Reviewer’s report

Title: The relationship between breastfeeding and reported respiratory and gastrointestinal infection rates in young children

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Reviewer: Caroline Lodge

Reviewer's report:

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This interesting article investigated the relationship between breastfeeding and respiratory and gastrointestinal infection in young children from 3 months of age up to 48 months of age in the Environmental Determinants of Diabetes (TEDDY) cohort. This prospective cohort started in 2004, recruiting infants at genetically high-risk for type 1 diabetes (8676 from 54,000 screened) across 6 centres (3 in US, and 3 in Europe (Germany; Finland; Malmo). They followed participants at 3 month intervals from 3 months of age until 4 years and 6 monthly thereafter.

The study sample investigated in this manuscript was limited to 6861 children followed to at least 18 months who had not developed antibodies. The longest time of follow-up was 48 months.

This study investigates 3 month windows of breastfeeding and infectious episodes, modelling the relationship between breastfeeding and infection for each 3 month period up to 18 months. It also looks at total breastfeeding duration and future risk of infection up to 18 months.

They found protection from respiratory and gastrointestinal illness between 3 and 6 months for children breastfed or partially breastfed, and some protection from otitis media up to 48 months even after breastfeeding cessation.

The relationship between breastfeeding and reduction in infection is not novel, however showing the presence of this relationship for both exclusively and partially breastfed babies between 3 and 6 months and for 3 month intervals up to 18 months for a range on respiratory and gastrointestinal infections strengthens the evidence for this time period.

Major comments

Methods
1. The timing of exposure and outcomes are not clear - would it be possible to further explain the temporal relationship of these variables. It is not clear if breastfeeding was categorized at the start of the 3 month period and infections after this - during the 3 month follow-up. These variables were obtained by the "TEDDY book questionnaire". Were discrete times recorded for cessation of exclusive and partial breastfeeding and for the occurrence of infections in each 3 month time interval. If so, why not use these times to explore the relationships between breastfeeding and infections?

2. Classification of infections is said to be from self-reported data - yet one of the outcomes is an ICD code(Line 216) Can you explain this further?

3. The study has been going since 2004 and has reported on some 6 year follow-ups in other publications. Why does this investigation only span to a maximum of 48 months?

4. Children not followed to 18 months were excluded - were there any differences for this portion of the cohort who were lost to follow-up?

5. Children with antibodies were excluded due to perceived introduction of bias - did this subset have different associations for the exposures/outcomes being investigated?

6. It is unclear why other variables were included in the models. Are all the variables included common cause confounders and do they have a plausible temporal relationship. For example - parental working status at 9 months is unlikely to be related to breastfeeding at 3 months. Season may be related to infection risk but is season related to breastfeeding?. Please indicate on what basis confounders were chosen to be added to the model. Was causal modelling theory involved, did the authors consider a directed acyclic graph?

7. Were any of the variables tested as modifiers - eg - sex, season. Most importantly, was centre tested. It is plausible that these relationships may differ by centre. I would like to see the relationships by centre before combining

8. I am a little confused by the statistical methods. The 3-6 month timepoint was investigated separately using a logistic regression model. All other timepoints with 3 month intervals from the 6 - 18 month timepoints were investigated using generalized estimating equations. Why were 2 different models used?. Why was the 3-6 month time period not included in the Gee with all the other times?

Does the Gee model assume that the relationship between breastfeeding and infection at each 3 month timepoint is the same? Is that a reasonable assumption?
Results

1. The increase in respiratory infectious episodes reported is curious. Apart from the selective reporting suggested in the discussion, could this be related to reverse causation? Additionally, could this be related to the manifestation of infection. If all babies are equally exposed to respiratory infections, and breast fed babies are relatively protected, might you see an "increase" in uncomplicated urtis in these babies whilst less protected babies manifest these infections as laryngitis/tracheitis/conjunctivitis/Om etc?

2. It is not clear what has been adjusted for in table 2 and figure 2. Would the authors list all adjustments at the bottom of these tables/figures?

Discussion

It is claimed that exclusive breastfeeding has a greater protective effect that non-exclusive breastfeeding. Would the authors provide evidence that the odds ratios for these two groups are significantly different for the outcomes investigated?

Limitations

The select nature of the cohort has not been discussed in terms of generalizability of results

Line 361 - The authors describe the study size as beneficial for investigating interactions - it is not clear which interactions have been investigated in this study

The Conclusions state only the benefits for exclusive breastfeeding - these benefits are seen also relating to non-exclusive breastfeeding and the authors have not shown that these effects are significantly different. This statement needs to include both exclusive and non-exclusive breastfeeding.

Minor Comments

3 decimal point in odds ratio in abstract. And line 258 - please change to 2

Numbers of children studied and outcome age to be included in the abstract

The word "Conflicive" on the flow chart needs to be changed - did the authors mean conflicting?
Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?  
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
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I recommend additional statistical review

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