PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
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<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Timing of probiotic milk consumption during pregnancy and effects on the incidence of preeclampsia and preterm delivery: a prospective observational cohort study in Norway</th>
</tr>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Nordqvist, Mahsa; Jacobsen, Bo; Brantsaeter, Anne-Lise; Myhre, Ronny; Nilsson, Staffan; Sengpiel, Verena</td>
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VERSION 1 – REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Kirsi Laitinen</th>
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<tbody>
<tr>
<td></td>
<td>Senior lecturer, University of Turku, Finland</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>02-Jul-2017</td>
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</table>

GENERAL COMMENTS

This paper studies from a Norwegian cohort study whether consumption of probiotic milk before, during early or late pregnancy influences associations with preeclampsia and preterm delivery. The paper is well written, utilizes data from a sizeable cohort study and draws conclusions that are reasonable considering the study setting and findings.

Comments:

Page 4, it is stated that the strength of the study is that is has subjects of “all ages”. Please correct. Also do not use abbreviations like MoBa in this section as this is not a generally known abbreviation.

Background, I would appreciate a little bit more detailed and specified description of the aberrations in inflammatory status in the two conditions studied, as this appears to be one key hypothesis behind the study (page 5, line 100-101). This is discussed in more detailed in the discussion section, but a brief statement here would be beneficial. Also considering a large number of references (5 to 16), some of which are from reviews, is included here, a more specified description is called for.

In the discussion, it would be beneficial to consider the normal changing inflammatory profile of pregnancy, regarding your own results considering the timing of probiotics consumption in the two different conditions studied.

The statement regarding diet effect (page 6, line 117-118). Briefly describe how maternal diet influences the pregnancy outcomes in concern.
It would be beneficial for the reader to describe clearly already at the introduction what was studied previously and what is studied now, is there an overlap between the reports.

Are Biola and Cultura market names? If so, this should be stated and also information on the manufacturers added.

What about consumption of sour products like yoghurt, sour milk, kefir. Was this asked in the questionnaire, I assume these would have contained probiotics too.

Also it should be discussed why the previous results differ to somewhat of these results considering early pregnancy consumption. Could one reason be that the ffq provided more accurate data of the diet. These issues should be explained and discussed in detail.

Further, I am not convinced if you can separate the specific probiotics consumed. Should you omit the results regarding this e.g. page 14, lines 297-

Also, are you confident in stating that no difference between the two probiotic products was found (page 16, lines 343-344), consider revising.

Can you provide percentages (%) to figure 2. Also discuss what is the impact of these patterns of consumption on the results.

**REVIEWER**

Dr Ellie Gresham  
Griffith University, Australia

**REVIEW RETURNED**

04-Jul-2017

**GENERAL COMMENTS**

A wonderfully written paper and important contribution to the literature. Some very minor comments:

Lines 43, 210-211 - Spontaneous term controls were defined as 'between gestational weeks 39+0-40+6; it wasn't clear why you had excluded women who had spontaneous births between 37+0 - 38+6 and 41+0 - 41+6 reflecting the WHO definition of term birth.

Lines 235 and 237 - Change '3' to three

Line 323 - Change '430' to Four hundred and thirty

Lines 376-377 - You refer to previous publications demonstrating that women adopt more health-conscious behaviours during pregnancy. Are you sure that this is the case? can this be substantiated - you have referenced one paper a prospective observational cohort.

Tables 2 and 3 - define PE, PTD, OR and CI

Figure 1 - Define Q1, Q3 and PTD

**REVIEWER**

Julian Crane  
University of Otago  
New Zealand

**REVIEW RETURNED**

20-Jul-2017

**GENERAL COMMENTS**

A well presented straightforward epidemiological study of a population based cohort of pregnant women showing significant associations between probiotic milk consumption at different periods of pregnancy and reduced preeclampsia and preterm delivery. The large sample size allows for a reasonable level of adjustment for confounding.
I have a few issues that the authors should consider:

1. The low participation rate is an obvious disappointment and as the authors acknowledge, potentially a significant problem. They have investigated this in a separate paper and shown that despite considerable selection bias there were no differences in a selection of exposure outcomes. However the differences between the participants and non participants are quite large and in general the participants are healthier and presumably more affluent.

