Author's response to reviews

Title: Dairy consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis

Authors:

Mu Chen (muc371@mail.harvard.edu)
Qi Sun (QISUN@hsph.harvard.edu)
Edward Giovannucci (egiovann@hsph.harvard.edu)
Dariush Mozaffarian (dmozaffa@hsph.harvard.edu)
JoAnn E. Manson (jmanson@rics.bwh.harvard.edu)
Walter C. Willett (wwillett@hsph.harvard.edu)
Frank B. Hu (nhbfh@channing.harvard.edu)

Version: 2
Date: 14 October 2014

Author's response to reviews: see over
Dear Dr. Barnard,


Thank you for your letter on Sept 23, 2014, in which you offered us the opportunity to revise our manuscript. We have taken the comments and suggestions of the reviewer into consideration and have revised the manuscript accordingly. On the following pages, please find our point-by-point responses to the reviewer’s concerns in the order they were originally listed, with details of the pages on which the changes have been made.

We have checked all the style requirements for *BMC Medicine* carefully. The manuscript has not been submitted to, nor is under consideration for publication by any other journal. All the authors have read the manuscript and are in agreement that the work is ready for submission to *BMC Medicine*. None of the authors have any conflicts of interest in the matter.

We hope that the revised manuscript is acceptable for publication in *BMC Medicine*. On behalf of all the authors, I thank the editor and reviewer for their comments and suggestions, which have helped us improve the quality of our manuscript.

Yours truly, (On behalf of the authors)
Frank B. Hu, MD, PhD
Professor of Nutrition and Epidemiology
Harvard School of Public Health
Professor of Medicine
Harvard Medical School
Tel: 617 432 0113; Fax: 617 432 2435; Email: nhbh@channing.harvard.edu.
Reviewers’ comments:

Reviewer #1: Dairy intake and development of type 2 diabetes is an important and timely issue. This paper presents the results of a meta-analysis of cohort studies on this topic and provides important data that will help shape public health policy. The data is well presented and appropriately discussed. The manuscript should be accepted for publication as written.

Reviewer #2: This is an updated analysis of the three Harvard cohorts on dairy intake and type 2 diabetes risk and an updated meta-analysis of cohort studies. In contrast to their previous analyses of these cohort studies the authors don’t find an inverse association between dairy products and type 2 diabetes, with the exception of yogurt and ice-cream. I have some questions that should be clarified below.

1. I wonder what is the reason for the difference in the current results compared to the previous results from these studies. Although the authors state in the discussion that this is not clear, perhaps some further analyses could clarify this. In two of the previous papers (Pittas, and Choi) from the NHS1 and HPFS, the multivariate models included nutrients and not food groups. In the current study analyses among females were also adjusted from hormone use and OC use, so the question is whether the current results are better adjusted compared to the previous results or whether there is a change in the risk with longer follow-up? If repeating the analyses with same study periods as the previous analyses – are the results similar to the previous results or still similar to the current results?

Multivariate models: in Choi’s paper, the dietary variables adjusted in the multivariate models were cereal fiber, trans FAs, PUFA:SFA ratio, glycemic load.
Aiming to investigate the association between vitamin D/calcium intake (rather than dairy intake) and type 2 diabetes, Pittas’ paper additionally adjusted for Mg and caffeine. In the current analysis, we also adjusted for glycemic load, trans-fat intake; however, we did not include Mg and saturated fatty acid because they are considered as dairy components. In addition, cereal fiber was removed from the adjustment because it was captured by glycemic load. Furthermore, we thought that coffee intake would be a better variable to adjust than caffeine because a recent meta-analysis (Ding M et al, *Diabetes Care* 2014) found that both caffeinated and decaffeinated coffee was associated with lower risk of type 2 diabetes. Hormone use and OC use (only for women) were included in the final models because they have been linked to T2D risk as well. However, the difference in covariates adjusted in the models does not explain the difference in our current and earlier findings.

