Iron Supplementation Benefits Physical Performance in Women of Reproductive Age: A Systematic Review and Meta-Analysis¹⁻³

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Abstract

Animal and human observational studies suggest that iron deficiency impairs physical exercise performance, but findings from randomized trials on the effects of iron are equivocal. Iron deficiency and anemia are especially common in women of reproductive age (WRA). Clear evidence of benefit from iron supplementation would inform clinical and public health guidelines. Therefore, we performed a systematic review and meta-analysis to determine the effect of iron supplementation compared with control on exercise performance in WRA. We searched the Cochrane Central Register of Clinical Trials, MEDLINE, Scopus (comprising Embase and MEDLINE), WHO regional databases, and other sources in July 2013. Randomized controlled trials that measured exercise outcomes in WRA randomized to daily oral iron supplementation vs. control were eligible. Random-effects meta-analysis was used to calculate mean differences (MDs) and standardized MDs (SMDs). Risk of bias was assessed using the Cochrane risk-of-bias tool. Of 6757 titles screened, 24 eligible studies were identified, 22 of which contained extractable data. Only 3 studies were at overall low risk of bias. Iron supplementation improved both maximal and submaximal exercise performance, demonstrated by an increase in maximal oxygen consumption (VO₂ max) [for relative VO₂ max, MD: 2.35 mL/(kg · min); 95% CI: 0.82, 3.88; P = 0.003, 18 studies; for absolute VO₂ max, MD: 0.11 L/min; 95% CI: 0.03, 0.20; P = 0.01, 9 studies; for overall VO₂ max, SMD: 0.37; 95% CI: 0.11, 0.62; P = 0.005, 20 studies], and submaximal exercise performance, demonstrated by a lower heart rate (MD: −4.05 beats per minute; 95% CI: −7.25, −0.85; P = 0.01, 6 studies) and proportion of VO₂ max (MD: −2.68%; 95% CI: −4.94, −0.41; P = 0.02, 6 studies) required to achieve defined workloads. Daily iron supplementation significantly improves maximal and submaximal exercise performance in WRA, providing a rationale to prevent and treat iron deficiency in this group. This trial was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/prospero.asp) as CRD42013005166. J. Nutr. 144: 906-914, 2014.

Introduction

Women of reproductive age (WRA)¹⁰ are at high risk of iron deficiency and iron deficiency anemia due to menstrual blood losses. Iron deficiency occurs when iron losses or requirements exceed iron intake, resulting in deficient tissue iron and iron stores, and may eventually produce iron deficiency anemia, in which hemoglobin concentrations are reduced. Female athletes are at particular risk because of diets deficient in iron, increased losses due to gastrointestinal bleeding, and reduced iron absorption due to subclinical inflammation (1). Iron deficiency and anemia are also highly prevalent among WRA in low- and middle-income settings, in which inadequate dietary iron content, consumption of poorly bioavailable iron, and parasitic infection with chronic blood loss contribute to the problem (2). Approximately 496 million nonpregnant women are anemic worldwide, with the prevalence approaching 50% in Africa and South Asia. Approximately 50% of anemia in nonpregnant women is thought to be amenable to iron (3).

Iron is essential for a range of functions relating to physical activity and exercise (4). Iron deficiency has been considered to impair physical exercise performance (5) and, consequently,
economic productivity, particularly in manual workers (6,7), especially female manual workers. These detrimental effects are considered important justifications to prevent or treat iron deficiency in women. The WHO recommends distribution of iron supplements to all women in populations in which the prevalence of anemia (in women) exceeds 20% (8). Likewise, the International Olympic Committee recommends screening female athletes for iron deficiency to target iron supplementation, with a view to improving performance (9).

However, randomized controlled trials (RCTs) investigating effects of iron supplementation on exercise performance have been small generally with equivocal results (10). This limits the capacity of primary and specialist clinicians and policymakers to anticipate potential benefits when considering strategies to prevent and treat iron deficiency. Therefore, we performed a systematic review and meta-analysis of RCTs to evaluate the effects of daily iron supplementation on physical performance in WRA.

