Author’s response to reviews

Title: Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders. A systematic review

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Author’s response to reviews:

One script: Reviewer comments. Three scripts: our response. We have not found other way to differentiate it

General review:

We have made the requested changes. All changes have been marked in the manuscript.

Reviewers’ comments:

Reviewer #1:

- Very interesting literature Review about on current and important topic in Addiction field.

The manuscript is focused on cannabis use during pregnancy.

The influence of the consumption of other substances (tobacco, alcohol) on development of foetus and children is not discussed in the results.

---Thank you for your observation. Although tobacco and alcohol are both possible confounding factors and could influence the development alterations, we have decided to focus just in cannabis use.
- Factors such as psychiatric diagnoses, social and health condition are associated with the consumption of THC and other substances during pregnancy? Some indicators of health or social factors may be associated with THC consumption during pregnancy?

---This remains controversial, while some authors associates being unmarried, unemployed or lower level of education, others find association with psychiatric diseases or ethnicity.

“While in UE, El Marroun associates being unmarried and lower education level as more likely in women that use cannabis during pregnancy, no association is found with demographic characteristics as age, employment or ethnicity[5]. In US, Martin finds association with young age, not unemployed and white non-Hispanic women, this study also find association with being unmarried and having lower educational level[65]. This also differ from other US study, which finds as more likely cannabis use during pregnancy women from multiracial origins, but no differences with age, employment or marital status[9]. This heterogeneity in findings across studies could be explained with the differences in study designs used, confounding factors, sample population and sample size.”

Reviewer #2:

- This systematic review of the effects of prenatal exposure of cannabis on infants, children and adolescents is well timed with regards to increasing cannabis use worldwide, including the US. Given the continually changing literature base on this topic, it is important that review papers are up to date, accurate in their conclusion statements based on the current literature. This manuscript needs substantial revisions in its structure, presentation of findings and writing before it should be published in order to allow the manuscript to be as acceptable as possible to the reading audience. In particular, the authors need to outline that (and include 'how' for some criteria) the PRISMA guidelines were implemented throughout the review, re-write many of their conclusion statements from factual to hypothesized ones, report on the strengths, weaknesses and bias of the studies reviewed, especially those related to the main take home messages of the manuscript. Lastly, the tables need to be re written to be similar to other review papers, again for easing the reading for the audience who is used to a certain format.

Introduction

- page 4, line 25: define EMCDDA.

---Due to the style requirements of the journal this is specified in the abbreviations section. We added the definition as you suggest.

- page 5, line 9: 'overall use of legal..." - also the authors present cannabis within the larger context of illegal drugs but the legality of cannabis in the US is changing &gt; so the paper needs
to be focused on Europe or if it is going to encompass the US in its background and conclusion statements, wording needs to be changed.

---Thank you for your appreciation, we have added a paragraph in order to clarify it.

“In Spain and most of Europe, cannabis continues to be an illegal substance, however, there are some regions in the western world where this has changed as some states of United States. Recently, other countries like Uruguay, or more recently, Canada have legalized their consumption [64].”

- page 5, line 14-15: ? differences...decrease with DECREASING age ?.

---Thank you for pointing it, we have corrected it. Now the sentence is:

“The differences in prevalence based on gender decrease with decreasing age, since in the population aged 14-18 almost no differences regarding gender were found [2].”

- page 5, line 26: again, this statement of few data on prevalence of cannabis use in pregnancy - this in Spain? Volkow's recent paper from the US does report on this for the US.

---We submitted this paper on January 2019. This paper was not in our review because of its publication date. Our search was carried on July 2018.

Thank you for your suggestion, we have added it.

“Volkow adds that in the US between 2002-2003 and 2016-2017, adjusted prevalence of past month cannabis use increased from 3.4% to 7.0% among pregnant women [64].”

- page 5, line 33-34: again, be careful about wording with illegal, and western countries - need to change manuscript to be European, Spain or worldwide & keep language consistent.

---Thank you for your appreciation, we have added a paragraph in order to clarify it.

