

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The relationship between breastfeeding and motor development in children: a protocol for a systematic review and meta-analysis.
AUTHORS	Hernández Luengo, Monserrat; Álvarez-Bueno, Celia; Pozuelo-Carrascosa, Diana P; Berlanga-Macías, Carlos; Martínez-Vizcaino, Vicente; Notario-Pacheco, Blanca

VERSION 1 – REVIEW

REVIEWER	Suzana Lins da Silva Instituto de Medicina Integral Prof. Fernando Figueira IMIP
REVIEW RETURNED	03-Mar-2019

GENERAL COMMENTS	The object of study is relevant for collective health, nowadays. From the perspective that outlines the protocol, it highlights the pertinence and the opportunity of its development. In the methodology: Include the date that the study will be carried out. I suggest that bibliographic research be done in databases of theses and dissertations, considering that, in many cases, results are not yet published in journals.
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REVIEWER	Bernardo Horta UFPEL
REVIEW RETURNED	04-Apr-2019

GENERAL COMMENTS	<ul style="list-style-type: none">- The references on the long-term consequences of breastfeeding should be updated.- In a systematic review, language bias is always a concern and the authors should include studies that have been published in other languages besides English and Spanish.- As previously reported, studies on the long-term consequences of breastfeeding are prone to residual confounding by socioeconomic status. Most of the studies on this subject have been carried out in high-income countries, a setting where breastfeeding duration is positively associated with socioeconomic status. Therefore, studies that failed to adjust the estimates to socioeconomic variables should be excluded from the review. Previously published reviews on the association between breastfeeding and performance in intelligence tests have reported that home environment is another confounding variable that should be taken into consideration. Therefore, the authors should clearly exclude studies that failed to adjust for confounding by socioeconomic status and home environment.- Linear regression is not the most appropriated method to assess the contribution of studies characteristics to the heterogeneity among the studies.
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	<ul style="list-style-type: none"> - The study methodology should clearly describe how the covariates will be evaluated. - In a meta-analysis of observational studies, heterogeneity should be assumed, and the estimates should be pooled using a random-effect model, as pointed by Borenstein. - In the discussion section, the authors pointed several limitations raised above and stated that these limitations will be overcome by carrying out the literature review with two independent evaluators. Independent assessment of the studies is a correct procedure, but it does not prevent the main limitation raised. Therefore, the authors should revise the review protocol.
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REVIEWER	Meghan Azad (with assistance from Sarah Turner) University of Manitoba, Canada
REVIEW RETURNED	14-Apr-2019

