

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The effects of prenatal cannabis exposure on fetal development and pregnancy outcomes: a protocol
AUTHORS	Ehiri, John; Gunn, Jayleen; Cecilia, Rosales; Center, Katherine; Nuñez, Annabelle; Gibson, Steven

VERSION 1 - REVIEW

REVIEWER	Prakesh Shah University of Toronto, Toronto, Canada
REVIEW RETURNED	26-Dec-2014

GENERAL COMMENTS	<p>This is a protocol for assessing effects of Cannabis on pregnancy outcomes. Overall it is a standard methodology protocol with some weaknesses and I am uncertain of its publication as this should be registered on the Prospero website rather than publishing as a manuscript. Suggestions for authors are included below.</p> <ol style="list-style-type: none">1. Restricting studies to effects of only cannabis alone would most likely to yield very poor results as it is well-known that women who use cannabis also use other agents.2. Most critical aspect was the statistical analyses in this review and it is not properly reported as to how it will be conducted. How will you combine data from case-control and cross sectional studies? How will you combine data from studies reporting adjusted OR, unadjusted OR and rates? Meta regression is mentioned but no details are given as to why and how it will be conducted. Heterogeneity assessment is unclear and guidelines for conducting and not conducting meta-analysis are not mentioned.
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REVIEWER	Anja Huizink VU University Amsterdam, The Netherlands
	I have recently published a review paper on a very similar topic with some overlap with the proposed study.
REVIEW RETURNED	06-Jan-2015

GENERAL COMMENTS	<p>This is a protocol paper on a future systematic review and meta-analysis to be conducted on the topic of the effects of prenatal cannabis exposure on pregnancy outcomes.</p> <p>It is an important topic, but whether this paper present a new approach is doubtful. First, a previous study already published a meta-analysis on maternal cannabis use and birth weight outcomes. The proposed study broadens this scope, but to my opinion, too widely, as it is not clear what the main outcome measures would be.</p>
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	<p>Second, a recent systematic review also described the most recent studies in this regard. It is unclear how this proposed study will add to those publications, and what the need is for this particular project.</p> <p>The proposed study has some major limitations:</p> <ul style="list-style-type: none"> - It does not refer to the available literature accurately. For instance, a reference is made to a design paper of the Generation R study (Hofman et al.), when discussing empirical findings on prenatal cannabis exposure and tobacco exposure from this cohort study that have been published elsewhere (see e.g. el Marroun et al.) - It is not very consistent in describing the proposed outcome measures for the meta-analysis (nor for the systematic review; how will both be combined into one study?). It is not feasible to run meta-analyses on the very long list of outcome measures provided on page 8. It is confusing for the reader whether or not infant measures will be focused on as well. See for instance the abstract, the aim is first described as focused on pregnancy outcomes, and later on is described as including outcomes of cannabis use for the infant or the mother. Also, some literature in the background section refers to infant behavioral outcomes, or neonatal neurological assessment. I would not include those outcomes under pregnancy outcomes. Perhaps, it would help if the authors more clearly describe or define what they regard as pregnancy outcomes. I would assume that pregnancy outcomes are related to birth outcomes. Maternal health issues may not be part of that, particularly during pregnancy, although they are listed under the outcome measures. It is simply too ambitious and too unfocused to include all this in one (?) meta-analysis. Moreover, "other maternal assessment measures", and "other fetal or neonatal assessment measures" need to be described more clearly. - Importantly, as can be learned from previous work in this field, and from other reviews recently published, it is very important to be very clear about potential confounders, which to include and how to account for them in the analyses. Some of these confounders are mentioned but a clear description on how to handle them, what to do with them in the analyses, etc, is missing.
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VERSION 1 – AUTHOR RESPONSE

REVIEWER 1:

Comment #1: This is a protocol for assessing effects of Cannabis on pregnancy outcomes. Overall it is a standard methodology protocol with some weaknesses and I am uncertain of its publication as this should be registered on the Prospero website rather than publishing as a manuscript.

Response: We anticipate that the review will be published in BMJ Open to ensure ease of reference and comparison to the protocol.

