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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: 02/10/2023
To: "Erin Delker" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-23-32

RE: Manuscript Number ONG-23-32

Prenatal exposure to cannabis and risk of major structural birth defects: a systematic review and meta-analysis

Dear Dr. Delker:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 03/03/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

* Please carefully review the Statistical Editor's comments. Several inconsistencies in the data were identified which should be carefully considered and addressed.

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Figure 1: Please check n values (articles retrieved adds up to 2,706; records retrieved less 505 equals 2,242; everything below this is off by 2). Please upload as a figure file on Editorial Manager.

* Figures 2-8: Please upload all figures as figure files on Editorial Manager.

REVIEWER COMMENTS:

Reviewer #1:

The authors present a meta-analysis of cohort studies evaluating the risk of congenital anomalies among patients reporting cannabis use. They identify a potential increased risk of Ebstein's anomaly and gastroschisis.

Abstract:
Line 25- include numbers in regards to the pooled positive associations.

Introduction:
Line 47- some of this section may be cut down for this obstetric journal

Methods:
Line 83- in this paragraph please state the exclusion criteria and inclusion criteria together. The authors can cut this section down a great deal by simply making one statement and listing all exclusion criteria and one statement with all inclusion criteria.

Line 102- If the authors did not search clinicaltrials.gov how do they know it is only being studied in observational settings?

Line 113- how was the disagreement resolved? Was this a third party decision?

Line 139- again please identify how disagreement was resolved?

Results:
Line 197- clarify that this is only the 9 studies evaluating cardiac anomalies.

Line 242- place a sub title her for gastroschisis to be consist with prior paragraphs

Discussion:
Some of the discussion should be cut down to focus on limitations and outcomes.

Line 352- did the authors perform an evaluation for publication bias?

Line 355- additional limitations include that many studies did not identify which trimester the exposure occurred (i.e. first trimester only would be associated with anomalies). And the potential for recall bias particularly regarding the use of alternative drugs.

Reviewer #2: Prenatal exposure to cannabis and risk of major structural birth defects: a systematic review and meta-analysis

The references do not appear to correlate with the footnote numbers in my manuscript and appear incomplete

The authors screened a large number of records (2240) to finally include 23 in the synthesis. They acknowledge studies were "...heterogeneous and difficult to aggregate"

The objectives were:
1. Aggregate published findings...and generate suggestions for future research

2. Answer the question, based on existing data, "Does cannabis exposure during pregnancy increase the risk of major structural birth defects?"

Data is aggregated and OR's and RR's discussed

However only 10 studies of those studies, per their table 2, noted first trimester use. Of those only 4 adjusted for alcohol and tobacco exposure and only 1 measured cannabis use during the pregnancy. Given the teratogenic window it would appear to be a jump to infer, no matter how likely, first trimester use in
all the 23, or a primary cannabinoid etiology.

The authors did not breakout the defined first trimester use but did note subgroups by defect associations, leading to some unusual result tabulations, Van Gelder 2014.2 with an unexposed cleft lip incidence of ~20% for example, demonstrating the difficulties of too specific a breakdown and potentially the primary article
Any potential meta analysis would seem to be dwarfed by the two large studies, Petrangelo and Bandoli, not included in the references, and thus require more directed and controlled studies rather than increasing depth of statistical analysis. (Only Bandoli was fully available on the internet for review)

Reviewer #3:

Manuscript number: ONG-23-32

"Prenatal exposure to cannabis and risk of major structural birth defects: a systematic review and meta-analysis"

General: The manuscript aggregates and reviews English language studies on association between prenatal cannabis use and major structural birth defects, commenting on strengths and limitations in and between the studies and possible areas warranting future investigation.

Introduction:
Line 65, 89: It appears as though the citation number/reference match-up was disrupted around this point in the article (citations 17-21), leading to an offset by one number in the reference list. Careful attention to accurate citations will decrease reader confusion when attempting to reference articles.

Methods:
Line 96: What was the reason for excluding studies not published in English? Was this exclusion implemented at the title/abstract screening or full text screening period? Cannabis has been legalized and decriminalized in many nations across the globe that are not primarily English-speaking. Data from these areas may vary significantly, and excluding studies in languages other than English may impact results for this particular topic. Consider mentioning the reason for this limitation in the methods or discussion and clarifying which stage of screening this particular exclusion impacted, given that it may affect generalizability.

