Author's response to reviews

Title: Dietary iron intake, body iron stores, and the risk of type 2 diabetes: a meta-analysis

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Author's response to reviews: see over
Dear Editors of *BMC Medicine*,

On behalf of our colleagues, I submit the revised manuscript entitled “**Dietary iron intake, body iron stores, and the risk of type 2 diabetes: a meta-analysis** (MS: 1853109037746342)” for publication in *BMC Medicine*.

We appreciate very much all you and the reviewers’ help with critical appraisals and constructive suggestions. Based on all the comments, we have revised our manuscript carefully and we believe it looks much better now. Please see our point-by-point responses to the reviewers as attached below.

All authors listed have contributed to the work, and all authors have agreed to submit the manuscript to *BMC Medicine*. No part of the work has been published before or been reviewed in other journals.

We appreciate your consideration and look forward to hearing from you.

Yours sincerely,

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Responses to Reviewers

Responses to Reviewer 1

Comment: The manuscript by Bao et al. “Dietary iron intake, body iron stores, and the risk of type 2 diabetes: a meta-analysis” has performed a comprehensive literature search and meta analysis of papers reporting on the risk of diabetes associated with iron. They find an association of diabetes with intake of heme iron and ferritin that is not accounted for by inflammation. This is a timely review as several papers have continued to report on the ferritin-diabetes association while still debating the causality of that relation. The conclusion about heme intake and independence from inflammation is a significant step toward demonstrating causality. The review is well done and I have no criticisms.

Response: Thanks very much for your nice appraisal.
Responses to Reviewer 2 (Statistical Reviewer)

Major compulsory revisions:

Comment 1: Unfortunately, comparing the highest category of exposure with the lowest for each study, fails to quantify the association fully. Different studies use different categorisations, introducing heterogeneity, and meaning that the definition of “highest category” is different for each study. This in turn makes it impossible to interpret the results, because we do not know what exposure the increased risk relates to. In addition, it ignores most of the data, so that the results are based on far fewer than the 9,269 incident T2DM cases from 197,488 participants quoted. Instead, the authors should model a dose-response trend over the intakes using methods such as that of Greenland and Longnecker, otherwise results are uninterpretable.

Response 1: Thanks very much for your comments. According to your suggestion, we conducted dose-response analyses for total iron and heme iron intake in association with T2DM risk (Please see Abstract, Page 2, Line 15-16; Methods section, Page 7, Line 17-21; Results section, Page 10, Line 3-6; and Figure 3). For body iron stores, we did not conduct such analysis, because the required data for a dose-response analysis were not available in most studies. Thus, we have acknowledged this point in the methods (Please see Page 7, Line 21-23) and discussions (Please see Page 15, Line 9-11). As you pointed out, “9,269 incident T2DM cases from 197,488 participants” may be misleading. It is a sum of all participants in the five studies, not the number of participants in highest and lowest category. Thus, we removed the statement in the abstract and the text (Please see Abstract, Page 2, Line 13; and Results, Page 9, Line 16).

Comment 2: Heterogeneity. There is heterogeneity, and the authors completely fail to address this. There should be a detailed analysis of potential sources of heterogeneity – this could explain some of the differences in results between the studies. Maybe there are too few studies to do this properly, but this is a weakness in the interpretation of the results.

Response 2: Thanks very much for your comments. As you said, due to the limited number of studies, it is not sufficient to conduct a formal meta-regression analysis for identifying potential sources of heterogeneity. Thus, we have acknowledged this point in the discussion (Please see Page 15, Line 12-13).
Comment 3: The abstract does not give the non-heme iron, supplemental iron and total iron intake results. The pooled RRs and confidence intervals for all meta-analyses must be included to give a balanced summary. The conclusion to the discussion also ignores all the non-significant results. Again, these should be given equal weight in the conclusions.

Response 3: Thanks very much for your comments. We have revised the conclusion in the abstract (Please see Page 3, Line 2-3) and text (Please see Page 16, Line 5-6) accordingly.

Minor compulsory revisions:

Comment 1: The authors used hand-searching, but have not included this in their flowchart. This is important as a measure of how good the original search strategy was.

Response 1: Thanks very much for your comments. When we developed the search strategy, we carried out an iterative process in which the search terms are modified again and again, based on what were retrieved from hand-searching of relevant studies and review papers. Thus, all the papers found in hand-searching were finally covered in the database search with refined terms. This is why we used hand-searching but did not included this in the flowchart.

Comment 2: Page 5. The model with the largest number of covariates is not necessarily the most appropriate, and may lead to over-adjustment.

