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Efficacy of iron supplementation on fatigue and physical capacity in non-anaemic iron-deficient adults: a systematic review of randomised controlled trials

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ABSTRACT

Objective Iron supplementation in iron-deficiency anaemia is standard practice, but the benefits of iron supplementation in iron-deficient non-anaemic (IDNA) individuals remains controversial. Our objective is to identify the effects of iron therapy on fatigue and physical capacity in IDNA adults.

Design Systematic review and meta-analysis of randomised controlled trials (RCTs).

Setting Primary care.

Participants Adults (≥18 years) who were iron deficient but non-anaemic.

Interventions Oral, intramuscular or intravenous iron supplementation; all therapy doses, frequencies and durations were included.

Comparators Placebo or active therapy.

Results We identified RCTs in Medline, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index of Nursing and Allied Health, SportDiscus and CAB Abstracts from inception to 31 October 2016. We searched the WHO's International Clinical Trials Registry Platform for relevant ongoing trials and performed forward searches of included trials and relevant reviews in Web of Science. We assessed internal validity of included trials using the Cochrane Risk of Bias tool and the external validity using the Grading of Recommendations Assessment, Development and Evaluation methodology. From 11 580 citations, we included 18 unique trials and 2 companion papers enrolling 1170 patients. Using a Mantel-Haenszel random-effects model, iron supplementation was associated with reduced self-reported fatigue (standardised mean difference (SMD) −0.38; 95% CI −0.52 to −0.23; I^2 0%; 4 trials; 714 participants) but was not associated with differences in objective measures of physical capacity, including maximal oxygen consumption (SMD 0.11; 95% CI −0.15 to 0.37; I^2 0%; 9 trials; 235 participants) and timed methods of exercise testing. Iron supplementation significantly increased serum haemoglobin concentration (MD 4.01 g/L; 95% CI 1.22 to 6.81; I^2 48%; 12 trials; 298 participants) and serum ferritin (MD 9.23 µmol/L; 95% CI 6.48 to 11.97; I^2 58%; 14 trials; 616 participants).

Conclusion In IDNA adults, iron supplementation is associated with reduced subjective measures of fatigue but not with objective improvements in physical capacity. 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 anaemia.

PROSPERO registration number CRD42014007085.

Strengths and limitations of this study

- ► We used a comprehensive search strategy, an a priori protocol and adhered to established methodological (eg, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, Grading of Recommendations Assessment, Development and Evaluation) guidelines.
- ► We identified an at-risk patient population, for whom iron deficiency is highly prevalent, but treatment is unknown.
- ► Our outcomes are clinically relevant and patient centred.
- ► Our search was limited to English studies.
- ► In an effort to quantify elemental iron administration, we did not include studies evaluating dietary iron fortification.

INTRODUCTION

Iron deficiency (ID) is estimated to affect two billion people and is the leading cause of anaemia worldwide.[1 2] Iron is necessary for cellular immune responses, oxidative metabolism within the mitochondria and production of haemoglobin and myoglobin. When iron losses exceed dietary iron absorption, iron stores become depleted resulting in impaired haemoglobin production and decreased red

blood cell haemoglobin content.[3] Reduction in haemoglobin concentration below a threshold (conventionally defined by the WHO as 120 g/L for women and 130 g/L for men) signifies anaemia.[4]

It is well established that anaemia results in decreased physical capacity and increased fatigue proportional to anaemia severity.[5–9] Unfortunately, patient-reported fatigue is common in community and primary care settings with a prevalence ranging from 7% to 45%.[10] It is estimated that the indirect annual economic consequence of chronic fatigue in the USA is 9.1 billion dollars.[11]

The clinical relevance of iron deficiency in the absence of anaemia is poorly understood but may impact well-being, perceptions of fatigue or contribute to decrements in physical performance through impairment in biochemical processes including tissue and mitochondrial oxidative capacity.[8] While iron replacement can normalise haemoglobin concentration, restore work capacity and improve fatigue in iron-deficiency anaemia, it is unclear if supplementation affects fatigue and physical capacity in iron-deficient but non-anaemic (IDNA) individuals. In the absence of compelling efficacy data on well-being or muscle function, the use of iron supplements is common in the general population and are routinely recommended to high performance athletes to enhance performance.