Materials and Methods

Protocol. The protocol of this review was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/prospero.asp) as CRD42013005166 (11).

Information sources. We searched the following electronic databases: 1) MEDLINE; 2) Scopus; 3) Cochrane Central Register of Clinical Trials (CENTRAL); 4) WHO regional databases (AIM, AFROMED, LILACS, IMEVAR, WPIM, and IMEMR); 5) the Proquest Digital Thesis database; and 6) OpenSIGLE (for gray literature). Electronic searches were undertaken on 28 July 2013. We also reviewed reference lists of identified articles and other systematic reviews. No language or date restrictions were applied. We searched the WHO International Clinical Trials Registry Platform for potentially eligible unpublished or ongoing trials. MEDLINE and Scopus search strategies are presented in the online material (Supplemental Fig. 1).

Study eligibility criteria. RCTs with randomization at any level were eligible if they administered oral iron supplementation daily (at least 5 d/wk) vs. control. Trials giving iron in combination with multiple micronutrients (excluding folate or vitamin C), parental iron, or iron by central or point-of-use fortification were excluded. Studies that included a cotreatment were included only if the cotreatment was applied identically in both study arms. Trials were eligible if they were performed in WRA (women beyond menarche and before menopause who are not pregnant or lactating). If this criterion was not explicitly stated, we included studies if results for females aged 12–50 y could be extracted separately or if >50% of participants fulfilled this criterion. Sensitivity analyses were performed if marginal decisions were made. Studies meeting these criteria were eligible regardless of participants and personnel, incomplete outcome data, selective outcome reporting, and other possible sources (14). Studies were considered at high overall risk of bias if randomization or allocation concealment was judged as being at high (or unclear) risk of bias or were either not blinded or had high or imbalanced attrition rates; otherwise, they were considered at low overall risk of bias. For outcomes containing >10 trials, funnel plots were examined for asymmetry to identify publication bias.

Synthesis of results. Meta-analysis was undertaken for outcomes reported by at least 2 studies. Mean difference (MD) and standardized mean difference (SMD; in which effect size is normalized to the standard deviation of the measurement scale) were determined for continuous data measured on the same scale and different scales, respectively. Statistically significant differences were defined when the 95% CI for the effect size did not cross 0 with $P < 0.05$.

Heterogeneity was quantified with the $I^2$ test. Significant heterogeneity was considered to exist when $I^2$ exceeded 50% and was explored by predefined subgroup analysis for outcomes containing ≥5 studies. Subgroups included the following: 1) age (adolescence, adulthood); 2) baseline anemia status (anemic, non-anemic, mixed/unspecified, as defined by trial authors); 3) baseline iron status (iron deficient, non-iron deficient, mixed/unspecified, as defined by trial authors); 4) dose of elemental iron per day (<30, 30–60, 61–100, >100 mg); 5) duration of supplementation (<1, 1–3, >3 mo); and 6) training status of women (trained: participants recruited because of a high level of physical fitness due to either membership of a defined sporting team or achievement of a defined high standard of physical performance, and both competitive and recreational athletes were included; women were also included in this group if they underwent a defined physical training program as part of the study). Differences between subgroup strata were formally investigated using the $\chi^2$ and $I^2$ methods of Borenstein et al. (15) in subgroups in which ≥2 strata contained ≥3 trials each. We anticipated clinical, methodologic, and thus statistical heterogeneity between studies, so all data were combined using random-effects meta-analysis with calculation of $\tau^2$.

Results

Study flow is presented in Figure 1. A total of 6757 titles were screened for eligibility. The WHO International Clinical Trials Registry Platform identified no unpublished or ongoing potentially eligible studies. After screening, 36 references were identified for full-text review. Five were excluded because they were not RCTs (16–20) [including 1 that was a quasi-RCT (19)], and 1 was excluded because the intervention was not an eligible iron supplement (21). One full-text paper could not be sourced (22). Twenty-nine references comprising 24 studies were considered eligible for inclusion. The full eligibility screen is presented in Supplemental Table 1. Two ostensibly eligible
studies were crossover trials that did not report on outcomes at the end of the first parallel time course, so data could be not extracted (23,24). Data were thus extracted from 22 studies (Table 1) recruiting 911 participants, of whom 464 were randomly assigned to take daily iron supplementation and 447 to the control group.

