PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Marijuana smoking and asthma: a protocol for a meta-analysis
AUTHORS	Lei, Jincheng; Shao, Mingjie

VERSION 1 – REVIEW

REVIEWER	Albertson, Timothy University of California Davis School of Medicine, Internal Medicine
REVIEW RETURNED	08-Feb-2021

GENERAL COMMENTS	a description of the plan for a meta-analysis offers the reader nothing. the formula for doing a meta-analysis is well described in the literature and does not require a publication as it lacks uniqueness. the topic is of interest but a paper on how you plan to do a meta-analysis lacks depth.

REVIEWER	Jarjou'i, Amir Shaare Zedek Medical Center
REVIEW RETURNED	01-May-2021

GENERAL COMMENTS	This study protocol addresses an important and interesting question concerning the association between asthma and marijuana smoking. I applaud the Authors for their well-written and intriguing study protocol. To correctly establish such an association between asthma and marijuana, several points need to be established/clarified. 1. The use of marijuana "use" instead of marijuana "smoking" can be misleading. Smoking marijuana, as well as smoking other plants, will expose the lungs to many combustion by-products that have many hazardous effects on the lungs. Marijuana use in the form of edibles or tinctures does not result in the same effects. I would ask the authors to use marijuana "smoking" instead of marijuana "use" throughout their protocol. Also, the authors should exclude marijuana use in the form of vaporizers, as that is a different question that needs to examined seperatly. 2. Please specify if only studies including exact joint years of marijuanna smoking will be included. Moreover, what standards will be used for choosing studies including a diagnosis of new onset asthma or worsening asthma. I think studies included in the meta-analysis should contain a precise and acceptable criteria when defining asthma as an outcome. Also, smoking marijuana has been associated with the development of COPD , it is important to include studies that defferentiae between the two entities based on acceptable sirometry criteria.

	3. There is an inherent major limitation when including studies examining different strains, or combination of the marijuanna plant. Unlike medications that are usually uniformal in their dose and composition, marijuana joints can include different strains and very different chemicals. This shouldd be noted in the discussion, although such a limitation can not be avoided currently, studies including medical grade marijuanna should be pointed out as well.

REVIEWER	Agrawal, Suneil Desert Regional Medical Center, Emergency Medicine
REVIEW RETURNED	02-May-2021

GENERAL COMMENTS	The date parameters for the database search are missing. Disagreements regarding study selection, data extraction and quality assessment are to be resolved by negotiation between the independent reviewers. This seems vague, prone to bias, and would be difficult to reproduce. The intenet is to examine the association between marijuana and asthma, but no clear hypothesis is laid out. What exact associations between marijuana use and asthma are the authors looking for?

REVIEWER	Witek, Theodore University of Toronto
REVIEW RETURNED	15-Apr-2021

GENERAL COMMENTS	This is a worthwhile venture with an important question. However, I do not see a method paper sufficient to publish as stand alone. Literature is not expansive (as pointed out). Resubmit when study complete.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Timothy Albertson, University of California Davis School of Medicine
Comments to the Author:
a description of the plan for a meta-analysis offers the reader nothing. the formula for doing a meta-analysis is well described in the literature and does not require a publication as it lacks uniqueness. the topic is of interest but a paper on how you plan to do a meta-analysis lacks depth.
Response: Thanks for the reviewer's comment.

Reviewer: 2
Dr. Amir Jarjou'i, Shaare Zedek Medical Center
Comments to the Author:
This study protocol addresses an important and interesting question concerning the association between asthma and marijuana smoking.
I applaud the Authors for their well-written and intriguing study protocol.
To correctly establish such an association between asthma and marijuana, several points need to be established/clarified.
Response: We appreciate the reviewer's comments. Please see the specific responses below.

