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BMJ Open

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

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Keywords:	PUBLIC HEALTH, Asthma < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine)

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Title: Marijuana use and asthma: a protocol for a meta-analysis

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Key words: Marijuana, Asthma, Meta-analysis

Abstract word count: 249 (BMJ Open: 300 or less)

Article word count: 1,239 (BMJ Open: 4,000 or less)

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17 **ABSTRACT**

18 **Introduction**

19 Recent studies have raised the concern about the risk of asthma in marijuana users;
20 however, the results remain controversial and warrant further investigation. With a
21 growing number of marijuana users, examining the association between marijuana use
22 with asthma, and quantifying such association through meta-analysis have important
23 implications for public health and clinical decision making. In view of this, the
24 present protocol aims to detail a plan of meta-analysis on the association
25 aforementioned. The findings of this study are expected to strengthen the current
26 knowledge base with respect to the potential adverse effects of marijuana use on
27 pulmonary health and to facilitate the development of prevention strategies for
28 asthma.

29 **Methods and analysis**

30 The MEDLINE/PubMed, Web of Science and EMBASE databases will be targeted
31 for comprehensive search to retrieve relevant observational studies focusing on the
32 association between marijuana use and asthma. Both unadjusted and adjusted effect
33 sizes, such as odds ratio, relative risk, hazard ratio, and the corresponding 95%
34 confidence intervals will be extracted for pooled analyses. Heterogeneity and
35 publication bias within the included studies will be examined. The Newcastle-Ottawa
36 Quality Scale will be used to examine the quality and risk of bias. Statistical software
37 Review Manager V.5.3 and Stata V.11.0 will be used for statistical analyses.

38 **Ethics and dissemination**

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4 39 Since no private and confidential patient data will be included in the reporting,
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6 40 approval from an ethics committee is not required. The results will be published in a
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9 41 peer-reviewed journal. The study raises no ethical issue.
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11 42 **OSF registration number**

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44 **Strengths and limitations of this study**

- 45 ● This is the first meta-analysis that aims to evaluate the association between
- 46 marijuana use and asthma. Our findings will strengthen the current knowledge
- 47 base with respect to the potential adverse effects of marijuana use on pulmonary
- 48 health and to facilitate the development of prevention strategies for asthma.
- 49 ● The study selection, data extraction and quality assessment will be performed by
- 50 two independent investigators, and disagreements, if any, will be resolved by
- 51 negotiation.
- 52 ● The study quality and risk of bias will be comprehensively evaluated by adopting
- 53 the Newcastle-Ottawa Quality Scale.
- 54 ● Since this meta-analysis will include both prospective and retrospective studies,
- 55 the final results may be subjected to bias to a certain extent. Meanwhile, the
- 56 variations in study design and sample characteristics might result in high
- 57 heterogeneity.
- 58 ● This meta-analysis intends to examine the associations between different
- 59 frequencies of marijuana use and asthma; however, such kind of subgroup
- 60 analyses may be challenging or even impossible due to the expected small
- 61 number of qualified articles.

INTRODUCTION

Marijuana is one of the most frequently administrated psychoactive drugs in the global context.¹ As reported, the number of current marijuana users aged ≥ 12 years in the United States (US) had grown from 6.2% in 2002 to 10.1% in 2018.² In view of the potential benefits of marijuana observed in several medical conditions (e.g., epilepsy, pain symptom, multiple sclerosis, anxiety and depression), 33 states in the US have legalized the use of marijuana for medical purposes; additionally, the District of Columbia and another 11 states have legalized marijuana for recreational purposes.³⁻⁵ Nevertheless, several adverse effects such as the risk of chronic psychiatric disorders, cognitive decline, malignancy, chronic bronchitis, addiction, and cardiovascular diseases are suspected to associate with marijuana use.⁶

