

# 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)\*
- Email correspondence between the editorial office and the authors\*

*\*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](mailto:obgyn@greenjournal.org).

**Date:** Aug 17, 2018  
**To:** "Michelle Ann Kominiarek" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-18-1402

RE: Manuscript Number ONG-18-1402

Child neurodevelopmental outcomes by pre-pregnancy body mass index and gestational weight gain

Dear Dr. Kominiarek:

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).

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 Sep 07, 2018, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

##### REVIEWER #1:

Comments to author:

Abstract:

1. Line: line 93-94. The conclusion doesn't support the results as written. The lack of association with cognitive performance is adjusted OR for BMI. This should be clarified in the abstract.

Introduction:

2. The introduction is well written. The pertinent information and background are concise and relevant. Biologic plausibility is referenced in line 114-117. Perhaps an expansion on the Barker's Hypothesis could be added for historic perspective to engage the reader early in the introduction.

3. Lines 122-124. The hypothesis of myelination and cognitive development at 20weeks needs to be clarified compared to prior studies focusing on intervention of thyroid function at 12 weeks. The avg age in the UK CATS trial referenced from the original article in the NEJM was 13 wks. with thyroid development.

Materials and methods:

4. Lines 141-142. There is potential bias in self reported BMI. For this reason it is unclear why underweight BMI is excluded. Although the number was low could they have been included in the analysis for normal BMI ? Is there any biologic basis for exclusion related to the outcome in question ie IQ or GWG?

5. Line 145-146. Was there a reason why there was limited data on weight after 36 weeks? If the data base was limited to term, or 37 weeks, the accuracy of the most important outcome being used in this study is questionable, particularly GWG.

6. Lines 157-163. How the IQ test results are being used is not clear. Score < 85 at 3 and 5 years seem to be separate categorical outcomes vs. the continuous scores. It seems to come out in the results section but not clear what is being done in the materials and method section.

7. Lines 193-196. The difference between subclinical hypothyroid and hypothyroxinemia suggest two difference populations to start. Although there were attempts to control for thyroid studies the original study did report different IQ scores by

category. median IQ score of the children was 97 (95% confidence interval [CI], 94 to 99) in the levothyroxine group and 94 (95% CI, 92 to 96) in the placebo group (P=0.71). In the hypothyroxinemia trial, the median IQ score was 94 (95% CI, 91 to 95) in the levothyroxine group and 91 (95% CI, 89 to 93) in the placebo group (P=0.30). Since these were separate parallel RCT with no comparison between RCT is it more appropriate to analyze each RCT separately regarding the question of both BMI and GWG?

Results:

The tables and legends stand by themselves and are clear

8. Given the high percent of Hispanic subjects is there any information on primary language and use of cognitive function testing validation? Were they conducted in both English and Spanish?

Comments:

9. The limitations of this trial were clearly stated. The multifactorial nature of IQ testing is problematic. Because these findings are from a subset of patients as mentioned in regards to subclinical hypothyroid replacement it may not be generalizable but could add to future systematic reviews.

REVIEWER #2:

This is a secondary analysis of data from a prior prospective randomized controlled study. The data set used in this study was unique in that it followed child neurodevelopmental outcomes out to 3 and 5 years. Using this valuable data to evaluate for another variable that could contribute to poor child neurological outcomes was an interesting evaluation of a prior data set. However, in an outcome that is multifactorial such as child neurodevelopment, it is difficult to make any association, even after correcting for confounding variables. Also, because this study was a secondary analysis, it was not properly powered to measure the outcome that was evaluated.

Abstract

1\* The objective of the paper is clearly stated and summarized.

Introduction

2\* The introduction explains clearly why BMI and GWG were the variables of concern in regards to child neurodevelopmental outcome.

3\* The definitions of the rates of GWG used from the Institute of Medicine standards should be outlined in the introduction to further provide background for the reader.

Materials and Methods

4\* The authors clearly explain how the original data set was pared down to the 948 patients, and why some patients were excluded from the secondary analysis.