Given the global prevalence of iron deficiency and impact of fatigue, the purpose of this systematic review is to identify, critically appraise and meta-analyse data from prospective randomised trials evaluating iron therapy in adults with IDNA.

METHODS

Using an a priori published protocol (CRD42014007085; available at https://www.crd.york.ac.uk/PROSPERO/),[12] we conducted a systematic review using methodological approaches outlined in the *Cochrane Handbook for Systematic Reviewers* and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis criteria.[12–14] A panel of experts from multiple fields (eg, internal medicine, haematology, kinesiology, gastroenterology, research methodology) formulated the research question, reviewed search strategies and methods and provided input throughout the review process.

Populations, interventions, comparators, outcome measures, setting and study designs

Our research question was 'In iron-depleted but non-anaemic adults, does iron supplementation improve fatigue and physical capacity?' We included randomised controlled trials (RCTs) of adults (≥18 years) who were iron deficient but non-anaemic (see online supplementary appendix 1). Interventions included oral, intramuscular or intravenous iron supplementation; all therapy doses, frequencies and durations were included. We included trials that evaluated outcomes at least 28 days from the initiation of iron therapy. Comparators included placebo or active therapy. Our exclusion criteria are presented in online supplementary appendix 2.

Our primary outcome measures were self-reported fatigue and objective measures of physical capacity. Secondary outcomes included the incidence of anaemia, change in haemoglobin concentration and serum ferritin and the incidence of adverse outcomes including iron toxicity, constipation, diarrhoea, gastrointestinal intolerance and nausea.

Search strategy for identification of studies

We searched Medline, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index of Nursing and Allied Health, SportDiscus and CAB Abstracts from inception to 31 October 2016 to identify relevant citations of published trials, using individualised systematic search strategies for each database. The Medline strategy is presented in online supplementary appendix 3. We searched the WHO's International Clinical Trials Registry Platform, clinicaltrials.gov and relevant conference proceedings to identify planned, ongoing or recently completed but unpublished trials. We performed forward searches of included trials and relevant reviews in Web of Science to identify additional citations and contacted study authors to request pertinent unpublished data or provide clarifications on study methods or results. Reference lists of narrative and systematic reviews and of the included trials were searched for additional citations. We performed reference management in EndNote V.X7 (Thomson Reuters).

Study selection, data extraction and quality assessment

We screened citations, selected studies and extracted data from included trials using standardised and piloted screening and data extraction forms. Citation screening, study selection and data extraction were performed in duplicate. The following data were extracted from each trial: author identification, publication year, publication language, trial location, source of trial funding, participant characteristics (age, sex, weight), intervention/comparator (drug used, dose (elemental iron), route of administration, duration), as well as results for the primary and secondary outcomes. We assessed the internal validity of included trials using the Cochrane Collaboration Risk of Bias tool.[13] Discrepancies between the two reviewers were resolved by consensus or by a third reviewer (RZ), as required. Data extraction and descriptive statistics were performed using Microsoft Excel 2016 V.15.

Data analysis

Data analysis was performed using Review Manager (RevMan V.5.3.5, The Nordic Cochrane Centre, The Cochrane Collaboration). Study level comparisons of dichotomous data were presented as risk ratios (RR) with 95% CI. Pooled continuous data were expressed as the mean difference (MD) or standardised mean difference (SMD). Change scores or post-treatment means were extracted to inform summary estimates for continuous

data. Pooled RRs and 95% CIs were calculated using Mantel-Haenszel random-effects model. Pooled MDs or SMDs were calculated using a random-effects model. 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. In studies evaluating exercise capacity, weight-based maximal oxygen consumption (VO_2 max) values were used preferentially if both absolute and weight-based VO_2 max results were provided. Statistical heterogeneity was quantified using the I^2 statistic.[15] For the primary outcomes of fatigue and work capacity, we evaluated potential publication bias using funnel plot analysis.[16] All tests of statistical inference reflect a two-sided alpha of 0.05.

Subgroup analyses

We performed subgroup analyses for fatigue and exercise capacity outcomes according to biological sex, athletic status (athlete or non-athlete), method of iron administration, duration of therapy, duration of study follow-up and risk of bias.