Cytologic variations in the respiratory tract, respiratory symptoms (e.g., wheezing, cough, sputum production, and shortness of breath), and impaired lung function are all potentially respiratory effects of marijuana use.⁷ Previous research suggested that marijuana use might expose users to carbon monoxide and tar deposition at a chance of 3-5 times higher than tobacco smokers, and the airflow obstruction produced by marijuana use was equivalent to 2.5-5 times of that produced by tobacco smoking, which is a recognized risk factor for the development of asthma.⁸⁻¹⁰ Thus, it has been speculated that marijuana use could increase the risk of developing asthma. On the contrary, other literatures have also reported that marijuana use does not necessarily have significant association with asthma.¹¹⁻¹⁵ A

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84 review concluded that even though a high frequency of marijuana use might lead to
85 respiratory symptoms in the general population, the association between marijuana
86 use and asthma should be further clarified.¹⁶ This association may be attributed to Δ9-
87 tetrahydrocannabinol (the physiologically-active bronchodilator compound in
88 marijuana), which has been illustrated to cause rapid reversal of bronchoconstriction
89 induced experimentally by exercises or methacholine inhalation in asthma patients,¹⁷
90 and may have a therapeutic potential for asthma.¹⁸

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92 Meta-analysis, an important and useful tool to reveal trends that may not be
93 straightforward, can effectively help researchers establish clinical policies and
94 guidelines. Therefore, we plan to perform a systematical meta-analysis on the existing
95 literature so as to test the hypothesis that there is a positive association between
96 marijuana use and asthma.

97

98 **METHODS**

99 **Literature search**

100 This protocol was designed by referencing to the Preferred Reporting Items for
101 Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015,¹⁹ and was
102 registered in the Open Science Framework (OSF) registries (osf.io/uptxc). A
103 comprehensive search will be performed across MEDLINE/PubMed database, Web of
104 Science and EMBASE database to retrieve the relevant studies focusing on the
105 association between marijuana smoking and asthma. Key words or medical subject

heading terms will be defined to identify qualified articles from the databases
aforementioned (see **Table 1** for the electronic search strategy). Appropriate adaption
will be made to all the search terms in order to cater different syntax rules of each
database.

Study selection

Two researchers will be engaged independently to identify observational studies for
inclusion according to the predetermined criteria. Disagreements, if any, shall be
resolved by negotiation as far as possible. Specifically, the inclusion criteria are: (1)
observational studies, including case-control studies, cohort studies, and cross-
sectional studies; (2) study exposure is marijuana use; (3) study outcome is diagnosis
of asthma; (4) studies reporting the prevalence of asthma both in the groups of
marijuana users and non-users, and (5) studies published in English. Meeting
abstracts, case reports, letters, reviews, cost-effective studies or non-human studies
will not be included.

Data extraction

The two researchers will be responsible for extracting the following data
independently using a standardized 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 use); and outcome information

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(diagnosis of asthma). Then, both unadjusted and adjusted effect sizes, such as odds ratio (OR), relative risk (RR) or hazard ratio (HR), will be extracted directly or, if not available, calculated per 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 researchers will be resolved by negotiation.

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 researchers independently, and disagreements, if any, will be resolved by negotiation.

Data analysis

Firstly, the study characteristics will be summarized with narrative texts and baseline tables, and the pooled OR, RR and HR, as well as the corresponding 95% confidence intervals (CIs) will be calculated. Both unadjusted and adjusted estimates will be pooled for analyses. Then, the heterogeneity across included studies will be examined using Cochrane’s Q test and I² statistics (p>0.05 for Q statistics and I²<50% indicating statistical homogeneity). If statistical homogeneity is confirmed, the fixed effects model will be applied to pool the data; otherwise, the random effects model will be applied. Statistical analyses will be performed using Stata V.11.0 and Review Manager V.5.3 (the Nordic Cochrane Centre, the Cochrane Collaboration,

Copenhagen, 2014), with $p < 0.05$ indicating statistical significance. Lastly, subgroup analyses will be performed (e.g., age, sex, ethnic group, economic condition, education restrictions, geographical limitations, frequency of marijuana use) whenever feasible in order to minimize the impact of heterogeneity.

