	MJ use had no association with PAD among nondiabetics, but the models were not adjusted for current smoking	High	Fondation de France
MIS									
Wolff et al, 2011 (43) Prospective cohort	Patients hospitalized for acute ischemic stroke	48	Mean: 35.5 ± 8	NS/smoke	A questionnaire on drug use was used but no detail given	2 y	Cannabis use had an association with MIS (OR, 113 [CI, 9-5047]; $P < 0.001$)	High	NS
SAH									
Rumalla et al, 2016 (44) Cross-sectional	Patients hospitalized for aneurysmal SAH	2104 users and 91 948 nonusers	15-54	NS/NS	Exposure status assessed using ICD-9 codes	NA	Cannabis use was an independent predictor of SAH (OR, 1.18 [CI, 1.12-1.24])	High	NS

AHA = American Heart Association; AHR = adjusted hazard ratio; AMI = acute myocardial infarction; CAD = coronary artery disease; CARDIA = Coronary Artery Risk Development in Young Adults; CVD = cardiovascular disease; DUI = driving under the influence; ECG = electrocardiogram; HR = hazard ratio; HTN = hypertension; ICD-9 = International Classification of Diseases, Ninth Revision; IRR = incidence rate ratio; MI = myocardial infarction; MIOS = Determinants of Myocardial Infarction Onset Study; MIS = multifocal intracranial stenosis; MJ = marijuana; NA = not applicable; NCHS = National Center for Health Statistics; NHANES = National Health and Nutrition Examination Survey; NHLBI = National Heart, Lung, and Blood Institute; NIA = National Institute on Aging; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIH = National Institutes of Health; NS = not specified; OR = odds ratio; PAD = peripheral arterial disease; PVD = peripheral vascular disease; RR = relative risk; SAH = subarachnoid hemorrhage; THC = Δ9-tetrahydrocannabinol; TIA = transient ischemic attack.

* Cumulative lifetime exposure listed if presented in study.

† Reported findings are adjusted for baseline factors unless otherwise indicated.