

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)*

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Date: Dec 04, 2020
To: "Beth Angela Plunkett" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2729

RE: Manuscript Number ONG-20-2729

Association of breastfeeding and child intelligence quotient score at age five

Dear Dr. Plunkett:

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 Dec 28, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a secondary analysis of two randomized, controlled trials of treatment of subclinical hypothyroidism that analyzes the association of breast feeding with intelligence quotients at 5 years of age in the resulting infants from singleton pregnancies. I appreciate the authors' important contribution to the field, and appreciate the chance to review this manuscript.

Strengths:

- * This is a set, rigorously followed population from two randomized, controlled trial, indicating to this review good reliability of the data and lack of measurement bias.
- * This is a large analysis, where there is significant power to detect associations, and is drawn from multiple centers and a geographically diverse population.
- * Solid statistical work, including considering the option of a curvilinear relationships between breast feeding duration and intelligence outcomes.

Limitations:

- * As this is a typical randomized, controlled trial population, it is very slanted toward affluent, Caucasian women, and therefore not as generalizable to general populations. That is most visible in the fact that the breast feeding prevalence in this population (80%!) is much higher than the general population.
- * This paper excludes infants that went to the NICU, which includes many infants that would benefit the most (potentially) from breast feeding and better neurodevelopment advantages, so this cannot be generalized to that population.
- * The analysis did not have data on important social determinants of health, like household income, parental intelligence or occupation, etc., so some determinants and confounders are limited. The authors acknowledge this in the Discussion.

Comments for authors by section:

Introduction:

- * Succinct and makes good use of the evidence and reviews the relevant physiology.
- * Clear objective and hypothesis presented

Methods:

- * Line 147-148: Be a bit more clear about what happened if death happened at less than age 3. From reading the

sentence, it seems like this indicates that the intelligence from 3 years would be used if the child dies before 3 years, which does not make sense.

* Line 154-156: I am curious why low intelligence, as opposed to overall intelligence score, was selected as the primary outcome. Was the primary outcome perhaps selected "post-hoc" after it was known what associations were significant?

* Good definitions and explanation of the outcomes.

* Lines 201-202: Why were no adjustments made for multiple comparisons? Was it because there was limited comparisons made, or was this just not deemed necessary for other reasons. It seems from reading the methods that many comparisons were necessary.

Results:

* Appropriate and helpful Table 1 with breakdown by breast feeding status.

* I would move up the primary outcome results to sooner, so they are discussed as soon as the patient characteristics are done being discussed. It is not mentioned until 3 paragraphs in.

Discussion:

* Line 282-284: I agree this is true, and that is why it might have been nice to see an analysis or sub-analysis of infants who did go to NICU or were more at risk for worse neurodevelopmental outcomes, as opposed to only those non-NICU infants.

* Line 301-304: Thanks to the authors for acknowledging the risk of residual confounding.

Reviewer #2:

Thank you for the opportunity to review this interesting study. This manuscript presents the findings of a secondary analysis of two RCTs that had a primary purpose of evaluating treatment of subclinical hypothyroidism in pregnancy. This analysis looked specifically at the relationship between breastfeeding, breastfeeding duration, and IQ scores at age 5 years. The study methodology appears sound and the variables identified for inclusion in the regression are valid. The manuscript is well organized. Two overarching concerns were of concern to this reader:

1. This is not a normal population, given all had subclinical hypothyroidism or hypothyroidoxemia. There is a clear relationship between overt hypothyroidism and subsequent IQ in offspring. Given all participants in this study were euthyroid by conventional measure (correct?) they may be a legitimate cohort for a study on breastfeeding and IQ, but the fact that these women were treated or not for hypothyroidism should be transparently acknowledged in each of the sections of the manuscript with text that reassures the reader that the hypothyroidism was not a confounding variable.

2. The variables controlled for in the primary analysis of WPPSI III < 85 score did not control for several variables (See Table 2) that have been identified as predictors of both low duration of breastfeeding or no breastfeeding and lower offspring IQ. (non-breastfeeding group were more likely to be Black, smoking in pregnancy, using public insurance (which often disappears after 6 weeks postpartum) etc. If true that these variables were not included in the regression for this primary analysis, that needs to be acknowledged and considered in the analysis.

