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Cannabis and adverse cardiovascular events: A systematic review and meta-analysis of observational studies

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ABSTRACT

Background: Cannabis is the most used illicit drug in the world. Global trends of decriminalization and legalization of cannabis lead to various forms of cannabis use and bring great concerns over adverse events, particularly in the cardiovascular (CV) system. To date, the association between cannabis and adverse CV events is still controversial.

Purpose: We aim to conduct a systematic review and meta-analysis to assess the adverse CV events from cannabis use.

Patients and methods: A systematic search for publications describing the adverse CV events of cannabis use, including acute myocardial infarction (MI) and stroke, was performed via PubMed, Scopus, and Cochrane Library databases. Data on effect estimates in individual studies were extracted and combined via random-effects meta-analysis using the DerSimonian and Laird method, a generic inverse-variance strategy.

Results: Twenty studies with a total of 183,410,651 patients were included. The proportion of males was 23.7%. The median age and follow-up time were 42.4 years old (IQR: 37.4, 50.0) and 6.2 years (IQR: 1.7, 27.7), respectively. The prevalence of cannabis use was 1.9%. Cannabis use was not significantly associated with acute MI (pooled odds ratio (OR): 1.29; 95%CI: 0.80, 2.08), stroke (pooled OR 1.35; 95%CI: 0.74, 2.47), and adverse CV events (pooled OR: 1.47; 95%CI: 0.98, 2.20).

Conclusion: The risk of adverse CV events including acute MI and stroke does not exhibit a significant increase with cannabis exposure. However, caution should be exercised when interpreting the findings due to the heterogeneity of the studies.

1. Introduction

Cannabis, also known as marijuana, is a plant-based preparation of *Cannabis sativa* and *Cannabis indica*. Cannabis use and cultivation were illegal and prohibited globally for its negative psychoactive properties in the past century [1,2]. However, given the millennium history of

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cannabis use and scientifically proven benefits, [3] cannabis has been increasingly decriminalized or legalized for medical and recreational purposes in many countries in recent decades [2, 4, 5]. Because of the lessened regulation, cannabis consumption has reached over 140 million people around the world [6].

Cannabis contains hundreds of chemical compounds, including the well-known and extensively studied tetrahydrocannabinol (THC) and cannabidiol (CBD). These chemicals can modulate the human endocannabinoid system and produce distinct neurological and cardiovascular responses [7,8]. Because THC is believed to be associated with cannabinoid receptor type 1 (CB_1R) mediated endothelial and autonomic dysfunction, concerns of acute and chronic effects, particularly cardiovascular (CV) adverse events ie, myocardial infarction (MI) and stroke, intensify as cannabis becomes less restricted [7,8].

Although published case reports and case series found links between adverse CV events and heavy cannabis use, [9] data from the large national databases and many cohorts are still controversial [5]. One of the largest United States databases showed that the frequency of MI and stroke were significantly higher in young cannabis users, [10] while the data from UK Biobank suggested that cannabis might reduce the risk of MI. [11] Many confounding factors may explain the conflicting data; for example, (i) the THC and CBD contents of the cannabis plant are various depending on each cultivation method, [12,13] (ii) the route of administration, dosage, duration, product preparation affect THC doses, and (iii) contamination of adulterants may contribute to significant CV side effects [8,14].

Considering the limitation to perform a randomized controlled trial due to ethical issues and data discrepancy, we aim to conduct a systematic review and the first meta-analysis to assess the adverse CV events from cannabis use.

2. Material and methods

2.1. Search strategy

We performed a systematic search from MEDLINE (PubMed), EMBASE (Scopus), and the Cochrane library databases from inception until July 2022 for publications that studied the adverse CV events of cannabis use. Two authors (N.T. and N.S.) independently gathered the systematic literature review using a search strategy that included the various terms representing 'cannabis' and 'adverse cardiovascular event' as stated in supplementary data 1. Reference lists of recognized citations were manually searched for relevant studies as well. This systematic review and meta-analysis follow the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) standards. In addition, it was conducted following the Preferred Reporting Items for Systematic Reviews, Meta-Analyses (PRISMA) statement. This review was not registered, however, the study protocol, data extraction forms, and data used for all analyses were located at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

2.2. Study eligibility

The inclusion criteria were cross-sectional, case-control, and prospective or retrospective cohort studies published in peer-review, English-language journals. The inclusion of studies was not restricted by sample size or population ethnicity. Cannabis use included all cannabis preparation, route of administration, dosage, and duration. Studies of FDA-approved cannabis drugs were excluded because these forms of cannabis have already been extensively examined under randomized controlled trials [15–20]. Editorials, reviews, conference abstracts, case reports, case series, systematic reviews, meta-analyses, and studies that the results could not be generated into a two-by-two table were also excluded. Any disagreements concerning study choices were settled through collaborative conversation.