GENERAL COMMENTS	<p>This protocol paper describes an ongoing systematic review and meta-analysis of the association between breastfeeding and motor development in children. Strengths include: an interesting topic, use of the PRISMA and MOOSE guidelines, use of validated quality assessment tools, and registration on PROSPERO. Overall, the research question needs to be more clearly defined, especially the breastfeeding exposure(s) of interest. I have several specific questions and suggestions.</p> <ol style="list-style-type: none"> 1. I am surprised that the review was registered a year ago (April 2018) and this protocol paper is only being submitted now. Why? 2. The research question is not adequately defined. What type of breastfeeding is included? In some instances, both duration and exclusivity are mentioned, but in another instance you state that studies will be excluded if breastfeeding is supplemented (which would be a very challenging criterion to apply). 3. Please include more background / rationale for the topic in the introduction. Why is motor development important? And why would breastfeeding influence it? 4. Please clarify the age range you are interested in; some places refer to infants and others refer to children. What age range(s) specifically? 5. Abstract/Introduction: Please carefully revise the opening statement. I do not think “scientific societies” are making breastfeeding recommendations (do you mean clinical societies?) – and the recommendation is not to “keep breastfeeding for 6 months” but rather to exclusively breastfeed for 6 months and keep breastfeeding for 1 or 2 years or longer. Also, I think that the nutritional benefits of breastfeeding should also be mentioned; I realize this is not the focus of the study, but alongside the other benefits that are listed, nutrition is a notable omission. 6. It would be very interesting and relevant to include an objective to assess the method of breast milk feeding (i.e. direct nursing at the breast vs. feeding pumped breast milk from a bottle). It may turn out that few or no eligible studies addressed this, but that in itself would be a relevant finding to report. Pumping is increasingly common and it is important to distinguish the act of breastfeeding from the consumption of breast milk. 7. While I agree that you are unlikely to find (m)any RCTs of breastfeeding, I don’t think you should exclude this study design. I am not sure if the PROBIT RCT assessed motor development, but if it did, this would be an important study to include.
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	<p>8. P2 – I agree that the results of this review could be used “to improve breastfeeding rates” but an equally important outcome would be informing future research on this topic. I think this should also be mentioned.</p> <p>9. P4 – I think it is too strong to say “There is no evidence against this recommendation” (referring to the WHO recommendation of 6 months exclusive BF). This is a point of controversy, especially regarding the early introduction of allergenic foods.</p> <p>10. I agree that confounding is a very important issue in BF research. Please elaborate on what confounders you feel are important for this particular research question. Which specific confounders will you ‘require’ in order to get full points on the quality assessment?</p> <p>11. The inclusion/exclusion criteria are confusing. If a study reports on BF duration OR exclusivity, but not both, will you exclude it? (Your criterion says “AND”). I don’t understand why or how you could include only studies where children have “not received supplementation” (during what time period?) - if you only include studies with exclusively breastfed infants, then how can you assess the impact of BF exclusivity? Finally, it absolutely does not make sense to exclude studies because they “have already been used in other similar reviews”. If you want to provide a comprehensive and unbiased overview of this topic, you need to include all relevant studies, regardless of whether they have been included in previous reviews.</p> <p>12. Search strategy: I’m not sure it is necessary or useful to include the study design terms. It’s possible that relevant studies might not include these terms in the abstract or keywords, and then you would miss these studies.</p> <p>13. Data extraction: you have not explicitly mentioned that effect estimates (i.e. study results) will be extracted. This should be mentioned.</p> <p>14. Statistical analysis: it is not true that “at least four studies” are required for meta-analysis. Why impose this limit? Also, how will you deal with studies that use different scales or measures? Can you convert them to a standardized score and still meta-analyze them?</p> <p>15. There are pros and cons to either approach, but I encourage you to consider using breastfed infants (rather than never-breastfed infants) as the reference group because breastfeeding is the biological norm.</p> <p>16. Some language editing is required.</p>
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REVIEWER	Kun Aristiati Susiloretni Semarang Health Polytechnic Indonesia
REVIEW RETURNED	09-May-2019

GENERAL COMMENTS	The topic of this manuscript is worthy to be investigated, however some points needs edits: Page 5 line 23, Please specify age of the child Page 5 line 57, Include randomized control trial and other intervention studies
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Reviewer's Comment:

The object of study is relevant for collective health, nowadays. From the perspective that outlines the protocol, it highlights the pertinence and the opportunity of its development. In the methodology: Include the date that the study will be carried out.

Authors: Done, thanks.

Reviewer's Comment:

I suggest that bibliographic research be done in databases of theses and dissertations, considering that, in many cases, results are not yet published in journals.

Authors: As suggested, we have included in the search description the most relevant grey literature databases, as well as clinical trial records ClinicalTrials.gov and EudraCT (methodology, section, page 6):

“Searches for unpublished studies will be conducted at: OPEN GRAY, ProQuest dissertations & Thesis Global, Theseo, Networked digital library of theses and dissertations (NDLTD), and Google Scholar. A search of ClinicalTrials.gov and EudraCT clinical trial records will also be conducted.”
Furthermore, we have removed from discussion the potential limitation regarding the exclusion of grey literature, page 11.

Reviewer#2

Reviewer's Comments:

The references on the long-term consequences of breastfeeding should be updated.

Authors: Thank you very much for your consideration. We have included in the manuscript the following references:

- In Introduction section, page 4:

“... Additionally, breastfeeding provides high quality nutrients, prevents gastrointestinal infection and decreases the risk of diseases later in life such as allergies, asthma, obesity and celiac disease.2,3,7,9,12,16-19”

- In Discussion section, page 10:

“...There is considerable evidence about the long- and short-term benefits of breastfeeding for infant health16-19.”

Included references are:

18. Umer A, Hamilton C, Edwards RA, et al. Association Between Breastfeeding and Childhood Cardiovascular Disease Risk Factors. *Matern Child Health J* 2019;23:228–39. doi:10.1007/s10995-018-2641-8.

19. Horta BL, de Lima NP. Breastfeeding and Type 2 Diabetes: Systematic Review and Meta-Analysis. *Curr Diab Rep* 2019;19:1. doi:10.1007/s11892-019-1121-x.