Assessment of publication bias

Publication bias will be examined when more than 10 studies are included by using funnel plot and Egger test. If the funnel plot demonstrates an asymmetric pattern, publication bias is confirmed, 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. 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 users, especially in adolescents,² examining the association between marijuana use and asthma, and quantifying such association through meta-analysis have important implications for public health and clinical decision making. As far as the authors know, at least 10 studies have examined the association between marijuana use and asthma, of which, five studies suggested that marijuana use was positively associated with asthma,^{12 23-26} but another five studies did not support such association.¹¹⁻¹⁴ Therefore, the association between marijuana use 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 in spite of an apparent trend. In view of the situation above, the proposed meta-analysis aims to summarize available evidence to comprehensively examine the association between marijuana use and asthma. The findings of this study will strengthen the current knowledge base with respect to the potential adverse effects of marijuana on pulmonary health and to facilitate the development of prevention strategies for asthma.

Contributors

194 Conceptualisation: JL and MS. Data curation: JL and MS. Methodology: JL and MS.

195 Writing of original draft: JL. Review and editing: MS.

196

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200

201 **Competing interests**

202 None declared.

203

204 **Patient and public involvement**

205 Patients and/or the public were not involved in the design, or conduct, or reporting, or

206 dissemination plans of this research.

207

208 **Patient consent for publication**

209 Not required.

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278 **Table 1 Electronic search strategy in PubMed**

Number	Search terms
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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

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10-11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7, 14
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	4, 8

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Smoking and tobacco
Keywords:	PUBLIC HEALTH, Asthma < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine)

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

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Key words: Marijuana, Asthma, Meta-analysis

Abstract word count: 257 (BMJ Open: 300 or less)

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17 **ABSTRACT**

18 **Introduction**

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

29 **Methods and analysis**

30 The MEDLINE/PubMed, Web of Science and EMBASE databases will be searched
31 systematically from inception to September 1, 2021 to retrieve the relevant
32 observational studies focusing on the association between marijuana smoking and
33 asthma. Both unadjusted and adjusted effect sizes, such as odds ratio, relative risk,
34 hazard ratio, and the corresponding 95% confidence intervals will be extracted for
35 pooled analyses. Heterogeneity and publication bias across the included studies will
36 be examined. The Newcastle-Ottawa Quality Scale will be used to assess the quality
37 and risk of bias. Statistical software Review Manager V.5.3 and Stata V.11.0 will be
38 used for statistical analyses.

39 **Ethics and dissemination**

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4 40 Since no private and confidential patient data will be included in the reporting,
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6 41 approval from an ethics committee is not required. The results will be published in a
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9 42 peer-reviewed journal or disseminated in the relevant conferences. The study raises no
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12 43 ethical issue.

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14 44 **OSF registration number**

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46 **Strengths and limitations of this study**

- 47 ● This is the first meta-analysis that aims to evaluate the association between
- 48 marijuana smoking and asthma. Our findings are expected to strengthen the
- 49 current knowledge base pertaining to the potential adverse effects of marijuana
- 50 smoking on pulmonary health and to facilitate the development of prevention
- 51 strategies for asthma.
- 52 ● The study selection, data extraction and quality assessment will be performed by
- 53 two independent investigators. Disagreements, if any, will be resolved by
- 54 consulting a third investigator.
- 55 ● The study quality and risk of bias will be comprehensively examined by adopting
- 56 the Newcastle-Ottawa Quality Scale.
- 57 ● Since this meta-analysis will include both prospective and retrospective studies,
- 58 the final results may be subjected to bias to a certain extent. Meanwhile, the
- 59 variations in study design and sample characteristics might result in a high level
- 60 of heterogeneity.
- 61 ● This meta-analysis intends to examine the associations between different
- 62 frequencies of marijuana smoking and asthma as a subgroup analysis; however, it
- 63 might be challenging or even impossible to implement due to the expected small
- 64 number of qualified articles.