Two independent reviewers (N.S. and A.M.) reviewed abstracts and full texts. The third reviewer (N.T.) will make the final decision when the consensus could not be determined. A study with the largest number of patients was selected for the analysis when two or more studies had an overlapping population.

2.3. Data extraction and outcomes

The extracted data were first author, publication year, study site and country, study design, major inclusion, and exclusion criteria, age, gender, comorbidities, and follow-up time. The cannabis exposure data namely cannabis preparation, route of administration, dosage, and duration were collected. CV adverse events included in the meta-analysis were acute MI, stroke including hemorrhagic, ischemic stroke, and transient ischemic attack (TIA), and composite adverse CV events by definition of the individual study (when the definition was not provided, composite adverse CV events was comprised of acute MI and stroke).

2.4. Pre-specified subgroups

Pre-specified subgroup analyses were planned to stratify by preparation of cannabis, route of administration, dose, duration, and purpose of cannabis use if data were available.

2.5. Quality assessment

The Newcastle-Ottawa quality assessment (NOS) scale for cross-sectional and cohort studies was used to assess the quality of included studies, respectively. The assessment is based on eight domains categorized into three categories: patient selection, comparability, and exposure or outcome [21]. Two reviewers (N.S. and A.M.) evaluated the study quality independently. Any disagreement was resolved by the consensus of the third reviewer (N.T.). Studies with a score of 6 or more were considered high-quality studies.

2.6. Statistical analysis

All statistical analyses were performed using R program version 4.2.0 (R Core Team, Vienna, Austria). A random-effects model was used to estimate the pooled odd ratios for all outcomes. DerSimonian and Laird's generic inverse variance technique was used to calculate adjusted point estimates from each study, which assigned a weight to each study based on its variance [22]. Between-subgroup heterogeneity is tested by considering the dispersal of subgroup-specific pooled effects from the weighted average of subgroup effects under the specified model. The funnel plot and Egger test are used to determine whether there is publication bias [23].

3. Results

A total of 2896 citations were acquired from a systematic search. Of these, 2753 citations were excluded by title and abstract screening, leaving 143 citations for full-text review. One hundred and twenty-three citations were excluded due to an ineligible population, incomplete raw data, redundant population, inappropriate outcome, and improper study design. Finally, 20 studies, which consist of 4 prospective cohorts, 9 retrospective cohorts, and 7 cross-sectional studies, were included in a systematic review. The urine toxicology screening, self-reporting to the interviewer or questionnaire, and the International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) coding were used to assess exposure to cannabis. [Fig. 1].

3.1. Characteristics of included studies

Of the 20 included studies, a total of 183,410,651 patients were enrolled with the number of participants in each study ranging from 51

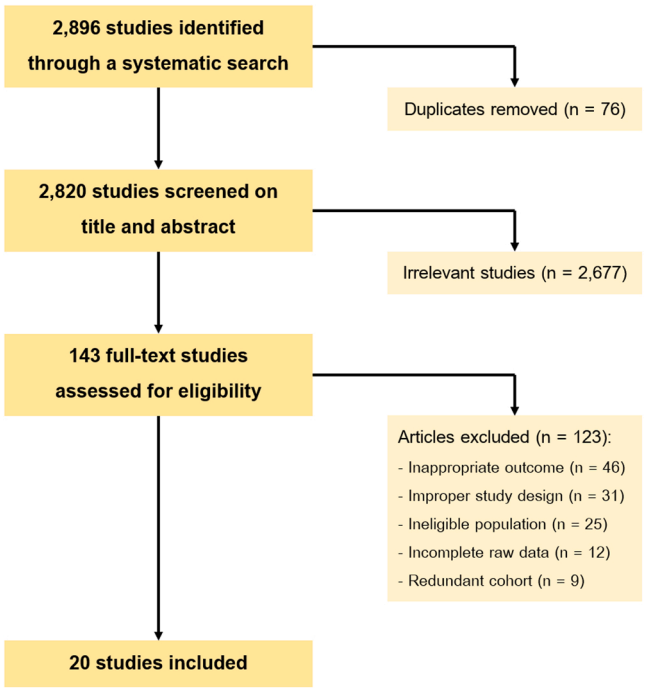

Fig. 1. Flow diagram of the selection of articles.