5\* The definitions of GWG used in this study are confusing for the reader and it is not clearly described how the "early" and "late" weekly rates of GWG were calculated and compared with the first, second, and third trimester GWG standards provided from the Institute of Medicine.

6\* As the primary outcome of the original trial was child IQ at 5 years, it is unclear why the authors have included the information from the DAS-III scores as well, especially because not all subjects had a DAS-III score documented.

Results

7\* As this was a secondary analysis, it was not possible to adjust and match patients for baseline differences and there were significant differences noted in race, education, insurance type, and parity - all of which were confounding factors that could affect child neurodevelopmental outcomes. However, the only confounding factors noted to be associated with the WPPSI-III scores were race, education, insurance type and infant sex. The confounding factors associated with the DAS-III were education, race, and infant sex.

8\* It is unclear why the unadjusted associations were included in the results. This especially makes the tables confusing to the reader.

Discussion

9\* The discussion accurately discusses the shortcomings of the study and the significant contribution that several

confounding factors have on the results of the study, specifically the multifactorial nature of child neurodevelopmental outcomes.

10\* The authors adequately position their findings in the current literature, specifically studies examining the effect of GWG on child neurodevelopmental outcomes.

11\* One of the largest pitfalls of this study was that the data set used was specifically a group of patients with either subclinical hypothyroidism or hypothyroxinemia, this was acknowledged accurately in the discussion, and with the disclosure that these results may not be generalizable.

12\* The authors acknowledge that the data set used was not adequately powered to address the hypothesis of this study.

#### Tables

13\* Tables 3 and 4 are confusing in that they contain both p values for the unadjusted and adjusted confounders using linear and/or logistic regression.

#### Figures

14\* Figure 1 is helpful in that it clearly depicts how patients were excluded from the data set for the final analysis.

#### REVIEWER #3:

The authors submit a study regarding child neurodevelopmental outcomes and prepregnancy body mass index and gestational weight gain.

1. Address the concern for bias as all subjects in this secondary analysis had either subclinical hypothyroidism or hypothyroxinemia. Are these results able to be generalized based on the data presented?
2. Describe more clearly as to how gestational weight gain (GWG) was determined. "Because of the high proportion of women who did not have a recorded weight after 36 weeks gestation, the GWG variable was calculated according to the Institute of Medicine (IOM) rates. . . ". Is this not a mathematical model for estimating of one of the independent variables in this study? How do the authors attest to the accuracy of this estimate?
3. More of description of the childhood testing needs to be included, perhaps in tabular form for the readership who are unlikely to be familiar with this testing.
4. This secondary analysis contradicts the results of recent literature looking at this question as a primary study outcome. This is problematic, raising the question of the validity of the results. See below.
5. The selection of references is both inadequate and biased.

#### STATISTICAL EDITOR'S COMMENTS:

1. lines 79-80: As space permits, should format proportions as n(%) to put the sample sizes in context.
2. lines 83, Table 2: The GWW groups differed by parity, proportion male and BW, not just by parity.
3. In Table 3, all of the sets and subsets have large samples and are adequate in size to allow adjustment for the number of cited adjusters.
4. However, for Table 4, some of the subsets have smaller samples and were insufficient to allow adjustment for the number of covariates included in the model. For example, total GWW, WPPSI-III at 5 years < 85 (inadequate n = 28) or DAS-II at 3 years < 85 for same subest of inadequate GWW had n = 37. For those comparisons, the aOR is potentially an over fitted model.

#### EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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, as well as subsequent author queries. 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:
  1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. Based on the forms that have been submitted, the following people have not met the criteria for authorship: Brian Casey, Baha Sibai, Jay Iams. On the third page of the form, under the section labeled "Authorship," items #2-4, in addition to 1a or 1b, MUST be checked off in order to qualify for authorship. These people should be moved to the acknowledgments, or they could resubmit a revised author agreement form if they filled it out erroneously the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

3. Please update the SMFM abstract number (says 502 in your paper but it is 654).

4. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

5. 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 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

6. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

8. 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.

9. 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.