Discussion:
Line 357: It may be of value to note here that studies conducted prior to the legalization of cannabis (i.e. those published over a decade ago) may miss the sampling of a portion of the population incarcerated for cannabis-related offenses. While most federal and state offenders sentenced for cannabis possession in the US are male, according to the United States Sentencing Commission, there remains a significant possibility of prenatal marijuana exposure in the incarcerated population, whether cannabis use is the reason for the sentencing or not. Line 363 does note that confounding factors that co-vary with use will change with increasing acceptance of cannabis, but it does not directly address idea of a change in the populations sampled over time due to incarceration.

Figures:
What is the rationale behind how the studies were listed in each figure? Figures 3 and 7 have studies listed chronologically per defect. The chronology in Figure 2 is the reverse of in other tables. Consider more consistency in how figures are organized, to improve easy of reading and comparison.

STATISTICAL EDITOR COMMENTS:

General: There were multiple errors in calculation of RRs, based on the data in the Tables.

For instance, Fig 3, the reference by Correa-Villasenor, the data entries 7/60 vs 40/354 results in RR = 1.0, not 2.4. In the article by Villasenor, the data are actually 7/44 vs 263/3572, which yields a RR = 2.2, not 2.4. Need to correct this. Also, in the article by Villasenor, the results are in format or ORs, not RRs. Similarly, for the article by Linn, the data 7/1246 vs 26/11178 results in RR = 0.4, not RR = 2.4.

in Fig 8, the study by Linn (hydrocephalus) with entries 6/1246 vs 2/11178 results in RR = 27, not 3. Need to reconcile.

Again, related to the study by Correa-Villasenor, several potential agents associated with later development of Ebstein's were explored and Cannabis had the lowest OR among benzodiazepines, GI medications, Varnishes, Cannabis and miscellaneous solvents. Moreover, although the finding of Ebstein's was carefully established, the exposure to drug or chemical agent was by self-recall. This clearly could be a result of recall bias.

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Sincerely,
Jason D. Wright, MD
Editor-in-Chief

The Editors of Obstetrics & Gynecology

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

RESPONSE TO REVIEWS for ONG-23-32

"Prenatal exposure to cannabis and risk of major structural birth defects: a systematic review and meta-analysis"

Thank you very much for the detailed feedback and opportunity to revise this manuscript. Below we explain how we address the reviewers' comments. Changes in the manuscript that address the reviewers' suggestions are highlighted in track changes.

Reviewer Comment	Response
Editor	
Please carefully review the Statistical Editor's comments. Several inconsistencies in the data were identified which should be carefully considered and addressed.	Yes, we appreciate the statistical editor identifying the issues. We have reviewed all estimates and corrected typos in the code used to generate data columns of the figures. We appreciate the opportunity to be able to revise after fixing these errors.
Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://urldefense.com/v3/__https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf__;!!LLK065n_VXAQ!hveZSeDSJ9a4VL6xUqdd84tkUdEgMNp96A9n31_TCye6bnu1lEtTHqnDl8UBGPbhNlYFF1lmv_wGUMzV0pg$ and making the applicable edits to your manuscript.	Thank you for the link. We have reviewed these guidelines.
Figure 1: Please check n values (articles retrieved adds up to 2,706; records retrieved less 505 equals 2,242; everything below this is off by 2). Please upload as a figure file on Editorial Manager.	This was fixed.
Figures 2-8: Please upload all figures as figure files on Editorial Manager.	Done. We have included them in the word doc in addition to uploading them as svg files
Reviewer 1	
Abstract: Line 25- include numbers in regards to the pooled positive associations.	We have added the pooled effect estimates for both Ebstein's anomaly and gastroschisis in the abstract.
Introduction: Line 47- some of this section may be cut down for this obstetric journal	We have removed some of the introductory material and as a result, the revised draft is more concise.

