Author's response to reviews

Title: The Association between Breastfeeding and Childhood Obesity: A Meta-Analysis

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Version: 3 Date: 1 November 2014

Author's response to reviews: see over
November 1, 2014

Dr. Meilin Zhang and Patricia Tucker
BioMed Center Public Health

Re: Manuscript # 2017387087140391

Dear Drs. Zhang and Tucker,

We appreciate the Editorial Board’s willingness to consider a resubmitted version of our manuscript entitled “The Association between Breastfeeding and Childhood Obesity: A Meta-Analysis”.

We are very grateful to the two reviewers for their admirable professionalism and knowledge. As a result, the revision has greatly benefited from their insightful, constructive, and specific comments on improving our work. We have carefully taken their comments into consideration in preparing our revision. We feel that we have adequately addressed the comments from both reviewers. In addition to the changes made in the body of this paper, we have also reformatted the manuscript and supplemented all necessary information as required by the journal.

Thank you very much for your editorial advice and efforts.

Sincerely,

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Reviewer 1- Meilin Zhang:

Major Compulsory Revisions:

Reviewer 1-1: In EMBASE PubMed, searching for (breastfed*) AND (obesity OR overweight OR adiposity) AND (child* OR infant) limited to date before 1st August 2014 resulted in 263 papers; similar search in EMBASE resulted in 362 results. It is unclear how the authors obtained only 428 studies.

Authors 1-1: Thank you for these comments. Based on our literature search, a total of 718 papers were yielded, including 263 studies from PubMed, 362 from EMBASE and 93 from CINAHL Puls with Full Text databases, but some papers were duplicates. After removing the duplicate studies, we obtained 428 unduplicated articles. This has been added to the results section.

“The comprehensive literature search of electronic databases, key journals, and cross-references yielded 718 publications, which included 428 unduplicated articles, regarding the association between obesity and breastfeeding published before 1st August 2014 as potentially relevant articles.” (line 233)

Reviewer 1-2: The authors haven’t presented any data on the relationship between breastfeeding and diet and sleep. Thus, there is no basis to conclude that the mechanism of breastfeeding’s influence later in life is complex.

Authors 1-2: We agree and thank the reviewer for kind reminding. This part has been removed from the discussion section.

Reviewer 1-3: The definition of obesity in each reference is different, what do you think about whether it will affect the result?

Authors 1-3: We agree and thank the reviewer for kind reminding. Thus, sensitivity analysis was performed to assess how results vary by study design, definitions of obesity and breastfeeding, type of breastfeeding, and adjustment for potential confounding factors. Findings of sensitivity analysis were showed in results section.

Reviewer 1-4: The duration of breastfeeding in each reference is also different. The authors stated that breastfeeding for <3 months showed slightly protective effect on childhood obesity, while breastfeeding for ≥7 months showed a significantly high protection. Generally speaking, the child for six months can add complementary. The authors should consider how this will influence the results.

Authors 1-4: Thank you for these comments. The difference of definitions of breastfeeding and the duration of breastfeeding in each study might affect the result, and the effects were analyzed by sensitivity analysis. Also, associations between
breastfeeding duration and childhood obesity were analyzed. Findings of sensitivity analysis were showed in results section. We agree with the reviewer that the child for six months can add complementary, however, due to the limitation of data collected, we could not analyze the effect of results. In further study, we should consider how this will influence the results.

**Major Essential Revisions:**

**Background:**

_Reviewer 1-5: Page 4, line 88: “between the two” changed into “between the breastfeeding and childhood obesity”_

Authors 1-5: As suggested, this has been revised.

**List of Abbreviations:**

_Reviewer 1-6: Page 16, line 365: delete the “;”_

Authors 1-6: We thank the reviewer for pointing the errors. This has been revised.

_Reviewer 1-7: Lowercases and uppercase of the total items should be consistent._

Authors 1-7: Thank you for pointing this out, this has been revised.

**Reviewer 2-Patricia Tucker:**

**Discretionary Revisions:**

_Reviewer 2-1: Abstract, line 55, more information regarding the sample of articles would be helpful (what was the range of publication dates, number of countries represented, etc.)_

Authors 2-1: Thank you for kind reminding, this has been added to the abstract.

