PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of iron supplementation on fatigue and physical capacity in non-anemic iron deficient adults: a systematic review of randomized controlled trials
AUTHORS	Houston, Brett; Hurrie, Daryl; Graham, Jeff; Perija, Brittany; Rimmer, Emily; Rabbani, Rasheda; Bernstein, Charles; Turgeon, Alexis; Fergusson, Dean; Houston, Donald; Abou-Setta, Ahmed; Zarychanski, Ryan

VERSION 1 – REVIEW

REVIEWER	Bernard Favrat Department of ambulatory care and community medicine, University of Lausanne, Switzerland
REVIEW RETURNED	22-Sep-2017

GENERAL COMMENTS	minor revision minor revision 1. In the abstract (conclusion section) : as you have only studied non-anemic adults, your last sentence should be “to improve symptoms of fatigue in absence of documented anemia.” Same comment at the end of the paper (page 15, last sentence) 2. Table 1 typo : Krayenbueh should be replaced by Krayenbuehl, idem for table 2

REVIEWER	Rune J. Ulvik, professor dr.med. Inst. of Clinical Science, University of Bergen, Norway
REVIEW RETURNED	29-Sep-2017

GENERAL COMMENTS	It was indeed a pleasure to read this thorough update on iron deficiency. As stated by the authors there is a lack of evidence in the literature to finally conclude if supplementation with iron salts should be recommend in the absence of anemia. This review marks the state of the art in the field and should inspire to future studies to strengthen the scientific basis for guidelines to be practised in the primary health care.

REVIEWER	Cesana Bruno Mario Formerly: University of Brescia, Italy
REVIEW RETURNED	06-Nov-2017

GENERAL COMMENTS	Efficacy of iron therapy (in the Title.) I would like to suggest: Effectiveness of iron therapy. Iron therapy I would like to suggest: Iron supplementation Page 8 "For the primary outcome of fatigue, if multiple scales were reported, fatigue-specific scores were preferred over general scores and the most commonly reported and clinically meaningful score was used to generate summary effect measures" Please give much more details about the scales used for the assessment of the fatigue and how the different rating scales have been actually combined. I usually ask some sensitivity analysis, particularly in the case of statistically significant result, but in this case with only 4 papers on the fatigue two for the oral and two for the Intravenous route it is practically not possible. In any case, some more details about these papers in the discussion could be useful for a better understanding of the results. Appendix 7. Subgroup Analysis for Fatigue uncategorized athletetic status Please correct.

REVIEWER	Niko Kaciroti University of Michigan, USA
REVIEW RETURNED	08-Nov-2017

GENERAL COMMENTS	The methods used for the review are appropriate.

REVIEWER	D Bandara University of Monash, Australia
REVIEW RETURNED	09-Nov-2017

GENERAL COMMENTS	Accept for publication with minor revision. Well-articulated publication and please consider minor corrections below. Clearly, state how/what methods have been used to perform subgroup analyses on Page 8. Results from small sample trails need to be considered with caution in the interpretation of meta-analyses. Therefore, I would prefer to see an inclusion criterion with a minimum trial sample size. Trial publication no 27 (sample of 15) and trial publication no 34 (sample of 16) has low patient numbers and follow up days are 28 (table 1). Also if the outcomes assessed from inclusion criteria is the same as follow up days from table 1, 28 days is not the same as one month. One month is reflected in 30.4 days (30 days). From table 1, total subjects/patients is 1178 (adding no of patients on iron and on control). Table 1 has a footnote to *, but it's not clear what is the total subjects in this trial. Should it be should be 8 in each group (therefore overall n=1170) or 8 overall (therefore overall n=1162 but then which group)? I would include the exact number of patients in each group and change the footnote so that it reflects details of the two intervention arms. N reported in the text needs to match to the table. Also in figure 1, I would prefer to see addition box at the end, which clearly shows the number of trials included as 18 and the total number of subjects included in these trials.

	In table 1, add a column at the start of the table, labeling it “number of trial” and list 1 to 18. This will avoid confusion and double counting of the publications as trials. It would be easy to refer to this trial number as the trial than publication number.