10. 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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

11. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, 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. If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance ([obgyn@greenjournal.org](mailto:obgyn@greenjournal.org)). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at <http://www.acog.org/Resources-And-Publications>.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at <http://ong.editorialmanager.com>. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 Sep 07, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

September 7, 2018

The Editor  
Obstetrics and Gynecology  
409 West 12th Street, SW  
Washington, DC 20024-2188

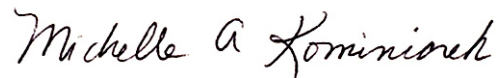
RE: Manuscript "Child neurodevelopmental outcomes by pre-pregnancy body mass index and gestational weight gain"

Dear Editor,

Thank you for the favorable review of our manuscript. Enclosed please find the manuscript entitled "Child neurodevelopmental outcomes by pre-pregnancy body mass index and gestational weight gain" which is being submitted to Obstetrics and Gynecology for publication as original research after addressing the reviewers' comments.

Each of the comments have been addressed in the following pages. Thank you for your consideration of this manuscript and I hope you will find this study acceptable for publication in your journal.

Sincerely,

A handwritten signature in black ink that reads "Michelle A Kominiarek". The script is cursive and fluid.

Michelle A. Kominiarek

## REVIEWER COMMENTS:

### REVIEWER #1:

Comments to author:

Abstract:

1. Line: line 93-94. The conclusion doesn't support the results as written. The lack of association with cognitive performance is adjusted OR for BMI. This should be clarified in the abstract.

Authors' Response: We clarified the conclusion section in the abstract to account for the findings from the adjusted OR.

Lines 92-94: **Conclusion:** In women with either subclinical hypothyroidism or hypothyroxinemia, neither pre-pregnancy BMI nor GWG were associated with neurodevelopmental outcomes among children born at term in adjusted analyses.

Introduction:

2. The introduction is well written. The pertinent information and background are concise and relevant. Biologic plausibility is referenced in line 114-117. Perhaps an expansion on the Barker's Hypothesis could be added for historic perspective to engage the reader early in the introduction.

Authors' Response: We added information regarding the Barker hypothesis to the introduction.

Lines 104-106: The developmental origins of health and disease hypothesis suggests that in-utero effects can have long-term consequences on offspring health.(5)

5. Barker DJ. The developmental origins of adult disease. Eur J Epidemiol 2003;18(8):733-6.

3. Lines 122-124. The hypothesis of myelination and cognitive development at 20weeks needs to be clarified compared to prior studies focusing on intervention of thyroid function at 12 weeks. The avg age in the UK CATS trial referenced from the original article in the NEJM was 13 wks. with thyroid development.

Authors' Response: Per reference #14 and 15, fetal brain myelination occurs after the 1<sup>st</sup> trimester of pregnancy. The participants in trials of interventions for thyroid disorders including the original trial from this manuscript were treated beginning at < 20 weeks. Because this was a secondary analysis, we did not have control over when the T4 treatment was started and it was



not the primary exposure of interest for this study. Instead, we hypothesized that there would be differences in neurodevelopmental outcomes depending on whether there was early or late excessive GWG. We hypothesized that underlying pathophysiological mechanism linking timing of GWG to neurodevelopmental outcomes is related to timing of fetal brain myelination. The references for these hypothesis were updated.

#### Materials and methods:

4. Lines 141-142. There is potential bias in self reported BMI. For this reason it is unclear why underweight BMI is excluded. Although the number was low could they have been included in the analysis for normal BMI ? Is there any biologic basis for exclusion related to the outcome in question ie IQ or GWG?

Authors' Response: Underweight women were primarily excluded due to the small sample size (n=17). Underweight women have different GWG goals than normal weight women, so they could not be combined with the normal weight women. Furthermore, underweight women may have different risks than normal weight women for offspring IQ. Participants may have underestimated their self-reported pre-pregnancy and therefore would have lower pre-pregnancy BMIs; however, we are not able to determine the accuracy of the self-reported weight values. We do not suspect that the exclusion of 17 underweight women significantly influenced our results.

5. Line 145-146. Was there a reason why there was limited data on weight after 36 weeks? If the data base was limited to term, or 37 weeks, the accuracy of the most important outcome being used in this study is questionable, particularly GWG.