“The studies’ publication dates ranged from 1997 to 2014, and they examined the population of 12 countries.” (line 55)

_Reviewer 2-2: Would have been interesting to test the association at different ages, rather than controlling for age as confounding variable. It is not clear to me if age was accounted for. Also, birth weight._

Authors 2-2: We agree and appreciate the reviewer’s comments. However, we could not obtain sufficient information from these published studies that allowed us to
analyze data in such manner. We hope these issues can be addressed in further study when more information becomes available.

**Reviewer 2-3:** Could add a footnote letting readers know that your search strategy is available should they contact you.

**Authors 2-3:** Thank you for this comment. This has been added underneath Figure 1 as suggested.

“Please contact the corresponding author for detailed search strategy.” (line 689)

**Reviewer 2-4:** You mentioned that you were only able to capture 1 study that was published in a language other than English, however, you have a number of countries represented where the primary language wouldn't be English (Germany, Brazil, Japan, etc.)

**Authors 2-4:** Yes, populations from 12 countries were included in this meta-analysis. While official languages vary across countries, all 24 articles were published in English.

**Major Essential Revisions:**

**Reviewer 2-5:** Title: I would suggest capitalizing “Analysis”

**Authors 2-5:** Change has been made as suggested.

**Reviewer 2-6:** Abstract, line 62, remove “for”

**Authors 2-6:** The word “for” has been removed.

**Reviewer 2-7:** Page 4, line 99, replace “children” with “childhood”

**Authors 2-7:** As suggested, this has been revised.

**Reviewer 2-8:** Page 4, line 108, insert “and” before “2)”

**Authors 2-8:** This has been revised as suggested.

**Reviewer 2-9:** Page 4, line 109, insert “of” between “search” and “key”

**Authors 2-9:** The word “of” has been inserted between “search” and “key”.

**Reviewer 2-10:** Page 5, line 121, insert “and” between “type” and “included”
Authors 2-10: This has been revised.

Reviewer 2-11: Page 5, line 122, remove “at least”

Authors 2-11: This has been removed.

Reviewer 2-12: Page 5, line 128, replace “or were not the type: reviews, commentaries, …” with “were not primary research (e.g., reviews, commentaries, …)”

Authors 2-12: As suggested, the sentence has been re-written as following:

“Studies were excluded on the basis of the following criteria: focused on other disease; were duplicates; provided incomplete data (e.g., no AOR, 95% CI) or insufficient data for calculation of these estimates; did not provide data on BMI; were not published as full text; were not primary research (e.g., reviews, commentaries, consultants’ corners, letters, conference abstracts).” (line 160)

Reviewer 2-13: Page 5, line 130, replace “would be” with “were”

Authors 2-13: Done.

Reviewer 2-14: Page 5, line 131, what did you do if a discrepancy occurred regarding article selection?

Authors 2-14: Thank you for kind reminding, the sentence has been added to study selection.

“If a discrepancy occurred regarding article selection, the 2 authors would discuss or refer to other authors.” (line 167)

Reviewer 2-15: Page 6, line 135, replace “literature” with “article”

Authors 2-15: Change has been made as suggested.

Reviewer 2-16: Page 6, line 136, please provide examples for feeding patterns

Authors 2-16: Thank you for this suggestion. The examples have been added.

“The following information from each article was extracted: first author, publication year, study design, study population characteristics of country, ethnicity, age, feeding patterns (e.g., never-ever breastfeeding, breastfeeding duration), BMI, sample size, and data provided such as AOR or data used to calculate the AOR, corresponding 95% CI, and confounding factors (e.g., birth weight, gender, age, maternal overweight,
maternal smoking, maternal education, socioeconomic status, dietary habits, exercise.” (line 171)

**Reviewer 2-17:** Page 6, line 138, please provide examples for confounding factors

Authors 2-17: The examples have been added. (See Reviewer 2-16)

**Reviewer 2-18:** Page 6, line 142, insert “was” between “which” and “calculated”

Authors 2-18: The word “was” has been inserted between “which” and “calculated”.

**Reviewer 2-19:** Page 6, line 147, change to BMI percentiles

Authors 2-19: Change has been made as suggested.

**Reviewer 2-20:** Page 6, line 147-153, discussion re the challenge of having different indicators for each study should be noted.