REVIEWER	Khitam Muhsen (PhD) Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University Tel Aviv, Israel.
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	Review of manuscript Efficacy of iron therapy on fatigue and work capacity in non-anemic iron deficient adults: a systematic review of randomized controlled trials. Manuscript ID bmjopen-2017-019240 In this well-designed study, the authors addressed the effects of iron therapy on fatigue and work capacity in non-anemic iron deficient adults. The analysis was based on results from randomized controlled trials. My comments refer to the methodological aspects of the study. Study objective in the abstract and introduction: Please rephrase according to "PICO". Please add the comparator. Abstract Please add the statistical model used to combine results from different studies. Data analysis Primary outcomes and results Most comparisons were made between the intervention control groups in continuous variables. Pooled MDs or SMDs were calculated using a random-effects model, which is suitable in this case. In secondary outcomes such as adherence to therapy, pooled risk ratios were calculated using Mantel-Haenszel random-effects model, which is appropriate for this kind of analysis. Page 8, lines 1-3 "Pooled risk ratios and 95% confidence intervals were "conducted" using Mantel-Haenszel random-effects model". Please change "conducted " to "calculated/obtained"… It is recommended to assess publication bias using formal statistical test, such as Egger regression intercept. Results section. Much of the important results were reported in appendices. It is highly recommended to restructure this section and move some important figures/tables to the results section, such as appendix 4. Figure legends and titles need to be improved. Figures should stand alone. For example, title of figure 2 can be changed to "Effect of iron supplementation compared to …. on difference in fatigue score between baseline and follow-up". Similarly, the title in appendix 4 should to be modified. Please define abbreviations in figure legend.

	Table 2: Please add text to the cells (low risk/ unclear risk) in addition to colors. Some readers are color blind (for example 4-10% of men in the USA).

VERSION 1 – AUTHOR RESPONSE

19-Dec-2017

Dear BMJ Editorial team,

Re: Manuscript ID bmjopen-2017-019240 entitled "Efficacy of iron supplementation on fatigue and physical capacity in non-anemic iron deficient adults: a systematic review of randomized controlled trials."

Thank-you for your interest in our manuscript. The reviewer's comments and suggestions to improve our manuscript have been acted upon and incorporated, without changes to the overall message. All comments have been addressed in full (below).

Comments from the Associate Editor:
This paper addresses one of the most clinically relevant questions I've seen for a long time in the BMJ Open papers I see, so I'd definitely work to take this. I see this all the time, and like the authors explain in the discussion, there's really not a lot of guidance on how to manage iron deficiency without anaemia.

I don't like the term "work capacity", they looked at measures of "work capacity" that are probably more relevant to athletes or people with predominantly physically demanding jobs, but which may not be very relevant to all those of us of have predominantly sedentary jobs. Wouldn't, say, "physical capacity" be more appropriate?

Thank-you for this comment. Throughout the manuscript, the term 'work capacity' has been changed to 'physical capacity.'

They should also describe what information was extracted from the individual studies, it is not clear.

Thank-you for this feedback. To clarify which information was extracted, we haveincluded the following statement on page 7, which now reads: "The following data were extracted from each trial: author identification, publication year, publication language, trial location, source of trial funding, patient characteristics (age, sex, weight), intervention/comparator (drug utilized, dose (elemental iron), route of administration, duration), as well as results for the primary and secondary outcomes."

I wonder if they could also include the findings for the secondary outcomes in the abstract, as serum haemoglobin and ferritin levels is really what we can mostly readily assess in clinical practice to gauge improvement. The authors ultimately call for supplementation to improve symptoms of fatigue, but it is not so straightforward, so they could explain the clinical implications a bit better. Patients with iron deficiency without anemia may not have fatigue at all and another option (which is probably the wisest thing to do first) is to promote ingestion of iron rich foods as sometimes iron deficiency without anemia reflects having a poor diet.

We agree with your comment. We have added the results of iron supplementation on serum hemoglobin and ferritin in the abstract. We also agree with your comment regarding dietary iron consumption, and have modified the abstract (and manuscript) to reflect this. The manuscript now reads: "Given the global prevalence of both iron deficiency and fatigue, patients and practitioners

could consider consumption of iron-rich foods or iron supplementation to improve symptoms of fatigue in the absence of documented anemia."