“In Spain and most of Europe, cannabis continues to be an illegal substance, however, there are some regions in the western world where this has changed as some states of United States. Recently, other countries like Uruguay, or more recently, Canada have legalized their consumption [64].”

- At the end of the introduction, the objectives of the study are NOT clear - from the background leading up to this it seems like the objectives are going to be a review of the prevalence of cannabis use in pregnancy (geography focus not clear though) & the effects on children of
cannabis prenatal exposure. But then this paragraph is not clear what are the primary and secondary objectives of the review. Please revise.

---Although we describe some data about prevalence, our objective is to describe associated factors to cannabis use during pregnancy and the consequences of prenatal exposure to this substance. We have removed screening methods from the objectives.

“For this reason, the objective of this study is to review the literature on the use of cannabis among pregnant women, its associated factors and its potential effects on the development of the fetus during the postnatal period, childhood and adolescence.”

Methods

- See above note about PRISMA guidelines. See above note about specifying geography of studies included - needs to be outlined in methods (and be consistent with introduction).

---We have not included any geographic limitations and we have tried to clarify inclusion and exclusion criteria.

“The inclusion criteria were: studies specifically focused on associated factors of cannabis use during pregnancy, effects of exposure to cannabis on the developing fetus and its mental health. The search revealed 491 potentially adequate articles, 377 of which did not meet the inclusion criteria after a review of their title and their abstract. 114 articles were selected, 73 of which were ruled out after a full reading. Ultimately, 41 articles from the original search were included[3-5,7-10,12-17,19-26,28,38,39,42-49,51,53-57,59-61], plus 24 articles which were added after appearing repeatedly in the list of references of the first group[1,2,6,11,18,27,29-37,40,41,50,52,58,62,63,64,65]. According to the PRISMA methodology [62], 73 articles were ruled out because of a small sample size, unclear designs or methods of study, not addressing review objectives or not specific information about cannabis.”

- The paragraph starting at line 41 should go after the subsequent paragraph - essentially the wording of the methods should match well with the flow of the figure but it does not right now.

---Thank you for the suggestion, we have fixed it.

“114 articles were selected, 73 of which were ruled out after a full reading. Ultimately, 41 articles from the original search were included[3-5,7-10,12-17,19-26,28,38,39,42-49,51,53-57,59-61], plus 24 articles which were added after appearing repeatedly in the list of references of the first group[1,2,6,11,18,27,29-37,40,41,50,52,58,62,63,64,65].”

Results

- please see above note about clarifying the objectives of the study from the beginning.
Thank you, clarified as previously indicated.

- In line with how the objectives are changed, please consider changing the subheading in line 22 on page 7 to something like 'Animal and human studies on the effects on children of prenatal cannabis exposure'. Please use further subheadings within this one to delineate animal vs. human data and the categories of effects.

---Thank you for your suggestion, we have organized it in a different way and with different subheadings.

“2.a Factors associated to cannabis use during pregnancy

2.b Animal studies on the effects on children of prenatal cannabis exposure

2.c Human studies on the effects on children of prenatal cannabis exposure”

- The last 2 paragraphs on page 7 need to be taken out - they are too generalized, and the wording used stereotypes women who use substances and perpetuates stigma they face seeking care - please consider rewriting with focus on the fact that all studies we have right now in humans are observational data, then outline the downsides to observational data - such as the existing data we have is not able to tease apart the effects of the drug itself (cannabis) from other factors from the environment in which the fetus then child matures that could also impact the outcomes assessed. The last sentence, page 8 line 5 is a good example of what should emphasized instead.

---Thank you for this observation, we have replaced these two paragraphs with:

“2.a Factors associated to cannabis use during pregnancy

Heterogeneous results have been obtained from different studies, this is probably related to differences in sample populations, study designs used and cultural differences from the geographical locations in which these studies are carried out.