Methods: Line 83- in this paragraph please state the exclusion criteria and inclusion criteria together. The authors can cut this section down a great deal by simply making one statement and listing all exclusion criteria and one statement with all inclusion criteria.	Thank you for the recommendation. We have revised accordingly.
Line 102- If the authors did not search clinicaltrials.gov how do they know it is only being studied in observational settings?	We made the a priori assumption that a clinical trial of cannabis exposure during pregnancy would not been allowed by institutional review boards and thus did not think to search clinicaltrials.gov for studies. We have removed the sentence related to ClinicalTrials.gov from our methods section. In response to this reviewer comment, we did now search clinicaltrials.gov and confirm that it is true that no experimental studies of cannabis use in pregnancy on birth defects has been carried out.
Line 113- how was the disagreement resolved? Was this a third party decision?	Almost always, disagreements were resolved once reviewers re-examined the title and abstracts. There was a few cases in which disagreement remained even after meeting together. In these cases, we deferred to the senior author (G.B.). We have added the following sentence to the manuscript, “In the few cases that the reviewers did not reach consensus after re-review, we consulted a third party (G.B.).”
Results: Line 197- clarify that this is only the 9 studies evaluating cardiac anomalies.	Thank you for noting this. The confusion in writing comes from the fact that some studies reported multiple estimates. We have added this sentence to clarify, “Nine studies evaluated associations between cannabis exposure and at least one cardiac defect. Across the nine studies, there were 24 unadjusted estimates and 12 adjusted estimates reported (Figure 3).”
Line 242- place a sub title her for gastroschisis to be consist with prior paragraphs	We have made this change.
Discussion: Some of the discussion should be cut down to focus on limitations and outcomes.	We have re-arranged the discussion section such that a large part of it focuses on both limitations of the included studies as well as limitations of our review process.
Line 352- did the authors perform an evaluation for publication bias?	We have added an evaluation for publication bias using Egger’s test. We have updated our methods to read: “Finally, we used Egger’s test of funnel plot asymmetry to evaluate potential for publication bias within each anatomic subgroup.”

	We have reported the results from each test in the results section by anatomic grouping We have updated our discussion of potential publication bias to read: ". For three of the outcome groupings – oral defects, digestive system defects, and cardiac defects – we found potential evidence for publication bias. This was because the studies that reported the largest measures of association, in general, were the most imprecise and those reporting the smallest measures of association had the tightest confidence intervals. If publication bias is present in these findings, we would expect the estimated pooled associations between cannabis use and each birth defect to be biased away from the null. "
Line 355- additional limitations include that many studies did not identify which trimester the exposure occurred (i.e. first trimester only would be associated with anomalies). And the potential for recall bias particularly regarding the use of alternative drugs.	Thank you for these comments. We have edited the discussion and included these additional limitations.
Reviewer 2	
The references do not appear to correlate with the footnote numbers in my manuscript and appear incomplete	Thank you for catching this! We have corrected all references
The authors screened a large number of records (2240) to finally include 23 in the synthesis. They acknowledge studies were "...heterogeneous and difficult to aggregate"	We are not sure how to interpret this reviewer comment, however, we have made the following edit to the sentence identified, which hopefully helps clarify. It now reads "the other published effect estimates were highly heterogeneous and difficult to aggregate"
Only 10 studies of those studies, per their table 2, noted first trimester use. Of those only 4 adjusted for alcohol and tobacco exposure and only 1 measured cannabis use during the pregnancy. Given the teratogenic window it would appear to be a jump to infer, no matter how likely, first trimester use in all the 23, or a primary cannabinoid etiology.	We agree this is a major limitation of these studies. We have added to our discussion section "Only 10 studies specifically measured first trimester exposure, the clinically relevant critical period for anomalies. Other studies that used a binary (any vs none) classification of prenatal cannabis exposure rely on the assumption that the exposure occurred during the first trimester. If incorrect, this assumption could lead to serious misclassification of the exposure variable and a biased effect estimate."
The authors did not breakout the defined first trimester use but did note subgroups by defect associations, leading to some unusual result tabulations, Van Gelder 2014.2 with an unexposed cleft lip incidence of ~20% for example, demonstrating the difficulties of too specific a breakdown and potentially the primary article Any potential meta analysis would seem to be dwarfed by the two large studies, Petrangelo and Bandoli, not included in the references, and thus require more	Van Gelder conducted a case-control study. They sampled on the outcome so incidence is set by design and should not be interpreted. For this reason, odds ratios rather than risk ratios are presented. We assume that the odds ratio is a reasonable approximation of risk given the rare incidence of the study outcome in the population. Regarding Petrangelo and Bandoli. We had a similar concern. This is why we re-ran our meta-analysis with