The following recommendations for improvement are offered:

Introduction, Abstract and Precis

These sections will be better linked to the study if the topic of hypothyroidism is introduced in each one given that disorder itself could independently affect breastfeeding and IQ scores. This population has an a priori increased risk for low IQ in children which should be acknowledged and addressed throughout the manuscript.

Methods

I recommend the addition of a few sentences that describe the outcomes of the parent study.

Results

Table 1. Gestational age at delivery might be better presented as a categorical variable so the reader can identify if one group had more preterm births.

Table 2A: It is not clear to this reader why some variables were included but not others in the final regression models. In particular the primary finding of a WPPSI III < 85 score was a significant finding of this study yet it appears that age, race and ethnicity, smoking and thyroid status were not included in the regression when all of these variables could affect the outcome.

Discussion

Suggest revising this section to address the findings better. The current discussion focuses on relating these findings to studies of preterm infants and studies of attention deficit disorder. Yet thyroid function and social determinants of health present in the differences in the no breastfeeding vs breastfeeding group within this cohort are likely more important for consideration.

Writing

This is an important topic but it can be a politically tricky one to address given the number of confounding variables that could affect breastfeeding choices and subsequent child IQ. Therefore the writing needs to be precise, accurate, but thorough. The current manuscript has several passages that deserve more text to contextualize the statement. For example:

Lines 110-111: "Short duration of breastfeeding has been reported as an independent predictor of low IQ scores and other cognitive problems." I recommend the authors add a few sentences that describe those populations and note what other factors were controlled for in those studies.

Lines 120-121. The myelination theory is the predominant theory for how breastfeeding enhances physiologic brain growth but because there are countless social determinants of health that affect breastfeeding and brain development, I suggest this section acknowledge that this theory is one theory and not the only possible mechanism.

In summary, I believe this manuscript will be of more value for a reader if the focus is shifted to address the variables present in this cohort in more detail, in all sections of the manuscript including the introduction, results and analysis of the results. Linking breastfeeding status to offspring IQ is a loaded topic with multiple possible etiologies that are interrelated. The current manuscript identified one finding with regard to IQ of < 85 at age 5 years and presented that finding as though it is solid evidence. However multiple variables that could interact were not addressed. A more nuanced and deeper analysis may be warranted.

Reviewer #3:

This is an important, difficult-to-conduct study that uses secondary data from ethnically and geographically diverse RCTs, and includes extensive 3 or 5-year child neurodevelopmental evaluation to assess breastfeeding and breastfeeding duration and IQ. The study is well-written, with good biologic plausibility for the study question and finding. The risk of unmeasured confounding is a limitation that the authors appropriately acknowledge. The dose-response relationship (breastfeeding months and risk of low IQ) strengthens the finding. Comments:

1. The finding that mean IQ score did not differ based on breastfeeding is buried in the paper, not mentioned until the discussion. Although not the primary outcome, readers of the study are likely to extrapolate the "low IQ" conclusion more broadly. Lack of difference in average IQ will be lost among those who read only the abstract; this relevant finding is also not presented in results section. The abstract conclusion "Breastfeeding and its duration are associated with lower odds of low IQ score at age 5" could easily be modified by adding "....but not mean IQ scores." That there might be a differential effect on low IQ versus average IQ is hypothesis generating.
2. Given the use of donor milk, did the authors distinguish "fed breastmilk" and "breastfed" given the biologic plausibility presented? Presumably donor milk is not in widespread use among term newborns and infants, but this detail should be included.
3. The numbers at later duration of breastfeeding are somewhat small to draw strong conclusions (n=141 breastfeeding > 12 months; n=34 breastfeeding at 2 years), limiting strong conclusions. The authors do acknowledge this, and the possibility of unaccounted for residual confounding from factors such as the home environment, parent-child interactions, etc.
4. Did the authors measure breastfeeding intent? Some women cannot breastfeed, and intent may account for some unmeasured confounding related to the home environment/parental engagement, etc.

STATISTICS EDITOR COMMENTS:

lines 91, 253-254: Should round all ORs and aORs to nearest 0.01, not to 0.001 precision.