El Marroun et al. can not find any strong association with demographic characteristics as age, ethnicity or presence of psychopathology with cannabis use during pregnancy in the study he performed in Rotterdam. But it is described a strong association with biological father’s cannabis use and being unmarried. Religion is described as a protective factor. From this sample 3’2% of women used cannabis before being pregnant, 2’9% before and during pregnancy, but just 0’6% of women decided to continue cannabis use throughout pregnancy. This last group had a lower educational level [5].

They also find out that history of cannabis addiction makes 2.77 times more likely to continue cannabis use during pregnancy; also, women with a frequent cannabis use (daily or weekly) are more likely to continue it than those who use it monthly[5].
However, Gray et al., in a study performed in US, can not describe strong associate with demographic characteristics as age, being unmarried or being employed. It is described that Hispanic women are less likely to use cannabis during pregnancy, but cannabis use was more likely in women from multiracial origin [9]. This differs from another study conducted in the US in which an association is found between cannabis use during pregnancy and characteristics such as being young, unmarried and non-Hispanic white. It is associated with having a psychiatric disease different from substance addiction and not having graduated from high school [65].

The knowledge of these associated factors to cannabis use during pregnancy may be useful in order to identify future mothers to provide with quality information about the possible consequences of prenatal exposure to cannabis.”

- See above note about changing way statements are written from factual ones to ones that give the findings of the evidence, the strengths and weaknesses of that evidence from which the statement comes. Examples of where this definitely needs to be done is page 9, line 49 that paragraph "cannabis causes...";

---Thank you for your observation, in Wang’s paper the sentence is: “These results document a different pattern of the anatomical organization of the CB1 mRNA expression in the mid-gestation fetal and adult human brain. Overall, the high CB1 mRNA expression in the fetal hippocampus and amygdala indicates that these limbic structures might be most vulnerable to prenatal cannabis exposure.” So, we have changed it to: “Intrauterine exposure to cannabis may causes different pattern of the anatomical organization of the CB1 mRNA expression in the mid-gestation fetal and adult human brain; has been found high CB1 mRNA expression in the fetal hippocampus and amygdala”

- page 10, line 7 paragraph of associations based on 1 to few studies;

---Thank you for making us know, we have corrected it.

“There is one study that assess the different consequences of the maternal use of cannabis in the newborn”

- page 10, line 46 paragraph - there is absolutely no grading of the evidence behind these associations outlined

---Thank you. Reviewed and corrected.

“There are few review studies suggesting prenatal exposure to cannabis may be associated with mood and behavioral alterations, that could be related with affective mental disorders, and depressive symptoms, as well as ADHD[21,45-48]. There are no studies that establish a connection with the presence of psychotic disorders [49]”
“Have been observed in two studies that the executive dysfunction could be present even into early adulthood [53,56].”

- Considering the cannabis detection review, see above notes about redoing the objectives of the study and consider not including this as a review objective. This information the way it is written ends up essentially just being repeated throughout the manuscript without actually 'reviewing' the data behind the different modalities, their specificities/sensitivities, etc.

--- We have eliminated detecting methods from subheadings, we keep some information about detection difficulties

- Also line 32, page 12 is not true & line 2, underreporting is not the only issue that needs to be considered when choosing a detection method…

--- Line 2. We agree, underreporting is not the only issue that needs to be considered when choosing a detection method, but it is an important reason for which detection methods need to be used.

Line 32. Two different authors (Garcia- Serra y García-Algar) in different papers, describe meconium as expensive and usually unavailable. Also, consider that for detection of exposure during first trimester maternal hair is more adequate. But we change de expression “is not sensitive” for more accuracy.

“Meconium is the most widely used fetal matrix to reveal prenatal exposure to drugs of abuse[5]. It can be easily obtained, but it has a collection window of 72 hours, it could be less sensitive for detection of exposure during the first trimester and testing is more expensive and less available [7,8].”

Discussion

- Paragraph 1 - please see above important notes about needing to reshape language from giving a hypothesized model of how cannabis and the environment together effect children & instead reporting on the bias, strengths and weaknesses of the existing observational evidence that struggles to be able to actually identify effects of the drug itself on the newborn given the multitude of multidimensional factors at play.