Reviewer's Comments:

In a systematic review, language bias is always a concern and the authors should include studies that have been published in other languages besides English and Spanish.

Authors: Thank you very much for your comment. We think that your consideration is right, and it is a lack of knowledge of the authors. For this reason, we have included a statement in the discussion section, limitation paragraph as follows:

- Discussion section, page 11:

“...Potential limitations of this research could include publication bias, information bias, inclusion of articles in English and Spanish only.”

Reviewer's Comments:

As previously reported, studies on the long-term consequences of breastfeeding are prone to residual confounding by socioeconomic status. Most of the studies on this subject have been carried out in high-income countries, a setting where breastfeeding duration is positively associated with socioeconomic status. Therefore, studies that failed to adjust the estimates to socioeconomic variables should be excluded from the review. Previously published reviews on the association between breastfeeding and performance in intelligence tests have reported that home environment is another confounding variable that should be taken into consideration. Therefore, the authors should clearly exclude studies that failed to adjust for confounding by socioeconomic status and home environment.

Authors: Thank you very much. The reviewer's comment seems judicious. As it has been indicated, it seems reasonable to adjust by covariates as socioeconomic status and home environment, and for that reason a subgroup analysis will be performed. We have added in exclusion criteria, methodology section the following, page 6:

“...Studies that don't adjust for confounding by socioeconomic status and home environment will be excluded.”

Reviewer's Comments:

Linear regression is not the most appropriated method to assess the contribution of studies characteristics to the heterogeneity among the studies.

Authors: We appreciate the reviewer's comment. According to Matthias Egger and acknowledging the limitations of unadjusted estimations, we add in subgroup analysis and meta-regression section the following statement, page 9:

“... Several meta-regressions will be performed on study and sample characteristics to investigate whether characteristics such as the type of motor development assessment (i.e., gross or fine motor), gender, age of study participants, birth weight, breastfeeding classification (never, less than 6 months or more than 6 months) and aspects related to motor skills were associated with the magnitude of effects and whether specific study characteristics can explain (some of) the observed statistical heterogeneity³⁴”

Moreover, we have modified reference number 34 (reference 37 now), that explains this meta-regression analysis.

Reviewer's Comments:

The study methodology should clearly describe how the covariates will be evaluated.

Authors: As suggested, we are going to list the covariates and describe how they are analysed and which instrument are used for their evaluation in the included papers in our review/meta-analysis.

Reviewer's Comments:

In a meta-analysis of observational studies, heterogeneity should be assumed, and the estimates should be pooled using a random-effect model, as pointed by Borenstein.

Authors: Thank you very much for your comment. According with revisor 3, RCT studies design will be included in search strategy. For that reason, it could be likely to find no heterogeneity and fixed-effect model could be performed. Hence, we think is correct to describe the heterogeneity analysis without changes (Statistical analysis section, page 9). Borenstein reference has been included:

...”To compute the pooled effect size (ES) estimates with 95% confidence intervals (CIs) fixed-effects models³³ will be used in the case of no heterogeneity; otherwise, random-effects model^{34,35} .”

Reviewer’s Comments

In the discussion section, the authors pointed several limitations raised above and stated that these limitations will be overcome by carrying out the literature review with two independent evaluators. Independent assessment of the studies is a correct procedure, but it does not prevent the main limitation raised. Therefore, the authors should revise the review protocol.

Authors: Thank you very much for your consideration. We have included the following statement in the discussion section, page 11:

“... To overcome these limitations, the study will be conducted and reported by two independent reviewers, and a third researcher will be consulted if inconsistencies exist in data collection or consensus is not reached. However, despite of implementing these strategies, is not possible to ensure the lack of risk of bias.”

Reviewer#3

Reviewer’s Comments:

I am surprised that the review was registered a year ago (April 2018) and this protocol paper is only being submitted now. Why?

Authors: Thank you for your comment and we would like to apologize for the inconvenience. Our first aim was to state that the completion date will be December 2019, but a typo error happened. We have asked to PROPERO data base to change the completion date to December 2019, that is the correct date.

Reviewer’s Comments:

The research question is not adequately defined. What type of breastfeeding is included? In some instances, both duration and exclusivity are mentioned, but in another instance you state that studies will be excluded if breastfeeding is supplemented (which would be a very challenging criterion to apply).

