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Marijuana smoking and asthma: a protocol for a meta-analysis

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ABSTRACT

Introduction Recent studies have raised the concern on the risk of asthma in marijuana smokers; however, the results remain controversial and warrant further investigation. With a growing number of marijuana smokers, examining the association between marijuana smoking and asthma and quantifying such association through meta-analysis have important implications for public health and clinical decision-making. In view of this, the present protocol aims to detail a comprehensive plan of meta-analysis on the association aforementioned. The findings are expected to strengthen the current knowledge base pertaining to the potential adverse effects of marijuana smoking on pulmonary health and to facilitate the development of prevention strategies for asthma.

Methods and analysis The MEDLINE/PubMed, Web of Science and EMBASE databases will be searched systematically from inception to 1 September 2021 to retrieve the relevant observational studies focusing on the association between marijuana smoking and asthma. Both unadjusted and adjusted effect sizes, such as OR, relative risk, HR and the corresponding 95% CIs will be extracted for pooled analyses. Heterogeneity and publication bias across the included studies will be examined. The Newcastle-Ottawa Quality Scale will be used to assess the quality and risk of bias. Statistical software Review Manager V.5.3 and Stata V.11.0 will be used for statistical analyses.

Ethics and dissemination Since no private and confidential patient data will be included in the reporting, approval from an ethics committee is not required. The results will be published in a peer-reviewed journal or disseminated in the relevant conferences. The study raises no ethical issue.

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INTRODUCTION

Marijuana is one of the most frequently administered psychoactive drugs in the global context.[1] As reported, the number of current marijuana smokers aged ≥12 years in the USA had grown from 6.2% in 2002 to 10.1% in 2018.[2] In view of the potential benefits of marijuana observed in a range of medical conditions (eg, epilepsy, pain symptom, multiple sclerosis, anxiety and depression), 33 states in the USA have legalised the use of marijuana for medical purposes; additionally, the District of Columbia and another 11 states have legalised marijuana for recreational

Strengths and limitations of this study

► This is the first meta-analysis that aims to evaluate the association between marijuana smoking and asthma. Our findings are expected to strengthen the current knowledge base pertaining to the potential adverse effects of marijuana smoking on pulmonary health and to facilitate the development of prevention strategies for asthma.

► The study selection, data extraction and quality assessment will be performed by two independent investigators. Disagreements, if any, will be resolved by consulting a third investigator.

► The study quality and risk of bias will be comprehensively examined by adopting the Newcastle-Ottawa Quality Scale.

► Since this meta-analysis will include both prospective and retrospective studies, the final results may be subjected to bias to a certain extent. Meanwhile, the variations in study design and sample characteristics might result in a high level of heterogeneity.

► This meta-analysis intends to examine the associations between different frequencies of marijuana smoking and asthma as a subgroup analysis; however, it might be challenging or even impossible to implement due to the expected small number of qualified articles.

purposes.[3–5] On the other hand, marijuana smoking is also suspected to be associated with several adverse effects such as the risk of chronic psychiatric disorders, cognitive decline, malignancy, chronic bronchitis, addiction and cardiovascular diseases.[6]

Cytologic variations in the respiratory tract, respiratory symptoms (eg, wheezing, cough, sputum production and shortness of breath) and impaired lung function are all potentially respiratory effects associated with marijuana smoking.[7] Previous research suggested that marijuana smoking might expose users to carbon monoxide and tar deposition at a chance of 3–5 times higher than tobacco smokers, and the incidence of airflow obstruction caused by marijuana smoking was equivalent to 2.5–5 times of that caused by tobacco smoking.[8–10] Since tobacco smoking is a recognised risk factor for the development of asthma, it has been speculated that marijuana

smoking could also increase the risk of developing asthma. On the contrary, some other studies reported that marijuana smoking was not necessarily associated with asthma.[11–15] A review concluded that even though a high frequency of marijuana smoking might lead to respiratory symptoms in the general population, the association between marijuana smoking and asthma should be further clarified.[16] This association may be attributed to Δ9-tetrahydrocannabinol (the physiologically active bronchodilator compound in marijuana), which has been demonstrated to cause rapid reversal of the bronchoconstriction induced experimentally by exercises or methacholine inhalation in asthma patients,[17] and may have a therapeutic potential for asthma.[18]

Meta-analysis, as an important and useful tool to reveal the trends that are not apparently straightforward, can effectively facilitate researchers to establish clinical policies and guidelines. Therefore, we plan to perform a systematical meta-analysis on the existing literature to test the hypothesis that marijuana smoking is associated with a significantly greater risk of asthma.

METHODS
Literature search
This protocol was designed by referencing to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015,[19] and was registered in the Open Science Framework registries (osf.io/uptxc). A systematical search will be performed across MEDLINE/PubMed, Web of Science and EMBASE from inception to 1 September 2021 to retrieve the relevant studies focusing on the association between marijuana smoking and asthma. Keywords or medical subject heading terms will be defined appropriately for the literature search (see table 1 for the detailed electronic search strategy), and necessary adaption will be made to all the search terms in order to cater the specific syntax rules of each database.

