Early reports

Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls

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Summary

Background Up to 25% of adolescent girls in the USA are iron deficient. This double-blind, placebo-controlled clinical trial assessed the effects of iron supplementation on cognitive function in adolescent girls with non-anaemic iron deficiency.

Methods 716 girls who enrolled at four Baltimore high schools were screened for non-anaemic iron deficiency (serum ferritin ⩽12 μg/L with normal haemoglobin). 98 (13·7%) girls had non-anaemic iron deficiency of whom 81 were enrolled in the trial. Participants were randomly assigned oral ferrous sulphate (650 mg twice daily) or placebo for 8 weeks. The effect of iron treatment was assessed by questionnaires and haematological and cognitive tests, which were done before treatment started and repeated after the intervention. We used four tests of attention and memory to measure cognitive functioning. Intention-to-treat and per-protocol analyses were done.

Findings Of the 81 enrolled girls with non-anaemic iron deficiency, 78 (96%) completed the study (39 in each group). Five girls (three control, two treatment) developed anaemia during the intervention and were excluded from the analyses. Thus, 73 girls were included in the per-protocol analysis. Ethnic distribution, mean age, serum ferritin concentrations, haemoglobin concentrations, and cognitive test scores of the groups did not differ significantly at baseline. Postintervention haematological measures of iron status were significantly improved in the treatment group (serum ferritin 27·3 *vs* 12·1 μg/L, p<0·001). Regression analysis showed that girls who received iron performed better on a test of verbal learning and memory than girls in the control group (p<0·02).

Interpretation In this urban population of non-anaemic iron-deficient adolescent girls, iron supplementation improved verbal learning and memory.

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Introduction

Iron deficiency is the most common nutritional disorder, which affects about 20% of the world population. This disorder is not limited to developing countries, and is the main cause of anaemia in the USA.[1] Iron deficiency is a systemic condition, which has many non-haematological consequences: it impairs physical endurance, work capacity, infant growth and development, and depresses immune function.[2,3]

Since the initial studies by Oski and Honig,[4] most research on the cognitive effects of iron deficiency has focused on infants and very young children (toddlers). Several studies have shown that iron deficiency causes changes in behaviour and lowers development test scores in infancy.[5,6] Animal models have revealed several mechanisms by which iron deficiency may affect cognition; these include changes in brain iron content and distribution, and in neurotransmitter function. Body iron stores, such as central nervous system iron, decrease before red blood cell production is affected by iron deficiency. Changes in cognition and behaviour may be independent of haemoglobin concentrations; for example, pica is a well-known manifestation of iron deficiency from which individuals recover soon after the start of iron therapy.[7,8] In addition, people who receive iron for iron-deficiency anaemia commonly report improved memory, attention, mood, and energy before any improvement in haemoglobin indices.[9] Decreased brain iron stores may impair the activity of iron-dependent enzymes necessary for the synthesis, function, and degradation of neurotransmitters, such as dopamine, serotonin, and noradrenaline.[10] During the past 10 years, the increased use of iron-fortified formulas and cereals has improved the iron status of children and reduced the prevalence of iron-deficiency anaemia.[11] However, adolescent girls and young women are still at high risk of developing iron deficiency because of increased iron demands during puberty, menstrual losses, and limited dietary iron intake. Prevalence estimates of iron deficiency in adolescent girls range from 9% to 40%, depending on the population studied and the criteria used to define iron deficiency.[12] The Second National Health and Nutrition Examination Survey (1976–80) found that 14·2% of adolescent girls in the USA were iron deficient.[13]

The non-haematological sequelae of iron deficiency in adolescents have not been well defined. A study by Groner et al[14] of pregnant young women found better performance on psychometric tests in women treated with iron than in controls. Ballin and colleagues[15] found that iron-treated adolescent girls reported decreased lassitude and improved mood and ability to concentrate. Many studies of the systemic effects of iron deficiency have focused on individuals with iron-deficiency anaemia. Webb and Oski[16] observed that anaemic students had

lower scores on a standardised scholastic achievement test than non-anaemic students. Thus, a better understanding of the possible cognitive effects of iron deficiency in the absence of anaemia is particularly important because of the high rate of this condition in adolescent girls.

The main aim of this randomised, double-blind, placebo-controlled trial was to examine the effects of iron supplementation on attention, memory, and learning in non-anaemic iron-deficient adolescent girls.