Characteristics of included studies are summarized in Table 1. Authors provided additional information for 2 trials (7,10). Risk of bias of included studies is summarized in Supplemental Figure 2. Only 3 studies were considered to be at overall low risk of bias (10,25,26). Findings from meta-analysis are summarized in Table 2. A comprehensive summary of results for all outcomes including subgroup analysis when appropriate is presented in Supplemental Table 2. Four trials were funded or supported by pharmaceutical companies (26–29), but only Jensen et al. (27) identified benefit from iron on exercise outcomes. Funding sources are presented in Supplemental Table 3.

Maximal exercise performance

Maximal aerobic capacity was measured in different studies using VO2 max or VO2 peak, which we combined by meta-analysis (termed hereafter as VO2 max). Both absolute and relative VO2 max were reported in eligible studies.

Relative VO2 max was reported in 18 studies recruiting 620 participants. Meta-analysis revealed a beneficial effect from iron [MD: 2.18 (95% CI: 1.35, 3.21), P < 0.00001, I2 = 10%] but not in nontrained [MD: 2.32 (3.38, 8.02), P = 0.43, I2 = 93%] women. When only the 3 studies at low risk of bias were included, no benefit from iron on VO2 max was seen [MD: 0.94 (95% CI: −2.06, 3.93), P = 0.54, I2 = 0%, 207 participants]. Analysis by age, dose, and type of iron compound could not be performed because of insufficient data in the subgroups.

Absolute VO2 max was reported by 9 studies recruiting 316 women, all of whom were iron deficient. Meta-analysis identified a benefit from iron among women randomly assigned to receive iron [MD: 0.11 L/min (95% CI: 0.03, 0.20), P = 0.01, I2 = 0%] (Fig. 2b). This effect was seen in anemic but not non-anemic women. The benefit from iron was seen only in trained women. No studies at overall low risk of bias reported this outcome.

When all studies reporting VO2 max were combined (20 studies, 737 participants, inclusion of relative VO2 max data if both absolute and relative data were reported), the SMD between iron and control was 0.35 (95% CI: 0.12, 0.58) (P = 0.004, I2 = 52%). When the 64 anemic women were removed from the analysis, a beneficial effect from iron remained [SMD: 0.26 (95% CI: 0.05, 0.47), P = 0.01, I2 = 38%]. Subgroup analysis showed that iron supplementation clearly benefited VO2 max in anemic women and in both iron-deficient women and women in whom baseline iron status was not established. Nonsignificant evidence of benefit was seen in participants who were non-anemic or in whom baseline anemia status was not established.

Iron improved VO2 max in trained but not nontrained women. For each of these subgroups, there was no evidence of a significant difference in effect between subgroup strata (Supplemental Table 2).

Other maximal exercise variables. There were no differences evident between women randomly assigned to take iron and control in other peak exercise variables, including respiratory exchange ratio or time (duration of maximal exercise) to exhaustion (Table 2).

One study reported effects of iron supplementation on muscle fatigability in non-anemic iron-depleted women: women randomly assigned to take iron experienced reduced attenuation of maximal voluntary contractions compared with women randomly assigned to the control group (P < 0.01) (32). One study reported the effects of iron on VT in peak exercise: women randomly assigned to take iron had significantly higher VT [31.54 vs. 24.27 mL/(kg·min) and 74.13% vs. 63.04% of VO2 max, both P < 0.05] (33).

Submaximal exercise

No studies reporting submaximal exercise outcomes were considered at low overall risk of bias.