Response 2: Thanks very much for your comments. The possibility of over-adjustment is really a concern that we have considered in our analysis. This is why we carefully evaluated and selected the multivariate models for body iron stores and iron intakes in association with T2DM risk. Because circulating ferritin may be influenced by inflammation, we separately extracted the risk estimates from the most fully-adjusted models except for other biomarkers, and the models with additional adjustment for inflammation markers (such as C-reactive protein, interleukin-6, fibrinogen, etc.). If available, we also extracted risk estimates from the models in which other metabolic biomarkers (such as HDL-C, TG, FPG, FPI, HbA1c, HOMA-IR, ALT, GGT, and adiponectin, etc.) were additionally adjusted for additional sensitivity analyses. For dietary iron intake, the most fully-adjusted models represented the model including other dietary factors as covariates, which we think are appropriate, and thus they were used for our analysis.
Comment 3: Page 6. HR are already RR, and need no rare disease assumption. You only need the rare disease assumption for OR. The authors argue that they can combine HR and OR with RR as they are all estimates of RR. However, that does not mean that the authors can refer to OR as RR, because they are not. Report OR as OR, but combine with HR and RR in the forest plots.
Response 3: Thanks very much for your comments. According to your suggestion, we have changed the wording to make it clear (Please see Page 7, Line 12-14).

Comment 4: Page 6. Funnel plots do not assess publication bias; they assess small study effects. One of which is publication bias. But in nutrition epidemiology the smaller studies may well have better methods of assessing the exposure, so it could be that the larger studies are the ones with greatest bias.
Response 4: Thanks very much for your comments. According to your suggestion, we have changed the wording to make it clear (Please see Page 8, Line 3-4).

Comment 5: The numbers of studies in the meta-analyses are too small for adequate assessment of small-study effects.
Response 5: Thanks very much for your comments. We have acknowledged this point in the discussion (Please see Page 15, Line 13-14).

Comment 6: Page 3, paragraph 2, line 2. “in human” should be “in humans”.
Response 6: Thanks very much for your comments. We have corrected it accordingly (Please see Page 4, Line 11).

Comment 7: Page 4, final line. “for EMBASE database” should either be “for the EMBASE database” or “for EMBASE”.
Response 7: Thanks very much for your comments. We have corrected it accordingly (Please see Page 5, Line 22).

Comment 8: Page 7, last paragraph, penultimate line. “one studies” should be “one study”.
Response 8: Thanks very much for your comments. We have corrected it accordingly (Please see Page 9, Line 6).
Comment 9: Page 8, first paragraph, last line. “noon-heme” should be “non-heme”.
Response 9: Thanks very much for your comments. We have corrected it accordingly (Please see Page 9, Line 15).

Comment 10: There is no need to quote I squared values to one decimal place, nor p-values to 3 decimal places. This creates a false sense of precision in these figures.
Response 10: Thanks very much for your comments. According to your suggestion, we have revised the text (Please see the Results section, Page 9-11).

Comment 11: To avoid reverse causality, the authors need to do more than just exclude retrospective studies, they should also consider exploring exclusion of studies with diabetes incident within, say, 2 years of iron intake being recorded.
Response 11: Thanks very much for your comments. Reverse causality is really a concern in prospective cohort studies with short follow-up. However, in the included studies for dietary iron intake, the follow-up durations were 5-20 years (Table 1), thus it is less likely to have such reverse causality. For the included studies of body iron stores, the follow-up duration were shorter (4, 10, 5.1, 7.9, 4.3-4.7, 2.8 years, respectively; Table 1). However, when we did sensitivity analysis excluding the studies with 2.8-year follow-up, there was no substantial change in the results.
Responses to Reviewer 3

Comment: The study summarized the longitudinal findings on iron intake, iron store in relation to the risk of diabetes. The findings are robust. It is well written. The main limitation of the study is that most of the studies are performed in Western population. There is only one study with small number of incident diabetes case from Asia. The findings may not be generalized. Major Asia has the highest number of diabetes patients in the world. Lack of adequate information in Asia is a major concern. However, several cross-sectional studies on iron and diabetes in Asia are available. A synthesis of these studies may help to support the findings. This information may have particular public health importance as anemia prevalence is very high in Asia.

Response: Thanks very much for your comments. As you said, lack of data, in particular prospective data, from Asian populations limited the direct generalization of the findings. We have acknowledged this point as a limitation in the discussion section (Please see Page 15, Line 14-19). However, it should be noted that the prospective cohort study by Shi et al found that heme iron intake was positively associated with the risk of T2DM among Chinese, although the sample size was small and more validation studies are needed.
**Responses to Reviewer 4**

**Comment:** The study presents important and relevant information about the relationship between iron and diabetes, as human epidemiologic studies linking body iron stores and iron intake to the risk of type 2 diabetes mellitus (T2DM) were conflicting. Thus, the article must be published as written.

**Response:** Thanks very much for your nice appraisal.