Authors' Response: Weight data was measured during monthly study visits. It was not abstracted from weights measured routinely during prenatal care. For this trial, study visits occurred up to 37 weeks and the last study visit occurred between 35-37 weeks and therefore GWG was calculated and then compared with the IOM recommended GWG based on weekly rates for the 2<sup>nd</sup> and 3<sup>rd</sup> trimester rather than total recommended GWG. Clarification was provided in the methods. Further information about the calculation of GWG was provided in Appendix B.

Lines 148-160: Total GWG was defined as the difference between the last study weight which typically occurred between 35-37 weeks, and pre-pregnancy weight. Because of the high proportion of women who did not have a recorded weight after 36 weeks gestation, the GWG variable was compared to the GWG guidelines based on weekly rates of GWG rather than total GWG.

6. Lines 157-163. How the IQ test results are being used is not clear. Score < 85 at 3 and 5 years seem to be separate categorical outcomes vs. the continuous scores. It seems to come out in the results section but not clear what is being done in the materials and method section.

Authors' Response: The IQ test results are reported as continuous and categorical (score <85) outcomes. Clarification was provided in the methods.

Line 175-176: A WPPSI-III score < 85 at 5 years and a DAS-II score < 85 at 3 years were also evaluated as categorical outcomes.

7. Lines 193-196. The difference between subclinical hypothyroid and hypothyroxinemia suggest two difference populations to start. Although there were attempts to control for thyroid studies the original study did report different IQ scores by category. median IQ score of the children was 97 (95% confidence interval [CI], 94 to 99) in the levothyroxine group and 94 (95% CI, 92 to 96) in the placebo group (P=0.71). In the hypothyroxinemia trial, the median IQ score was 94 (95% CI, 91 to 95) in the levothyroxine group and 91 (95% CI, 89 to 93) in the placebo group (P=0.30). Since these were separate parallel RCT with no comparison between RCT is it more appropriate to analyze each RCT separately regarding the question of both BMI and GWG?

Authors' Response: Although the original trial presented the IQ findings separately from each parallel RCT, we opted to combine the two trials into one for this analysis. The rationale for this approach was due to the lack of a statistically significant difference between treatment groups in IQ outcomes in both of the original trials. We examined the interaction of thyroid status (subclinical hypothyroidism or subclinical hypothyroxinemia) and BMI with the IQ outcomes and found that the interaction was not significant. Therefore, we combined the two trials and examined thyroid status as an independent covariate in the regression analysis. Similarly, there were no significant differences between the interaction of GWG and thyroid status with the IQ outcomes.

Results:

The tables and legends stand by themselves and are clear

8. Given the high percent of Hispanic subjects is there any information on primary language and use of cognitive function testing validation? Were they conducted in both English and Spanish?

Authors' Response: Information on primary language was not available. Participants who preferred to complete the IQ tests in Spanish had certified interpreters available.

Lines 177-178: Spanish language study materials and certified medical interpreters were available to participants whose preferred language was Spanish.

Comments:

9. The limitations of this trial were clearly stated. The multifactorial nature of IQ testing is problematic. Because these findings are from a subset of patients as mentioned in regards to subclinical hypothyroid replacement it may not be generalizable but could add to future systematic reviews.

## REVIEWER #2:

This is a secondary analysis of data from a prior prospective randomized controlled study. The data set used in this study was unique in that it followed child neurodevelopmental outcomes out to 3 and 5 years. Using this valuable data to evaluate for another variable that could contribute to poor child neurological outcomes was an interesting evaluation of a prior data set. However, in an outcome that is multifactorial such as child neurodevelopment, it is difficult to make any association, even after correcting for confounding variables. Also, because this study was a secondary analysis, it was not properly powered to measure the outcome that was evaluated.

### Abstract

1\* The objective of the paper is clearly stated and summarized.

### Introduction

2\* The introduction explains clearly why BMI and GWG were the variables of concern in regards to child neurodevelopmental outcome.