2. It is not clear exactly what the definition of a probiotic milk consumer is? Presumably there is considerable variation with occasional and regular users – should there be some sort of cut off? What about the middle period of pregnancy – might this also have an impact on some of the outcomes? As the authors suggest pregnancy is a time of considerable variation in appetite and interests in food.

3. The main population characteristics table, Table 1 is not to my mind especially helpful. Rather, I would have liked to see the overall cohort data and then two columns of probiotic milk users and non users. This is what is of interest here in terms of the possibilities that other factors associated with probiotic milk consumption might be at play. It is not clear to me exactly what the p values refer to in this table.

4. If the hypothesised effect is on systemic inflammatory responses why are there no dose response effects?

5. The most significant issue that does not receive very much comment is that 60% of the population questioned consumed yoghurt but this consumption data was missing for 60% of the whole population. Yoghurt is made from probiotic organisms indeed that is where many probiotics come from, and is very similar to probiotic milk (unless it is pasteurised as in the US) and therefore represents a major confounding factor here. Obviously much data is missing but an analysis by yoghurt consumption controlling for probiotic milk would be interesting. Otherwise I think the authors need to acknowledge that the effects might well be yoghurt and/or probiotic milk.

REVIEWER

Dr. M.A. Oudijk
Department of Obstetrics
Academic Medical Center Amsterdam
The Netherlands

REVIEW RETURNED

27-Jul-2017

GENERAL COMMENTS

The authors have performed an interesting analysis from a professional national database/research project on the effect of probiotic milk intake and the two most important pregnancy complications, PTD and PE.

I would like to compliment the authors for their work, and it has been a pleasure to read. Very rarely I review an article that is well constructed, interesting and of possible major importance for obstetricians and their patients.

I have no comments or any questions (which rarely happens). It has been a joy to read.
Reviewer: 1, Kirsi Laitinen

This paper studies from a Norwegian cohort study whether consumption of probiotic milk before, during early or late pregnancy influences associations with preeclampsia and preterm delivery. The paper is well written, utilizes data from a sizeable cohort study and draws conclusions that are reasonable considering the study setting and findings.

Comments:

1) Page 4, it is stated that the strength of the study is that it has subjects of "all ages". Please correct. Also do not use abbreviations like MoBa in this section as this is not a generally known abbreviation.

Response: We have changed "all" to "different" (page 4 line 67) and written out the abbreviation (page 4 lines 70-71 and 74-75).

2) Background, I would appreciate a little bit more detailed and specified description of the aberrations in inflammatory status in the two conditions studied, as this appears to be one key hypothesis behind the study (page 5, line 100-101). This is discussed in more detailed in the discussion section, but a brief statement here would be beneficial. Also considering a large number of references (5 to 16), some of which are from reviews, is included here, a more specified description is called for.

Response: The accepted explanation of inflammatory changes in preeclampsia is summarized on page 5 lines 101-106. We have now given a brief but more detailed description of inflammatory changes behind preterm delivery on pages 5-6, lines 109-115. A more detailed discussion of the inflammatory processes in pregnancy and pregnancy complications such as preeclampsia and preterm delivery and the possible effect of probiotics was beyond the scope of this observational study.

3) In the discussion, it would be beneficial to consider the normal changing inflammatory profile of pregnancy, regarding your own results considering the timing of probiotics consumption in the two different conditions studied.

Response: Under Discussion, on page 23, lines 523-525, we have mentioned changes during a normal pregnancy: "These results are very interesting since it is known that during pregnancy, the mother’s immune system changes from Th1-dominated cellular immunity to Th2-dominated humoral immunity in order to accept the fetal “semi-allograft”. Since this an observational study that cannot investigate or explain the mechanisms behind our findings, we have decided not to focus more on the normal inflammatory changes.

4) The statement regarding diet effect (page 6, line 117-118). Briefly describe how maternal diet influences the pregnancy outcomes in concern..

Response: A brief description is now given on page 6, lines 124-128: “Growing evidence suggests that maternal diet influences pregnancy outcome, for example dietary pattern characterized by high intake of vegetables, fruits, and vegetable oils, which is associated with reduced risk of preeclampsia and preterm delivery.”
5) It would be beneficial for the reader to describe clearly already at the introduction what was studied previously and what is studied now, is there an overlap between the reports.

