

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Breast milk and cognitive development – the role of confounders: A systematic review
AUTHORS	Walfisch, Asnat; Sermer, Corey; Cressman, Alex; Koren, Gideon

VERSION 1 - REVIEW

REVIEWER	Eyal Sheiner MD PHD Director, maternity D, Sorok, Beer Sheva, ISRAEL
REVIEW RETURNED	25-May-2013

GENERAL COMMENTS	<p>This manuscript was aimed to determine the association between breastfeeding and child cognitive development controlling for factors associated with breastfeeding, specifically maternal socioeconomic class, IQ and education.</p> <p>A systematic review of the literature investigating the association between breastfeeding and cognitive outcomes of healthy infants born at term was performed.</p> <p>84 studies met inclusion criteria with 34 rated as high quality, 26 as moderate and 24 as low quality. Critical assessment of accepted studies revealed the following associations: 14 (null), 25 (positive), 15 (null after adjusting for confounders), 14 (positive - diminished after adjusting for confounders), and 16 with mixed results with positive associations in sub-group analysis. Directionality of effect did not correlate with study quality, however studies showing a decreased effect after multivariate analysis were of superior quality compared to other study groupings (i.e. 12/14 high quality). Further, studies that showed null or diminished effect after multivariate analysis corrected for significantly more confounders (7.9 ± 3.4) as compared to those that found no change following adjustment (4.8 ± 4.1) ($p = 0.001$).</p> <p>Authors concluded that the results support a conclusion that much of the reported effect of breastfeeding on child neurodevelopment may be due to confounding.</p> <p>I found this study as interesting and extremely important and relevant. I am sure that it will be highly cited. Accordingly, I recommend acceptance in its current form.</p>
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REVIEWER	Janis Baird Senor Lecturer MRC Lifecourse Epidemiology Unit University of Southampton I have no competing interests
REVIEW RETURNED	13-Jun-2013

THE STUDY	While the methods for the review are rigorous, the date limits for the search are not stated. It is not clear whether the search is up to date. An article which appears to meet the inclusion criteria published in 2011 is not included - Brion et al IJE. The timing of the search needs to be clarified.
RESULTS & CONCLUSIONS	<p>The results section is too brief. There is no description of the included studies and the main findings in relation to the association of breastfeeding with cognition are summarised in a couple of sentences. The table summarising studies gives detailed information but I think there needs to be something more in the results section. For example, some additional summary tables giving the direction of association, study ids for the studies showing the association and corresponding quality. At the moment there are just unreferenced statements that, for example, '14 studies showed no association between breastfeeding and IQ'. Readers have to work their way through the long table to find out which studies these were, where they were set, what was the age at follow up etc.</p> <p>I would also have liked to see more general description of the studies reviewed. For example, there is little comment on setting - developed vs developing country studies and how the findings varied accordingly. The setting is not always clear in the table of studies either. For example, Amanda et al Andres et al. It would be helpful if setting was stated in the second column for all included studies. I would also have liked to see narrative in relation to the age at outcome measurement and whether findings varied according to the timing of follow up. From the table it is clear that assessment of cognition was carried out at ages ranging from infancy up to teenage. It may also be helpful if the direction of association is recorded in bold in descriptive table.</p> <p>The discussion is also somewhat brief in places. The final sentence of the third paragraph needing to be explained.</p>
GENERAL COMMENTS	<p>This is a good systematic review. It has followed rigorous methods and presents a comprehensive collation of relevant literature. It is not, however, clear whether the searches are up to date.</p> <p>I believe the results section needs revision</p>

VERSION 1 – AUTHOR RESPONSE

Janis Baird, Senior Lecturer, MRC Lifecourse Epidemiology Unit
University of Southampton:

2a) “ While the methods for the review are rigorous, the date limits for the search are not stated. It is not clear whether the search is up to date. An article which appears to meet the inclusion criteria published in 2011 is not included - Brion et al IJE. The timing of the search needs to be clarified.

Response: Our original search was done from inception to July 2011. A second literature search was done in April 2013 for all studies published during the period August 2011-December 2012. In the Methods section of the manuscript, we stated that:” Searches were conducted in the following databases (all from inception to December 2012)”. The study by Brion et al was evaluated, in the original search, and rejected because it involved a statistical manipulation of previously published studies and cohorts. In fact, we included in our review (and table) one study describing one of the cohorts discussed in the Brion et al publication (steer et al, ref 92). According to the reviewer request, we have now expanded the description of the search dates.

2b) "The results section is too brief. There is no description of the included studies and the main findings in relation to the association of breastfeeding with cognition are summarised in a couple of sentences. The table summarising studies gives detailed information but I think there needs to be something more in the results section. For example, some additional summary tables giving the direction of association, study ids for the studies showing the association and corresponding quality. .."

Response: Thank you for this comment. We have now added a second table summarizing the directionality of the different studies and the corresponding distribution of study quality (Table 2). In order to make it easier for the reader we have also divided the directionality of the studies' results into 4 groups only (rather than 5) and the "mixed results" group was divided between the other 4 categories as appropriate.

2c) "... there is little comment on setting - developed vs developing country studies and how the findings varied accordingly. The setting is not always clear in the table of studies either. For example, Amanda et al Andres et al. It would be helpful if setting was stated in the second column for all included studies."

Response:

We appreciate this comment. We have therefore added more settings details to the third column of Table 1. Additionally, we have added a separate table dividing the different studies into developed and developing world with the related directionality of outcome and quality grading (Table 3). Not surprisingly, the majority of the included studies were set in the developed world (71/84, 84.5% vs. 13/84, 15.5%). We also noticed that the quality of studies set in the developing countries was generally poorer given our criteria: A + B- 6/13 (46%) in the developing countries vs. 54/71 (76%) in the developed countries. Of interest, developing country studies were more likely to find a null association or null association after adjustment for confounding compared with developed country studies (8/13 (61%) v. 31/84 (37%)). We have added discussion to address possible reasons for this trend.

We have added the table and the related observations mentioned here to the results and discussion sections.

2d) "... I would also have liked to see narrative in relation to the age at outcome measurement and whether findings varied according to the timing of follow up. From the table it is clear that assessment of cognition was carried out at ages ranging from infancy up to teenage.

Response:

To address this point, we have added a separate table (Table 4) dividing the included studies into three age groups (infancy, childhood and adulthood) with the corresponding results and quality grading. The majority of included studies measured intelligence during the childhood period (age 1-18 years: 70/93 studies, 75%). Studies performed during childhood and reaching an initial positive association, weakened after adjustment, were generally of higher quality than other studies (12/14 quality grade A, 86%). Studies performed during infancy or adulthood were more likely to find a null association (before or after adjustment) as compared with studies performed during childhood (Infancy group - 61%, adulthood - 60%, childhood 43%). We have added the table and the related observations mentioned here to the results section and discussed these findings.

2e) "...The discussion is also somewhat brief in places. The final sentence of the third paragraph needing to be explained."

Response:

We have rephrased the sentence to: "Unfortunately, the few studies that have followed this design

reached conflicting results.” 13, 40

We have also expanded the discussion relating to our findings of the comparison between developed and developing world and between different age groups.