Efficiency: HR. Six studies recruiting 172 participants reported HR during submaximal exercise (28,33–36). Women administered iron had a significantly lower HR during submaximal exercise compared with women randomly assigned to the control group [MD: −4.05 beats per minute (95% CI: −7.25, −0.85), P = 0.01, F = 0%] (Fig. 3a). The reduction was seen only in trained women. All studies reporting this outcome were performed in iron-deficient women.

Efficiency: percentage of VO2 max. Six studies comprising 167 participants reported on percentage of VO2 max required by participants as they undertook a defined submaximal exercise
<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Country</th>
<th>Participant age</th>
<th>Baseline anemia, iron deficiency status</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brutsaert et al. (32)</td>
<td>Mexico</td>
<td>18–45 y</td>
<td>Non-anemic (Hb &gt; 120 g/L); iron deficient (ferritin &lt; 20 μg/L)</td>
<td>10 mg/d elemental iron as FeSO₄ (n = 10)</td>
<td>Placebo (n = 10)</td>
<td>6 wk</td>
<td>U, U, L, U, L</td>
</tr>
<tr>
<td>Dieu et al. (62)</td>
<td>United States</td>
<td>&gt;18 y</td>
<td>Non-anemic (Hb &gt; 120 g/L); mixed iron status: 58% iron depleted (ferritin &lt; 20 μg/L)</td>
<td>30 mg/d elemental iron as FeSO₄ (n = 21)</td>
<td>Placebo (n = 19)</td>
<td>6 wk</td>
<td>L, L, L, L, L</td>
</tr>
<tr>
<td>Fogelholm et al. (25)</td>
<td>Finland</td>
<td>17–31 y</td>
<td>Non-anemic (Hb &gt; 120 g/L); iron depleted (ferritin &lt; 25 μg/L)</td>
<td>100 mg/d elemental iron as FeSO₄, with vitamin C supplement (n = 14)</td>
<td>Placebo + vitamin C supplement (n = 17)</td>
<td>8 wk</td>
<td>L, L, U, L, L</td>
</tr>
<tr>
<td>Friedmann et al. (31)</td>
<td>Germany</td>
<td>13–25 y (58% females)</td>
<td>Non-anemic (Hb &gt; 117 g/L for females, 135 g/L for males); iron depleted (ferritin &lt; 20 μg/L)</td>
<td>200 mg/d elemental iron as FeSO₄ (n = 20)</td>
<td>Placebo (n = 20)</td>
<td>12 wk</td>
<td>U, U, U, U, L</td>
</tr>
<tr>
<td>Hinton (34); Brownlie et al. (53,54)</td>
<td>United States</td>
<td>18–33 y</td>
<td>Non-anemic (Hb &gt; 120 g/L); iron depleted (ferritin &lt; 16 μg/L)</td>
<td>20 mg/d elemental iron as FeSO₄ (n = 14)</td>
<td>Placebo (n = 17)</td>
<td>6 wk</td>
<td>U, U, L, U, L</td>
</tr>
<tr>
<td>Hinton and Sinclair (33)</td>
<td>United States</td>
<td>18–41 y</td>
<td>Non-anemic (Hb &gt; 120 g/L); iron depleted (ferritin &lt; 16 μg/L, or raised sTfR or sTfR-F index)</td>
<td>30 mg/d elemental iron as FeSO₄ (n = 10)</td>
<td>Placebo (n = 10)</td>
<td>6 wk</td>
<td>U, U, L, U, L</td>
</tr>
<tr>
<td>Jensen et al. (27)</td>
<td>United States</td>
<td>18–25 y</td>
<td>Non-anemic</td>
<td>50 mg/d elemental iron as FeSO₄ (n = 7)</td>
<td>Placebo (n = 6)</td>
<td>12 wk</td>
<td>U, U, L, U, L</td>
</tr>
<tr>
<td>Klingshirn et al. (37)</td>
<td>United States</td>
<td>22–39 y</td>
<td>Non-anemic (Hb &gt; 120 g/L); iron depleted (ferritin &lt; 20 μg/L)</td>
<td>50 mg/d elemental iron as FeSO₄ (n = 9)</td>
<td>Placebo (n = 9)</td>
<td>8 wk</td>
<td>U, U, U, U, L</td>