Response: Thank you for highlighting the need for clarification regarding this. We have now clarified this in the introduction, page 7, lines 138-139: "Two previous studies in the Norwegian Mother and Child Cohort Study (MoBa) showed associations between intake of milk containing probiotics during the first half of pregnancy and reduced risk of preeclampsia and spontaneous preterm delivery. Since pregnancy is a time of rapid development and differentiation, the aim of this study was specifically to investigate whether there might be a certain time window before, during early or late pregnancy for a probiotic exposure effect on these two adverse pregnancy outcomes."

6) Are Biola and Cultura market names? If so, this should be stated and also information on the manufacturers added.

Response: Thank you so much for reminding us about this very important aspect. We have now specified this in the manuscript, pages 8-9, lines 178-181: "The probiotic milk products were product A (Biola®, all types, manufactured by Tine SA, Oslo), containing Lactobacillus acidophilus (LA-5), Bifidobacterium lactis (Bb12), and Lactobacillus rhamnosus GG (LGG); and product B (Cultura®, all types, manufactured by Tine SA, Oslo),"

7) What about consumption of sour products like yoghurt, sour milk, kefir. Was this asked in the questionnaire, I assume these would have contained probiotics too.

Response: The consumption of other milk products, both regular milk, sour milk and kefir was asked in the questionnaires. Two questions assessed intake (frequency) of the standardized probiotic products (Biola® and Cultura®), and two other questions assessed intake of other milk. Of these questions, one assessed regular milk and the other asked for all types of sour milk including kefir. While this study strictly investigated bacteria strains defined as probiotic through laboratory research, we acknowledge that many bacteria in diet have probiotic properties without being registered as such. In particular, it is assumed, as the reviewer points out, that many lactic acid bacteria have probiotic properties. Kefir is a sour milk that contain several lactic acid bacteria including species which are similar to some with known probiotic effect and could contain probiotic properties. However, since we are investigating bacteria strains strictly defined as probiotic, all sour milk is included in the variable "non-probiotic milk" used as a confounder in our study. This may result in misclassification of the exposure and thereby lead to more conservative results. We have added to the methods (page 11, lines 235-236 and page 12 lines 259-260) that additional sour milk products were classified as non-probiotic milk (see answer to comment 5 from reviewer 3) and elaborated the text about possible misclassification of the exposure in the discussion (page 26, lines 592-594): "Another source of misclassification is that sour milk was included in "non-probiotic milk". This misclassification of the exposure would most likely contribute to attenuation of a potential association with the outcomes studied."

8) Also it should be discussed why the previous results differ to somewhat of these results considering early pregnancy consumption. Could one reason be that the ffq provided more accurate data of the diet. These issues should be explained and discussed in detail.

Response: The aim of this study was to analyze if one time point is of more importance than another, which is why we used consumption in early pregnancy as a confounder to consumption in late pregnancy, in the logistical regression model. This does not contradict the results from our previous study where an association was found between consumption during early-mid pregnancy and preeclampsia (Brantsæter et al., AJE 2011).
9) Further, I am not convinced if you can separate the specific probiotics consumed. Should you omit the results regarding this e.g. page 14, lines 297-

Response: We reported that significantly reduced risk of preeclampsia and preterm delivery was seen for each of the products when analyzed as separate exposures, but no statistically significant difference was seen when included into the same model. These results are presented with the following text on page 18, lines 385-386: "...however, there was a substantial overlap between consumers of the two products". We reported these results in order to highlight that it was not possible to separate the specific probiotics consumed. Therefore, we would like to keep this text. We would appreciate a more specific comment on how to clarify this better if we did not understand your comment correctly. Please see further answer to comment 10.

10) Also, are you confident in stating that no difference between the two probiotic products was found (page 16, lines 343-344), consider revising.

Response: The text has been revised, page 21, lines 471-472, instead of saying that there was no difference between the two probiotics we have now written that "In this study we were not able to separate the impact of the specific probiotic products".

11) Can you provide percentages (%) to figure 2. Also discuss what is the impact of these patterns of consumption on the results.

Response: Percentages are now added to Figure 2. The patterns of consumption reveal an expected non-random overlap for the three periods, causing substantial confounding. We have thus handled them as three separate predictors in the same logistic regression model to sort out during which period the consumption makes an independent contribution to the risk for preeclampsia or preterm delivery. While we find evidence for association with consumption of probiotics in late pregnancy and preeclampsia, and early pregnancy and preterm delivery it cannot be excluded that consumption in other periods matter to a lesser extent as well.