They don't seem to have acknowledged this review:

Br J Nutr. 2017 May;117(10):1422-1431. doi: 10.1017/S0007114517001349. Epub 2017 Jun 19.
Iron deficiency without anaemia is a potential cause of fatigue: meta-analyses of randomised controlled trials and cross-sectional studies.
https://www.ncbi.nlm.nih.gov/pubmed/28625177

Thank-you for noting this new publication: The review by Yokoi et al has been included in the discussion (page 14), and now reads: "Two systematic reviews included studies of pregnant women, blood donors and children, and included data from both randomized and non-randomized controlled trials38,39. These studies concluded benefit of iron supplementation, although in the review by Yokoi et al, the benefit was limited to randomized controlled trials."

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Bernard Favrat
Institution and Country: Department of ambulatory care and community medicine, University of Lausanne, Switzerland
Please state any competing interests: BF was author or co-author in three studies described in this review
BF received study grants and lecture/consultant fees from Vifor Pharma Ltd. and Pierre Fabre Médicament;

Please leave your comments for the authors below

minor revision
minor revision
1. In the abstract (conclusion section) : as you have only studied non-anemic adults, your last sentence should be "to improve symptoms of fatigue in absence of documented anemia." Same comment at the end of the paper (page 15, last sentence)

Thank-you for this feedback. We have reviewed the manuscript, and the last sentence of the abstract and last paragraph have been modified to read: "Given the global prevalence of both iron deficiency and fatigue, patients and practitioners could consider a course of iron supplementation to improve symptoms of fatigue in the absence of documented anemia."

2. Table 1 typo : Krayenbueh should be replaced by Krayenbuehl, idem for table 2

Thank-you for this detailed observation. The typos have been adjusted in both Table 1 as well as Table 2.

Reviewer: 2
Reviewer Name: Rune J. Ulvik, professor dr.med.
Institution and Country: Inst. of Clinical Science, University of Bergen, Norway
Please state any competing interests: None declared

Please leave your comments for the authors below
It was indeed a pleasure to read this thorough update on iron deficiency. As stated by the authors there is a lack of evidence in the literature to finally conclude if supplementation with iron salts should be recommend in the absence of anemia. This review marks the state of the art in the field and should inspire to future studies to strengthen the scientific basis for guidelines to be practised in the primary health care.

Thank-you for these supportive comments.

Reviewer: 3
Reviewer Name: Cesana Bruno Mario
Institution and Country:Formerly: University of Brescia, Italy
Please state any competing interests or state: I have no competing interest to declare. None declared

Please leave your comments for the authors below

Efficacy of iron therapy (in the Title.)
I would like to suggest: Effectiveness of iron therapy.
Iron therapy I would like to suggest: Iron supplementation
Page 8 "For the primary outcome of fatigue, if multiple scales were reported, fatigue-specific scores were preferred over general scores and the most commonly reported and clinically meaningful score was used to generate summary effect measures" Please give much more details about the scales used for the assessment of the fatigue and how the different rating scales have been actually combined. I usually ask some sensitivity analysis, particularly in the case of statistically significant result, but in this case with only 4 papers on the fatigue two for the oral and two for the Intravenous route it is practically not possible. In any case, some more details about these papers in the discussion could be useful for a better understanding of the results.

Thank-you for your comments. Given that all included studies were in fact randomized controlled trials, our author group feels that efficacy is a more accurate representation of effect. As per reviewer suggestion, we have changed iron therapy to 'supplementation' throughout the manuscript. The title has been modified to read "Efficacy of iron supplementation on fatigue and exercise capacity in non-anemic iron deficient adults: a systematic review of randomized controlled trials."

We agree that sensitivity analysis was not feasible given the number of included trials evaluating iron deficiency and fatigue.

Appendix 7. Subgroup Analysis for Fatigue
uncategorized athletetic status Please correct.

Thank-you for this observation. Appendix 7 has been modified, and athletetic has been corrected to "athletic."

Reviewer: 4
Reviewer Name: Niko Kaciroti
Institution and Country: University of Michigan, USA
Please state any competing interests: None

Please leave your comments for the authors below
The methods used for the review are appropriate.

Thank-you.

Reviewer: 5
Reviewer Name: D Bandara
Institution and Country: University of Monash, Australia
Please state any competing interests: None declared

Please leave your comments for the authors below
Accept for publication with minor revision.

Well-articulated publication and please consider minor corrections below.

Clearly, state how/what methods have been used to perform subgroup analyses on Page 8.