Authors 2-20: Thank you this comment, this has been added. Also, the challenge of having different indicators for different studies has been addressed in the sensitivity analysis of results section and discussion section.

“Given these diverse criteria for obesity, we considered whether they might affect the accuracy of our estimate, and conducted sensitivity analysis to evaluate the influence.” (line 193)

**Reviewer 2-21:** Page 7, a number of instances, please replace “vs” with “versus”

Authors 2-21: Thank you for these comments. All “vs” has been replaced with “versus”.

**Reviewer 2-22:** Page 7, line 159, define never-ever

Authors 2-22: This has been added as suggested.

“Data were categorized according to various breastfeeding variables, and information regarding breastfeeding was typically obtained from the parents. Several studies grouped infants into “ever breastfed” versus “never breastfed”, or “exclusively breastfed” versus “mixed fed” versus “exclusively formula fed”. Ever breastfeeding was defined as any attempt at breastfeeding, even if only for a short time; never breastfeeding was defined as no breastfeeding; exclusively breastfeeding was defined as breastfeeding without supplementation (e.g., no solid food, tea, herbal preparation or liquids); mixed feeding was defined as a combination of breastfeeding and formula feeding; and exclusively formula feeding was defined as only formula feeding [15,
Other studies classified children in terms of the duration of breastfeeding, which was measured in weeks or months. Therefore, we stratified the included articles for the subgroup analysis as never-ever breastfeeding (i.e., ever breastfed versus never breastfed, exclusively breastfed versus exclusively formula fed) and breastfeeding duration.

**Reviewer 2-23**: Page 7, line 175, small p? and drop extra 0 before decimal –p<0.05

**Authors 2-23**: We thank and well took the reviewer’s suggestion.

**Reviewer 2-24**: Page 8, line 185, remove “finally”

**Authors 2-24**: The word “finally” has been removed.

**Reviewer 2-25**: Page 8, line 186, remove “were”

**Authors 2-25**: The word “were” has been removed.

**Reviewer 2-26**: Page 8, line 195, insert a space between “studies” and “defined”

**Authors 2-26**: Thank you for pointing the error. This has been corrected in the revision.

**Reviewer 2-27**: Page 9, line 202-203, the language is not clear to me.

**Authors 2-27**: We have reworded this sentence in the following way:

“Additionally, we analyzed unadjusted data of results.” (line 260)

**Reviewer 2-28**: Page 10, line 225, insert “a” between “used” and “funnel”. I would also suggest moving this section; it doesn’t really fit at this point in the results.

**Authors 2-28**: As suggested, the sentence has been removed.

**Reviewer 2-29**: Page 10, line 231-232 — you report 17 studies and 9 studies, but this actually equals 26 studies, not 25 for which you have reported including in the analysis. Did one study do both or is this a typo?

**Authors 2-29**: Thank you for kind reminding. These 9 studies were included in the 17 studies. We have re-written this sentence in the following way:

“Seventeen studies analyzed the association between breastfeeding duration and obesity, and 9 of these studies presented 2 or more categories for breastfeeding durations.” (line 289)
Reviewer 2-30: Authors information — need "the" in line 388, between "in" and "faculty" (should Faculty of Medicine be capitalized)? Also, need a space before GWH in line 389 and replace "in" with "at" on line 291.

Authors 2-30: We thank and well took the reviewer’s comments.

Reviewer 2-31: Acknowledgements, line 395, you thank participants for their time and effort. Given this was a secondary analysis, not sure this is appropriate.

Authors 2-31: We appreciate the reviewer’s comment. The words “time, efforts” have been removed from acknowledgements.

Reviewer 2-32: Table 1 — change “study size” to “sample size”

Authors 2-32: This comment has been well taken.

Reviewer 2-33: Table 2, change to “FindingS”

Authors 2-33: Change has been made as suggested.

Reviewer 2-34: Table 2, reword “watching TV” to “TV viewing”

Authors 2-34: This has been revised.

Major Compulsory Revisions:

Reviewer 2-35: While this is an interesting article which I believe would be an important contribution to the literature, the quality of writing is unacceptable in some instances. I think the writing could be improved, which would make the readability of the document easier (for example, the first sentence in the methods section of the abstract).