</tr>
<tr>
<td>LaManca and Haynes (28)</td>
<td>United States</td>
<td>18–35 y</td>
<td>Anemia status unknown; iron depleted (ferritin &lt; 20 μg/L)</td>
<td>60 mg/d (non-anemic, mild anemic or 120 mg/d (moderate anemia) elemental iron as FeSO₄ (n = 40)</td>
<td>Placebo (n = 10)</td>
<td>8 wk</td>
<td>U, U, U, U, L</td>
</tr>
<tr>
<td>Li et al. (7,55); Li (50)</td>
<td>China</td>
<td>19–44 y</td>
<td>Iron deficient (ferritin &lt; 12 μg/L); non-anemic (n = 18); anemic (Hb &lt; 120 g/L) (n = 22)</td>
<td>50 mg/d elemental iron as FeSO₄ (n = 40)</td>
<td>Placebo (n = 40)</td>
<td>8 wk</td>
<td>U, U, U, U, L</td>
</tr>
<tr>
<td>Lyle et al. (56)</td>
<td>United States</td>
<td>College age</td>
<td>Anemia status unknown; iron status unknown</td>
<td>10 or 50 mg/d elemental iron as FeSO₄ + low-iron diet + exercise regimen</td>
<td>Placebo + unrestricted diet + exercise regimen</td>
<td>12 wk</td>
<td>U, U, H, H, L</td>
</tr>
<tr>
<td>Magazanik et al. (57)</td>
<td>Israel</td>
<td>19 y</td>
<td>Anemia status unknown; iron status unknown</td>
<td>15 mg/d elemental iron as FeSO₄ (n = 13)</td>
<td>Placebo (n = 13)</td>
<td>7 wk</td>
<td>U, U, U, L, L</td>
</tr>
<tr>
<td>McClung et al. (58)</td>
<td>United States</td>
<td>Mean age: 21 y</td>
<td>Anemia status unknown; iron status unknown</td>
<td>15 mg/d elemental iron as FeSO₄ (n = 86)</td>
<td>Placebo (n = 86)</td>
<td>9 wk</td>
<td>U, U, U, L, L</td>
</tr>
<tr>
<td>Newhouse et al. (29)</td>
<td>Canada</td>
<td>18–40 y</td>
<td>Non-anemic (Hb &gt; 120 g/L); iron depleted (ferritin &lt; 20 μg/L)</td>
<td>100 mg/d iron twice per day as FeSO₄ (n = 19)</td>
<td>Placebo (n = 21)</td>
<td>8 wk</td>
<td>U, U, U, L, L</td>
</tr>
<tr>
<td>Rajaram et al. (59)</td>
<td>United States</td>
<td>College age</td>
<td>Non-anemic iron deficiency (Hb &gt; 120 g/L, ferritin &lt; 12 μg/L, transferrin saturation &lt; 16%)</td>
<td>Iron deficiency anemia (n = 10); non-anemic iron deficiency (n = 9); 50 mg/d elemental iron as FeSO₄ (low-iron diet) (n = 16)</td>
<td>Placebo (n = 10); non-anemic iron deficiency (n = 9); placebo (normal-iron diet) (n = 13)</td>
<td>24 wk</td>
<td>U, H, H, L, L</td>
</tr>
<tr>
<td>Rowland et al. (33)</td>
<td>United States</td>
<td>Adolescents</td>
<td>Non-anemic (Hb &gt; 120 g/L); iron deficient (ferritin &lt; 20 μg/L)</td>
<td>325 mg/d elemental iron as FeSO₄ (n = 7)</td>
<td>Placebo (n = 7)</td>
<td>4 wk</td>
<td>U, U, U, U, L</td>
</tr>
<tr>
<td>Taniguchi et al. (59)</td>
<td>Japan</td>
<td>18–22 y</td>
<td>Non-anemic (Hb &gt; 120 g/L); iron deficient (ferritin &lt; 6 μg/L)</td>
<td>1 mg/d elemental iron as ferric ammonium citrate + vitamin C (n value not stated, assume 27)</td>
<td>Placebo + vitamin C (n value not stated, assume 27)</td>
<td>9 wk</td>
<td>U, U, H, H, L</td>
</tr>
</tbody>
</table>
iron deficiency could improve performance in female athletes who compete in a wide range of sports requiring either or all of endurance, maximal power output, and strength. The magnitude of increase in performance, even in non-anemic individuals.