Comment #2: Restricting studies to effects of only cannabis alone would most likely to yield very poor results as it is well-known that women who use cannabis also use other agents.

Response: This is very important, and we thank the reviewer for the suggestion. We agree with the reviewer that women who use cannabis also use other agents; however, we believe it is important to try to control for the confounding effects of other illicit drug use on women and their infants.

Furthermore, we believe that in order to understand the true effects of cannabis on women and their infants, we ought to study the effects of cannabis exclusive of other illicit substances. It has been well-documented that substances such as tobacco and alcohol consumption may also be confounding factors. Therefore, we will take the most adjusted measure of association as possible (see Data Synthesis page 11).

Comment #3: Most critical aspect was the statistical analyses in this review and it is not properly reported as to how it will be conducted. How will you combine data from case-control and cross sectional studies? How will you combine data from studies reporting adjusted OR, unadjusted OR and rates? Meta regression is mentioned but no details are given as to why and how it will be conducted. Heterogeneity assessment is unclear and guidelines for conducting and not conducting meta-analysis are not mentioned.

Response: This is an excellent observation for which we are grateful. We have clarified these in our discussion of the analyses. We have added information under: Measures of treatment effect, assessment of heterogeneity, and data synthesis (Page 11).

REVIEWER 2:

Comment #1: This is a protocol paper on a future systematic review and meta-analysis to be conducted on the topic of the effects of prenatal cannabis exposure on pregnancy outcomes. It is an important topic, but whether this paper present a new approach is doubtful. First, a previous study already published a meta-analysis on maternal cannabis use and birth weight outcomes. The proposed study broadens this scope, but to my opinion, too widely, as it is not clear what the main outcome measures would be. Second, a recent systematic review also described the most recent studies in this regard. It is unclear how this proposed study will add that those publications, and what the need is for this particular project.

Response: We agree with the reviewer that this study broadens the scope of prior studies. We anticipate that limiting this search to studies that report outcomes of prenatal cannabis use while excluding other illicit substances will restrict the number of studies included in this study. Therefore, we will include as many maternal, fetal, and neonatal outcomes as possible in our search. However, we anticipate a manageable number of eligible studies for inclusion the review.

Comment #2: It does not refer to the available literature accurately. For instance, a reference is made to a design paper of the Generation R study (Hofman et al.), when discussing empirical findings on prenatal cannabis exposure and tobacco exposure from this cohort study that have been published elsewhere (see e.g. el Marroun et al.)

Response: We have modified this citation as shown on page 14 (references).

Comment #3: It is not very consistent in describing the proposed outcome measures for the meta-analysis (nor for the systematic review; how will both be combined into one study?). It is not feasible to run meta-analyses on the very long list of outcome measures provided on page 8. It is confusing for the reader whether or not infant measures will be focused on as well. See for instance the abstract, the aim is first described as focused on pregnancy outcomes, and later on is described as including outcomes of cannabis use for the infant or the mother. Also, some literature in the background section refers to infant behavioral outcomes, or neonatal neurological assessment. I would not include those outcomes under pregnancy outcomes. Perhaps, it would help if the authors more clearly describe or define what they regard as pregnancy outcomes. I would assume that pregnancy outcomes are related to birth outcomes. Maternal health issues may not be part of that, particularly during pregnancy, although they are listed under the outcome measures. It is simply too ambitious and too

unfocused to include all this in one (?) meta-analysis. Moreover, "other maternal assessment measures", and "other fetal or neonatal assessment measures" need to be described more clearly.

Response: We have checked all through the manuscript and modified these for clarification. We are including as many maternal, fetal, and neonatal outcomes as possible in our search. However, we expect that there will not be very many studies that meet our stringent inclusion criteria.

Comment #4: Importantly, as can be learned from previous work in this field, and from other reviews recently published, it is very important to be very clear about potential confounders, which to include and how to account for them in the analyses. Some of these confounders are mentioned but a clear description on how to handle them, what to do with them in the analyses, etc, is missing.

Response: This concern has been addressed and the paper modified to state that the data will be combined using the most adjusted measure of association when this is possible. (see page 11 - Measures of treatment effect).