Grading the evidence

We graded the strength of evidence for our primary outcomes using the Grading of Recommendations Assessment, Development and Evaluation methodology. This approach classifies the strength of evidence as 'high', 'moderate', 'low' or 'very low.'

RESULTS

Trial characteristics and study populations

Of the 11 580 citations identified, we included 18 unique trials and 2 companion papers,[17 18] enrolling 1170 subjects (figure 1; table 1). Trials were published between 1989 and 2015, and all trials were published in peer-reviewed journals. Eight trials[19–26] were from North America, seven trials[27–33] were from Europe, two trials[18 34] were from Australia and one trial[35] was from Asia.

Exclusively healthy women (aged 17 to 55 years old) with varying levels of fitness (sedentary to well trained) were enrolled in all but three studies.[22 27 29] The WHO cut-off for anaemia (haemoglobin concentration ≥130 g/L (males) and ≥120 g/L (females)) was used by nine studies,[19 22–25 30–32 35] whereas seven studies used lower values ranging from ≥110 to <120 g/L,[20 21 27 28 33 34 36] and baseline haemoglobin concentration was not provided in two trial reports.[26 29]

All trials were placebo controlled. In 13 of 18 trials (72%), we considered the blinding of participants and personnel to be adequate. Likewise, 10 trials (55%) adequately incorporated blinded outcome assessment. One trial[29] was considered to have a low risk of bias (table 2). The remainder of the trials were considered unclear risk of bias due to unclear processes of randomisation (12 trials[19–27 30 33 34]) or allocation concealment (13 trials[19–27 30 31 34 35]).

Interventions

Iron interventions consisted of iron supplementation administered orally, intramuscularly or intravenously. Of the trials evaluating oral supplements, all but one[29] used ferrous sulfate (13 trials,[19–26 30 32 33 35 36] 713 participants). Intravenous iron was administered in three trials[27 28 31] (395 participants), and intramuscular iron in one trial[34] (16 participants). In trials using oral iron,[19–26 29 30 32 33 35 36] the mean daily elemental iron dose was 86.9 mg (±49.1 mg; range: 16–200 mg). In trials reporting intravenous iron,[27 28 31] the mean daily elemental iron dose was 566 mg (±330 mg; range 200–1000 mg) and mean total elemental iron dose 767 mg (±206 mg; range 500–1000 mg). Among all studies, the mean duration of iron therapy was 46 days (±30 days; range 1–112 days), and mean duration of follow-up was 57 days (±24 days; range 28–112 days).

Primary outcomes

Fatigue

Four trials[28 31–33] enrolling 714 participants were eligible for meta-analysis. Iron supplementation was associated with a reduction in subjective measures of fatigue when assessed by either the Piper Fatigue Scale,[28] the Current and Past Psychological State scale,[32] visual analogue scale[33] or Brief Fatigue Inventory questionnaire (BFI)[31] (SMD −0.38; 95% CI −0.52 to −0.23; I^2 0%) (figure 2). In one trial using the BFI score, fatigue was not significantly different between groups after 12 weeks, although it was improved in the subgroup of participants with the lowest iron stores (ferritin ≤15 ng/mL or transferrin saturation ≤20%).[31] Evaluation of publication bias was not possible due to the low number of included trials. Given that the majority of trials were of unclear risk of bias, we graded the overall strength of evidence as moderate.

Physical capacity

Physical capacity was reported in 10 trials[19 20 22–27 30 34] (291 participants); all but one[20] of the trials employed at least one of three common aerobic tests of physical capacity: time trial,[22 25] time to exhaustion[23 26 27 34] or VO_2 max[19 22–27 30 34] performance from a graded exercise test. In two trials (79 participants) that used 15 km time trials,[22 25] iron supplementation was not associated with improved exercise capacity (SMD −0.09; 95% CI −0.53 to 0.35; I^2 0%) (figure 3A). In four trials[23 26 27 34] (69 participants) that used time-to-exhaustion tests, iron supplementation did not significantly improve physical capacity (SMD 0.25; 95% CI −0.22 to 0.73; I^2 0%) (figure 3B). Nine trials[19 22–27 30 34] (235 participants) reported VO_2 max as a surrogate measure of physical capacity. Iron supplementation did not increase VO_2 max (SMD 0.11; 95% CI −0.15 to 0.37; I^2 0%) (figure 3C). We found no evidence of funnel plot asymmetry to suggest publication bias for this outcome (see online supplementary appendix 4). The overall strength of the evidence for time trial, time