Table 1: As noted by the Authors, these cohorts were statistically different in multiple baseline characteristics. Of particular importance, insurance status (likely a surrogate for income or SES), education (I assume this is maternal, but need to clarify) etc. An important missing covariate would be maternal IQ, which correlates strongly with infant IQ.

Table 2: Among the many secondary outcomes, those that are statistically associated with breastfeeding do not retain that association when adjusted for the various variables listed in Table 2A. The primary outcome, which does retain statistical significance after adjustment, has been adjusted for only three baseline covariates in the final model. This association may be due to unmeasured covariates or to non inclusion of important known variables. The Authors should corroborate the multivariable regression model with a matching algorithm, e.g., propensity score matching. Should also show more detail

with regards to the relationship between the primary outcome vs maternal education level and primary outcome vs insurance status, when stratified by duration of breastfeeding. There may be a strong association between duration and insurance status or duration vs maternal education, and those may be more directly linked to the primary outcome than duration of breastfeeding itself.

EDITOR 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. 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.
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2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. 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.

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 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.

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 print appendixes) but exclude references.

6. 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).

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 limit for Original Research articles is 300 words; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 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. 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%).

11. 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.

12. 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 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 (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 (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at <https://www.acog.org/clinical> (click on "Clinical Guidance" at the top).

13. Figures 1-2: Please upload as figure files on Editorial Manager.

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

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.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. 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 Dec 28, 2020, we will assume you wish to withdraw the manuscript from further consideration.

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

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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December 29, 2020

Dear Editors:

Thank you for considering our manuscript, ONG-20-2729, entitled, "Association of breastfeeding and child intelligence quotient age five." I have read the instruction for authors. Please find below our italicized responses to the reviewer's and editor's comments. All authors have approved the responses and updated version of the manuscript.

Sincerely,

Beth A. Plunkett, MD, MPH

REVIEWER COMMENTS:

Reviewer #1:

This is a secondary analysis of two randomized, controlled trials of treatment of subclinical hypothyroidism that analyzes the association of breast feeding with intelligence quotients at 5 years of age in the resulting infants from singleton pregnancies. I appreciate the authors' important contribution to the field, and appreciate the chance to review this manuscript.

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- * This is a set, rigorously followed population from two randomized, controlled trial, indicating to this review good reliability of the data and lack of measurement bias.
- * This is a large analysis, where there is significant power to detect associations, and is drawn from multiple centers and a geographically diverse population.
- * Solid statistical work, including considering the option of a curvilinear relationships between breast feeding duration and intelligence outcomes.

We appreciate the reviewer's summary and comments.

Limitations:

- * As this is a typical randomized, controlled trial population, it is very slanted toward affluent, Caucasian women, and therefore not as generalizable to general populations. That is most visible in the fact that the breast feeding prevalence in this population (80%!) is much higher than the general population.

We respectfully disagree with the reviewer's comments. The U.S. Census bureau data (<https://www.census.gov/quickfacts/fact/table/US#>) demonstrate that 12% of the US persons age 25 or older in 2019 had less than a high school degree whereas 43% of our subjects had less than a high school degree (Table 1). Similarly, the proportion of our subjects who were Caucasian (31.8%) is considerably lower than the 76.3% of the population reported by the Census bureau.

- * This paper excludes infants that went to the NICU, which includes many infants that would benefit the most (potentially) from breast feeding and better neurodevelopment advantages, so this cannot be generalized to that population.

Thank you. We have included this exclusion as one of the limitations of the study. "Similarly, it must be noted that infants who were admitted to the ICU were excluded from our analyses and

thus our conclusions cannot be applied to this population.” (p. 9)

* The analysis did not have data on important social determinants of health, like household income, parental intelligence or occupation, etc., so some determinants and confounders are limited. The authors acknowledge this in the Discussion.

Thank you for your comment. As noted, these factors are included as limitations of the study.

Comments for authors by section:

Introduction:

* Succinct and makes good use of the evidence and reviews the relevant physiology.
* Clear objective and hypothesis presented

Thank you for your comments.