Authors 2-35: Thank you for the kind reminder and this has been addressed. For example, the first sentence in the methods section of the abstract has been reworded.

“The PubMed, EMBASE and CINAHL Plus with Full Text databases were systematically searched from start date to 1st August 2014.” (line 48)

Reviewer 2-36: Background, page 3, first paragraph — the focus on adult obesity isn’t really necessary in my opinion, given the focus of this paper is on the child’s health, not the nursing mothers. I would suggest removing.

Authors 2-36: This part has been removed from the background.
Reviewer 2-37: Background, page 3, line 78, I think acknowledging psychological problems associated with obesity is necessary. Currently you state that mental health problems are possible, but only list sleep trouble as a non-physical example.

Authors 2-37: Thank you for pointing this out, other psychological examples have been added.

“Unfortunately, childhood obesity is linked to several physical and mental health conditions, including orthopedic problems, menstruation problems, sleep trouble, depression, anxiety and diabetes in childhood [8, 9].” (line 74)

Reviewer 2-38: Page 3, line 82, what do you mean by personal behaviors? Please provide an example.

Authors 2-38: Thank you for this comments, the examples have been added.

Childhood obesity has multiple causes, including genetic factors, personal behaviors (e.g., exercise, sleep duration, and TV viewing), dietary habits, and their interactions [11-15], and many researchers have investigated various possible interventions to prevent childhood obesity. (line 80)

Reviewer 2-39: The introduction is quite brief, I think the addition of literature regarding influencing factors on women’s decision to breastfeed, along with current rates of breastfeeding are necessary. Also, might be helpful to discuss the different forms of infant feeding (exclusive breastfeeding, exclusive formula, combined, etc.).

Authors 2-39: We thank and well took the reviewer’s comments. These have been added to the background.

“Among these, breastfeeding has been associated with a decreased risk of obesity, along with other health benefits for the child and mother. According to the WHO recommendations, infants should be exclusively breastfed for the first 6 months, and breastfeeding should be supplemented with additional foods for the first 2 years (or beyond) [15]. Breast milk is considered the ideal food for infants, as it provides adequate energy and nutrients to meet the infants’ needs. In addition, as breast milk is safe and contains antibodies, breastfeeding could reduce the risk of neonatal infection, gastrointestinal infection, and pneumonia during infancy [9, 10]. It has been indicated that approximately 45% of neonatal infectious deaths, 30% of diarrhoeal death and 18% of respiratory death among children <5 years old are associated with suboptimal breastfeeding [15]. Moreover, breastfeeding has long-term benefits throughout a child’s lifetime. Children and adults who were breastfed have lower rates of overweight/obese, type-2 diabetes, hypertension, and are known score higher on intelligence tests than persons who were formula-fed [12, 15]. Based on the WHO
report, if every child in the world was exclusively breastfed for the first 6 months, followed by breastfeeding until 2 years, the lives of 800,000 children would be saved each year [16]. Additionally, breastfeeding protects mothers against breast cancer, ovarian cancer, and obesity. Exclusive breastfeeding also is an effective, natural method of birth control, providing 98% protection between birth and 6 months postpartum [15].

In 2012, approximately 38% of infants who were under 6 months old were exclusively breastfed worldwide [15], with additional feeding methods including partial breastfeeding and exclusively formula feeding [9, 12]. The major factors that affect prevalence and duration of breastfeeding include maternal race/ethnicity, education, breast diseases, inadequate breast milk production, employment, length of maternity leave, inadequate knowledge regarding breastfeeding, lack of familial and societal support, and lack of guidance and encouragement from health care professionals [9, 15]. To strengthen breastfeeding practices, families, employers, professional workers and society as a whole should fully support to breastfeeding mothers.” (line 83)

Reviewer 2-40: Page 4, line 99-103, I think the need for this work could be more strongly articulated. The fact that it hasn’t been done since 2005 to me isn’t really a good argument. But, perhaps, because breastfeeding rates have changed since then, or more social awareness has transpired, resulting in changing norms re: breastfeeding.