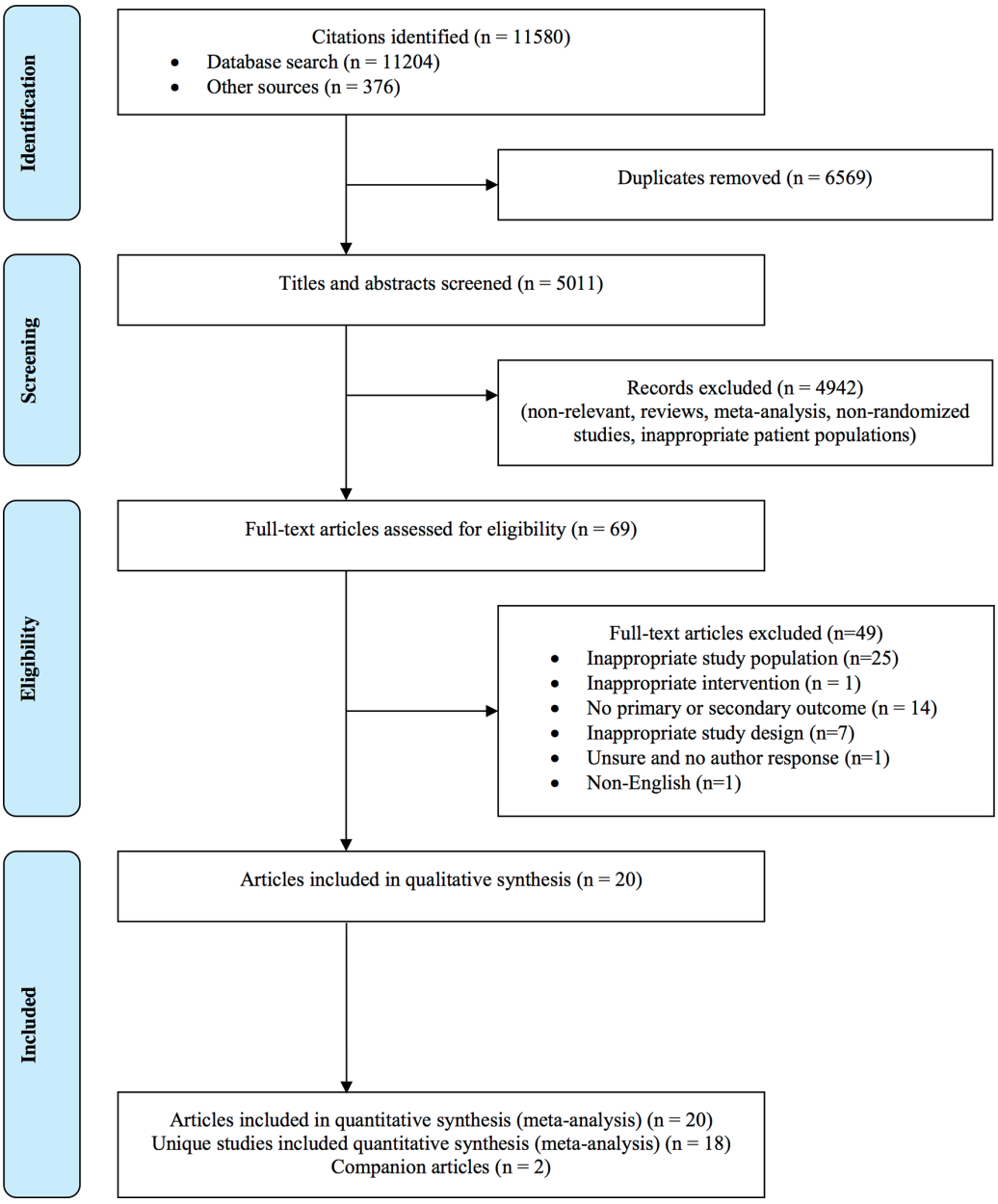


Figure 1 Study flow diagram following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[14] with modifications. Of the 11 580 citations identified, we included 18 unique trials and 2 companion papers.

to exhaustion and VO_2 max outcomes were low, given the imprecision of effect estimates and that the majority of trials were of unclear risk of bias.