to 118,659,619 patients. [10, 11, 24–41] The median age was 42.4 years old (IQR: 37.4, 50.0). The proportion of males was 23.7%. The median follow-up time was 6.2 years (IQR: 1.7, 27.7, range from 242 days to 38 years). The prevalence of cannabis use was 3,549,117 patients (1.9%). All varieties of cannabis preparation, route of administration, and dosage are counted as cannabis use in all studies. Moreover, the details of these varieties are not well summarized. [Table 1].

3.2. Cannabis use and acute myocardial infarction

Ten studies with a total of 64,602,083 patients reported acute MI, which occurred in 144,716 patients (0.22%) [10, 11, 24, 26, 30, 31, 34, 35, 38, 40]. The pooled OR and rates of acute MI were shown in [Fig. 2]. Cannabis use predicted acute MI with a pooled OR of 1.29 (95%CI: 0.80, 2.08). The heterogeneity I^2 and τ were 99% and 0.30 ($p < 0.01$), respectively.

3.3. Cannabis use and stroke

Thirteen studies with a total of 172,285,631 patients reported stroke, which occurred in 248,563 patients (0.14%) [10, 24, 25, 27–29, 33–38, 40]. The pooled OR and rates of stroke were shown in [Fig. 3]. Cannabis use predicted stroke with a pooled OR of 1.35 (95%CI: 0.74, 2.47). The heterogeneity I^2 and τ were 97% and 0.74 ($p < 0.01$), respectively.

Regarding the separate analyses of ischemic stroke including TIA and hemorrhagic stroke, the pooled OR were 1.52 (95%CI: 0.66, 3.51) and 2.03 (95%CI: 0.65, 6.34), respectively. The population heterogeneities

Table 1
Characteristics of included studies.

Author	Year	Study Design	Exposure assessment	Population	N	Age (years)	Male (%)	Outcome	Follow-up (years)
Auger [24]	2020	Retrospective cohort	ICD code	Pregnant women	1,247,035	-	0	MI, stroke, composite CV	30
Barber [25]	2013	Case-control	Urine test	Hospitalized patients aged 18–55 years	320	44.8 ± 8.5	60.6	Stroke	-
Chami [26]	2019	Letter to editor, Retrospective cohort	N/A	N/A	10,835,118	37.4 ± 15	59.2	MI	3
Desai [10]	2019	Case-control	ICD code	Hospitalized patients aged 18–39 years	52,290,927	27.3 ± 5.9	16.7	MI, stroke	-
Dutta [27]	2021	Case-control	Self-report	Patients with first ischemic stroke aged 15–49 years	1,564	39.2	44.4	Stroke	-
Falkstedt [28]	2017	Retrospective cohort	Self-report	Young adults aged 18–20 years conscripted to military service	45,081	-	100	Stroke	38
Hemachandra [29]	2016	Cross-sectional	Self-report	Adults aged 20–64 years	7,455	-	49.1	Stroke	-
Karki [30]	2022	Retrospective cohort	Urine test	Hospitalized patients aged 18–54 years	14,490	46.3 ± 6.6	-	MI	-
Ladha [31]	2021	Case-control	Self-report	Adults aged 18–44 years	33,173	-	50.5	MI	-
Lehrer [11]	2022	Case-control	N/A	Adults	157,111	58	-	MI	-
Lorenz [32]	2017	Prospective cohort	Self-report	HIV infected patients	414	41	-	Composite CV	6.59
Malhotra [33]	2018	Retrospective cohort	ICD code	Hospitalized patients aged 15–54 years	118,659,619	50	-	Stroke	-
Phillips [34]	2022	Prospective cohort	ICD code	Adults aged ≥ 50 years	550	62.8 ± 7.3	69.5	MI, stroke	2
Reis [35]	2017	Prospective cohort	Self-report	Young adults aged 18–30 years	5,113	25	-	MI, stroke, composite CV	26.9
San [36]	2020	Cross-sectional	Urine test	Patients with urine drug screening on admission	9,350	44	53.9	Stroke	-
Sarmiento [37]	2021	Retrospective cohort	Urine test	Type A aortic dissection	51	54.7	74.5	Stroke	0.08
Stupinski [38]	2020	Retrospective cohort	ICD code	Traumatic patients	678	34 ± 15	83.0	MI, stroke	-
Sun [39]	2020	Prospective cohort	Self-report	Adults	14,818	38.2 ± 11.3	50.7	Composite CV	5.8
Winhusen [40]	2020	Retrospective cohort	ICD code, urine test	Adults aged ≥ 18 years	17,888	42.4 ± 13.6	56.8	MI, stroke	7.5
Zongo [41]	2021	Retrospective cohort	N/A	Adults with cannabis authorization for medical uses	69,896	-	54.6	Composite CV (MI and stroke)	0.66