1. The use of marijuana "use" instead of marijuana "smoking" can be misleading. Smoking marijuana, as well as smoking other plants, will expose the lungs to many combustion by-products that have many hazardous effects on the lungs. Marijuana use in the form of edibles or tinctures does not result in the same effects. I would ask the authors to use marijuana "smoking" instead of marijuana "use" throughout their protocol. Also, the authors should exclude marijuana use in the form of vaporizers, as that is a different question that needs to examined seperatly.
Response: We appreciate the reviewer's comment, and we have revised the text, and modified the exclusion criteria as suggested in the revised manuscript.
Action: "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." (Line 126-128 in the revised manuscript)

2. Please specify if only studies including exact joint years of marijuanna smoking will be included. Moreover, what standards will be used for choosing studies including a diagnosis of new onset asthma or worsening asthma. I think studies included in the meta-analysis should contain a precise and acceptable criteria when defining asthma as an outcome. Also, smoking marijuana has been associated with the development of COPD , it is important to include studies that defferentiae between the two entities based on acceptable sirometry criteria.
Response: Thanks for the reviewer's comment, we have modified the inclusion and exclusion criteria according to the previous published studies [1, 2] in the revised manuscript.
Action: "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."
References: 1. Mehrnaz G , Brooke B , Samuel L , et al. Association Between Marijuana Use and Risk of Cancer: A Systematic Review and Meta-analysis. JAMA Network Open, 2019, 2(11):1-28; 2. M. Pérez-Ríos, A. Ruano-Ravina, Etminan M , et al. A meta-analysis on wood dust exposure and risk of asthma. Allergy, 2010, 65(4).

3. There is an inherent major limitation when including studies examining different strains, or combination of the marijuanna plant. Unlike medications that are usually uniformal in their dose and composition, marijuana joints can include different strains and very different chemicals. This shouldd be noted in the discussion, although such a limitation can not be avoided currently, studies including medical grade marijuanna should be pointed out as well.
Response: Per the reviewer's comment, we have added the limitation in the Discussion section in the revised manuscript.
Action: "However, unlike medications that are usually standardized 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." (Line 197-201 in the revised manuscript)

Reviewer: 3
Dr. Suneil Agrawal, Desert Regional Medical Center
Comments to the Author:
The date parameters for the database search are missing.
Response: Thanks for the reviewer's comment, we have added the data parameters for the database

search in the revised manuscript.
Action: “The MEDLINE/PubMed, Web of Science and EMBASE databases will be searched systematically from inception to September 1, 2021 to retrieve the relevant observational studies focusing on the association between marijuana smoking and asthma.” (Line 30-33 in the revised manuscript)
“A systematical search will be performed across MEDLINE/PubMed, Web of Science and EMBASE from inception to September 1, 2021 to retrieve the relevant studies focusing on the association between marijuana smoking and asthma.” (Line 106-109 in the revised manuscript)

Disagreements regarding study selection, data extraction and quality assessment are to be resolved by negotiation between the independent reviewers. This seems vague, prone to bias, and would be difficult to reproduce.
Response: We appreciate the reviewer’s comment, we have revised the process in the revised manuscript.
Action: “Disagreements, if any, will be resolved by consulting a third investigator.” (Line 53-54 in the revised manuscript)
“Disagreements, if any, shall be resolved by consulting a third investigator as far as possible.” (Line 117-118 in the revised manuscript)
“Any disagreements between the two investigators will be resolved by consulting a third investigator.” (Line 141-142 in the revised manuscript)
“The risk of bias will be evaluated by the two investigators independently, and disagreements, if any, will be resolved by consulting a third investigator.” (Line 146-147 in the revised manuscript)

The intenet is to examine the association between marijuana and asthma, but no clear hypothesis is laid out. What exact associations between marijuana use and asthma are the authors looking for?
Response: Per the reviewers’ comment, we have revised the study hypothesis in the revised manuscript.
Action: “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.” (Line 98-100 in the revised manuscript)

Reviewer: 4
Dr. Theodore Witek, University of Toronto
Comments to the Author:
This is a worthwhile venture with an important question. However, I do not see a method paper sufficient to publish as stand alone.
Literature is not expansive (as pointed out). Resubmit when study complete.
Response: Thanks for the reviewer’s comment.

VERSION 2 – REVIEW

REVIEWER	Jarjou'i, Amir Shaare Zedek Medical Center
REVIEW RETURNED	18-Sep-2021

GENERAL COMMENTS	I am pleased with the revisions and corrections