

OBSTETRICS & GYNECOLOGY



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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: Sep 17, 2021
To: "Marcela C Smid" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1635

RE: Manuscript Number ONG-21-1635

Association Between Prenatal Nicotine or Cannabis Exposure and Adverse Neurobehavioral Outcomes in Offspring

Dear Dr. Smid:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in *Obstetrics & Gynecology* in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Oct 01, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Methods

Line 55 - I personally would like the authors to state that this is a retrospective cohort study and secondary analysis. I recognize that this may vary with personal style. This should also be considered in the title and abstract as it is in the STROBE guidelines.

Line 103 - I would like to question the validity of using a Conner's Rating Scale in a 48-month-old child. Generally, this questionnaire is validated for children as young as age 6. Modifications of this survey have been made to include children in preschool years. These children may be followed longer, and that is why this questionnaire was used.

Line 121 - The sample size appears appropriate. The incidence of marijuana/nicotine use is similar to what the authors anticipated.

Results

Line 170 - I agree that the adjusted median difference in the Conner score is higher in children whose mothers had a positive urine test compared to negative urine mothers. What is not clear to readers is that median scores for both groups are considered normal. The interquartile range is not higher than what would be regarded as a positive Conner test (65). Would any of the children ultimately need to be treated with interventions or medications? Intervention is unlikely necessary at the age of assessment. I agree with the authors that is preliminary results and a separate study is needed.

Figure 1

Typo in the lower-left box "self-ported."

Reviewer #2:

Objective: Secondary analysis of two parallel multi-center randomized controlled trials of treatment for hypothyroxinemia or subclinical hypothyroidism among pregnant individuals enrolled at 8-20 weeks gestation. All maternal-infant dyads with a maternal urine sample at enrollment and child neurodevelopmental testing were included (n= 1197)

1. Precis is very confusing to read as there are three negatives: Neither, nor and not. Please state simply
2. Well written, easy to read
3. Discussion: I would recommend that the discussion expand and develop as a major weakness of the study (Not the last paragraph but perhaps the first paragraph of the weaknesses in the discussion) the lack of data for Adverse Childhood Experiences (ACE). I dont think that a neurobehavioral study can look at a single exposure whether it is THC or cotinine without looking at ACEs and their plausible neuro pathways.
4. line 171 please add "at 48 months" to your positive finding
5. You have a negative study regarding your primary outcome yet the emphasis of your discussion is on the positive secondary outcome. What other associations have been linked to childhood impulsivity: genes, childhood trauma etc, I would develop this in the discussion

Reviewer #3:

Lines 2-3: Worded as a double negative, need to clarify.

lines 24-26: Should change to something like, "Among the 24 separate secondary outcomes tested, the children with THC-COOH exposure compared with unexposed children had higher (worse) attention scores at age 48 months (57 vs 49, AD 6.0 (95% CI 1.1 to 10.9)".

lines 136-137, Table 1: Since the inference threshold was defined as $p < 0.05$, need to clarify whether the difference in maternal age for cotinine groups was statistically significant.

Tables 2, 3: Since there are actually 2 primary outcomes (comparisons of WPPSI III IQ @ 60 months for (1) cotinine and (2) THC-COOH, the inference threshold should be stricter, i.e., based on 97.5% CI, which will likely make the unadjusted difference in medians NS for cotinine, just as the other unadjusted comparison and both adjusted comparisons are.

Also, the statistically significant difference in the Conners test at 48 months for THC-COOH is (1) a secondary outcome and (2) one of a multiple of secondary outcomes tested, without any adjustment for multiple hypothesis testing. That is, it is likely that at least one comparison would be significant at $p < .05$ level, given the number of comparisons. It may be spurious and not reproducible.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

- * Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
- * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
- * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
- * Name the IRB or Ethics Committee institution in the Methods section (if applicable).
- * Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

4. If your study is based on data obtained from the National Center for Health Statistics, please review the Data Use Agreement (DUA) for Vital Statistics Data Files that you or one of your coauthors signed. If your manuscript is accepted for publication and it is subsequently found to have violated any of the terms of the DUA, the journal will retract your article. The National Center for Health Statistics may also terminate your access to any future vital statistics data.

5. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

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7. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data

definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions> and the gynecology data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

8. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

9. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
- * If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

10. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

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In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

12. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

13. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

14. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).

15. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

16. Please review examples of our current reference style at <http://ong.editorialmanager.com> (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources"). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at <https://www.acog.org/clinical> (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

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If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

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Kluwer, and instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line, "Please Submit Your Open Access Article Publication Charge(s)." Please complete payment of the Open Access charges within 48 hours of receipt.

If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and

* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 01, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
John O. Schorge, MD
Associate Editor, Gynecology

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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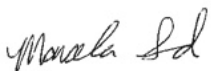
September 28th, 2021

Dear Editors of the *Obstetrics and Gynecology*:

On behalf of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, we are pleased to resubmit our revised manuscript entitled, "**Association Between Prenatal Nicotine or Cannabis Exposure and Adverse Neurobehavioral Outcomes in Offspring**" for consideration for publication in *Obstetrics and Gynecology*.

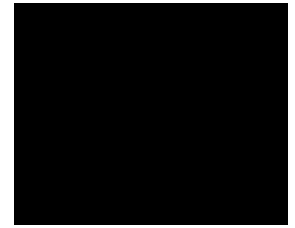
We thank the reviewers for their comments and have responded to each one. The comments and responses can be found at the end of this letter. Thank you for your consideration of our manuscript for publication. We look forward to hearing from you at your earliest convenience.

Sincerely,



Marcela Smid, MD MA MS
University of Utah Department of Obstetrics and Gynecology
30 N 1900 E, Suite 2B200
Salt Lake City, Utah 84132
Marcela.Smid@hsc.utah.edu
Office: 801-581-8425 Fax: 801-585-2594





REVIEWER COMMENTS:

Reviewer #1, Comment #1:

Line 55 - I personally would like the authors to state that this is a retrospective cohort study and secondary analysis. I recognize that this may vary with personal style. This should also be considered in the title and abstract as it is in the STROBE guidelines.

Authors' response: We appreciate the reviewer's suggestion and are willing to edit the title if that is the editor's preference. However, we did not make a change prior to resubmission as this is not typically done for secondary analyses.

Manuscript edits:

Title: Prenatal Nicotine or Cannabis Exposure and Offspring Neurobehavioral Outcomes

Reviewer #1, Comment #2:

Line 103 - I would like to question the validity of using a Conner's Rating Scale in a 48-month-old child. Generally, this questionnaire is validated for children as young as age 6. Modifications of this survey have been made to include children in preschool years. These children may be followed longer, and that is why this questionnaire was used.

Authors' response: The Conner's Rating Scale at 48 months was included in the original trial to answer the secondary research question "Does thyroxine administration to pregnant women with subclinical hypothyroidism or hypothyroxinemia affect attention deficit in their offspring, as measured by the Conner's Rating Scales and the DAS subsets at 48 months?" There are several studies that have validated the use of Conner's Rating Scale for attention problem at this age.

Manuscript edits:

Lines 160-161: Notably, the Conners Rating Scales is validated for use at 48 months of age.^{30,31}

30. DuPaul, G. J., Power, T. J., McGoey, K. E., Ikeda, M. J., & Anastopoulos, A. D. (1998). Reliability and validity of parent and teacher ratings of attention-deficit/hyperactivity disorder symptoms. *Journal of Psychoeducational Assessment*, 16(1), 55-68.

31. Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N. (1998). The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *Journal of abnormal child psychology*, 26(4), 257-268.

Reviewer #1, Comment #3:

Line 121 - The sample size appears appropriate. The incidence of marijuana/nicotine use is similar to what the authors anticipated.

Authors' response: We thank the reviewer for this comment.