CV = cardiovascular; ICD = International Classification of Diseases; MI = myocardial infarction; N/A = not applicable
Notes:
Abbreviations: CV = cardiovascular; ICD = International Classification of Diseases; MI = myocardial infarction; N/A = not applicable

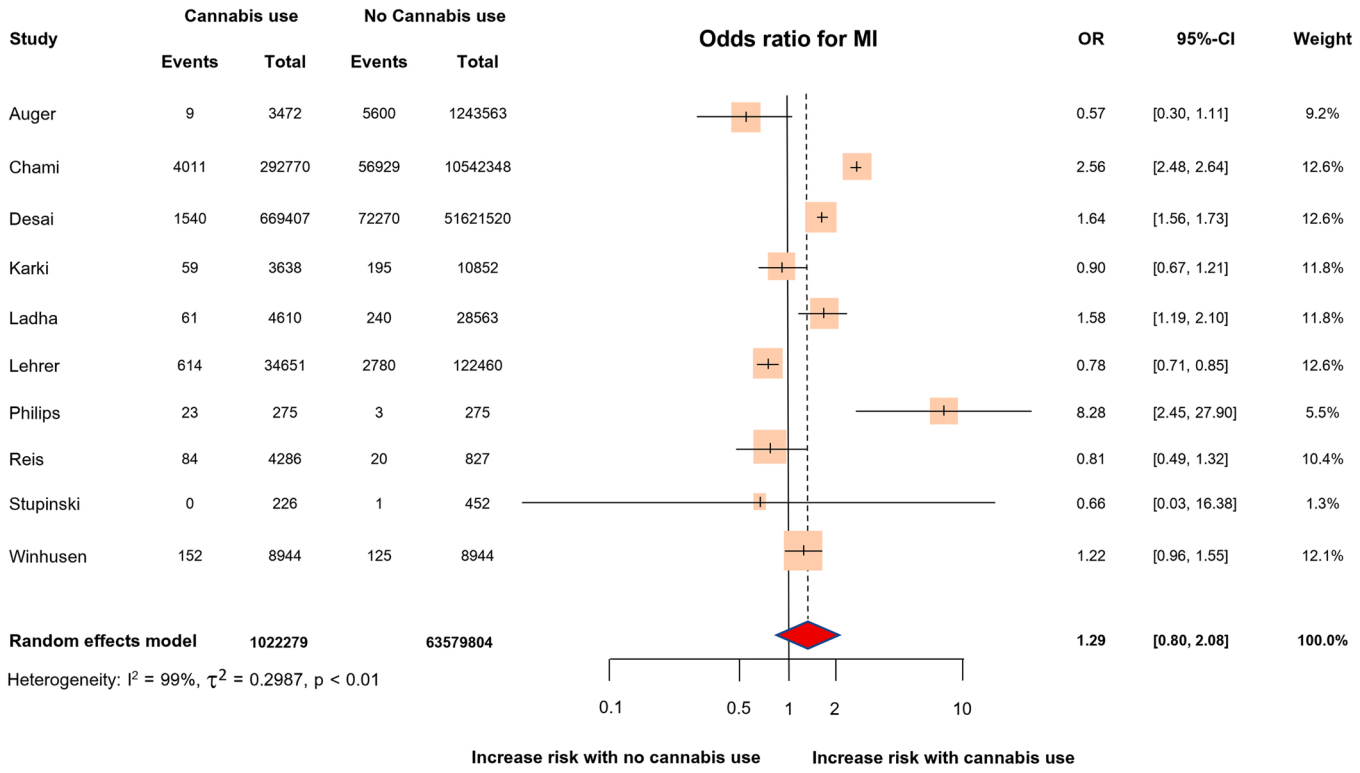

Fig. 2. Forest plot of analysis regarding myocardial infarction. Individual trials and pooled analyses revealed an insignificant increase risk of acute MI in the cannabis use group. CI = confidence interval; MI = myocardial infarction; OR = odds ratio.