Thank-you for this feedback. All subgroup analysis were established a priori. Summary effect estimates were calculated using Mantel-Haenszel random-effects model. Test for subgroup differences were performed using chi2 statistics.

Results from small sample trails need to be considered with caution in the interpretation of meta-analyses. Therefore, I would prefer to see an inclusion criterion with a minimum trial sample size. Trial publication no 27 (sample of 15) and trial publication no 34 (sample of 16) has low patient numbers and follow up days are 28 (table 1). Also if the outcomes assessed from inclusion criteria is the same as follow up days from table 1, 28 days is not the same as one month. One month is reflected in 30.4 days (30 days).

Thank-you for this attention to detail. To clarify, the inclusion criteria in the manuscript have been modified to read “We included trials that evaluated outcomes at least 28 days from the initiation of iron therapy.”

From table 1, total subjects/patients is 1178 (adding no of patients on iron and on control). Table 1 has a footnote to *, but it's not clear what is the total subjects in this trial. Should it be should be 8 in each group (therefore overall n=1170) or 8 overall (therefore overall n=1162 but then which group)? I would include the exact number of patients in each group and change the footnote so that it reflects details of the two intervention arms. N reported in the text needs to match to the table. Also in figure 1, I would prefer to see addition box at the end, which clearly shows the number of trials included as 18 and the total number of subjects included in these trials.

Thank-you for your comment. The total number of subjects is 1170. The footnote refers to a trial with two iron intervention arms (each arm enrolled 8 patients). To clarify this, we have amended the footnote to read: “*Trial included two intervention arms, with 8 patients enrolled in each arm; represents weighted averages between two iron treatment groups.” A column summarizing the number of trials as well as participants has also been included for clarity.

In table 1, add a column at the start of the table, labeling it “number of trial” and list 1 to 18. This will avoid confusion and double counting of the publications as trials. It would be easy to refer to this trial number as the trial than publication number.

Thank-you for this feedback. A separate column indicating trial number has been added to Table 1.

In primary outcome fatigue, 4 trials add to 722 (144, 146, 43, 47, 102, 96, 75, 69). Check reporting of 714. Also be consistent as to what term to use for those included. Use of different terms such subjects, patients and participants, makes it difficult to read.

The number of patients included in the fatigue trials is 714, and an error in Table 1 has been corrected to ensure consistency. The total number of included patients is 1170.

I can't find the output results for discussion on page 12, secondary outcomes and adverse events section, 1st paragraph. Similarly, can't find the results outputs for of RR on page 13? Also, it is not clear how one could generate the statement relating to current appendix 10. Include results outputs to confirm statement in the text.

As per reviewer feedback, forest plots for changes in hemoglobin and ferritin were added to the Supplementary Appendices (Appendix 9 and 10). To increase readability, Appendix references regarding subgroup analyses were moved.

Reviewer: 6
Reviewer Name: Khitam Muhsen (PhD)
Institution and Country: Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.
Please state any competing interests: None

Please leave your comments for the authors below
Review of manuscript Efficacy of iron therapy on fatigue and work capacity in non-anemic iron deficient adults: a systematic review of randomized controlled trials. Manuscript ID bmjopen-2017-019240

In this well-designed study, the authors addressed the effects of iron therapy on fatigue and work capacity in non-anemic iron deficient adults. The analysis was based on results from randomized controlled trials.

My comments refer to the methodological aspects of the study.

Study objective in the abstract and introduction: Please rephrase according to "PICO". Please add the comparator.

Thank-you for this comment. Our abstract had previously been formatted according to prior feedback from the BMJ Open Editorial Office. We have modified the abstract to include 'comparator' as a subtitle, to more closely reflect PICO terminology.

Abstract
Please add the statistical model used to combine results from different studies.

Thank-you. As per reviewer feedback, we have made the following modification to the abstract, which now reads: "Using a Mantel-Haenszel random-effects model.."

Data analysis
Primary outcomes and results
Most comparisons were made between the intervention control groups in continuous variables. Pooled MDs or SMDs were calculated using a random-effects model, which is suitable in this case.

In secondary outcomes such as adherence to therapy, pooled risk ratios were calculated using Mantel-Haenszel random-effects model, which is appropriate for this kind of analysis.
Page 8, lines 1-3 "Pooled risk ratios and 95% confidence intervals were "conducted" using Mantel-Haenszel random-effects model". Please change "conducted " to "calculated/obtained"…

Thank-you for this comment. This has been modified, and now reads: “Pooled risk ratios and 95% confidence intervals were calculated using Mantel-Haenszel random-effects model.”