Authors: The reviewer’s comment seems judicious. We have changed the title, in order to include all type of breastfeeding:

“The relationship between breastfeeding and motor development in children: a protocol for a systematic review and meta-analysis”.

Moreover, we have removed the following inclusion criteria “i) participants, children who have not received supplementation in feeding”, to avoid misunderstandings.

Reviewer's Comments:

Please include more background / rationale for the topic in the introduction. Why is motor development is important? And why would breastfeeding influence it?

Authors: Done, thanks:

“... Motor development allows the acquisition of skills that will contribute to a child's full participation in activities, avoiding sedentary behaviours and will help to establish a direct and active relationship with the environment.^{20,21}”

Included references are:

20. Pollitt E, Caycho T. Desarrollo motor como indicador del desarrollo infantil durante los primeros dos años de vida. *Revista de Psicología*: 2010;28:381–409. Available at: <http://www.redalyc.org/articulo.oa?id=337829515007>> ISSN 0254-9247. Accessed on 26 August 2018.

21. Michels KA, Ghassabian A, Mumford SL, Sundaram R, Bell EM, Bello SC, et al. Breastfeeding and motor development in term and preterm infants in a longitudinal US cohort. *Am J Clin Nutr*. 2017;106(6):1456–1462.

Reviewer's Comments:

Please clarify the age range you are interested in; some places refer to infants and others refer to children. What age range(s) specifically?

Authors: We have specified the age range in inclusion criteria, pages 5-6:

“... (i) children age 0 to 10 years old.”

Reviewer's Comments:

Abstract/Introduction: Please carefully revise the opening statement. I do not think “scientific societies” are making breastfeeding recommendations (do you mean clinical societies?) – and the recommendation is not to “keep breastfeeding for 6 months” but rather to exclusively breastfeed for 6 months and keep breastfeeding for 1 or 2 years or longer. Also, I think that the nutritional benefits of breastfeeding should also be mentioned; I realize this is not the focus of the study, but alongside the other benefits that are listed, nutrition is a notable omission.

Authors: The reviewer's comment seems judicious. Done, thank you.

Reviewer's Comments:

It would be very interesting and relevant to include an objective to assess the method of breast milk feeding (i.e. direct nursing at the breast vs. feeding pumped breast milk from a bottle). It may turn out that few or no eligible studies addressed this, but that in itself would be a relevant finding to report. Pumping is increasingly common and it is important to distinguish the act of breastfeeding from the consumption of breast milk.

Authors: Thank you very much for your comment. It could be interesting to include the method of breast milk feeding. A subgroup analysis will be done if we have enough dates.

Reviewer's Comments:

While I agree that you are unlikely to find (m)any RCTs of breastfeeding, I don't think you should exclude this study design. I am not sure if the PROBIT RCT assessed motor development, but if it did, this would be an important study to include.

Authors: Thank you very much. We agree that PROBIT is a very important study and the results are very useful for the scientific community. However, after a thorough evaluation, we should not include this RCT because the motor development variable assessment is not included.

Reviewer's Comments:

P2 – I agree that the results of this review could be used “to improve breastfeeding rates” but an equally important outcome would be informing future research on this topic. I think this should also be mentioned.

Authors: Thank you very much. We agree to revisor's comment. Longitudinal studies should be conducted in order to confirm the duration effect of breastfeeding in motor development.

Reviewer's Comments:

P4 –I think it is too strong to say “There is no evidence against this recommendation” (referring to the WHO recommendation of 6 months exclusive BF). This is a point of controversy, especially regarding the early introduction of allergenic foods.

Authors: Thank you very much for your comment. Certainly, there is a point controversy and differences exist in the recommendations to pinpoint the ideal time for starting complementary feeding, thus we have modified the sentence justifying it with the reference:

7. Fewtrell M, Bronsky J, Campoy C, Domellöf M, Embleton N, Fidler Mis N, et al.

Complementary feeding: A position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on nutrition. *J Pediatr Gastroenterol Nutr.* 2017;64:119–132.

“... There is no evidence against this recommendation,1-4 which is also supported by many health organizations. 5-7” This sentence has been modified as follow:

The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life as an ideal feed, and continuation of breastfeeding for at least the first and second years which is also supported by many health organizations.1-6 However, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) differs in the recommendations of the age when of introduction of complementary feed should be included because of the risk of food allergies.7

Reviewer’s Comments:

I agree that confounding is a very important issue in BF research. Please elaborate on what confounders you feel are important for this particular research question. Which specific confounders will you ‘require’ in order to get full points on the quality assessment?