Reviewer 2, Ellie Gresham:

A wonderfully written paper and important contribution to the literature. Some very minor comments:

1) Lines 43, 210-211 - Spontaneous term controls were defined as 'between gestational weeks 39+0-40+6; it wasn't clear why you had excluded women who had spontaneous births between 37+0 - 38+6 and 41+0 - 41+6 reflecting the WHO definition of term birth.

Response: Thank you for pointing this out, we agree that it is important to explain and motivate the background. In order to be able to compare our results with our previous study, we decided to use the same gestational weeks for the control group. Originally, the full term control group was chosen in order to create a distinct and homogenous control group. We have now clarified this under Methods, page 10, line 222: "As in our previous study, the comparison group in the preterm delivery analysis consisted of spontaneous term pregnancies delivered at gestational week 39+0-40+6, resulting in a total of 34,458 women included in the preterm delivery analysis."

2) Lines 235 and 237 - Change '3' to three

Response: Thank you! Changed. Page 12, lines 249 and 251.
3) Line 323 - Change '430' to Four hundred and thirty

Response: Thank you! Changed. Page 20, line 450.

4) Lines 376-377 - You refer to previous publications demonstrating that women adopt more health-conscious behaviours during pregnancy. Are you sure that this is the case? Can this be substantiated - you have referenced one paper a prospective observational cohort.

Response: Pregnancy is a time when women are highly motivated for dietary improvements. The MoBa FFQ included separate questions pertaining to changes in diet after becoming pregnant. Analysis of these questions confirmed that a number changes appear to take place for a large percentage of pregnant women. The most substantial changes were seen for coffee and alcohol intake, but large changes were also seen for the other major food groups, e.g. less sweet beverage, more fruit and vegetables. Similar changes from before to early pregnancy have been reported from other studies of pregnant women. We thank you for highlighting the need for clarification and have revised the sentence (page 6 lines 124-128) and added more references: “Growing evidence suggests that maternal diet influences pregnancy outcome, for example dietary pattern characterized by high intake of vegetables, fruits, and vegetable oils, which is associated with reduced risk of preeclampsia and preterm delivery.”

5) Tables 2 and 3 - define PE, PTD, OR and CI

Response: The abbreviations have now been written out in the tables, including Supplemental table 1.

6) Figure 1 - Define Q1, Q3 and PTD

Response: The abbreviations have now been written out in the figure.

Reviewer 3, Julian Crane

A well presented straightforward epidemiological study of a population based cohort of pregnant women showing significant associations between probiotic milk consumption at different periods of pregnancy and reduced preeclampsia and preterm delivery. The large sample size allows for a reasonable level of adjustment for confounding.

I have a few issues that the authors should consider:

1) The low participation rate is an obvious disappointment and as the authors acknowledge, potentially a significant problem. They have investigated this in a separate paper and shown that despite considerable selection bias there were no differences in a selection of exposure outcomes. However, the differences between the participants and non participants are quite large and in general the participants are healthier and presumably more affluent.

Response: Yes, we agree and thus acknowledged this in our manuscript, pages 24-25, lines 558-562: “The participation rate is 40.6%. Self-selection bias has been investigated, showing that single women under the age of 25 are underrepresented in MoBa. However, differences regarding preterm delivery incidence were minor and no differences in preeclampsia incidence were found. No bias was found in eight selected exposure-outcome associations. (Nilsen et al Pediatr Perinatal Epidem 2009)”
Beside from the youngest women, Nilsen et al found a strong underrepresentation of those living alone, mother with more than two previous births and with previous stillbirths. An underrepresentation with a relative deviation of 22-43% was also found for smokers, women with stillbirths, and neonatal death, while multivitamin and folic acid supplement users were over-represented. Despite this, no differences in association measures were found between participants and the total population regarding the eight well known exposure-outcome associations, suggesting that prevalence estimates of exposures and outcomes, but not estimates of exposure-outcome associations are biased due to self-selection.

2) It is not clear exactly what the definition of a probiotic milk consumer is? Presumably there is considerable variation with occasional and regular users – should there be some sort of cut off? What about the middle period of pregnancy – might this also have an impact on some of the outcomes? As the authors suggest pregnancy is a time of considerable variation in appetite and interests in food.

