**Author’s response to reviews**

**Title:** The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis

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**Version:** 2 **Date:** 9 November 2009

**Author’s response to reviews:** see over
Dear Nutrition Journal Editorial Team,

Re: The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis

Thank you to both of our reviewers for their thorough and thoughtful comments, which have been very helpful to us in revising and improving this systematic review. The individual points are answered below, and changes in the manuscript are highlighted/tracked.

Reviewer: Nicola M Lowe
Reviewer's report:
This is a well written, thoroughly undertaken review. The introduction outlines the rationale for the question addressed by this review and the aims of the study are clearly defined. A number of reviews of Iron supplementation have already been conducted, however the uniqueness of this review in terms of the specific age range studied, is adequately justified. The methods used are appropriate and well described. The discussion is well balanced and is supported by the data. The points listed below are discretionary revisions. Thank you for your positive comments.

Methods
1. The authors stated that the “search was not limited by language”, was translation of papers or abstracts therefore required, and if so, how was this undertaken? No, none of the potential studies for inclusion were published in a language other than English. We have inserted ‘None of the studies identified required translation’ to clarify this in the results section (page 12).

Results
2. Page 13 refers to funding bias, how was this assessed? Very good suggestion - how did we miss this? thanks! The method of assessment of funding source has been added below table 2.

3. Table 3. It would be useful to have the P values to indicate which of the cognitive domains Iron had a significant effect on. When the 95% CI of the standardized mean difference includes zero then the p-value is >0.05, when it does not include zero then the p-value is <0.05, so I have indicated by using an ‘*’ in table 3 where <0.05.

Discussion
4. it is well established that Zn also plays a role in cognitive function. Do the
authors think that the lack of affect of Fe supplementation on many of the
cognitive domains may be due to a concurrent Zn deficiency, possibly worsened
by the Fe supplementation? Good thought, thanks, we have added this possibility to
discussion, page 22-3

5. Page 22, paragraph 3, second sentence “……This was because the outcomes
were reported as z-scores or were adjusted, which were highly appropriate, or
because of lack of variance data”. This sentence does not make sense to me?? Ooops, we
have rewritten this and hope it makes more sense now.

Reviewer: Katalin Fekete
Reviewer’s report:
This is clearly structured manuscript, addressing a highly relevant and actual
question. Falkingham et al collected and evaluated all relevant randomised
controlled trials concerning the effects of iron supplementation on cognition in
children aged at least 6 years and in adults. I feel that this paper maybe suitable
for publication in the Nutrition Journal; however I have a few minor comments
and suggestions.
Minor comments:
1. Page 2, line 24. Abbreviation of intelligence quotient is used although it has
not been previously defined. Thank you for pointing this out, IQ is replaced by intelligence in
the abstract and the next use of IQ is defined.

2. Page 2, last sentence. This is redundant. We think you are referring to “The limited number
of included studies were generally small, short and methodologically weak.” This sentence is
important to express the validity of the included studies – the answer that the systematic
review provides needs to be mediated by the risk of bias of the included studies, so this
sentence contextualizes the other information in this paragraph. For this reason we have
retained this sentence.

3. In its present form the introduction is nearly four manuscript pages. I feel that
some data of the literature may either be placed into the discussion or omitted. In
my view, the Introduction should be limited to 2 manuscript pages. We have shortened the
introduction by over a page and some of the additional material has been added to the
discussion section (comparing this review’s results with previous research).