The difference between current results and previous results: When we repeat the analyses with same study periods as the previous analyses, the results are similar to the previous results. The reason for the difference between current results and previous results might be that during the 10 additional years of follow-up, the number of T2D cases has tripled in HPFS / doubled in NHS. For HFPS, there were 1,243 T2D cases during the 12-year follow-up in the Choi et al, compared with 3,364 T2D cases during the 24-year follow-up in current analysis; for NHS, there were 4,843 T2D cases during 20 years of follow-up in Pittas et al, compared with 7,841 T2D cases during 30 years of follow-up in current analysis.
Accordingly we added the following sentence in the discussion section: “The reason for the discrepancy between our earlier and current results was probably due to longer follow-up (10 more years) of the NHS and HPFS cohorts, and our meta-analysis suggests that potential benefits of dairy were less evident with long-term follow-up.”

2. How was total dairy calculated? Were the different items contributing to total dairy summed up as standard servings (which differed for each item) or was the gram weight of each item summed up and results presented for a specific serving high-fat and low-fat dairy products.

Different types of dairy were summed up as standard servings, which differed for each item. For example, the standard serving size was 8oz. glass for skim, low fat milk, or whole milk, Tbs from cream, sour cream, ½ cup for sherbet or frozen yogurt, ice cream, cottage or ricotta cheese, 1 oz. for cream cheese or other cheese. We have mentioned this in the assessment of dairy consumption in the “Method” section.

3. What is the average serving size for total dairy, high-fat and low-fat dairy? Did the authors use the same serving sizes as in their own cohorts for re-calculation of studies that reported results by frequency of intake or grams per day to a common scale?

In studies that reported the intakes by servings/d, we directly extracted and used the numbers; for studies that reported the intakes by gram, we used 177g as a
serving size for total dairy products, and 244g as a serving size for milk and yogurt intake to recalculate the intakes to a common scale (serving/d).

4. Table 1 and footnotes to table 2, 3, and 4: is it red AND processed meat?

Yes, it is red meat and processed meat. To clarify this, we have changed “red processed meat” to “red and processed meat” in all the table footnotes.

5. Add the median of dairy intake for each quintile/category in table 2, 3, 4

Done.

6. Would it be possible to adjust for BMI in a separate step in the final model? It was argued that yogurt consumption was associated with less weight gain in a previous study by the authors and this could be a potential mechanism.

As shown in the following table, the hazard ratio of a one serving/d increase of yogurt intake for not adjusting time-varying BMI was 0.82, 95% CIs (0.74, 0.91), compared with the HR for adjusting BMI of 0.83, 95% CIs (0.75, 0.92). We have mentioned this in the fourth paragraph in the discussion section: “However, adjusting for BMI in the multivariate model did not alter the inverse association between yogurt intake and T2D risk.”

<table>
<thead>
<tr>
<th>Yogurt Intake (servings)</th>
<th>P for trend</th>
<th>HR (95% CI) for one serving/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1/mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3/mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not adjusting time-varying BMI</td>
<td>1.00</td>
<td>1.01 (0.97, 1.06)</td>
</tr>
<tr>
<td>Adjusting time-varying BMI</td>
<td>1.00</td>
<td>1.00 (0.96, 1.05)</td>
</tr>
</tbody>
</table>
Also, we conducted a stratified analysis on yogurt by baseline BMI (<25 kg/m$^2$ or $\geq 25$ kg/m$^2$), and no significant interaction of yogurt consumption with baseline BMI was observed (see Table S3 under “Supplemental data”). This was also mentioned in the second paragraph in the results section.

7. In Choi et al, sour cream was analyzed separately from cream. Clarify if cream refers to total intake or specific items, and consider presenting results separately as well if it refers total intake.

For HPFS, in 1986 and 1990, sour cream, non-dairy whitener, and cream were 3 separate items in the FFQs; whereas in 1994, 1998, 2002, and 2006 these 3 items were combined as one food item “cream” in the FFQs. Choi estimated sour cream in 1994 and 1998 using total cream consumption. Thus, in this paper we did not separate specific items and cream refers to total intake.

8. The authors elegantly show that reverse causation may explain some of the associations in Table 5. It would also be interesting to know if there are particular lag-times where associations between yogurt and dairy intakes and type 2 diabetes are stronger than others. The authors can feel free to ignore this if it is a large amount of work, but just asking out of curiosity.