3\* The definitions of the rates of GWG used from the Institute of Medicine standards should be outlined in the introduction to further provide background for the reader.

Response: In order to meet the word count limitations of the introduction, we opted to keep the definitions of the rates of GWG in the methods section. In the methods section, the GWG rates are clearly defined and referenced.

### Materials and Methods

4\* The authors clearly explain how the original data set was pared down to the 948 patients, and why some patients were excluded from the secondary analysis.

5\* The definitions of GWG used in this study are confusing for the reader and it is not clearly described how the "early" and "late" weekly rates of GWG were calculated and compared with the first, second, and third trimester GWG standards provided from the Institute of Medicine.

Response: The GWG definitions were clarified in the materials and methods section.

6\* As the primary outcome of the original trial was child IQ at 5 years, it is unclear why the authors have included the information from the DAS-III scores as well, especially because not all subjects had a DAS-III score documented.

Response: Scores from the WPPSI-III at 5 years were available for 948 participants. Scores from the DAS-II at 3 years were available for 915 participants. In the original trial, the primary outcome was either the WPPSI-III or the DAS-II score if the WPPSI-III was missing. We opted to include both IQ measures because they were readily available for analysis and both were important outcomes to evaluate for neurodevelopmental outcomes.

## Results

7\* As this was a secondary analysis, it was not possible to adjust and match patients for baseline differences and there were significant differences noted in race, education, insurance type, and parity - all of which were confounding factors that could affect child neurodevelopmental outcomes. However, the only confounding factors noted to be associated with the WPPSI-III scores were race, education, insurance type and infant sex. The confounding factors associated with the DAS-III were education, race, and infant sex.

8\* It is unclear why the unadjusted associations were included in the results. This especially makes the tables confusing to the reader.

Response: We opted to include the unadjusted associations in the results because several of them were statistically significant, especially for the BMI exposures. Furthermore, we wanted to show how the analysis changed after adjustments for confounders. The unadjusted p-values were kept in the results, but removed from the tables.

## Discussion

9\* The discussion accurately discusses the shortcomings of the study and the significant contribution that several confounding factors have on the results of the study, specifically the multifactorial nature of child neurodevelopmental outcomes.

10\* The authors adequately position their findings in the current literature, specifically studies examining the effect of GWG on child neurodevelopmental outcomes.

11\* One of the largest pitfalls of this study was that the data set used was specifically a group of patients with either subclinical hypothyroidism or hypothyroxinemia, this was acknowledged accurately in the discussion, and with the disclosure that these results may not be generalizable.

12\* The authors acknowledge that the data set used was not adequately powered to address the hypothesis of this study.

## Tables

13\* Tables 3 and 4 are confusing in that they contain both p values for the unadjusted and adjusted confounders using linear and/or logistic regression.

Response: Please see response #8 above.

## Figures

14\* Figure 1 is helpful in that it clearly depicts how patients were excluded from the data set for the final analysis.

## REVIEWER #3:

The authors submit a study regarding child neurodevelopmental outcomes and prepregnancy body mass index and gestational weight gain.

1. Address the concern for bias as all subjects in this secondary analysis had either subclinical hypothyroidism or hypothyroxinemia. Are these results able to be generalized based on the data presented?

Response: We acknowledge that all participants in this study had either subclinical hypothyroidism or hypothyroxinemia. These results may not be generalizable to all populations, as we address as a limitation in the discussion.

2. Describe more clearly as to how gestational weight gain (GWG) was determined. "Because of the high proportion of women who did not have a recorded weight after 36 weeks gestation, the GWG variable was calculated according to the Institute of Medicine (IOM) rates. . . ". Is this not a mathematical model for estimating of one of the independent variables in this study? How do the authors attest to the accuracy of this estimate?

Authors' Response: In the materials and methods section, we provided further clarification on how the GWG was determined. Further information about the calculation of GWG was also provided in Appendix B.

