Author's response to reviews

Title: How well do blood folate concentrations predict dietary folate intakes in a sample of Canadian lactating women exposed to high levels of folate? An observational study.

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Author's response to reviews: see over

Dr. Lolu da-Silva
Assistant Editor, BMC-series journals

Dear Dr. da-Silva:

Please find below a point-by-point response to the reviewer comments to our manuscript entitled, “How well do blood folate concentrations predict dietary folate intakes in a sample of Canadian lactating women exposed to high levels of folate? An observational study” (MS: 1947964852129440). We believe the revisions made in response to the reviewers’ comments have strengthened the manuscript.

Many thanks again for granting us an extension in returning this revision given the travel schedules of the authors. This allowed us to check out some statistical questions posed by one of the reviewers.

Do not hesitate to let us know if there are any further comments to be responded to in reference to this manuscript.

Sincerely,

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RESPONSE TO REVIEWERS COMMENTS

REVIEWER 1: Marie Caudill

Major Compulsory Revisions

Dr. Caudill asked that we make three major revisions to the paper. We agree with these recommendations and have made the requisite changes in the revised version of the manuscript as detailed below.

First, Dr. Caudill asked us to consider an alternative interpretation of our data. In the original version of the manuscript we concluded that, “blood folate concentrations are not reliable predictors of folate intake”. Dr. Caudill suggests that we consider the alternative interpretation that “folate intake estimated via food composition tables is not a reliable predictor of folate status”. We agree and have qualified our statements in the following sections in our revision.

Abstract: Page 3, beginning line 1
Discussion: Page 11, beginning line 12
Conclusion Page 16, beginning line 1

Second, Dr. Caudill asks that we present a more balanced view of the strength of the relationship between blood folate levels and dietary intake. Specifically she recommends we include data from controlled folate feeding studies that demonstrate that serum and red blood cell folate are sensitive and specific indicators of dietary intake. We suspect that differences in the baseline folate status of women in our study versus those of the controlled trials, lack of a folate depletion phase in our study, and the noise introduced by the significantly larger number of folate-containing foods (and variability in the quality of the folate content found for each food in the Canadian Nutrient file) in our work versus the controlled feeding trials account for the differences in the strength of the relationship between blood folate values and dietary folate intake. We have discussed the controlled folate feeding studies in the following sections of the revised manuscript.

Background: Page 5, beginning line 2

Third, Dr. Caudill recommended modifying the conclusions to our paper, and we have done so in both the abstract and conclusion to our discussion.

REVIEWER 2: Paul F Jacques

Major Compulsory Revisions

1. Page 5, lines 6-19 (original manuscript): Dr. Jacques expressed confusion regarding the rationale for the study. In hindsight, as originally written, we concur. The overall goal of this study was to examine how predictive blood folate concentrations and folate intakes are of each other in a sample of Canadian lactating women exposed to high levels of folate. Our intention
was not to establish this relationship in the general population, and trust the revisions to our manuscript in the title, and objectives statement in the abstract (Page 2, lines 10-12) and background (Page 6, beginning line 1) have clarified this. While it is true women in our sample had high baseline folate concentrations, from the perspective of clinical practice in Southern Ontario they are not unusual. We receive a large volume of inquires from health care professionals, government agencies and well-educated women seeking direction on whether, or not, if women already have high RBC folate concentrations they should consume a folic acid-containing supplement for NTD prevention. These inquires have increased with calls to increase the amount of folic acid provided in prenatal supplements, and reports that chronic ingestion of folic acid may have some undesirable health consequences. As the original impetus for public health initiatives regarding folic acid supplementation and food fortification were the randomized clinical trials linking folate intake to NTD prevention, one of many strategies of addressing the aforementioned health care professional question is to assess whether blood folate concentrations and folate intake are predictive of each other; the rationale for the current study.

Dr. Jacques provides an excellent discussion of why or why not post-fortification of the food supply the association between folate intake and blood folate concentrations might or might not improve. We think this information strengthens the rationale for the study and we have added it to the background and discussion sections of the revised manuscript (Page 5, beginning line 10 and Page 12, beginning line 20).

2. Page 6, line 13 (original manuscript): Dr. Jacques point out that it wasn’t until page 15 of the original manuscript that we make it clear that the lactating women in our study were exposed to high levels of folic acid. In the revised version of the manuscript we make this clear much earlier—specifically in the title and in the “objective of the study” statements in the abstract (Page 2, lines 10-12) and in the background (Page 6, beginning line 1).

We concur with the reviewer that extrapolating our finding for the lactating women exposed to high levels of folate herein to the general population would be inappropriate. We trust with the aforementioned changes to the manuscript it is clear that our target population is lactating women chronically exposed to high levels of folate. As noted in section 1 above, while it is true lactating women in our sample had high baseline folate concentrations; from the perspective of clinical practice in Southern Ontario they are not unusual.

3. Page 10, lines 12-23 and Page 11, lines 1-2 (original manuscript): As noted by the reviewer, the relationship between folate intakes and blood folate concentrations did not improve between 4 and 16 weeks lactation---note they did not diminish either. As noted in the revised discussion section, we speculate that the contribution of liver folate stores accumulated prior to and during pregnancy when folic supplement use was high (ie 1000 ug/d) could partially be responsible for this observation (Page 15, beginning line 12).

4. Page 11, lines 3-10 (original manuscript): We believe that Dr. Jacques is asking us to make the text description of our findings illustrated in Figure 1 consistent with our statistics. In the revised manuscript we have modified the text so that we conclude that there is little benefit in terms of RBC folate concentration from synthetic folic acid intakes above151 ug/d.
We believe Dr. Jacques comments here have been addressed in response to his earlier comments as we have revised the title, and objectives statements of the manuscript to make it clear that lactating women exposed to high levels of folate are our target population. We have revised the first sentence of the original discussion (Page 11, lines 12-13) that Dr. Jacques objected to.

**Minor Essential Revisions**

1. **Page 8, lines 18-21 (original manuscript):** In response to Dr. Jacques comment, in the statistical comparison of red blood cell folate concentrations by quartile of synthetic folate intake we included an interaction term for quartile of synthetic folate intake and type of supplement (placebo, 5-methyl-tetrahydrofolate, folic acid). We did not find a statistically significant interaction (P value > 0.20).

2. **Page 11, lines 15-19 (original manuscript):** We added a statement to the revised discussion to acknowledge the possibility that post-folic acid fortification of the food supply RBC levels might be a better predictor of NTD risk than supplement use (Page 11, beginning line 23).

3. **Page 12, lines 12-15 (original manuscript):** The data used to calculated intakes from fortified foods was based on calculated estimates (food composition tables) and were not measured. This information can be found on Page 8, beginning line 1 (revised manuscript).

4. **Page 15, line 5 (original manuscript):** We concur with Dr. Jacques’s statement. We have elaborated on the possible contribution of folate stores amassed during the preconceptional period and pregnancy beginning on Page 15, beginning line 12 (revised manuscript).