One trial[20] (20 participants) used dynamic knee extension exercise to evaluate changes in physical capacity. In this trial, the decline in maximum voluntary contraction after 6 min of exercise was significantly less in participants randomised to receive iron. Among 16 other unique measures of physical capacity, 19% (3 of 16) found statistically significant increases in measures of physical capacity with iron supplementation (see online supplementary appendix 5).

Subgroup analysis

Subgroup analyses based on method of iron administration and duration of follow-up demonstrated no statistically significant differences in subjective fatigue (see online supplementary appendix 6). Biological sex, athletic status (athlete vs non-athlete) and risk of bias could not be evaluated as all trials contributing data to the meta-analyses enrolled women of uncharacterised athletic status and were of unclear risk of bias.[28 31–33] Subgroup analyses evaluating athletic status and method of iron administration demonstrated no statistically significant differences in objective physical capacity (see online supplementary appendix 7). Biological sex, duration of follow-up and risk of bias were unevaluable as all trials enrolled women with follow-up of less than 2 months and all were of unclear risk of bias.[19 22–27 30 34]

Secondary outcomes and adverse events

Despite the absence of baseline anaemia, iron supplementation significantly increased serum haemoglobin

Table 1 Characteristics of individual trials, patient populations and interventions

Trial #	Source	Population	No. of patients (iron)	No. of patients (control)	Control	Age (range)	Minimum Hb (g/L)	Maximum ferritin (ug/L)	Iron type	Daily iron dose (mg)	Iron route	Iron duration (days)	Follow-up (days)
1	Brownlie *et al*[17 19]	Physically active untrained women	22	19	Placebo	18–33	120	16	Ferrous sulfate	16	PO	42	42
2	Brutsaert *et al*[20]	Untrained women	10	10	Placebo	18–45	110	20	Ferrous sulfate	18.1	PO	42	42
3	Burden *et al*[27]	University endurance runners	7	8	Saline		120	30 (F); 40 (M)	Ferric carboxymaltose	500	Intravenous	1	28
4	Donangelo *et al*[21]	Young women	12	11	Zinc gluconate	20–28	110	20	Ferrous sulfate	100	PO	56	70
5	Favrat *et al*[28]	Premenopausal women with fatigue	144	146	Saline		115	15	Ferric carboxymaltose	1000	Intravenous	1	56
6	Flink *et al*[29]	Individuals with low unstimulated salivary flow	25	21	Placebo	15–46		30 (F); 50 (M)	Ferrous fumarate	120	PO	90	90
7	Fogelholm *et al*[30]	Female athletes	17	14	Placebo	17–31	120	25	Ferrous sulfate	100	PO	56	56
8	Hinton and Sinclair[22]	Recreationally trained individuals	9	8	Placebo	18–41	120 (F); 130 (M)	16	Ferrous sulfate	30	PO	42	42
9	Klingshirn *et al*[23]	Female endurance runners	9	9	Placebo	22–39	120	20	Ferrous sulfate	100	PO	56	56
10	Krayenbuehl *et al*[31]	Premenopausal women with fatigue	43	47	Saline		120	50	Venofer	200	Intravenous	4	84
11	LaManca and Haymes[26]	Healthy females	28	28	Placebo			20	Ferrous sulfate	100	PO	56	56
12	Leonard *et al*[18 36]*	Young women	16*	8	Placebo	18–35	115	20	Ferrous sulfate	60/80	PO	112	112
13	Moafi *et al*[35]	Female students	36	36	Placebo	18–35	120	20	Ferrous sulfate	50	PO	42	42
14	Newhouse *et al*[24]	Young women	19	21	Placebo	18–40	120	20	Ferrous sulfate	200	PO	56	56
15	Peeling *et al*[34]	Well-trained female athletes	8	8	Saline		115	35	Ferrum H	100	Intramuscular	5	28
16	Vaucher *et al*[32]	Women with fatigue from clinic	102	96	Placebo	18–50	120	50	Ferrous sulfate	80	PO	84	84
17	Verdon *et al*[33]	Women with fatigue from clinic	71	65	Placebo	18–55	117		Ferrous sulfate	80	PO	28	28
18	Zhu and Haas[25]	Physically active women	20	17	Placebo	19–36	120	16	Ferrous sulfate	135.3	PO	56	56
Total			598	572									

*Trial included two intervention arms, with eight patients enrolled in each arm; represents weighted averages between two iron treatment groups.
F, female; Hb, haemoglobin; M, male; PO, oral (per os).