We did a 4-year lag analysis to investigate the association between yogurt/total dairy intakes and risk of diabetes 4 years later. As shown in the table below, the association between yogurt consumption and type 2 diabetes was still significant
(pooled HR for one serving/d: 0.87, 95% CIs (0.78, 0.96)) but slightly attenuated compared with the original approach (pooled HR for one serving/d: 0.83, 95% CIs (0.75, 0.92)). For total dairy intake, the association between its consumption and type 2 diabetes did not change.

**Multivariate Relative Risk (RR) of Type 2 Diabetes According to intakes of yogurt intake using 4-year lag analysis**

<table>
<thead>
<tr>
<th>Yogurt Intake (servings)</th>
<th>HPFS 4-year lag analysis</th>
<th>Current analysis</th>
<th>P for trend</th>
<th>HR (95% CI) for one serving/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1/mo</td>
<td>1.00</td>
<td>1.00</td>
<td>0.51</td>
<td>0.90 (0.72, 1.13)</td>
</tr>
<tr>
<td>1-3/mo</td>
<td>1.00</td>
<td>0.97 (0.88, 1.06)</td>
<td>0.30</td>
<td>0.85 (0.68, 1.06)</td>
</tr>
<tr>
<td>1/wk</td>
<td>0.91 (0.81, 1.02)</td>
<td>0.89 (0.80, 0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/wk</td>
<td>0.97 (0.85, 1.12)</td>
<td>0.95 (0.84, 1.08)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Multivariate Relative Risk (RR) of Type 2 Diabetes According to intakes of dairy intake using 4-year lag analysis**

<table>
<thead>
<tr>
<th>Dairy Intake (servings)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P for trend</th>
<th>HR (95% CI) for one serving/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPFS</td>
<td>1.00</td>
<td>1.05 (0.94, 1.18)</td>
<td>0.98 (0.87, 1.11)</td>
<td>0.95 (0.84, 1.07)</td>
<td>0.96 (0.85, 1.08)</td>
<td>0.21</td>
<td>0.98 (0.95, 1.01)</td>
</tr>
<tr>
<td>4-year lag analysis</td>
<td>1.00</td>
<td>1.08 (0.97, 1.21)</td>
<td>1.01 (0.91, 1.13)</td>
<td>0.99 (0.88, 1.11)</td>
<td>0.99 (0.88, 1.11)</td>
<td>0.38</td>
<td>0.98 (0.95, 1.01)</td>
</tr>
<tr>
<td>Current analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHS</td>
<td>1.00</td>
<td>0.97 (0.9, 1.05)</td>
<td>0.99 (0.92, 1.07)</td>
<td>1.0 (0.92, 1.08)</td>
<td>1.04 (0.95, 1.13)</td>
<td>0.27</td>
<td>1.02 (0.99, 1.05)</td>
</tr>
<tr>
<td>4-year lag analysis</td>
<td>1.00</td>
<td>1.00 (0.93, 1.07)</td>
<td>0.98 (0.91, 1.06)</td>
<td>1.03 (0.95, 1.11)</td>
<td>1.05 (0.97, 1.14)</td>
<td>0.15</td>
<td>1.02 (0.99, 1.05)</td>
</tr>
<tr>
<td>Current analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHS II</td>
<td>1.00</td>
<td>1.03 (0.93, 1.14)</td>
<td>1.02 (0.92, 1.13)</td>
<td>1 (0.9, 1.12)</td>
<td>1.04 (0.92, 1.16)</td>
<td>0.75</td>
<td>0.99 (0.96, 1.02)</td>
</tr>
<tr>
<td>4-year lag analysis</td>
<td>1.00</td>
<td>1.08 (0.98, 1.18)</td>
<td>1.04 (0.94, 1.15)</td>
<td>0.99 (0.89, 1.10)</td>
<td>1.00 (0.89, 1.11)</td>
<td>0.46</td>
<td>0.98 (0.95, 1.01)</td>
</tr>
<tr>
<td>Current analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>1.00</td>
<td>1.01 (0.95, 1.06)</td>
<td>1.00 (0.94, 1.05)</td>
<td>0.99 (0.93, 1.04)</td>
<td>1.02 (0.96, 1.08)</td>
<td>0.83</td>
<td>1.00 (0.98, 1.01)</td>
</tr>
<tr>
<td>4-year lag analysis</td>
<td>1.00</td>
<td>1.04 (0.98, 1.09)</td>
<td>1.00 (0.95, 1.06)</td>
<td>1.01 (0.96, 1.07)</td>
<td>1.02 (0.96, 1.08)</td>
<td>0.99</td>
<td>0.99 (0.98, 1.01)</td>
</tr>
<tr>
<td>Current analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. Figure 2: Ericson et al, 2013 should be removed
We have removed Ericson et al, 2013 and the summarized HR from the random-effects model for one serving of total dairy intake does not change (0.98, 95% CI (0.96, 1.01)).