Response: Thank you for pointing out the need for clarification regarding the definition of consumers. This has now been clarified under Methods, page 8, lines 176-178: "The participant is defined as a probiotic consumer if she has written any number larger than zero, with no cut off." About the middle part of the pregnancy: we agree that it would be very interesting to study this time period, but MoBa does not include any questionnaire that only asks about consumption during these weeks. As stated under Methods: In Q1, the women were asked to report their consumption both prior to becoming pregnant and during pregnancy up until the time that the questionnaire was completed (on average around week 17), while Q3 (answered around week 30) asked about consumption from week 13 and until answering the questionnaire. So the questionnaires do not have boxes for each week, but ask for an "average daily consumption" during the three time periods mentioned above.

3) The main population characteristics table, Table 1 is not to my mind especially helpful. Rather, I would have liked to see the overall cohort data and then two columns of probiotic milk users and non users. This is what is of interest here in terms of the possibilities that other factors associated with probiotic milk consumption might be at play. It is not clear to me exactly what the p values refer to in this table.

Response: Our aim with Table 1 was to present maternal characteristics of the studied population and also to visualize how probiotic consumption might differ in relation to maternal characteristics. So the table really gives information about both the consumers and the non consumers. To clarify this, we have specified that column one presents the study population, and we have changed the percentages in column two (probiotic consumers) from percentage within the category, to percent of the probiotic consumer population. I.e instead of presenting that 41.5% of women who are under 19 years old are consumers, we have written that 0.5% of the probiotic consumers are women under 19 years old. So by comparing the percentage in column two with the percentage in column one, a comparison can easier be made between consumers and non consumers according to maternal characteristics.

4) If the hypothesized effect is on systemic inflammatory responses why are there no dose response effects?

Response: In the two previous publications a dose response effect could be found. One explanation could be that the participants had the possibility to give more detailed answers about their consumption behavior in the FFQ, than in Q1 and Q3 that we have studied.
5) The most significant issue that does not receive very much comment is that 60% of the population questioned consumed yoghurt but this consumption data was missing for 60% of the whole population. Yoghurt is made from probiotic organisms indeed that is where many probiotics come from, and is very similar to probiotic milk (unless it is pasteurized as in the US) and therefore represents a major confounding factor here. Obviously much data is missing but an analysis by yoghurt consumption controlling for probiotic milk would be interesting. Otherwise I think the authors need to acknowledge that the effects might well be yoghurt and/or probiotic milk.

Response: Thank you for pointing out this, which shows that we need to more clearly define and present the exposure. The questions that form the basis for this study separated clearly between milk products enriched with probiotic bacterial strains and other sour milk products/yoghurt. Similar species might be found in sour milk products. However, this study aims to investigate strictly those strains with confirmed probiotic effect from laboratory studies. According to FAO, probiotics are defined as “live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host”. Only bacterial strains that colonize in the gut are able to confer health benefits. We have added this definition to the introduction, page 6, lines 127-128. Further, we would like to point out that the other milk/yoghurt items were included in the variable “non-probiotic milk products” and included as a confounder in our analyses. In the revised manuscript, we have added information under Methods that non-probiotic milk products comprise regular milk and sour milk products including kefir and yoghurt. page 11, lines 235-236 and page 12 lines 259-260, and elaborated the text about possible misclassification of the exposure in the discussion (page 26, lines 592-594): “Another source of misclassification is that sour milk was included in “non-probiotic milk”. However, this misclassification of the exposure would most likely contribute to attenuation of a potential association with the outcomes studied.”

Reviewer 4, Martijn A Oudijk

The authors have performed an interesting analysis from a professional national database/research project on the effect of probiotic milk intake and the two most important pregnancy complications, PTD and PE.

Comment: I would like to compliment the authors for their work, and it has been a pleasure to read. Very rarely I review an article that is well constructed, interesting and of possible major importance for obstetricians and their patients.

I have no comments or any questions (which rarely happens). It has been a joy to read.

Response: Thank you so much for your positive feedback! We have worked with this study for a long time and made a huge effort to present a qualitative and useful study and it is very heartwarming to receive such feedback.
**VERSION 2 – REVIEW**

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<th>Ellie Gresham</th>
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**GENERAL COMMENTS**

Changes made with thanks. A very well written manuscript. Thank you.