Table 2 Cochrane risk of bias summary

	Overall	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other
Brownlie *et al*[17 19]	?	?	?	+	?	?	+	+
Brutsaert *et al*[20]	?	?	?	+	?	?	+	+
Burden *et al*[27]	?	?	?	+	+	+	+	+
Donangelo *et al*[21]	?	?	?	?	?	+	+	+
Favrat *et al*[28]	?	+	+	?	?	?	+	+
Flink *et al*[29]	+	+	+	+	+	+	+	+
Fogelholm *et al*[30]	?	?	?	+	+	+	+	+
Hinton and Sinclair[22]	?	?	?	?	?	+	+	+
Klingshirn *et al*[23]	?	?	?	+	?	+	+	+
Krayenbuehl *et al*[31]	?	+	?	+	+	+	?	+
LaManca and Haymes[26]	?	?	?	?	?	+	+	+
Leonard *et al*[18 36]	?	+	+	+	+	?	+	+
Moafi *et al*[35]	?	+	?	+	+	+	+	+
Newhouse *et al*[24]	?	?	?	+	+	?	+	+
Peeling *et al*[34]	?	?	?	?	?	+	+	+
Vaucher *et al*[32]	?	+	+	+	+	?	+	+
Verdon *et al*[33]	?	?	+	+	+	+	+	+
Zhu and Haas[25]	?	?	?	+	+	+	+	+

Green (+)=low risk of bias; Yellow (?)=unclear risk of bias.

concentration (MD 4.01 g/L; 95% CI 1.22 to 6.81; I^2 48%; 12 trials; 298 participants)[18–27 30 34] (see online supplementary appendix 8). In two trials,[25 28] reporting incident anaemia, a new diagnosis of anaemia at trial completion was less common in patients randomised to receive iron supplementation. Iron supplementation also significantly increased serum ferritin (MD 9.23 µmol/L; 95% CI 6.48 to 11.97; I^2 58%; 14 trials; 616 participants) (see online supplementary appendix 9).

Adverse events were sparsely reported. Gastrointestinal intolerance was reported in three trials[23 29 32] and was significantly increased in one trial[29] using intramuscular iron administration but not in the two trials[23 32] that used oral administration. Nausea was reported in four trials[18 28 31 33]; two trials[28 31] using intravenous administration of iron reported significantly increased nausea, whereas nausea was not increased in patients who received iron by oral administration.[18 33] Constipation was reported in one trial[18] and diarrhoea in two trials[18 31] (see online supplementary appendix 10). Adherence with the study intervention was reported in 13 trials.[18 19 22–29 32 33 35] Iron supplementation was not associated with differential rates of medication adherence (RR 1.0; CI 95% 0.99 to 1.01; I^2 0%; 12 trials; 958 participants). The route of administration of the study intervention was also not associated with differences in adherence (see online supplementary appendix 11).

DISCUSSION

In iron-deficient but non-anaemic adults, we found iron supplementation was associated with reduced subjective measures of fatigue but had no significant impact on objective physical capacity. Given iron deficiency is the most prevalent micronutrient deficiency worldwide,[2] there is a discrepant lack of robust evidence evaluating iron supplementation in the absence of anaemia across important patient populations. Despite rigorous and systematic methodology, we were only able to identify 18