Methods

The study was based at two public (ie, state-supported) high schools and two private Catholic high schools in Baltimore, Maryland, USA. During August and September, 1993, girls who enrolled at the four schools (grades 9–12 [ages 13–18]) were asked to take part in a voluntary screening for iron deficiency, which consisted of a complete blood count and measurement of serum ferritin concentration. An explanatory letter and consent form were sent to all girls who attended the schools, and distributed at school open-houses and in science and health classes. Written consent from a parent or guardian was required for participation in the screening.

Students completed a brief demographic and medical history questionnaire before blood samples were taken at the school by venepuncture. Haemoglobin concentrations were obtained from a complete blood count, and serum ferritin was measured by chemiluminometric immunoassay (CIBA Corning Diagnostic Corporation, Norwood, Massachusetts, USA). All laboratory tests were done by SmithKline Beecham Clinical Laboratories.

We used established race-adjusted and age-adjusted values for haemoglobin and serum ferritin. Girls were classified as normal (non-iron deficient), non-anaemic iron-deficient, or anaemic. Anaemia was defined as a haemoglobin concentration of less than 11·5 g/dL for African American girls or less than 12·0 g/dL for white girls.[17] Non-anaemic iron deficiency was defined as a serum ferritin concentration of less than 12·0 µg/L with a normal haemoglobin concentration.[18,19] Only girls with non-anaemic iron deficiency were eligible for enrolment in the trial.

After we obtained written informed consent from the student and a parent or guardian, eligible participants were randomly assigned to a treatment or control group. Assignment was done by computer-generated random number lists, in blocks of four with stratification by school. Participants and investigators were unaware of group assignment. Participants were asked not to take any vitamins or iron supplements during the trial.

After randomisation, baseline cognitive functioning was assessed. Standard cognitive tests were administered by trained research assistants at the participants' schools; three measures of attention and one multicomponent test of verbal learning and memory were used. The Brief Test of Attention (BTA)[20] is a measure of auditory divided attention, in which participants listen to a tape of letters and numbers (eg, 4-A-8-G-3-2) and are asked to report how many numbers or letters they hear. The Symbol Digit Modalities Test (SDMT)[21] is a timed measure of visual attention, motor speed, and rapid coding, in which participants print the number that corresponds to a written symbol listed at the top of the test page and the task is then repeated with the participant saying the digits. The Visual Search and Attention Test (VSAT)[22] is a timed test of visual scanning, target detection, and cancellation, in which participants locate and cross out letters or symbols that look like the target. The Hopkins Verbal Learning Test (HVLT)[23] is a 12-item, semantically categorised word-list learning test with three free recall trials, a delayed recall trial, and yes/no recognition; participants are read the same list of words three times and each time are asked to repeat as many words as they can recall, 20 min later they are asked to say which words they remember, and are read 24 words which include the original 12 words plus 12 semantically related and unrelated words.

Participants were randomly allocated a non-prescription ferrous sulphate preparation (Feosol, SmithKline Beecham) or placebo for 8 weeks. Two 325 mg tablets of ferrous sulphate were taken twice daily; the daily dose of 1300 mg was equivalent to 260 mg elemental iron daily. Iron and placebo (SmithKline Beecham) tablets were identical in appearance and dose regimen. Research assistants were unaware of treatment allocation throughout the study; treatment received was not disclosed until all subjects had completed postintervention testing.

We ensured optimum compliance in several ways. Research assistants administered one dose of treatment or placebo every schoolday; on weekends and holidays girls were contacted at home and reminded to take their tablets. In addition, researchers worked closely with girls and their families to encourage continuing participation, monitor compliance, and ask about side-effects. Every week girls received their supply of tablets and were asked to report any doses that they had not taken. Finally, participants were given small prizes at school, which they could receive only at the time scheduled for that day's regimen.

After treatment had stopped, haematological and cognitive tests were repeated and participants completed a brief questionnnaire about their group assignment (iron, placebo, don't know), any side-effects (nausea, stomach ache, headache, diarrhoea, change in stool colour, constipation, other); and behavioural and cognitive changes in energy, attention, memory, mood, and sleep pattern (more/better, the same, less/worse).