5. Page 4, line 25. Please move the dot behind the reference number. Added
6. Page 5, line 11-12. “children aged 0 to 59 month” should be changed into
“infants and children aged under 5 years”. Altered
7. Page 5, line 18-19. “very young children” should be changed into “infants and
young children”. Modified throughout this paragraph (several instances!)
8. Page 6, line 21. Abbreviation of World Health Organization is used although it
has not been previously defined. This text has now been deleted from the manuscript
9. Page 6, line 24. Abbreviation of World Health Organization should be used. This text has
now been deleted from the manuscript
10. Page 8, line 8. Please write "additional file" in capital letter. Done, and we have altered the
number of this file as the reference to Additional File 1 on PRISMA has been added in before
this reference.
11. I did not find the reference of Additional file 2 in the text. **Added, now Additional File 1.**
12. Page 9, line 3. What denotes “similarity to the control”? Could the author please clarify this? **We used this as a double-check on masking of participants and researchers - if the form of the intervention and placebo were different (for example, one capsule and one powder) then the study was not felt to be adequately masked.**
13. Page 10, line 4. Abbreviation of haemoglobin and serum ferritin is used although it has not been previously defined. **Thanks, the definitions have been added in the text.**
14. Please write figures and tables in capital letters in the text. Please be consistent. **Done**
15. Page 10, line 15. “Reference manager” should be “Reference Manager” **Done**
16. Page 10, line 18. Abbreviation of World Health Organization should be used. **As the name now only appears once in the paper we have dropped the abbreviation**
17. Page 10, line 18. Please move the dot behind the reference number. **Done**
18. Please write space between amount and unit. Please use the format throughout the paper. **Done**
19. Page 11, line 10. “I2” should be changed into “I2 test” or “I2 statistic”. **Done**
20. Page 12, line 4. From the 1554 titles and abstracts were identified… (Do not include the duplicates). **Altered**
21. Page 12, line 6. The Lambert paper [31] was not used in the analysis. Please exclude it from the references. **Amended as suggested**
22. Page 12, line 16. “anaemic women” should be changed into “anaemic non-pregnant women”. **Changed**
23. Page 13, line 16. “There were dropouts in 11 studies (none in one study, unclear in 2 studies)…” reported in Table 2. **This has been altered to include the data from Tables 1 (on dropouts) and 2 (on analysis), as in some studies participants completed the intervention (did not drop out) but were not included in the analysis.**
24. Page 14, line 16. Two dots at the end of the sentence. **You have good eyes, done!**
25. Page 14, line 19. “premenopausal” should be “pre-menopausal” **Done**
26. Page 15, line 12. The origin of this result is unclear. How was it calculated? **Good idea - we have added a description and reference for the method.**
27. Page 16, last sentence. Missing reference number. **Added as suggested**
29. Page 20, line 23-24. Page numbers are unnecessary and should be eliminated. **removed**
30. Table 1 and 2. Need to be re-formatted, as several columns are too crowded. **We believe these will be fine when formatted into pdf with smaller text and without double spacing.**
31. Table 1. Misspelling – Study duration **Shortened version used to allow the column width to be narrow, to reduce table crowding**
IQ: intelligence quotient **Added**
32. Table 2. Please define here low, moderate and high funding bias. **Very good suggestion - how did we miss this? thanks! The method of assessment of funding source has been added below table 2.**
Misspelling – Allocation concealment **As before, now added with a hyphen**
Abbreviation of haemoglobin and serum ferritin is used although it has not been defined. **These are defined in the main text, under table 1 and in the abbreviations section**
33. Table 3. would be more impressive with a “Number of studies” column. **Done**
34. Please take care to follow the reference style precisely. **We have used the offered reference manager style**
35. Figure 1. Missing downwards arrow between “Titles and abstracts screened”
and “Full papers and…” textboxes.  

36. Figures. “Total” columns should be changed into “N” (number of participants). The first columns should include not only the name and year but also the reference number.  Reference Manager 5 gives the column heading as ‘total’ rather than ‘N’, and we feel that this is self explanatory.  The studies in this review did not have reference numbers, so are named by the first author (of the main paper) and year of publication. Not complete names of the X axes.  These have been modified.  

37. The “Year” column in Figure 2 and 5 is unnecessary and should be omitted. Done  

38. Figure 3. “Favours iron supplementation” was used in the other forest plots. All now read ‘favours iron’ as otherwise part of the text is lost. 

Thank you again for your helpful comments; we trust you find the revised version of this manuscript covers your points adequately, 

With all best wishes, 

Lee Hooper, Martin Falkingham, Asmaa Abdelhamid, Peter Curtis, Susan Fairweather-Tait and Louise Dye