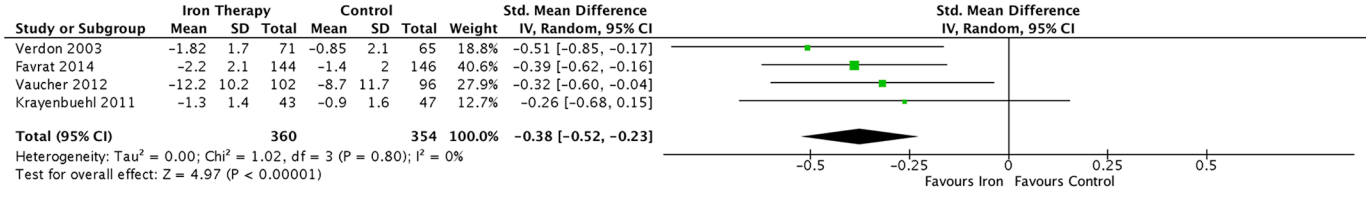
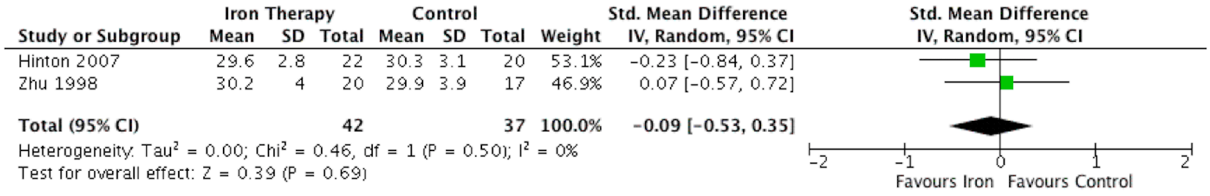
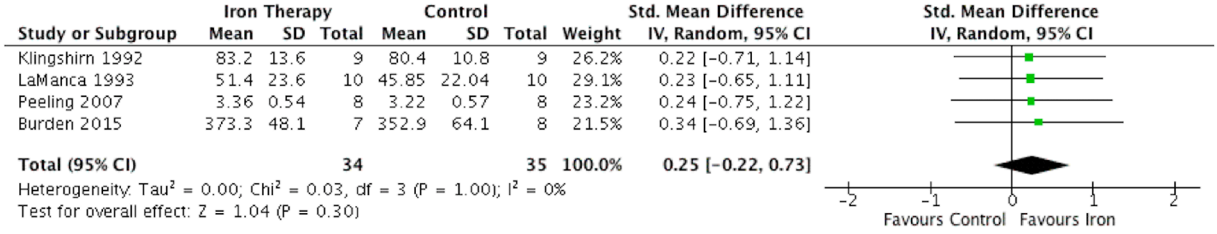


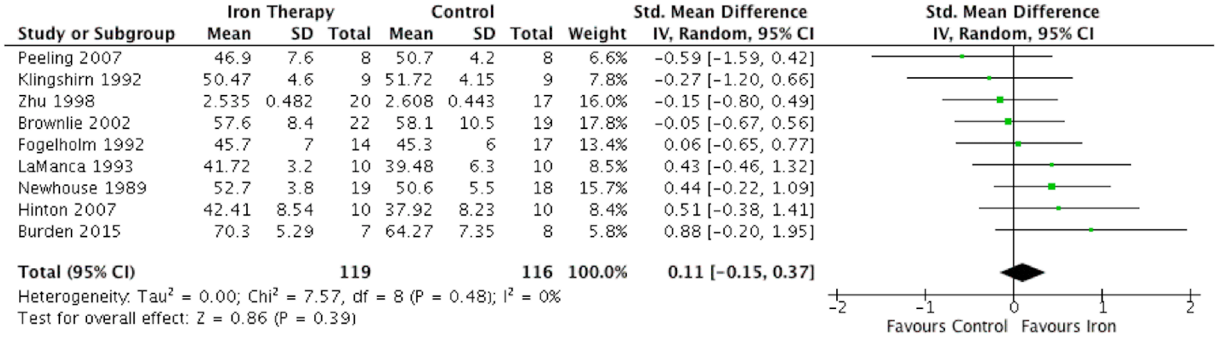
Figure 2 The effect of iron supplementation on patient-reported fatigue using validated fatigue scores. Iron supplementation was associated with a reduction in subjective measures of fatigue when assessed by either the Piper Fatigue Scale, the Current and Past Psychological State Scale, visual analogue scale or Brief Fatigue Inventory questionnaire.



3A. 15 km time trial



3B. Time to exhaustion



3C. Oxygen consumption (VO_2 max)

Figure 3 The effect of iron supplementation on measures of physical capacity. Iron supplementation was not associated with a reduction in objective measures of physical capacity when assessed by either maximal oxygen consumption and timed methods of exercise testing.

trials enrolling 1170 adults, representing a minute fraction of affected individuals.