Other submaximal outcomes. No differences between women randomly assigned to the iron and control groups were seen in energy consumption (kilojoules per minute), work (watts), or respiratory exchange ratio during submaximal exercise (Table 2). One study reported an improvement in 3.2 km (2 miles) run time among iron-deficient anemic female soldiers randomly assigned to take iron, although data for the overall group were not presented (38).

Other outcomes

Although not a prespecified outcome, we collected data on reported adverse events that were reported in detail by only 1 trial (26): women randomly assigned to take iron experienced increased undesirable gastrointestinal events (P = 0.001), “hard stools” (P = 0.015), and “any events” (P = 0.002).

Discussion

Daily oral iron supplementation in WRA improves both maximal and submaximal exercise performance. These benefits are clearest in iron-deficient and trained women. Our findings have implications for clinical management of patients, nutritional optimization for athletes, and rationale and design of public health anemia control programs. These results also begin to define the physiologic deficits induced by iron deficiency.

To our knowledge, this is the first published meta-analysis to provide evidence of beneficial effects of iron supplementation on physical performance. Gera et al. (39) reviewed effects of iron administration on physical performance in children but included only 3 studies, which was too few for meta-analysis. An unpublished meta-analysis by Casgrain et al. (40) that evaluated effects of iron (through different delivery strategies) on physical performance (in males and females) performed a meta-analysis of 8 studies reporting VO2 max, finding a significant benefit (2.68% (95% CI: 0.39, 2.83) for iron vs. placebo). These authors also identified a significant reduction in HR during submaximal exercise (4 studies, MD: 5.57 beats per minute (95% CI: −10.38, −0.76)).

Iron supplementation benefits maximal aerobic capacity (VO2 max) and efficiency of submaximal exercise (i.e., reduces the required percentage of VO2 max and HR), with 1 study also suggesting that it improves strength. The physiologic mechanism for these effects may reflect a range of processes. Raised hemoglobin concentrations may improve oxygen-carrying capacity and hence tissue oxygenation during exercise. Meta-analysis of hemoglobin data from studies reporting on VO2 max in this review showed a clear increase in hemoglobin with iron compared with control [MD: 6.79 g/L (95% CI: 4.29, 9.30), 19 studies]. Animal studies suggest that even non-anemic iron deficiency severely affects exercise performance in rats, restored by iron repletion (41). Iron is important in muscle metabolism with critical roles in the mitochondrial respiratory chain (cytochrome oxidase) and myoglobin (4,42). Improved tissue iron may thus improve tissue oxygen utilization and hence exercise performance, even in non-anemic individuals.

Our findings indicate that prevention and treatment of iron deficiency could improve performance in female athletes who compete in a wide range of sports requiring either or all of endurance, maximal power output, and strength. The magnitude of increase in