directed and controlled studies rather than increasing depth of statistical analysis. (Only Bandoli was fully available on the internet for review)	these studies removed. In the results section, we report: "Two administrative studies with large sample sizes were heavily weighted in the adjusted analyses (Bandoli, 2021: 22.7% Petrangelo, 2018: 21.7%).26,32 After removing these 2 studies from the analysis, we saw little change in the pooled effect estimates (OR = 1.3, 95%CI 1.0, 1.7; aOR = 1.3, 95%CI 1.0, 1.8), but observed lower I-squared values (47.2% for unadjusted random effects model and 63.0% for adjusted random effects model)."
Reviewer 3	
Introduction: Line 65, 89: It appears as though the citation number/reference match-up was disrupted around this point in the article (citations 17-21), leading to an offset by one number in the reference list. Careful attention to accurate citations will decrease reader confusion when attempting to reference articles.	Thank you for catching this! We have double checked and corrected all references
Methods: Line 96: What was the reason for excluding studies not published in English? Was this exclusion implemented at the title/abstract screening or full text screening period? Cannabis has been legalized and decriminalized in many nations across the globe that are not primarily English-speaking. Data from these areas may vary significantly, and excluding studies in languages other than English may impact results for this particular topic. Consider mentioning the reason for this limitation in the methods or discussion and clarifying which stage of screening this particular exclusion impacted, given that it may affect generalizability.	Thank you for raising this important point. We have added a statement in the information sources and search strategy statement that "all search terms were developed in the English language". We have also added to our discussion section, "Finally, we note that our search was limited to published studies identified using English language search terms. This may have caused studies published in other languages to drop out of the sample. It is possible that there are factors that modify the effect of cannabis on birth defects and vary across contexts. This would reduce the ability to generalize findings to those contexts." We note to the reviewers that we did not come across any non-English titles/abstracts in our review. This is likely due to our decision to only search using English terns
Discussion: Line 357: It may be of value to note here that studies conducted prior to the legalization of cannabis (i.e. those published over a decade ago) may miss the sampling of a portion of the population incarcerated for cannabis-related offenses. While most federal and state offenders sentenced for cannabis possession in the US are male, according to the United States Sentencing Commission, there remains a significant possibility of prenatal marijuana exposure in the incarcerated population, whether cannabis use is the reason for the sentencing or not. Line 363 does note that confounding factors that co-	We agree that legalization plays an important role in the study of cannabis use. We have added the below to our discussion section to acknowledge that legalization will not only affect how confounding factors co-vary in the population, but also who is willing / able to participate in research studies. "Recent legalizations of both medical and recreational cannabis have led to increased accessibility and more normative use in some regions. As cannabis use becomes more normative, the confounding factors that co-vary with use across the population will change. The characteristics of individuals enrolling in studies on

vary with use will change with increasing acceptance of cannabis, but it does not directly address idea of a change in the populations sampled over time due to incarceration.	cannabis use in pregnancy may change too. These changes should be leveraged to improve internal validity in future research.
Figures: What is the rationale behind how the studies were listed in each figure? Figures 3 and 7 have studies listed chronologically per defect. The chronology in Figure 2 is the reverse of in other tables. Consider more consistency in how figures are organized, to improve easy of reading and comparison.	We have updated the ordering of all studies in all figures to be chronological (oldest to newest). We agree that this consistency makes the figures easier to follow.
Statistical Editor	
General: There were multiple errors in calculation of RRs, based on the data in the Tables. For instance, Fig 3, the reference by Correa-Villasenor, the data entries 7/60 vs 40/354 results in RR = 1.0, not 2.4. In the article by Villasenor, the data are actually 7/44 vs 263/3572, which yields a RR = 2.2, not 2.4. Need to correct this. Also, in the article by Villasenor, the results are in format or ORs, not RRs. Similarly, for the article by Linn, the data 7/1246 vs 26/11178 results in RR = 0.4, not RR = 2.4.	Thank you very much for catching these errors. These issues have been corrected. Regarding estimation of the RRs vs ORs. When hand calculating, we estimated RRs for studies with a cohort study design and ORs for studies with a case control study design. These are the estimates reported in Table 1. For the figures, we have updated our analyses to estimate pooled ORs rather than pooled RRs and write in our methods section, “When aggregating results, we did not distinguish between ORs and RRs because all structural birth defects evaluated were rare, suggesting that the ORs were reasonable approximations of the RRs. “
in Fig 8, the study by Linn (hydrocephalus) with entries 6/1246 vs 2/11178 results in RR = 27, not 3. Need to reconcile.	This resulted from a typo in the data entry column. It has been corrected.
Again, related to the study by Correa-Villasenor, several potential agents associated with later development of Ebstein's were explored and Cannabis had the lowest OR among benzodiazepines, GI medications, Varnishes, Cannabis and miscellaneous solvents. Moreover, although the finding of Ebstein's was carefully established, the exposure to drug or chemical agent was by self-recall. This clearly could be a result of recall bias.	Thank you for these points. We were hesitant not to compare the effect estimate for marijuana with other exposures in the multivariable model because our goal was only to report on marijuana. We have made sure to include what other variables were included in the regression model when describing results from Correa-Villasenor study in our discussion. Regarding potential for recall bias, we agree that this is an issue, and is relevant to most included studies. As such, we have added to your discussion section “Additionally, many studies used retrospective case-control study designs. While these designs provide excellent capture of the outcome, there is potential recall bias of exposure and covariate data. For example, it is