--- We find your point of view quit interesting, so we have changed this paragraph in that perspective.
“There is a high prevalence of cannabis use during pregnancy, despite the difficulties to detect its consumption among pregnant women. However, it is difficult to describe factors associated to cannabis use during pregnancy due to the different results obtained in different studies. While in EU, El Marroun et al. associates being unmarried and lower education level as more likely in women that use cannabis during pregnancy, no association is found with demographic characteristics as age, employment or ethnicity[5]. In US, Martin et al. finds association with young age, not unemployed and white non-Hispanic women, this study also find association with being unmarried and having lower educational level[65]. This also differ from other US study, which finds as more likely cannabis use during pregnancy women from multiracial origins, but no differences with age, employment or marital status[9]. This heterogeneity in findings across studies could be explained with the differences in study designs used, confounding factors, sample population and sample size.”

- Page 13, first paragraph - needs to be re written - line 2 'causes alterations' is not clear, ; line 9 'are neurocognitive…” again problem with factual statements when data is lacking, and the last sentence is not stated appropriately.

---Thank you, we have re written it.

“So according to this hypothesis there could be neuro-cognitive consequences to the exposure, some of which may remain present even in early adulthood, such as executive dysfunction, with repercussions on the daily life[16,17, 63].”

- Page 13, line 29 - this is good example of how throughout the manuscript since animal and human data are both included, it needs to be extremely clear when one vs the other are being reviewed.

---Thank you, we have emphasized throughout the manuscript by using different subheadings differentiating data.

- The paragraph line 37, page 13 - this sentence does not add anything the way it is right now.

---Thank you, we have eliminated it.

- Line 45, this paragraph is the points that should be emphasized actually throughout the manuscript - see above notes about this please!

---Thank you. It also has been done above, throughout the manuscript.

- Page 14, line 12 onward - this is all the same info already presented in the results - see above note about considering taking this out of review and just including in the discussion within the discussion of the strengths/weaknesses of the evidence reviewed.
---Thank you, we have reduced the amount of repeated information and we have added information about the design of the studies.

“Therefore, screening with blood and urine samples is used during pregnancy because it is easier and more readily available, in spite of the fact that these tests only provide information about use in the last 24-48 hours[10,11]. There are few studies using detection methods, each of them with different methods and designs. More homogeneously design studies are needed in order to develop sensitive and available methods for substances use detection”

Discussion

- First line "has been proven" - this is untrue.

---Conclusions have been rewritten:

“The use of cannabis during pregnancy could produce neurochemical alterations both in humans and in research animals. From a clinical perspective, medical and psychiatric alterations have been described both in cross-sectional and in cohort studies.

Although there is some controversial findings, some regional differences and there are methodological limitations of the studies, early detection is fundamental. It is also important to warn women about the risks of using cannabis during pregnancy in order to minimize the possible consequences, which mainly include affective disorders and ADHD and which depend on duration and intensity of the prenatal exposure. In this regard, awareness campaigns may be an essential tool.

An active involvement is required from primary care, obstetricians, pediatric, mental health and drug dependence services. Longitudinal prospective studies need to be designed to finally identify all the consequences of prenatal exposure to cannabis regarding developmental alterations, neuro-cognitive side effects and mental disorders among the exposed population.”

Tables

- See above comments about changing how the manuscript is written to review the evidence, not just give conclusion statements with citations, on the topic. Table 1 makes it seem like you did a meta-analysis. Table 2 is poorly done & again does not review any evidence. Please take these tables out & replace it with tables of the evidence, reviewing it, organized by topic or study design (and human vs animal) as is done in other review papers.

---Table 1 have been deleted. Table 2 have been updated.

- Figure 1 - needs footnotes about methodology & needs editing to be more appropriate for a journal publication format wise (please do review of other review papers for examples).
---Thank you, we add a new Figure 1

- Figure 2 - see above comments - consider taking this out & replacing with evidence/bias review as outlined above

---Thank you, we have taken it out.