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TABLE 1 Continued

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Country</th>
<th>Participant age</th>
<th>Baseline anemia, iron deficiency status</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration</th>
<th>Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Waldvogel et al. (26)</td>
<td>Switzerland</td>
<td>18–50 y</td>
<td>Non-anemic (Hb ( \geq 120 ) g/L); iron deficient</td>
<td>80 mg/d elemental iron as FeSO4 (( n = 76 ))</td>
<td>Placebo (( n = 10 ))</td>
<td>4 wk</td>
<td>L, L, U, L, L, L</td>
<td></td>
</tr>
<tr>
<td>Walsh and McNaughton (60,61)</td>
<td>United States</td>
<td>Adolescents</td>
<td>Anemia status unknown; iron status unknown</td>
<td>60 mg/d elemental iron as ferrous ammonium citrate + multivitamin (( n = 10 ))</td>
<td>Placebo (( n = 10 ))</td>
<td>12 wk</td>
<td>U, U, L, U, L, L</td>
<td></td>
</tr>
<tr>
<td>Yoshida et al. (62)</td>
<td>Japan</td>
<td>Not reported</td>
<td>Anemia status unknown; iron status unknown</td>
<td>60 mg/d elemental iron as FeSO4 (( n = 20 ))</td>
<td>Multivitamin alone (( n = 6 ))</td>
<td>8 wk</td>
<td>U, U, L, U, U, L</td>
<td></td>
</tr>
<tr>
<td>Zhu et al. (36); Zhu and (38)</td>
<td>United States</td>
<td>19–36 y</td>
<td>Non-anemic (Hb ( \geq 120 ) g/L); iron deficient</td>
<td>Placebo (( n = 17 ))</td>
<td>Placebo (( n = 10 ))</td>
<td>8 wk</td>
<td>U, U, L, U, L, L</td>
<td></td>
</tr>
</tbody>
</table>

1 Overall risk of bias was defined as follows: high risk of bias (cohorts, high risk of selection bias; RCTs, high risk of performance bias; high risk of detection bias; high risk of attrition bias; high risk of reporting bias; high risk of other bias), low risk of bias (otherwise), and unclear risk of bias.

2 The letters correspond to random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, and selective reporting, respectively.
relative VO$_2$ max from iron [0.82–3.88 mL/(kg · min)] is in the range of improvements that can be achieved by exercise training (43). Female athletes experience a higher prevalence of iron deficiency compared with the general population (44) because of inadequate iron intake in athletes attempting to achieve or maintain a defined body weight and composition, foot-strike

### TABLE 2
Summary of effects of daily iron supplementation on exercise performance in women of reproductive age

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials</th>
<th>Participants</th>
<th>Difference [mean (95% CI)]</th>
<th>P-effect</th>
<th>I$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative VO$_2$ max, mL/(kg · C1 · min)</td>
<td>18</td>
<td>620</td>
<td>2.35 (0.82, 3.88)</td>
<td>0.003</td>
<td>71</td>
</tr>
<tr>
<td>Absolute VO$_2$ max, L/min</td>
<td>9</td>
<td>316</td>
<td>0.11 (0.03, 0.20)</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>VO$_2$ max, all studies, SMD</td>
<td>20</td>
<td>737</td>
<td>0.34 (0.11, 0.57)</td>
<td>0.004</td>
<td>52</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>4</td>
<td>112</td>
<td>0.01 (0.02, 0.03)</td>
<td>0.60</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>5</td>
<td>152</td>
<td>1.27 (1.08, 3.61)</td>
<td>0.29</td>
<td>0</td>
</tr>
<tr>
<td>Blood lactate at longest time point, mmol/L</td>
<td>4</td>
<td>106</td>
<td>-0.00 (0.72, 0.72)</td>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td>Time to exhaustion, min</td>
<td>2</td>
<td>49</td>
<td>1.08 (0.48, 2.66)</td>
<td>0.17</td>
<td>41</td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>6</td>
<td>172</td>
<td>-4.05 (7.25, -0.85)</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>%VO$_2$ max</td>
<td>6</td>
<td>167</td>
<td>-2.68 (4.94, -0.41)</td>
<td>0.02</td>
<td>46</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>5</td>
<td>136</td>
<td>-0.01 (0.02, 0.01)</td>
<td>0.28</td>
<td>0</td>
</tr>
<tr>
<td>Energy consumption, kJ/min</td>
<td>3</td>
<td>98</td>
<td>-0.48 (1.65, 0.68)</td>
<td>0.42</td>
<td>67</td>
</tr>
<tr>
<td>Workload, W</td>
<td>3</td>
<td>99</td>
<td>-6.64 (19.15, 5.88)</td>
<td>0.30</td>
<td>10</td>
</tr>
<tr>
<td>Time to exhaustion, min</td>
<td>3</td>
<td>52</td>
<td>1.23 (0.41, 2.87)</td>
<td>0.14</td>
<td>0</td>
</tr>
</tbody>
</table>