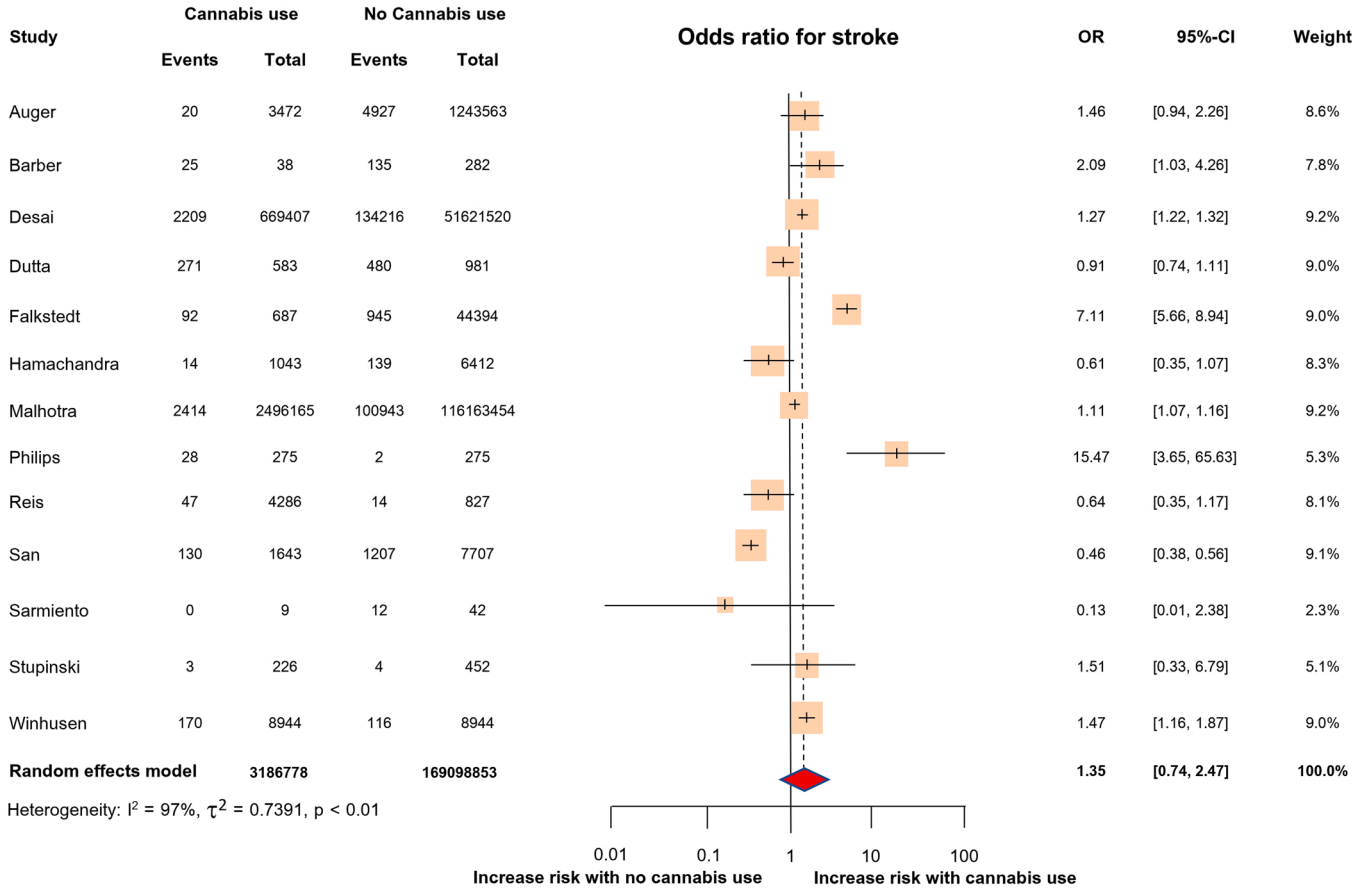

Fig. 3. Forest plot of analysis regarding stroke. Individual trials and pooled analyses revealed an insignificant increase risk of stroke in the cannabis use group. CI = confidence interval; OR = odds ratio.

in both analyses were shown in Supplementary figures 1 and 2.

3.4. Cannabis use and composite adverse cardiovascular event

Twenty studies with a total of 183,410,651 patients reported composite adverse CV events, which occurred in 313,703 patients (0.17%) [10, 11, 24–41]. The pooled OR and rates of composite adverse CV events were shown in [Fig. 4]. Cannabis use predicted composite adverse CV events with a pooled OR of 1.47 (95%CI: 0.98, 2.20). The heterogeneity I^2 and τ were 99% and 0.61 ($p < 0.01$), respectively.

Four studies provided their own definition for composite cardiovascular events [Supplementary data 2] [24, 32, 35, 39]. The summation of acute MI and stroke was used as a composite cardiovascular event in the remaining studies. Since there were different definitions among studies, the sensitivity analysis was performed by analyzing only sixteen studies with similar definitions of a composite cardiovascular event. The sensitivity analysis result was not different from the main analysis [Supplementary figure 3].

3.5. Quality assessment and risk of publication bias

All included studies had a NOS score of 6 or more and were considered high-quality studies. [Supplementary tables 1 and 2]. The funnel plots of acute MI and stroke appeared symmetrical consistent with the Egger test results (p-value = 0.188 and 0.058, respectively). However, the funnel plot and Egger test for composite adverse CV events showed evidence of publication bias (p-value = 0.005) [Supplementary figures 4–8].

4. Discussion

Contrary to the notions based on previous literature and biological explanations, this meta-analysis found that cannabis use insignificantly predicts all major cardiovascular adverse events. During the median follow-up time of 6.2 years, the pooled ORs were 1.29 (95%CI: 0.80, 2.08) for acute MI, 1.35 (95%CI: 0.74, 2.47) for stroke, and 1.47 (95%CI: 0.98, 2.20) for composite adverse CV events. This study gathers 20