Authors 2-40: This has been added to the background as suggested:

Moreover, the prevalence of breastfeeding is changing, and there are unique trends emerging in different countries. For example, the prevalence of breastfeeding is increasing in the UK [26], while the prevalence of exclusive breastfeeding is declining in China [27]. Thus, this review provides important updated data to reflect the changing of breastfeeding throughout the world.” (line 133)

Reviewer 2-41: Would be helpful to know which journals were manually searched for appropriate studies to include (page 4, line 109).

Authors 2-41: This has been added as suggested.

“2) literature search, including both electronic databases, hand-search of key journals (e.g., Obesity, International Journal of Obesity, Pediatric Obesity, International Journal of Pediatric Obesity) and the references from the retrieved papers.” (line 143)

Reviewer 2-42: Page 5, line 114-115, “all retrieved articles were hand-searched by 2 different authors” — what does this mean? Do you mean the articles were screened by 2 authors? If so, what screening process did you undertake?
Authors 2-42: We thank the reviewer for pointing this error. The re-worded sentence is as follows.

“All retrieved articles were screened according to pre-defined inclusion and exclusion criteria (described below) by two authors. Any disagreement was resolved in discussion with the project lead.” (line 151)

Reviewer 2-43: Page 5, line 121, you haven’t defined breastfeeding type, so this isn’t clear.

Authors 2-43: Thank you for the comments. The breastfeeding type was defined in “obesity and breastfeeding definition” of methods section. (See Reviewer 2-22)

Reviewer 2-44: Page 5, line 122-124, it is not clear to me which four major confounders were accounted for, or why they needed to account for four? Additional information would be helpful. I also noticed that this list did not include child’s age — was this not accounted for?

Authors 2-44: Thank you for pointing this out. When we formulated inclusion criteria, we decided to include studies with adjustment for four or more confounding factors. Because all retrieved studies provided AOR with adjustment for more than four confounders, none of the studies was excluded because of this criterion. To avoid any possible confusion, this sentence has been removed in the revised manuscript.

Reviewer 2-45: I found it interesting that the authors used funnel plots to assess publication bias, rather than the Fail Safe N. My experience in meta-analyses is that the Fail Safe N is used to explore publication bias. Insight into why this was not used might be helpful.

Authors 2-45: We appreciate the reviewer’s comments and as a result, the Fail Safe N has been added to the revised manuscript.

“Funnel plots and Fail-safe N were used to assess publication bias and reliability of results, and results from both Egger test and Bagg test were reported.” (line 52)

“Reliability of results were examined for each job satisfaction predictor though Fail-safe N.” (line 227)

“The result of Fail-safe N (N_{\text{Fs0.05}}=939.78) indicated high reliability of results.” (line 284)

Reviewer 2-46: Page 8, would be helpful if you start your results section with some summary data on the included studies — publication date range, countries accounted
for, study design, etc. while the information is available in the table, it puts the onus on the reader to have to count this information.

Authors 2-46: We thank and well took the reviewer’s comments.

“The comprehensive literature search of electronic databases, key journals, and cross-references yielded 718 publications, which included 428 unduplicated articles, regarding the association between obesity and breastfeeding published before 1st August 2014 as potentially relevant articles. A total of 25 studies with 226,508 subjects [39-63] were included in the present meta-analysis. The publication dates for these studies ranged from 1997 to 2014, and involved the population of 12 countries, including 5 German studies, 5 American studies, 3 British studies, 3 Australian studies, 2 Chinese studies, 1 Japanese study, 1 Irish study, 1 Greek study, 1 Brazilian study, 1 Dutch study, 1 Czech study, and 1 Canadian study. Of these, 24 included studies published in English and 1 study in Chinese. Ten studies were cross-sectional surveys and 15 were cohort studies, which included 10 prospective cohort studies and 5 indicate historical cohort studies. The selection process is detailed in Figure 1.” (line 233)

Reviewer 2-47: The authors provide a summary of the different definitions used by the authors of the primary studies for obesity, they don’t, however, provide this information for infant feeding. I would suggest adding.

Authors 2-47: We thank the reviewer’s suggestion, and we have added the information for infant feeding. (See Reviewer 2-22)

Reviewer 2-48: Page 11, line 257-264, this is the first time benefits of breastfeeding are discussed. I think this would be more useful to be first introduced in the background section.

Authors 2-48: Thank you for pointing this out, this has been added to the background section. (See Reviewer 2-39)