10. Do the authors have any data on high-fat and low-fat cheese and yogurt?

Cheese: there were 3 questionnaire items on cheese, “cottage/ricotta cheese”, “cream cheese”, and “other cream”. The multivariate relative risks (RRs) of type 2 diabetes according to these 3 types of cheese were shown in Supplementary table S5. Neither cottage cheese (pooled HR for one serving/d:1.02, 95% CIs (0.92, 1.14)) nor other cheese (pooled HR for one serving/d:1.01, 95% CIs (0.96, 1.06)) was significantly associated with risk of type 2 diabetes. Cream cheese was associated with higher T2D risk (pooled HR for one serving/d:1.44, 95% CIs (1.25, 1.66)). We subsequently conducted a stratified analysis on cream cheese by glycemic load and found a significant interaction between cream cheese consumption and glycemic load (GL) (low GL: HR=1.36, 95% CIs (1.14, 1.61); and high GL: HR=1.86, 95% CIs (1.45, 2.37)). As cream cheese intake was relatively low and usually consumed with bagels, the positive association of cream cheese is likely to be confounded by high-GL carbohydrate intakes and thus not included in the main manuscript.
Yogurt: we were unable to evaluate separately high/low fat yogurt. U.S. consumption patterns would suggest that most participants chose nonfat or low-fat yogurt.

11. Second last paragraph of the results: no significant heterogeneity for yogurt was found when one study [33] was removed. Perhaps rephrase to heterogeneity was reduced or moderate as $I^2=40.7\%$.

We have rephrased the sentence to “heterogeneity for yogurt was reduced when one study was removed ($I^2=40.7\%$; $P=0.063$)”.

12. Missing volume and page number for reference 27.

Done.

13. Supplemental table S6: suggest to order the studies by publication year rather than alphabetically.

Done.

14. Supplemental table S6: add explanations for abbreviations

Done.

Editorial changes:
1. Please ensure the meta-analysis part of your manuscript adheres to the PRISMA reporting guidelines. It would be most helpful if you could submit a completed PRISMA checklist with your revised manuscript.

We have checked the meta-analysis part’s adherence to the PRISMA reporting guidelines with a completed checklist attached. In addition, we added “This meta-analysis was conducted following a review protocol [26]. For study selection, we included prospective studies with cohort, case cohort, or nest case-control design investigating the association between intake of dairy products and the risk of type 2 diabetes.” in the methods section.

2. We notice that the additional files in your manuscript are labelled "PLOS Medicine". Please be aware the manuscript is currently under consideration at BMC Medicine. We notice your cover letter is addressed to BMC Medicine, but thought it best to check you intended to submit your manuscript to BMC Medicine rather than PLOS.

We apologize for the confusion and revised it accordingly.

3. Please include a statement in the methods section about whether informed consent was obtained from the participants in your study. If the requirement for consent was waived by the ethics committee, a statement to this effect should appear in the methods section.

We have added a statement in the methods section: “The completion of the self-administered questionnaire was considered to imply informed consent.”
4. Please include authors’ contributions and acknowledgements sections at the end of your manuscript. More information can be found at: http://www.biomedcentral.com/bmcmed/authors/instructions/researcharticle# formatting-contributions

Done

5. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

Done.