Reviewer #1, Comment #4:

Line 170 - I agree that the adjusted median difference in the Conner score is higher in children whose mothers had a positive urine test compared to negative urine mothers. What is not clear to readers is that median scores for both groups are considered normal. The interquartile range is not higher than what would be regarded as a positive Conner test (65). Would any of the



children ultimately need to be treated with interventions or medications? Intervention is unlikely necessary at the age of assessment. I agree with the authors that is preliminary results and a separate study is needed.

Authors' response: We thank the reviewer for this comment. We have added additional discussion about interpretation of the median T scores

Manuscript edits:

Lines 236-241: These results should be interpreted with caution. While the difference between exposed and unexposed children was statistically significant, both groups' median T score was within the average range 40-59 (16-83 percentile) which is associated with typical levels of attention concern for the child's age and sex.³⁹ In addition, we did not adjust for multiple comparisons as this analysis was intended to be hypothesis-generating in order to guide future work in this area.

39. Conners Comprehensive Behavior Rating Scales. Conners CBRS Update. Accessed at <https://www.acer.org/files/CBRS-Supplement.pdf> on September 27th, 2021.

Reviewer #1, Comment #5:

Figure 1: Typo in the lower-left box "self-ported."

Authors' response: We thank the reviewer for noting this typo. This has been edited to read "self-reported".

Reviewer #2

Objective: Secondary analysis of two parallel multi-center randomized controlled trials of treatment for hypothyroxinemia or subclinical hypothyroidism among pregnant individuals enrolled at 8-20 weeks gestation. All maternal-infant dyads with a maternal urine sample at enrollment and child neurodevelopmental testing were included (n= 1197)

Reviewer #2, Comment #1:

Precis is very confusing to read as there are three negatives: Neither, nor and not. Please state simply

Authors' response: We thank Reviewer #1 and #3 for this comment and have edited for clarity.

Manuscript edits:

Lines 55-56: Neither nicotine nor cannabis exposure in the early prenatal period was associated with a difference in child intelligence quotient at 5 years of age.

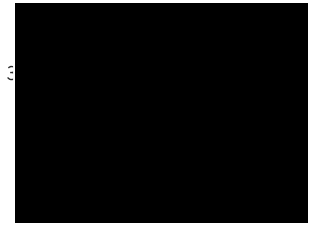
Reviewer #2, Comment #2:

Well written, easy to read

Authors' response: We thank the reviewer for this comment.

Reviewer #2, Comment #3:

Discussion: I would recommend that the discussion expand and develop as a major weakness of the study (Not the last paragraph but perhaps the first paragraph of the weaknesses in the discussion) the lack of data for Adverse Childhood Experiences (ACE). I don't think that a neurobehavioral study can look at a single exposure whether it is THC or cotinine without looking at ACEs and their plausible neuro pathways.



Authors' response: We appreciate that adverse childhood events are increasingly recognized as important exposure when studying child neurodevelopmental outcomes. We have added discussion of ACEs and that this is a common weakness of all studies on this topic, including our own.

Manuscript edits:

Lines 333-337: Other significant risk factors for attention disorders include environmental exposures such as high levels of lead,⁶⁴ mercury⁶⁵ and polychlorinated biphenyls (PCBs)⁶⁶, fetal alcohol exposure,⁶⁷ adverse childhood events (ACE)⁶⁸⁻⁷⁰ and gene susceptibility⁷¹ which were not systematically collected as part of the parent study.

Reviewer #2, Comment #4:

Line 171 please add "at 48 months" to your positive finding

Authors' response: This has been edited.

Manuscript edits:

Lines 224-227:: However, after adjustment for confounders, the only finding that remained significant was that children exposed to THC-COOH compared with unexposed children had higher adjusted medians for the Conners' Attention Scale score at 48 months of age.

Reviewer #2, Comment #5:

You have a negative study regarding your primary outcome yet the emphasis of your discussion is on the positive secondary outcome. What other associations have been linked to childhood impulsivity: genes, childhood trauma etc., I would develop this in the discussion

Authors' response: We agree with the reviewer's comment and have included a more robust discussion of other associations with attention problems.