INTRODUCTION

Marijuana is one of the most frequently administrated psychoactive drugs in the global context.¹ As reported, the number of current marijuana smokers aged ≥ 12 years in the United States (US) 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 (e.g., epilepsy, pain symptom, multiple sclerosis, anxiety and depression), 33 states in the US have legalized the use of marijuana for medical purposes; additionally, the District of Columbia and another 11 states have legalized marijuana for recreational 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 (e.g., 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 recognized 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

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87 associated with asthma.¹¹⁻¹⁵ A review concluded that even though a high frequency of
88 marijuana smoking might lead to respiratory symptoms in the general population, the
89 association between marijuana smoking and asthma should be further clarified.¹⁶ This
90 association may be attributed to $\Delta 9$ -tetrahydrocannabinol (the physiologically-active
91 bronchodilator compound in marijuana), which has been demonstrated to cause rapid
92 reversal of the bronchoconstriction induced experimentally by exercises or
93 methacholine inhalation in asthma patients,¹⁷ and may have a therapeutic potential for
94 asthma.¹⁸

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

102 **METHODS**

103 **Literature search**

104 This protocol was designed by referencing to the Preferred Reporting Items for
105 Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015,¹⁹ and was
106 registered in the Open Science Framework (OSF) registries (osf.io/uptxc). A
107 systematical search will be performed across MEDLINE/PubMed, Web of Science
108 and EMBASE from inception to September 1, 2021 to retrieve the relevant studies

focusing on the association between marijuana smoking and asthma. Key words 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 1 joint-year exposure (equivalent to 1 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 vaporizers 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 standardized 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 odds ratio (OR), relative risk (RR) or hazard ratio (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

Firstly, the study characteristics will be summarized with narrative texts and baseline tables, and the pooled OR, RR and HR as well as the corresponding 95% confidence intervals (CIs) will be calculated. Both unadjusted and adjusted estimates will be

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4 153 pooled for analyses. Then, the heterogeneity across the included studies will be
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6 154 examined using Cochrane's Q test and I^2 statistics ($p > 0.05$ for Q statistics and $I^2 < 50\%$
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9 155 indicating statistical homogeneity). If statistical homogeneity is confirmed, the fixed
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12 156 effects model will be applied, and otherwise, the random effects model will be applied
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15 157 to pool the data. Statistical analyses will be performed using Stata V.11.0 and Review
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17 158 Manager V.5.3 (the Nordic Cochrane Centre, the Cochrane Collaboration,
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20 159 Copenhagen, 2014), with $p < 0.05$ indicating statistical significance. Lastly, subgroup
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22 160 analyses will be performed (e.g., age, sex, ethnic group, economic condition,
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32 164 **Assessment of publication bias**

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35 165 Publication bias will be examined if more than 10 studies are included by using the
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37 166 funnel plot and Egger test. Publication bias is confirmed if the funnel plot
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40 167 demonstrates an asymmetric pattern, and accordingly, the bias will be discussed and
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48 170 **Patient and public involvement**

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51 171 Given that this systematic review will be carried out based on published studies,
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53 172 patients and members of the public will not be involved directly. Only data from
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56 173 published literature and/or the aforementioned sources will be used.
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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, 5 suggested that marijuana smoking was positively associated with asthma,^{12 23-26} but such association was not supported by another 5 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

197 summarize the available evidence to date to comprehensively examine the association
198 between marijuana smoking and asthma. However, unlike medications that are
199 usually standardized in their dose and composition, marijuana joints can be composed
200 of different strains and chemicals. Thus, this study will review the strains or
201 composition of marijuana plants used in the included studies and examine whether
202 marijuana belongs to medical grade. The findings of this study are expected to
203 strengthen the current knowledge base pertaining to the potential adverse effects of
204 marijuana on pulmonary health and to facilitate the development of prevention
205 strategies for asthma.

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207 **Contributors**

208 Conceptualisation: JL and MS. Data curation: JL and MS. Methodology: JL and MS.
209 Writing of original draft: JL. Review and editing: MS.

210

211 **Funding**

212 This work was supported by the National Natural Science Foundation of China
213 (82000585).

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215 **Competing interests**

216 None declared.

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218 **Patient and public involvement**

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219 Patients and/or the public were not involved in the design, or conduct, or reporting, or
220 dissemination plans of this research.
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222 **Patient consent for publication**
223 Not required.

For peer review only

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292 **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]
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10-11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7, 14
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	4, 8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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