Methods:

* Line 147-148: Be a bit more clear about what happened if death happened at less than age 3. From reading the sentence, it seems like this indicates that the intelligence from 3 years would be used if the child dies before 3 years, which does not make sense.

Thank you. We have corrected the sentence.

* Line 154-156: I am curious why low intelligence, as opposed to overall intelligence score, was selected as the primary outcome. Was the primary outcome perhaps selected "post-hoc" after it was known what associations were significant?

As described in the Introduction, the data with regard to average IQ and breast feeding has been mixed. However, recent studies have found meaningful relationships between no breastfeeding and low-IQ. We focused our attention on this primary outcome and selected other developmental problems as secondary outcomes (p. 5).

* Good definitions and explanation of the outcomes.

* Lines 201-202: Why were no adjustments made for multiple comparisons? Was it because there was limited comparisons made, or was this just not deemed necessary for other reasons. It seems from reading the methods that many comparisons were necessary.

Thank you for your comment. We planned this secondary analysis with a nominal p-value of 0.05 as significant to examine whether a possible association between breastfeeding and any neurodevelopmental outcomes in this population was evident. We have pointed this out as a limitation to the study (p. 9), “Finally, no statistical adjustments were made for multiple comparisons. As a result, the conclusions should be interpreted accordingly.”

Results:

* Appropriate and helpful Table 1 with breakdown by breast feeding status.

Thank you for your comment.

* I would move up the primary outcome results to sooner, so they are discussed as soon as the patient characteristics are done being discussed. It is not mentioned until 3 paragraphs in.

We respectfully disagree with this stylistic comment. We chose to present the characteristics of the study population before presenting the results of the analysis so that the results may be interpreted more meaningfully and within the context of the available data.

Discussion:

* Line 282-284: I agree this is true, and that is why it might have been nice to see an analysis or sub-analysis of infants who did go to NICU or were more at risk for worse neurodevelopmental outcomes, as opposed to only those non-NICU infants.

Thank you. As noted above, we have included this gap as a limitation to the study.

* Line 301-304: Thanks to the authors for acknowledging the risk of residual confounding.

Thank you for your comment.

Reviewer #2:

Thank you for the opportunity to review this interesting study. This manuscript presents the findings of a secondary analysis of two RCTs that had a primary purpose of evaluating treatment of subclinical hypothyroidism in pregnancy. This analysis looked specifically at the relationship between breastfeeding, breastfeeding duration, and IQ scores at age 5 years. The study methodology appears sound and the variables identified for inclusion in the regression are valid. The manuscript is well organized. Two overarching concerns were of concern to this reader:

1. This is not a normal population, given all had subclinical hypothyroidism or hypothyroidism. There is a clear relationship between overt hypothyroidism and subsequent IQ in offspring. Given all participants in this study were euthyroid by conventional measure (correct?) they may be a legitimate cohort for a study on breastfeeding and IQ, but the fact that these women were treated or not for hypothyroidism should be transparently acknowledged in each of the sections of the manuscript with text that reassures the reader that the hypothyroidism was not a confounding variable.

Thank you for your comments. We have clarified in the Methods section (page 5-6) that overt thyroid disease was excluded from the original trial and have explicitly stated the conclusions of the trial which were as follows: "The study's conclusions were that neither treatment for subclinical hypothyroidism nor hypothyroxinemia beginning between 8 and 20 weeks of gestation resulted in significantly better cognitive outcomes in children through age 5 as compared to no treatment for these conditions."

2. The variables controlled for in the primary analysis of WPPSI III < 85 score did not control for several variables (See Table 2) that have been identified as predictors of both low duration of breastfeeding or no breastfeeding and lower offspring IQ. (non-breastfeeding group were more likely to be Black, smoking in pregnancy, using public insurance (which often disappears after 6 weeks postpartum) etc. If true that these variables were not included in the regression for this primary analysis, that needs to be acknowledged and considered in the analysis.

As described in the methods, step-wise backward preceding multivariable regression models were used in which all eligible variables –including those cited by this reviewer--were evaluated and only those that reached a P-value of <0.1 were included in the final model. We have

clarified the text to state that all variables that did not reach this level of significance were excluded (p.7).