	possible that the presence of a birth defect how the study participant recalls and reports exposure information”

Date: 03/29/2023
To: "Erin Delker" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-23-32R1

RE: Manuscript Number ONG-23-32R1

Prenatal exposure to cannabis and risk of major structural birth defects: a systematic review and meta-analysis

Dear Dr. Delker:

Your revised manuscript has been reviewed by the Statistical Editor. The Editors would like to invite you to respond to additional comments before we can proceed with making a final decision.

Each point raised by the Statistical Editor's R1 review requires a response by revising your manuscript. The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by 04/12/2023, we will assume you wish to withdraw the manuscript from further consideration.

STATISTICAL EDITOR:

First, I thank the Authors for their corrections to their data entry that resulted in several discrepancies between the data columns and the corresponding ORs and RRs.

However, some issues remain re: Fig 3, section on Ebstein's anomaly. There were two studies cited, Downing and Correa-Villasenor. The study by Downing found NS association between cannabis and Ebstein's, while the study by Correa-Villasenor purportedly did show a significant association, with a pooled association that was statistically significant. However, I believe the results from the Correa-Villasenor study were misinterpreted and did not actually show a statistically significant association.

First, in Tables 5 and 6 and on page 141 of that reference (# 28), the Authors list the crude and then the adjusted ORs for the associations with Ebstein's anomaly. The strongest univariate associations were with family history of cardiovascular malformation, maternal hx of miscarriage and maternal age, followed by maternal exposures (in rank order) to benzodiazepines, varnishes, miscellaneous solvents, gastrointestinal medications and cannabis.

Then, several multivariable regression models were evaluated (Table 6) and described as "The model that explained the data best included family history of CVM, number of previous miscarriages treated as a score (i.e., 0, 1, and greater than 1, benzodiazepines, and varnishing (Table 6, model B); maternal age and marijuana no longer improved the fit of the model."

In Table 6, the Authors also provided 99% CIs for the ORs, since there was a multiplicity of variables retained in the model, with relatively few total cases (N = 44) of Ebstein's. If that inference threshold were applied, then cannabis would not have been retained in any of the multivariable models.

So, since neither study actually concluded that a statistically significant association between cannabis and Ebstein's existed, it seems inappropriate to state that this review and meta-analysis would come to a contrary conclusion.

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Sincerely,
Jason D. Wright, MD
Editor-in-Chief

The Editors of Obstetrics & Gynecology

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

RESPONSE TO REVIEWS for ONG-23-32

"Prenatal exposure to cannabis and risk of major structural birth defects: a systematic review and meta-analysis"

Thank you for the opportunity to revise our manuscript. We sincerely appreciate the statistical editor's additional feedback. A description of how we responded to their comment is below.

Statistical Editor

First, I thank the Authors for their corrections to their data entry that resulted in several discrepancies between the data columns and the corresponding ORs and RRs.

However, some issues remain re: Fig 3, section on Ebstein's anomaly. There were two studies cited, Downing and Correa-Villasenor. The study by Downing found NS association between cannabis and Ebstein's, while the study by Correa-Villasenor purportedly did show a significant association, with a pooled association that was statistically significant. However, I believe the results from the Correa-Villasenor study were misinterpreted and did not actually show a statistically significant association.