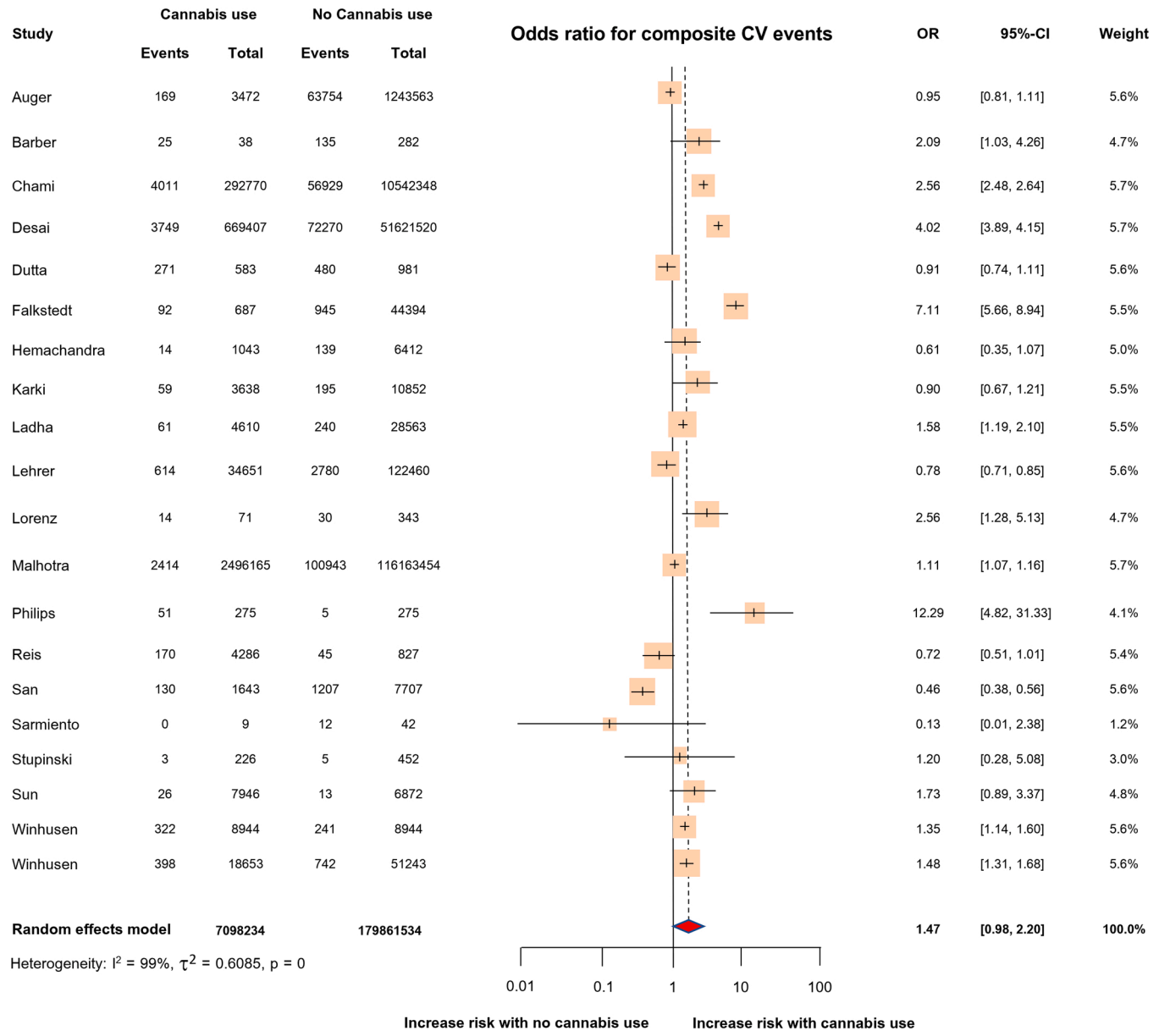

Fig. 4. Forest plot of analysis regarding composite adverse cardiovascular events. Individual trials and pooled analyses revealed an insignificant increase risk of composite adverse CV events in the cannabis use group. CI = confidence interval; CV = cardiovascular; OR = odds ratio.

studies with over 183,000,000 patients, including 4 prospective cohorts, 9 retrospective cohorts, and 7 cross-sectional studies. The prevalence of cannabis use was 3,549,117 patients (1.9%), ranging from 0.3% to 83.8%. Most studies did not clearly demonstrate cannabis preparation, route of administration, dosage, duration, and purpose of use (medical or recreational) in their study participants, which may influence the study results.

To the best of our knowledge, the current study is the first meta-analysis regarding cannabis-related adverse cardiovascular events, including acute MI and stroke, though, there are some systematic reviews on this topic. From the latest systematic review [42], 3 studies demonstrated the association between cannabis use and myocardial infarction [43–45]. One of 3 studies found that the risk of MI increased 4.8 times within the first hour after cannabis exposure and 1.7 times in the second hour, emphasizing the significant relation between time after cannabis exposure and risk of MI. [45] Supported by the previous systematic review of case series and case reports, the average onset of MI was within 5 h after the last cannabis exposure. [9] Platelet activation, aggregation, and vasospasm play a central role in the pathogenesis of myocardial infarction and ischemic stroke. THC has been found to be a prothrombotic substance by inducing platelet aggregation. Although the mechanism of this effect is unclear, in vitro study demonstrated that CB_1R and CB_2R are both present on platelet membranes. During the activation of CB_1R, moreover, fibrinogen receptors, glycoprotein IIb-IIIa and P-selectin expression on platelet membranes also increase in a dose-dependent fashion which may initiate a coagulation cascade. [46] THC may also induce endothelial irritation and autonomic nervous system dysfunction resulting in vasospasm [8,47]. However, long-term exposure to THC leads to the downregulation of CB_1R and physiologic response to THC [48]. This meta-analysis found a trend, but not statistically significant, toward MI in the cannabis-using group. The insignificant result might be influenced by the higher proportion of patients who reported chronic cannabis use in the included studies than in the published case reports and case series.