While treatment of iron deficiency in the absence of anaemia is associated with reduced subjective fatigue, whether this translates to clinically meaningful outcomes, including quality of life, work absenteeism, job or athletic performance is uncertain. Contrary to iron deficiency with established anaemia, lack of robust data in iron-deficient but non-anaemic individuals is reflected in the under-representation of guideline recommendations pertaining to this larger population. The proportion of iron-deficient, non-anaemic individuals who receive supplementation is further unknown.

Our systemic review builds on the results of three published evidence syntheses evaluating iron supplementation.[37–39] In a systematic review of healthy menstruating women, iron supplementation, irrespective of iron status or anaemia, improved haemoglobin and measures of iron stores.[37] Two systematic reviews included studies of pregnant women, blood donors and children and included data from both randomised and non-randomised trials.[38 39] These studies concluded benefit of iron supplementation, although in the review by Yokoi and Konomi[39], the benefit was limited to randomised controlled trials. Despite the high prevalence of iron deficiency, significant heterogeneity in patient populations and study designs and absence of data pertaining to objective muscle performance limits the generalisability of these findings.

In trials where a proportion of participants were anaemic at enrolment and with the knowledge that anaemia results in decreased physical capacity, iron supplementation has previously been associated with improved maximal and submaximal exercise performance.[5–8] We found insufficient evidence to suggest that iron supplementation improves exercise capacity in iron-depleted non-anaemic adults, differing from the results of physiological experiments that describe VO_2 max improvements with iron

supplementation, independent of haemoglobin.[40] These findings were postulated to be secondary to iron-mediated improvements in muscle oxidative capacity and improved mitochondrial function, the validity of which is unclear.[40]

A potential weakness our systematic review is the difficulty masking oral iron due to predictable gastrointestinal side effects and changes in stool colour and the impact of imperfect blinding on subjective measures of fatigue. However, despite this, fatigue was consistently reduced in trials evaluating both oral (n=2) and intravenous (n=2) iron preparations. Healthy women comprised the study population in 15 of 18 included trials; subjective measures of fatigue may not consistently apply to other at-risk populations. The duration of follow-up was relatively short (57 days; range 28–112 days) and perhaps too brief to expect significant changes in muscle metabolism or function. Finally, the lack of systematic reporting of adverse events impairs our ability to draw conclusions regarding the incidence of these events and tolerability of iron therapy.

The strengths of this review include the comprehensiveness of the search strategy, which included electronic databases, trial registries and forward searches. We used an a priori published protocol and followed established methodological guidelines concerning the conduct and reporting of this review. We synthesised patient-centred outcomes and evaluated efficacy in the context of relevant safety outcomes and adverse events. In contrast to the systematic review of Low *et al*,[37] we excluded studies that enrolled patients with anaemia at baseline.[37] While cut-offs for anaemia varied slightly among included trials, this important inclusion criteria reduces (but may not eliminate) the probability that changes in fatigue or muscle function are due to correction of anaemia. While the duration of follow-up in most studies was modest, the mean daily elemental iron dose (86.9±49.1 mg) reflects a recommended 'treatment' for patients with iron-deficiency anaemia.[41]

In IDNA adults, iron supplementation is associated with reduced subjective measures of fatigue but not with objective improvements in physical capacity. 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 anaemia.

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Contributors All authors meet ICMJE criteria for authorship. Two researchers (BH and DH) lead and coordinated all aspects of the review, including but not limited to preparation of the literature search, screening relevant material, data analysis and extraction, interpretation of the results of the meta-analytic procedures, bias investigation and preparation of the final report; three second reviewers (JG, ER, BP) conducted independent screening of relevant material, extracted and analysed data and aided in report preparation; one haematologist/ intensivist (RZ), methodologist (DAF) and anaesthetist/intensivist (AFT) with expertise in systematic reviews provided content expertise and methodological input and resolved disagreement among reviewers; one systematic review expert (AMAS) provided methodological input; two haematologists (DSH and ER), one gastroenterologist (CNB) and one statistician (RR) provided content expertise. All authors were involved in the process of study design and manuscript review.

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