The following recommendations for improvement are offered:

Introduction, Abstract and Precis

These sections will be better linked to the study if the topic of hypothyroidism is introduced in each one given that disorder itself could independently affect breastfeeding and IQ scores. This population has an a priori increased risk for low IQ in children which should be acknowledged and addressed throughout the manuscript.

Thank you for your comments. Because subject with overt hypothyroidism were excluded from both the primary analysis and our secondary analysis, we do not believe a discussion on hypothyroidism is relevant. We hope that we have sufficiently clarified this point in the methods section as described above.

Methods

I recommend the addition of a few sentences that describe the outcomes of the parent study.

Thank you. We have done so as described above (p.6).

Results

Table 1. Gestational age at delivery might be better presented as a categorical variable so the reader can identify if one group had more preterm births.

Thank you. We have added a row to describe preterm birth <37 weeks in each group (Table 1).

Table 2A: It is not clear to this reader why some variables were included but not others in the final regression models. In particular the primary finding of a WPPSI III < 85 score was a significant finding of this study yet it appears that age, race and ethnicity, smoking and thyroid status were not included in the regression when all of these variables could affect the outcome.

Please see above response regarding statistical methods. These variables were included in the original models but not in the final models based on the regression analysis. Thyroid status and treatment have been included in revised models as a sensitivity analyses (see methods p. 7, results p.9 and supplementary tables 1 and 2).

Discussion

Suggest revising this section to address the findings better. The current discussion focuses on relating these findings to studies of preterm infants and studies of attention deficit disorder. Yet thyroid function and social determinants of health present in the differences in the no breastfeeding vs breastfeeding group within this cohort are likely more important for consideration.

Thank you for your comments. Because overt hypothyroidism was an exclusion, we did not address it in the discussion. We hope that this topic has been sufficiently clarified. Our data set has limited information regarding social determinants of health and this is acknowledged in the limitations section of the discussion.

Writing

This is an important topic but it can be a politically tricky one to address given the number of confounding variables that could affect breastfeeding choices and subsequent child IQ. Therefore the writing needs to be precise, accurate, but thorough. The current manuscript has several passages that deserve more text to contextualize the statement. For example: Lines 110-111: "Short duration of breastfeeding has been reported as an independent predictor of low IQ scores and other cognitive problems." I recommend the authors add a few sentences that describe those populations and note what other factors were controlled for in those studies. Lines 120-121: The myelination theory is the predominant theory for how breastfeeding enhances physiologic brain growth but because there are countless social determinants of health that affect breastfeeding and brain development, I suggest this section acknowledge that this theory is one theory and not the only possible mechanism.

Thank you for these comments. We have made the suggested changes and specifically pointed out that the myelination pathway is theoretical (p. 5).

In summary, I believe this manuscript will be of more value for a reader if the focus is shifted to address the variables present in this cohort in more detail, in all sections of the manuscript including the introduction, results and analysis of the results. Linking breastfeeding status to offspring IQ is a loaded topic with multiple possible etiologies that are interrelated. The current manuscript identified one finding with regard to IQ of < 85 at age 5 years and presented that finding as though it is solid evidence. However multiple variables that could interact were not addressed. A more nuanced and deeper analysis may be warranted.

We respectfully disagree. The analytic approach of step-wise backward preceding regression analyses was selected to provide a nuanced analysis and to adjust for covariates that were potentially important, specifically those with a P-value <0.1 in univariable analyses. The limitations of the study are discussed and include potential unmeasured confounders.

Reviewer #3:

This is an important, difficult-to-conduct study that uses secondary data from ethnically and geographically diverse RCTs, and includes extensive 3 or 5-year child neurodevelopmental evaluation to assess breastfeeding and breastfeeding duration and IQ. The study is well-written, with good biologic plausibility for the study question and finding. The risk of unmeasured confounding is a limitation that the authors appropriately acknowledge. The dose-response relationship (breastfeeding months and risk of low IQ) strengthens the finding. Comments:

Thank you for your comments.