Manuscript edits:

Lines 333-337: Other significant risk factors for attention disorders include environmental exposures such as high levels of lead,⁶⁴ mercury⁶⁵ and polychlorinated biphenyls (PCBs)⁶⁶, fetal alcohol exposure,⁶⁷ adverse childhood events (ACE)⁶⁸⁻⁷⁰ and gene susceptibility⁷¹ which were not systematically collected as part of the parent study.

Reviewer #3:

Reviewer #3, Comment #1:

Lines 2-3: Worded as a double negative, need to clarify.

Authors' response: We thank Reviewer #1 and #3 for this comment and have edited for clarity.

Manuscript edits:

Lines 55-56: Neither nicotine nor cannabis exposure in the early prenatal period is associated with difference in child intelligence quotient at 5 years of age.

Reviewer #3, Comment #2:

Lines 24-26: Should change to something like, "Among the 24 separate secondary outcomes tested, the children with THC-COOH exposure compared with unexposed children had higher (worse) attention scores at age 48 months (57 vs 49, AD 6.0 (95% CI 1.1 to 10.9))".



Authors' response:

Manuscript edits:

Lines 77-79: In secondary outcome analysis, the children with THC-COOH exposure compared with those unexposed had higher (worse) attention scores at 48 months of age (57 versus 49, ADM 6.0 (95% CI 1.11 to 10.89)).

Reviewer #3, Comment #3:

Lines 136-137, Table 1: Since the inference threshold was defined as $p < 0.05$, need to clarify whether the difference in maternal age for cotinine groups was statistically significant.

Authors' response: As Reviewer #3 points out, our threshold for statistical significance was $p < 0.05$. Therefore, we did not consider difference in maternal age in the cotinine groups to be significant.

Reviewer #3, Comment #4:

Tables 2, 3: Since there are actually 2 primary outcomes (comparisons of WPPSI III IQ @ 60 months for (1) cotinine and (2) THC-COOH, the inference threshold should be stricter, i.e., based on 97.5% CI, which will likely make the unadjusted difference in medians NS for cotinine, just as the other unadjusted comparison and both adjusted comparisons are.

Authors' response: We thank Reviewer #3 for this comment and recognize that we have tested the relationship between the primary outcome and two different substances of exposure. This is an unplanned secondary analysis with two exposure and one primary outcome, which is why we opted not to adjust the p-value.

Reviewer #3, Comment #5:

Also, the statistically significant difference in the Conners test at 48 months for THC-COOH is (1) a secondary outcome and (2) one of a multiple of secondary outcomes tested, without any adjustment for multiple hypothesis testing. That is, it is likely that at least one comparison would be significant at $p < .05$ level, given the number of comparisons. It may be spurious and not reproducible.

Authors' response

We discussed adjusting our p-value of significance given the multiple secondary outcomes prior to submission of the manuscript. We decided not to make an adjustment as we included all available outcomes in the parent trial, and instead emphasized that this is a secondary analysis and exploratory. We added further language to make this clear to the reader as noted below.

In the methods, we state that we did not adjust for multiple comparisons.

Manuscript edits:

Lines 193-195: No corrections were made for multiple comparisons as this was a secondary (hypothesis-generating) analysis using all available neurodevelopmental outcomes in the parent trials.

In the discussion, we noted that this could be a spurious result given the multiple comparisons, but is consistent with other studies related to in utero marijuana exposure.

Lines 293-295: "Because this secondary analysis is exploratory, we did not adjust for multiple comparisons which may have resulted in alpha error."



In response to reviewer comments, we now emphasize that these results should be interpreted with caution in the first paragraph of the Discussion.

Lines 237-241: “These results should be interpreted with caution. While the difference between exposed and unexposed children was statistically significant, both groups’ median T score was within the average range 40-59 (16-83 percentile) which is associated with typical levels of attention concern for the child’s age and sex. In addition, we did not adjust for multiple comparisons as this secondary analysis was intended to be hypothesis-generating in order to guide future work in this area.”