We estimated that 70 participants (35 in each group) were required to detect a 0·5 SD change in cognitive test scores by a one-tailed Students' *t* test (α=0·05, β=0·1). The initial intention-to-treat analyses were done by χ^2, Student's *t* test, and linear regression; a per-protocol analysis was then done.[24]

The study was approved by the Department of Research and Evaluation of the Baltimore City Public Schools, the Division of Schools of the Archdiocese of Baltimore, and the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

Results

Signed consent forms for the screening blood tests were obtained from 803 of about 2000 female students who enrolled at the four schools (figure 1). 716 girls were

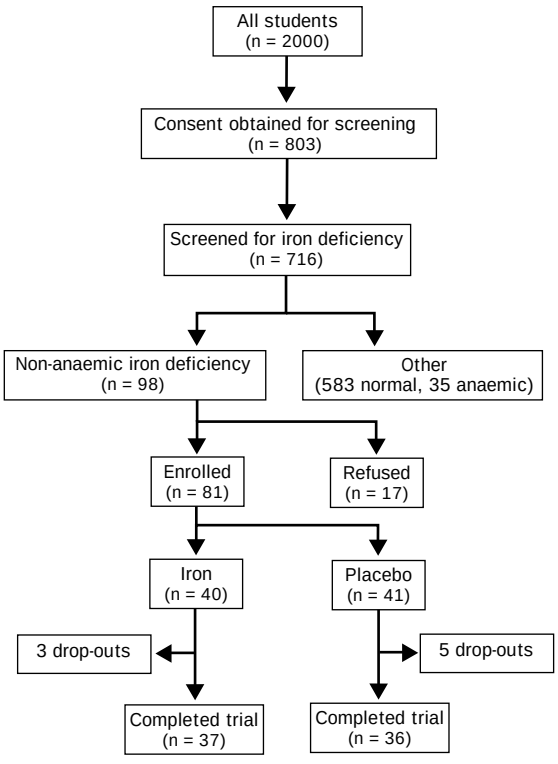

Figure 1: **Profile for randomisation into iron versus placebo**

	Treatment (n=37)	Control (n=36)	p*
Age (years)	16·2 (1·1)	157 (1·2)	0·06
Ethnic origin			
African American	16 (43%)	20 (56%)	
White	21 (57%)	16 (44%)	0·29
School			
Public	14 (38%)	16 (44%)	
Private	23 (62%)	20 (56%)	0·56
Haematological measurements			
Haemoglobin concentration (g/dL)	13·1 (0·7)	13·0 (0·7)	0·49
Mean cell volume (fL)	86·1 (3·8)	84·4 (4·8)	0·10
Red cell distribution width (%)	13·2 (0·9)	13·5 (1·1)	0·16
Serum ferritin concentration (μg/L)	9·1 (2·2)	8·5 (2·6)	0·28
Cognitive functioning test scores			
SDMT	118·1 (19·3)	115·1 (14·9)	0·46
VSAT	125·4 (22·5)	130·0 (22·9)	0·39
BTA	16·1 (2·6)	16·1 (2·7)	0·96
HVLT	25·2 (4·3)	24·9 (4·1)	0·72

Data are mean (SD) unless otherwise shown. *Two-tailed Student's *t* test or χ^2. SDMT=Symbol Digit Modalities Test; VSAT=Visual Search and Attention Test; BTA=Brief Test of Attention; HVLT=Hopkins Verbal Learning Test.

Table 1: **Characteristics of patients at start of treatment**

subsequently tested for iron deficiency (87 were absent or refused to take part). Of these 716 girls, 112 (16%) were iron deficient—14 had iron-deficiency anaemia and 98 were not anaemic and therefore eligible to enrol in the trial. 17 of the 98 non-anaemic iron-deficient girls did not want to take part in the trial. Of the 81 girls who enrolled, 78 (96%) completed the intervention (two girls transferred to other schools, one withdrew on the first day of the intervention) and were included in the initial intention-to-treat analyses. Five girls (three control, two treatment) developed anaemia during the intervention and were, therefore, excluded. 73 girls were therefore included in the final per-protocol analyses.

Both groups were well matched in terms of ethnic distribution, mean age, and school attended (table 1). Baseline haematological and cognitive measures were similar in both groups at the start of treatment. After the 8-week intervention, the treatment group had a significantly higher mean serum ferritin concentration than the control group (18·2 [SD 12·6] *vs* 3·5 [6·6] μg/L, p<0·001; table 2). Similarly, girls who took iron had a significantly higher mean haemoglobin concentration than the control group (13·5 [0·8] *vs* 12·7 [0·7] g/dL, p<0·001).