First, in Tables 5 and 6 and on page 141 of that reference (# 28), the Authors list the crude and then the adjusted ORs for the associations with Ebstein's anomaly. The strongest univariate associations were with family history of cardiovascular malformation, maternal hx of miscarriage and maternal age, followed by maternal exposures (in rank order) to benzodiazepines, varnishes, miscellaneous solvents, gastrointestinal medications and cannabis.

Then, several multivariable regression models were evaluated (Table 6) and described as "The model that explained the data best included family history of CVM, number of previous miscarriages treated as a score (i.e., 0, 1, and greater than 1, benzodiazepines, and varnishing (Table 6, model B); maternal age and marijuana no longer improved the fit of the model."

In Table 6, the Authors also provided 99% CIs for the ORs, since there was a multiplicity of variables retained in the model, with relatively few total cases (N = 44) of Ebstein's. If that inference threshold were applied, then cannabis would not have been retained in any of the multivariable models.

So, since neither study actually concluded that a statistically significant association between cannabis and Ebstein's existed, it seems inappropriate to state that this review and meta-analysis would come to a contrary conclusion.

Author's Response

Thank you very much for your detailed look at the Correa-Villasenor study. For marijuana, we reported the crude estimate reported in Table 5 (OR = 2.4, 95%CI 1.0 to 5.4) and the adjusted estimate reported in Table 6 Model A (OR = 2.8, 95% CI 1.2 to 6.5). We selected the estimate from Model A because, per our review protocol, it was the most fully adjusted model that included marijuana. However, we agree that by doing so we may have overstated the findings from that paper. We have made the following adjustments to our manuscript to both temper our conclusions and be more transparent about what was presented in the original article.

Abstract (additions are highlighted in yellow)

- Highlight that data were limited for Ebstein's anomaly and gastroschisis: "Only two specific anomalies, with limited data, had pooled effect estimates that did not attenuate to the null after adjustment: Ebstein's anomaly (2 studies, aOR = 2.2 (95% CI 1.3, 3.8)) and gastroschisis (5 studies, aOR = 2.5 (95% CI 1.1, 5.7))."
- Highlight that there was not high-quality evidence. "Overall, we found no convincing evidence to suggest that prenatal cannabis exposure causes birth defects. Though, findings related to gastroschisis

and Ebstein's anomaly should be considered in further research."

Tables (additions are highlighted in yellow)

- We initially only recorded 95% confidence intervals in Table 1. Because Correa-Villasenor also presents 99% CIs, we have added those to Table 1 for transparency.
- "M1 aOR = 2.8 (95% CI 1.2, 6.5) (99% CI 0.9, 8.4)"
- "M2 aOR = 3.6 (95% CI 1.6, 8.5) (99%CI 1.2, 11.1)"

Manuscript Discussion Section (additions are highlighted in yellow)

- We have tempered our overall conclusions:
  - "Overall, there was no convincing evidence that prenatal cannabis exposure causes birth defects. There were only two specific outcomes where effect estimates did not attenuate to the null after adjustment: Ebstein's anomaly (2 studies) and gastroschisis (5 studies). We reported 2.5 times higher risk of each outcome in pregnancies with prenatal cannabis exposure compared to those with no exposure, however, evidence was limited and should be interpreted with caution."
- We have added more detail about the Correa-Villasenor modeling approach
  - "Two observational studies specific to Ebstein's anomaly were included in this review. The first was a case-control study including 47 Ebstein's anomaly cases and 3,572 controls born between 1981-1989. That study reported an aOR of 2.8 (95% CI 1.2, 6.5) after adjustment for family history of cardiovascular malformations, maternal age, benzodiazepine exposure, and exposure to paint varnish.[28] Notably, the measure of association for marijuana was smaller than for all other environmental exposures examined. Also, the authors examined multiple logistic regression models and reported that the model that best explained odds of Ebstein's anomaly included adjustment for previous miscarriages, and in that model, marijuana was left out because it did not improve model fit. [28]"
- We are cautious not to overstate these findings in our discussion section. At the end of the section on Ebstein's Anomaly, we write:
  - "We note that both studies scored poorly (1 out of 5 points) on our risk of bias assessment. Neither study measured cannabis use prospectively, considered frequency or quantity of use, or adjusted for alcohol or tobacco exposure. Due to these limitations, results should not be overinterpreted. Further research may be warranted."