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<th>Julian Crane</th>
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<tbody>
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**GENERAL COMMENTS**

In general the authors have responded appropriate to the issues I raised. However I still have concerns re the possibility of confounding by other fermented foods. While these have been included as confounders in the adjustments, Table 1 shows that this data was missing on 60% of the population - so how could it be adjusted for? I still see this as a possible weakness. In the covering letter the authors mention probiotics with confirmed laboratory study effects but these are not likely to have much bearing on the protective effect here. Also I disagree with their idea that any of these probiotics regularly colonise the human gut.

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 2
Reviewer Name: Ellie Gresham
Institution and Country: NSW Health, Australiia
Please state any competing interests: None declared

Please leave your comments for the authors below
Changes made with thanks. A very well written manuscript. Thank you.

Thank you!

Reviewer: 3
Reviewer Name: Julian Crane
Institution and Country: University of Otago
Please state any competing interests: None

Please leave your comments for the authors below
In general the authors have responded appropriate to the issues I raised. However I still have concerns re the possibility of confounding by other fermented foods. While these have been included as confounders in the adjustments, Table 1 shows that this data was missing on 60% of the population - so how could it be adjusted for? I still see this as a possible weakness.
Response: As described in statistical methods (page 12, line 258), for categorical variables missing data is assigned a category of its own to avoid large loss of data in multivariable analysis, and it is thus still possible to adjust for.

However, we thank you very much for highlighting the high number of missing values (60%) for the variable “non probiotic yoghurt”. This is a variable that summarizes the consumption of "non probiotic yoghurt" during the three time periods (before, during early and late pregnancy), and a consumer at any of the three periods is defined as consumer in this variable. Upon recreating the variable, we found that when the original variable was created, a substantial part of the non consumers were misclassified as missing values. As can be seen from the estimates of cups/day in Table 1, the category representing the remaining (true) missing values is as expected similar to the category “no”. Also, a substantial part of this population (missing values) are probiotic consumers, confirming the probability that some individuals have not written the value zero stating non consumption, but have only written values for consumption behavior (>0). Sensitivity analysis, with missing values in variables regarding food/beverage frequency recoded as non consumers, resulted in similar results as when missing values were coded as a separate category: preeclampsia and probiotic consumption in late pregnancy: aOR: 0.79 (0.69 to 0.92); preterm delivery and probiotic consumption in early pregnancy: aOR: 0.79 (0.66 to 0.93).

There are three more variables that represent a summarized consumption during different time periods: summarized consumption of probiotic milk products and non probiotic milk products during all three time periods, and alcohol consumption during pregnancy. All these variables were created with the same error, creating large numbers of missing values due to misclassification. All of these four variables were used for analysis in Table 1. The summarized variables representing non probiotic milk/yoghurt consumption and alcohol consumption during pregnancy were used as confounders in all logistic regressions. All analyses have been rerun with the corrected variables. The new results are presented in the revised manuscript. The results remain nearly the same as in the previous analyses, with exception that when preeclampsia is categorized into mild and severe, we only find a statistically significant association for severe preeclampsia, as compared to before when both subgroups were significantly associated with probiotic consumption. These new results are actually more in alignment with our previous study, as we now have stated in the discussion, page 22 lines 505-509:

“Increased inflammatory response seems to play a greater role especially in severe preeclampsia [1-3], which might explain our finding of a significant association only between probiotic intake and severe preeclampsia. These results are also in alignment with our previous study. [4]”

Within the limits of this study, we have tried to adjust for confounders such as non probiotic dairy products as good as possible, however, as we have stated clearly in the manuscript under limitations (page 25 lines 572-573), unmeasured confounding cannot be ruled out.

In Table 1, we decided to follow your suggestion to present data for both consumers and non consumers, making it easier for the reader to make a comparison.

In the covering letter the authors mention probiotics with confirmed laboratory study effects but these are not likely to have much bearing on the protective effect here. Also I disagree with their idea that any of these probiotics regularly colonise the human gut

We agree that colonization properties of probiotics and its impact on the gut microbiota are highly species specific. Their survivability throughout the gut, number of viable bacteria per dosage and product shelf life are among different variables of importance for their potential health benefit effect. In this study our aim was to look at the impact of products classified as probiotics according to the joint FAO/WHO working group definition: “live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host”.
The two products in the study were the only probiotic products (according to the definition above) available on the Norwegian market while there might have been bacteria with probiotic properties in some of the other milk products available (kefir for example), and individuals consuming these other products might be classified as non consumers of probiotics in our study. This would however lead to an attenuation of the results in this study.