1 SMD, standardized mean difference; VO$_2$ max, maximal oxygen consumption.

### FIGURE 2
Effects of daily iron supplementation on maximal exercise performance in women of reproductive age. Daily iron supplementation improved relative VO$_2$ max, maximal oxygen consumption. (A) and absolute VO$_2$ max (B). IV, inverse variance; Random, random effects; VO$_2$ max, maximal oxygen consumption.
hemolysis, and increased iron losses in sweat, urine, and feces (44). Iron status may also be impaired in athletes by high-altitude training with enhanced erythropoiesis, gastrointestinal bleeding after severe endurance exercise (45), and elevated hepcidin after exercise (46). Hepcidin regulates systemic iron homeostasis and is induced by inflammation [including intensive exercise (47)] and storage iron; suppressed hepcidin facilitates iron absorption and utilization, whereas elevated hepcidin prevents it (48), suggesting that restitution of iron stores with oral iron may be less effective in the immediate postexercise period. Our data indicate that detection, treatment, and prevention of iron deficiency in this population can improve physical performance.

Iron supplementation was shown clearly in trials and meta-analyses to benefit hemoglobin and iron stores (49), but evidence for benefits on functional outcomes, which are a key rationale for controlling iron deficiency, has been difficult to ascertain. Measurement of exercise performance (e.g., VO2 max) has been consistent over time and between studies, enabling meta-analysis, unlike other variables (e.g., cognitive performance, psychologic health, fatigue) that have been measured in different studies using differing techniques and scales. Therefore, to the best of our knowledge, this is 1 of the first reports to document a nonhematologic benefit from iron. Improvements in physical performance from iron supplementation may extend to broader benefits. For example, Li et al. (7) showed that female cotton-mill workers randomly assigned to take iron experienced improved productivity and earnings and also had reduced HR during work compared with women in the control group (potentially reflecting our finding that iron reduces HR during submaximal exercise). Unpublished data from the same trial (included in this meta-analysis) revealed a significant improvement in absolute VO2 max in women randomly assigned to take iron (42,50). Given the beneficial effect from iron supplementation in women in whom baseline iron or anemia status was not measured, our data support, in populations in which iron deficiency and anemia are highly prevalent, implementation of public health measures to alleviate the burden of iron deficiency (such as daily or intermittent iron supplementation, staple food fortification, and deworming) (2) and, in settings in which iron deficiency is less prevalent, clinical measures to prevent, detect, and treat iron deficiency in individuals at risk (51), especially athletes.

Our conclusions are limited by heterogeneity and the paucity of highly eligible quality trials. We found that only 3 studies could be considered at low overall risk of bias: only a minority of studies reported methodology for randomization and allocation concealment. However, it is possible that other studies indeed used appropriate methods for prevention of bias but did not present these in the manuscript. Heterogeneity appears partially explained by variation in baseline anemia, iron deficiency, and training status of participants in trials. Few trials reported adverse effects. Estimates from our meta-analysis suggest that studies would need to recruit at least 142 participants to each arm (assuming a power of 0.80 to detect the difference). However, individual studies had an average size of just 41 participants, and 17 of the 22 included studies allocated #20 women to each arm. Combination of studies using meta-analysis has been useful in increasing the power to detect clinically significant differences in exercise-related outcomes. However, additional evidence is required to clarify the effects of iron on other exercise variables, such as endurance, and for other functional outcomes, including work performance and productivity and adverse effects.

Our data establish evidence of a beneficial effect from iron supplementation on exercise performance in women. Effect estimates can be used to determine the expected benefit to individual women and perhaps populations from alleviation of iron deficiency. They may also be used to guide iron deficiency prevention programs, especially among physically active women, and to design adequately powered RCTs to confirm our observations in specific settings.

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Literature Cited