Study selection
Two investigators will be engaged independently to identify observational studies for inclusion according to the predetermined criteria. Disagreements, if any, shall

be resolved by consulting a third investigator as far as possible. Specifically, the inclusion criteria are: (1) observational studies including case–control studies, cohort studies and cross-sectional studies; (2) studies with at least one joint-year exposure (equivalent to one joint per day for 1 year) or more cumulative marijuana smoking (defined as ever smoking); (3) studies with clear diagnostic criteria for asthma (either clinically diagnosed or self-reported through interview; asthma-like disorders were not considered as asthma); (4) studies reporting the prevalence of asthma both in the groups of marijuana smokers and non-smokers and (5) studies published in English. Meeting abstracts, case reports, letters, reviews, cost-effective studies or non-human studies will not be included. In addition, studies setting marijuana use in the form of vaporisers as the study exposure will also be excluded, as this configuration is beyond the scope of the proposed meta-analysis.

Data extraction
The same two investigators will be responsible for extracting the following data independently using a standardised data collection form: publication information ((author(s) and year of publishing)); study information (country of origin, data sources, study setting and study period); demographics (age, sex distribution and sample size); exposure information (marijuana smoking) and outcome information (diagnosis of asthma). Then, both unadjusted and adjusted effect sizes, such as OR, relative risk (RR) or HR, will be extracted directly or, if not available, calculated based on the relevant data in the original studies. If such data for calculation cannot be found, the author(s) of the concerned study will be contacted directly to request for the missing information whenever possible. Any disagreements between the two investigators will be resolved by consulting a third investigator.

Assessment of risk of bias
The study quality will be examined by adopting the Newcastle-Ottawa Quality Scale.[20] The risk of bias will be evaluated by the two investigators independently, and disagreements, if any, will be resolved by consulting a third investigator.

Data analysis
First, the study characteristics will be summarised with narrative texts and baseline tables, and the pooled OR, RR and HR as well as the corresponding 95% CIs will be calculated. Both unadjusted and adjusted estimates will be pooled for analyses. Then, the heterogeneity across the included studies will be examined using Cochrane's Q test and I^2 statistics ($p > 0.05$ for Q statistics and $I^2 < 50\%$ indicating statistical homogeneity). If statistical homogeneity is confirmed, the fixed-effects model will be applied, and otherwise, the random-effects model will be applied to pool the data. Statistical analyses will be performed using Stata V.11.0 and Review Manager V.5.3 (the Nordic Cochrane Centre, the Cochrane Collaboration,

Table 1	Electronic search strategy in PubMed
Number	**Search terms**
1	marijuana(MeSH Terms) or marijuana(tiab) or cannabis(tiab) or hemp(tiab) or mariguana(tiab) or marihuana(tiab) or dronabinol(tiab) or cannabichromene(tiab) or tetrahydrocannabivarin(tiab) or nabilone(tiab)
2	asthma(MeSH Terms) or bronchial spasm(tiab) or wheez*(tiab) or bronchospas?(tiab) or bronchoconstrict?(tiab) or bronchial hyperreactivity(tiab) or respiratory hypersensitivity(tiab)
3	1 AND 2

Copenhagen, 2014), with p<0.05 indicating statistical significance. Finally, subgroup analyses will be performed (eg, age, sex, ethnic group, economic condition, education restrictions, geographical limitations, frequency of marijuana smoking) whenever feasible in order to minimise the impact of heterogeneity.

Assessment of publication bias

Publication bias will be examined if more than 10 studies are included by using the funnel plot and Egger test. Publication bias is confirmed if the funnel plot demonstrates an asymmetric pattern, and accordingly, the bias will be discussed and explained in detail.

Patient and public involvement

Given that this systematic review will be carried out based on published studies, patients and members of the public will not be involved directly. Only data from published literature and/or the aforementioned sources will be used.

Ethics and dissemination

This meta-analysis will be performed on published studies without involving any private and confidential patient data, so no approval is required from an ethics committee. The results will be reported by publishing in a peer-reviewed journal or disseminated in the relevant conferences. No ethical issues will be raised.

DISCUSSION

Asthma, a prevalent disease in children and adolescents, is deemed to be linked with significant health, social and financial issues.[21 22] With a growing number of marijuana smokers, especially in adolescents,[2] examining the association between marijuana smoking and asthma and quantifying such association through meta-analysis have important implications for public health and clinical decision-making. To the best knowledge of the authors, at least 10 studies have examined the association between marijuana smoking and asthma, of which, five suggested that marijuana smoking was positively associated with asthma,[12 23–26] but such association was not supported by another five studies.[11–14] Therefore, the association between marijuana smoking and asthma remains controversial, and the inconsistency among different studies may be attributed to the variations in study design and sample characteristics. It is noteworthy that the sample size of many previous studies might be too small to achieve a sufficiently strong statistical power, which explains, at least in part, why statistical difference was not reached in some instances despite an apparent trend. In view of the situation above, the proposed meta-analysis aims to summarise the available evidence to date to comprehensively examine the association between marijuana smoking and asthma. However, unlike medications that are usually standardised in their dose and composition, marijuana joints can be composed of different strains and chemicals. Thus, this study will review the strains or composition of marijuana plants used in the included studies and examine whether marijuana belongs

to medical grade. The findings of this study are expected to strengthen the current knowledge base pertaining to the potential adverse effects of marijuana on pulmonary health and to facilitate the development of prevention strategies for asthma.

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