Authors: : Thank you very much. We agree to revisor’s comment. The main confounders will require to get points on the quality assessment could be: social class, mother’s and father’s education level, maternal age, home stimulation and maternal smoking during pregnancy.

Reviewer’s Comments: The inclusion/exclusion criteria are confusing. If a study reports on BF duration OR exclusivity, but not both, will you exclude it? (Your criterion says “AND”). I don’t understand why or how you could include only studies where children have “not received supplementation” (during what time period?) – if you only include studies with exclusively breastfed infants, then how can you assess the impact of BF exclusivity? Finally, it absolutely does not make sense to exclude studies because they “have already been used in other similar reviews”. If you want to provide a comprehensive and unbiased overview of this topic, you need to include all relevant studies, regardless of whether they have been included in previous reviews.

Authors: Thank you very much for your consideration. We have changed the inclusion criteria as follow:

“... Studies will be retrieved from the literature by searching for studies which measure the effects of breastfeeding duration and type (exclusive, even if it is little, or no exclusive breastfeeding).”

Regarding the comment: “does not make sense to exclude studies because they “have already been used in other similar reviews”, it is true. It is a drafting error. We want to specify that multiple publication derived from a single study (salami publication) will be excluded.

Reviewer’s Comments:

Search strategy: I’m not sure it is necessary or useful to include the study design terms. It’s possible that relevant studies might not include these terms in the abstract or keywords, and then you would miss these studies.

Authors: Thank you very much. The reviewer’s comment is absolutely right. We have removed the study design terms.

Reviewer’s Comments:

Data extraction: you have not explicitly mentioned that effect estimates (i.e. study results) will be extracted. This should be mentioned.

Authors: Done, thank you.

Reviewer’s Comments:

Statistical analysis: it is not true that “at least four studies” are required for meta-analysis. Why impose this limit? Also, how will you deal with studies that use different scales or measures? Can you convert them to a standardized score and still meta-analyze them?

Authors: We would like to thank the thoughtful reviewer’s comment. As it states in “Meta-analysis in context” recommendations, two studies are enough to perform a meta-analysis by using fixed-effects models. However, for random-effects models this fact is not so clear because we are assuming that the estimate of the between-studies variance may be substantially in error, specially using small number of studies. Following Cochrane Handbook, we tried to perform the meta-analysis to add information to our review with the aim to increase its power and precision. Unlikely, no book or study on meta-analysis methods fixes a minimum number of studies to conduct random-effects model meta-analyses in order to standardized a protocol. Taking into account the previous references and the characteristics of our review, we considered that four studies were a reasonable number to calculate a summarize effect size.

Regarding the comment: how will you deal with studies that use different scales or measures? Can you convert them to a standardized score and still meta-analyze them? As the reviewer says, studies that will be included in the review and meta-analysis have used different instrument and scales. For that reason, the standardized mean difference will be calculated for motor development variable in the group of children never been breastfed, and in the group of children who have been exclusively breastfed or breastfed for any length of time, as an estimate of ES using Cohen’s d index as the ES statistic.

Reviewer’s Comments:

There are pros and cons to either approach, but I encourage you to consider using breastfed infants (rather than never-breastfed infants) as the reference group because breastfeeding is the biological norm.

Authors: Done, thank you.

Reviewer’s Comments: Some language editing is required.

Authors: Done, thank you.

Reviewer#4

Reviewer’s Comments:

Page 5 line 23, Please specify age of the child.

Authors: Done, thank you.

Reviewer’s Comments:

Page 5 line 57, Include randomized control trial and other intervention studies.

Authors: Thank you. We have considered that it may be better to remove from the strategy search the type of study design. In that way, articles which don’t specify in title, abstract or keywords the study design, could be elected without reject any relevant studies.

VERSION 2 – REVIEW

REVIEWER	Bernardo Horta UFPel
REVIEW RETURNED	13-Jul-2019
GENERAL COMMENTS	In the revised version of this manuscript, the authors have managed to address the main critics that were raised by the reviewers

VERSION 2 – AUTHOR RESPONSE

Reviewer#2

Reviewer's Comments:

Please state any competing interests or state 'None declared': None

Authors:

Thank you very much. Done