Seven of 9 studies from the previous review [42] showed the association between cannabis use and stroke (3 with ischemic stroke, 1 with hemorrhagic, and 3 with all stroke forms) [29, 44, 49, 50, 51, 52, 53], while 2 studies (1 with ischemic stroke and 1 with all stroke forms) were not [25,28]. However, it is noteworthy that the participants in 5 of 7 positive studies were the United States population and 4 studies used data from the national registry, the nationwide inpatient sample, which can result in overlapping enrollment [49, 50, 51, 52, 53]. There was evidence that the frequency of cannabis use was related to the risk of stroke [29]. Our result found that the stroke risk; including ischemic stroke, TIA, and hemorrhagic stroke, increased in the cannabis-using group, despite, insignificant results.

This study has several limitations. First, although we performed an extensive systematic search via several large databases, the results are still subject to publication bias as demonstrated by asymmetrical funnel plots and the Egger test result of a composite adverse CV event. Second, there was population heterogeneity in the analysis for acute MI, stroke, and composite adverse CV events. Not only the inclusion and exclusion criteria in the individual studies are varied, but the diversity of cannabis use is also a great contributor to heterogeneity. Thus, we used the random-effect model in our meta-analysis for this reason. Third, most of the included studies are cross-sectional and retrospective studies which include participants from the pre-existing cohort, national registry, and survey [10, 11, 24, 26–31, 33–41]. Hence, the data recorded in these studies were not pre-specified for cannabis use and could lead to information bias. Fourth, only five studies used urine toxicology tests to identify cannabis users [25, 30, 36, 37, 40] while other studies collected data using participants' self-report in questionnaires or interviews, which could be the source of recall bias. Fifth, the analysis of arrhythmia, another commonly reported CV event [54], was not included due to a limited number of previous studies. [55,56] Exploring the association between cannabis and arrhythmia with an appropriate methodological approach is encouraged. Lastly, most studies included in this meta-analysis did not specifically describe how cannabis was used (e.g., preparation, route, dose, duration, and usage purpose). Five studies had reported the frequency of cannabis use. [28, 29, 31, 32, 35] However, given the small number of studies and different units of frequency reported, a subgroup analysis stratified by these factors cannot be performed even if it has already pre-specified.

We believe the plausible explanation for the inconsistent association between cannabis exposure and adverse CV events is mainly attributed to how cannabis is consumed in each study because the route of administration, dosage (including THC percentage), duration, and time after exposure greatly affect adverse events [5, 7, 9, 29]. Future research should focus on specific exposure conditions to cannabis that leads to serious outcomes.

5. Conclusion

The risk of adverse CV events, including acute MI and stroke, is not significantly increased with cannabis exposure. However, considering the heterogeneity among studies, it is vital to take a cautious stance toward the findings. Specific conditions of cannabis use such as cannabis preparation, route of administration, dosage, duration, and time after exposure can affect outcomes, and further investigations are needed.

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CRediT authorship contribution statement

Conception and design of study: N. Theerasuwipakorn, R. Chokesuwattanasakul, N. Siranart; acquisition of data: N. Theerasuwipakorn, A. Marsukjai; analysis and/or interpretation of data: N. Theerasuwipakorn, S. Prechawat, R. Chokesuwattanasakul, N. Siranart, A. Marsukjai, S. Thumtecho, V. Rungpradubvong. Drafting the manuscript: N. Theerasuwipakorn, A. Marsukjai; revising the manuscript critically for important intellectual content: N. Theerasuwipakorn, S. Prechawat, R. Chokesuwattanasakul, N. Siranart, A. Marsukjai, S. Thumtecho, V. Rungpradubvong. Approval of the version of the manuscript to be published (the names of all authors must be listed): N. Theerasuwipakorn, S. Prechawat, R. Chokesuwattanasakul, N. Siranart, A. Marsukjai, S. Thumtecho, V. Rungpradubvong.

Declaration of Competing Interest

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

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the

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