1. The finding that mean IQ score did not differ based on breastfeeding is buried in the paper, not mentioned until the discussion. Although not the primary outcome, readers of the study are likely to extrapolate the "low IQ" conclusion more broadly. Lack of difference in average IQ will be lost among those who read only the abstract; this relevant finding is also not presented in results section. The abstract conclusion "Breastfeeding and its duration are associated with lower odds of low IQ score at age 5" could easily be modified by adding "....but not mean IQ scores." That there might be a differential effect on low IQ versus average IQ is hypothesis generating.

Thank you for your comments. We have made the suggested edit in the abstract and added a similar comment to the results section (p. 8).

2. Given the use of donor milk, did the authors distinguish "fed breastmilk" and "breastfed" given the biologic plausibility presented? Presumably donor milk is not in widespread use among term newborns and infants, but this detail should be included.

Thank you for your comment. This information was not included in our data set and we have updated the discussion to include this item as a limitation (p. 9).

3. The numbers at later duration of breastfeeding are somewhat small to draw strong conclusions (n=141 breastfeeding > 12 months; n=34 breastfeeding at 2 years), limiting strong conclusions. The authors do acknowledge this, and the possibility of unaccounted for residual confounding from factors such as the home environment, parent-child interactions, etc.

Thank you for your comment.

4. Did the authors measure breastfeeding intent? Some women cannot breastfeed, and intent may account for some unmeasured confounding related to the home environment/parental engagement, etc.

Thank you for your comment. Our data set did not include breastfeeding intent which may be an unmeasured confounder.

STATISTICS EDITOR COMMENTS:

lines 91, 253-254: Should round all ORs and aORs to nearest 0.01, not to 0.001 precision.

These edits have been made (abstract and p. 8).

Table 1: As noted by the Authors, these cohorts were statistically different in multiple baseline characteristics. Of particular importance, insurance status (likely a surrogate for income or SES), education (I assume this is maternal, but need to clarify) etc. An important missing covariate would be maternal IQ, which correlates strongly with infant IQ.

We have specified "Maternal education." We agree that maternal IQ is an important missing covariate as specifically cited in the limitations section of the discussion (p.9).

Table 2: Among the many secondary outcomes, those that are statistically associated with breastfeeding do not retain that association when adjusted for the various variables listed in Table 2A. The primary outcome, which does retain statistical significance after adjustment, has been adjusted for only three baseline covariates in the final model. This association may be due to unmeasured covariates or to non inclusion of important known variables.

Our original regression model examined several potential confounders including maternal age, race and ethnicity, pre-pregnancy body mass index (BMI), parity, education level, insurance type, smoking, alcohol use, thyroid status, treatment group, gestational age at delivery, birth weight <10th percentile, infant sex, and age at neurodevelopmental exam. We used the step-wise regression procedure to generate a final parsimonious model. For the outcome of WPPSI III Score <85 this resulted in three covariates that were included in the final regression model.

The Authors should corroborate the multivariable regression model with a matching algorithm, e.g., propensity score matching. Should also show more detail with regards to the relationship between the primary outcome vs maternal education level and primary outcome vs insurance status, when stratified by duration of breastfeeding. There may be a strong association between duration and insurance status or duration vs maternal education, and those may be more directly linked to the primary outcome than duration of breastfeeding itself.

Thank you for your suggestions. We have included a propensity score matching analysis (see methods, results and discussion). We have also added a sensitivity analysis that included treatment and group assignment (see methods, results, discussion and supplementary tables as described above).

Our central hypothesis was that breastfeeding and its duration may be associated with low IQ or other neurodevelopmental problems. Thus, our objective was not to assess all factors that may be associated with low-IQ, rather to assess the association between breastfeeding and its duration and low-IQ. It is well-established in the literature that other factors, as the statistical editor suggests, may also be associated with IQ. However, we acknowledge that the full results of our multivariable analyses may be of interest to the readership. We have included the full results of these multivariable analyses for our primary outcome (breastfeeding and low IQ) Supplemental Table 1 and for breastfeeding duration and low IQ in Supplemental Table 2.

EDITOR COMMENTS:

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Thank you. We have checked with the authors.

3. 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.

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The methods (p. 6) and Table 1 have been updated with these details.

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 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.

We use standard reVITALize data definitions in our manuscript.

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Our manuscript is within the limits (17 pages).

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