It is recommended to assess publication bias using formal statistical test, such as Egger regression intercept.

Thank-you for this feedback. Given the limited number of included trials, statistical analysis of publication bias was not feasible. We analyzed the potential for publication bias using Funnel plot analysis (Appendix 5). (Ioannidis JP et al. CMAJ, 2007).

Results section.
Much of the important results were reported in appendices. It is highly recommended to restructure this section and move some important figures/tables to the results section, such as appendix 4.

Thank-you for this comment. We are happy to make any modifications the editor wishes with regards to the number of included figures. We were careful to include all outcomes of Appendix Figure 4 within the manuscript body, with appropriate references to the Appendix. Please let us know if Appendix Figure 4 is preferred in the manuscript, and we would be happy to make this modification.

Figure legends and titles need to be improved. Figures should stand alone.
For example, title of figure 2 can be changed to "Effect of iron supplementation compared to …. on difference in fatigue score between baseline and follow-up". Similarly, the title in appendix 4 should to be modified.
Please define abbreviations in figure legend.

Thank-you for this feedback. The title of Figure 2 has been modified to read: “The effect of iron supplementation on patient-reported fatigue, using validated fatigue scores.” Similarly, Appendix Figure 4 has been modified to read: “The effect of iron supplementation on measures of physical capacity.”

Table 2: Please add text to the cells (low risk/ unclear risk) in addition to colors. Some readers are color blind (for example 4-10% of men in the USA).

Thank-you for this comment. We have added “?” and “+” annotations (consistent with Cochrane annotation) to the unclear and low risk boxes resolve this issue.

VERSION 2 – REVIEW

REVIEWER	Bernard FAVRAT Department of Ambulatory Care and Community Medicine, University of Lausanne
REVIEW RETURNED	22-Dec-2017

GENERAL COMMENTS	very interesting and important paper

REVIEWER	Cesana Bruno Mario formerly University of Brescia, Italy
REVIEW RETURNED	22-Dec-2017

GENERAL COMMENTS	No further comments

REVIEWER	Khitam Muhsen (PhD) Tel Aviv University
REVIEW RETURNED	12-Jan-2018

GENERAL COMMENTS	The authors addressed the reviewers' comments. Please consider adding appendix Figure 4 in the manuscript and not as an appendix. If the Journal's policy does not allow, please move table 1 or 2 to the appendix.

VERSION 2 – AUTHOR RESPONSE

30-Jan-2018

Dear BMJ Editorial team,

Re: Manuscript ID bmjopen-2017-019240 entitled "Efficacy of iron therapy on fatigue and work capacity in non-anemic iron deficient adults: a systematic review of randomized controlled trials." Responses to reviewer comments are included below:

Thank-you for your interest in our manuscript. The reviewer's comments and suggestions to improve our manuscript have been acted upon and incorporated, without changes to the overall message. All comments have been addressed in full (below).

Editorial Requirements:
- Please revise the Strengths and Limitations section (after the abstract) to focus on the methodological strengths and limitations of your study rather than summarizing the results.

Thank-you for this feedback. We have revised our Strengths and Limitations section to focus on the methodological strengths and limitations of the study.

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Bernard FAVRAT
Institution and Country: Department of Ambulatory Care and Community Medicine, University of Lausanne
Please state any competing interests: My institution has received money from pharmaceuticals companies to perform research on iron

Please leave your comments for the authors below
very interesting and important paper

Thank-you for your feedback.

Reviewer: 3

Reviewer Name: Cesana Bruno Mario
Institution and Country: formerly University of Brescia, Italy
Please state any competing interests: No further comments/requests

Please leave your comments for the authors below
No further comments

Reviewer: 6
Reviewer Name: Khitam Muhsen (PhD)
Institution and Country: Tel Aviv University
Please state any competing interests: None

Please leave your comments for the authors below
The authors addressed the reviewers' comments.
Please consider adding appendix Figure 4 in the manuscript and not as an appendix. If the Journal's policy does not allow, please move table 1 or 2 to the appendix.

Thank-you for this comment. We have added appendix Figure 4 to the manuscript.