Lines 147-166: Pre-pregnancy weight and study measured weights were used to calculate GWG. Total GWG was defined as the difference between the last study weight which typically occurred between 35-37 weeks, and pre-pregnancy weight. Because of the high proportion of women who did not have a recorded weight after 36 weeks gestation, the GWG variable was compared to the GWG guidelines based on weekly rates of GWG rather than total GWG. We also calculated GWG according to the timing during gestation (at  $\leq 20$  weeks "early" or  $> 20$  weeks "late") (See Appendix B for sample calculations). For all BMI categories, the first

trimester GWG range is 0.5-2 kg whereas second and third trimester GWG rate varies by BMI category (normal weight 0.35-0.50 kg/week; overweight 0.23-0.33 kg/week; obese 0.17-0.27 kg/week).(17) The total GWG and GWG for the early and late gestational age periods were compared with expected GWG based on these guidelines.

3. More of description of the childhood testing needs to be included, perhaps in tabular form for the readership who are unlikely to be familiar with this testing.

Authors' Response:

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) and subscales is a 1½-hour examination of the child by a developmental specialist that measures IQ (primary variable) and other cognitive abilities. The Differential Ability Scales (DAS) is a 1-hour examination of the child by a developmental specialist that measures cognitive and achievement levels of children and correlates highly with the WPPSI. Results are expressed as age standardized scores, with an expected population mean of 100 and a standard deviation of 15. Further information was added to the methods.

4. This secondary analysis contradicts the results of recent literature looking at this question as a primary study outcome. This is problematic, raising the question of the validity of the results. See below.

Authors' Response: See response to #5 below.

5. The selection of references is both inadequate and biased.

Authors' Response: In the discussion section, we highlight the results of other studies that found different results than ours (e.g., higher BMI associated with cognitive delay) including a meta-analysis published in 2017 and other study from the Collaborative Perinatal Project in 2014. We also recognize that there are other studies on the topic of maternal BMI and GWG and offspring neurodevelopment, but did not present all such studies in our discussion section as our intent was to highlight only a few of the selected studies that both support and contradict our findings.

#### STATISTICAL EDITOR'S COMMENTS:

1. lines 79-80: As space permits, should format proportions as n(%) to put the sample sizes in context.

Response: The data was formatted with n(%).

2. lines 83, Table 2: The GWW groups differed by parity, proportion male and BW, not just by parity.

Response: The data in the abstract was edited to reflect the correct information for maternal characteristics.

3. In Table 3, all of the sets and subsets have large samples and are adequate in size to allow adjustment for the number of cited adjustors.

4. However, for Table 4, some of the subsets have smaller samples and were insufficient to allow adjustment for the number of covariates included in the model. For example, total GWW, WPPSI-III at 5 years < 85 (inadequate n = 28) or DAS-II at 3 years < 85 for same subset of inadequate GWW had n = 37. For those comparisons, the aOR is potentially an over fitted model.

Response:

The final model for WPPSI-III at 5 years < 85 included five covariates: gestational weight gain, race, education, infant sex, and insurance type. The final model for DAS-II at 3 years < 85 included four covariates: gestational weight gain, race, education, and infant sex. The models were re-run using Firth's penalized likelihood estimation method, an approach that addresses separability, small sample size, and bias in parameter estimates. (Firth D. "Bias reduction of maximum likelihood estimates", 1993 Biometrika 80, 27 – 38). Adjusted odds ratios and 95% confidence intervals have been updated in Table 4.

Response:

FIGURE 1: Please consider adding exclusion boxes.

Response: Exclusion boxes were added to Figure 1.

#### EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

Response: Our response is OPT-IN.

2. Based on the forms that have been submitted, the following people have not met the criteria for authorship: Brian Casey, Baha Sibai, Jay Iams. On the third page of the form, under the section labeled "Authorship," items #2-4, in addition to 1a or 1b, MUST be checked off in order to qualify for authorship. These people should be moved to the acknowledgments, or they could

resubmit a revised author agreement form if they filled it out erroneously the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

Response: Updated authorship forms for Brian Casey, Baha Sibai, and Jay Iams were provided.  
3. Please update the SMFM abstract number (says 502 in your paper but it is 654).

Response: The abstract number was updated.

4. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

Response: We reviewed the reVITALize definitions for obstetrics and applied them as appropriate.

5. 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 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

Response:

The total number of pages is 26.

The word count in the introduction is <250.

The word count in the discussion is <750.

6. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

Response: All acknowledgements are appropriately referenced and written permission was obtained from all individuals named.

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

Response: The abstract is accurate and contains <300 words.

8. 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.

Response: Standard abbreviations are used.

9. 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.

Response: Where appropriate, the virgule symbol was removed.

10. 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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

Response: The tables conform to the checklist.

11. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, 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. 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 a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at <http://www.acog.org/Resources-And-Publications>.

Response: We verified our ACOG reference in this revision.

## Daniel Mosier

---

**From:** Kominiarek, Michelle [REDACTED]  
**Sent:** Thursday, September 13, 2018 3:55 PM  
**To:** Daniel Mosier  
**Subject:** RE: Manuscript Revisions: ONG-18-1402R1

Hi Daniel,

I reviewed the edited manuscript that you sent and I have no further changes to it and I agree with the changes. Brian Casey's new email is [REDACTED] – can you send the authorship request to the new email? I will send Marcela's and Uma's authorship forms once I receive them.

Thanks.

---

**From:** Daniel Mosier [mailto:dmosier@greenjournal.org]  
**Sent:** Monday, September 10, 2018 2:10 PM  
**To:** Kominiarek, Michelle [REDACTED]  
**Subject:** Manuscript Revisions: ONG-18-1402R1

**WARNING: External email, please be mindful before clicking or replying.**

Dear Dr. Kominiarek,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 4: Please ask the following authors to respond to their authorship confirmation email. We emailed them at the email addresses below. The email contains a link that needs to be clicked on. The sender of the email is [EM@greenjournal.org](mailto:EM@greenjournal.org).
  - Brian Casey  
[REDACTED]
  - Jay Iams  
[REDACTED]
3. LINE 5: Please provide completed author agreement forms for the following authors using the latest version of our author agreement form, which can be found at <http://edmgr.ovid.com/ong/accounts/agreementform.pdf>. Note that both the "Authorship" and "Disclosure of Potential Conflicts of Interest" sections need to be completed, along with providing a signature. Please read the form carefully.
  - Marcela C. Smid MD,
  - Uma M Reddy MD MPH (only the NIH form was received)

Each of these points are marked in the attached manuscript. Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the "Accept all Changes" function in Microsoft Word.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Wednesday, September 12<sup>th</sup>**.

Sincerely,  
-Daniel Mosier

**Daniel Mosier**

Editorial Assistant

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**From:** [REDACTED]  
**To:** [Stephanie Casway](mailto:Stephanie.Casway)  
**Subject:** RE: O&G Figure Revision: 18-1402  
**Date:** Thursday, September 13, 2018 3:44:50 PM

---

Hi Stephanie,

I reviewed the figure.

The correct number for pre-pregnancy BMI is 980, but in the exclusion box before it, it should be 37 instead of 35 excluded for missing or underweight BMI.

Please let me know if this makes sense.

Michelle.

---

**From:** Stephanie Casway [mailto:SCasway@greenjournal.org]  
**Sent:** Wednesday, September 12, 2018 8:17 AM  
**To:** [REDACTED]  
**Subject:** O&G Figure Revision: 18-1402

**WARNING:** External email, please be mindful before clicking or replying.

Good Morning Dr. Kominiarek,

Your figure has been edited, and a PDF of the figure is attached for your review. Please review the figure CAREFULLY for any mistakes. In addition, please see our query below.

AQ1: Please confirm or explain n values for examination at 5 years of age (n=1,017), excluded for BMI (n=35), and prepregnancy BMI (n=980). With the current n values, prepregnancy BMI appears that it should be 982 (1,017-35=982)

PLEASE NOTE: Any changes to the figures must be made now. Changes made at later stages are expensive and time-consuming and may result in the delay of your article's publication.

To avoid a delay, I would be grateful to receive a reply no later than Friday, 9/14. Thank you for your help.

Best wishes,

Stephanie Casway, MA  
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