Factor analysis of the cognitive tests showed four distinct factors; therefore, each test was analysed separately. We used multiple-linear regression analysis to assess the effect of iron treatment on postintervention cognitive test scores, after adjustment for baseline scores (table 3). Iron treatment had no significant effect on postintervention BTA, SDMT, or VSAT scores (the three measures of attention). However, on the total recall score

Cognitive test	R^2	R^2 change attributable to iron therapy	Baseline score	p
Attention				
SDMT	0·49	N/A*	−0·43	0·90
VSAT	0·41	N/A*	−1·39	0·75
BTA	0·21	N/A*	−0·23	0·64
Learning				
HVLT	0·25	0·07	1·79	<0·02

Independent variables: group assignment and baseline score; dependent variable: postintervention score. *Not applicable because independent variable did not reach significance for entry into equation. SDMT=Symbol Digit Modalities Test; VSAT=Visual Search and Attention Test; BTA=Brief Test of Attention; HVLT=Hopkins Verbal Learning Test.

Table 3: **Summary of stepwise linear-regression analysis of group assignment on postintervention cognitive test scores**

of the HVLT (sum of trials 1–3), girls who took iron showed significant improvement over baseline and end of treatment compared with the control group (p<0·02). Baseline performance on the HVLT accounted for 93% of the variability in postintervention scores, whereas treatment condition accounted for the remainder. However, there were no significant differences between groups in other components of the HVLT (delayed recall, yes/no recognition). With the exception of one outlier, analysis of residuals showed no deviations from linear regression assumptions of linearity, constant variance, and normal distribution of standardised residuals. After adjustment for baseline scores, the correlation between the change in serum ferritin and postintervention score on the HVLT was 0·21 (p=0·04).

We compared preintervention and postintervention scores on each trial of the HVLT to assess differences detected between groups in total HVLT scores. The sum of the three learning trials of the HVLT is the HVLT total score (maximum score 36). We used ANOVA to analyse the HVLT learning curve by group assignment (treatment or control), session (baseline or postintervention), and trial (three free recall trials per test; figure 2). At baseline, both groups had similar learning curves. All girls recalled more words at each successive trial ($F_{2,142}$=273·70, p<0·001) with no significant differences between groups. Although both groups did better after the intervention ($F_{1,71}$=6·30, p<0·02), girls who took iron recalled more words at each successive trial than girls in the control group. However, the effect of group assignment on session did not achieve significance ($F_{1,71}$=2·67, p=0·106). The three-way interaction of group by session by trial was not significant ($F_{2,142}$ p=0·85).

65 of 73 subjects were available to complete the postintervention questionnaire on side-effects, subjective behaviour, and cognitive changes (table 4). Blinding to group assignment was successful. There was no significant difference between groups when girls were

	Treatment (n=37)	Control (n=36)	p*
Haemoglobin concentration (g/dL)			
Mean	13·5 (0·8)	12·7 (0·7)	<0·001
Change since start of intervention	0·4 (0·8)	−0·3 (0·5)	<0·001
Mean cell volume (fL)	88·5 (3·6)	85·1 (4·8)	0·001
Red cell dustribution width (%)	13·3 (1·2)	13·6 (1·0)	0·41
Serum ferritin concentration (μg/L)			
Mean	27·3 (13·2)	12·1 (7·6)	<0·001
Change since start of intervention	18·2 (12·6)	3·5 (6·6)	<0·001

*Two-tailed Student's *t* test. Data are mean (SD).

Table 2: **Haematological measurements at end of treatment**

	Treatment (n=34)	Control (n=31)	p*
Correctly guessed treatment	21 (61·8%)	14 (45·2%)	0·18
Side-effects			
Constipation	2 (5·9%)	1 (3·2%)	0·61
Change in stool colour	22 (64·7%)	3 (9·7%)	<0·001
Reported improvements			
Energy	12 (35·3%)	7 (22·6%)	0·26
Mood	5 (15·2%)	6 (16·7%)	0·87
Concentration	8 (25·8%)	6 (20·0%)	0·59
Memory	7 (21·2%)	3 (9·7%)	0·20

*χ^2.

Table 4: **Postintervention questionnaire**

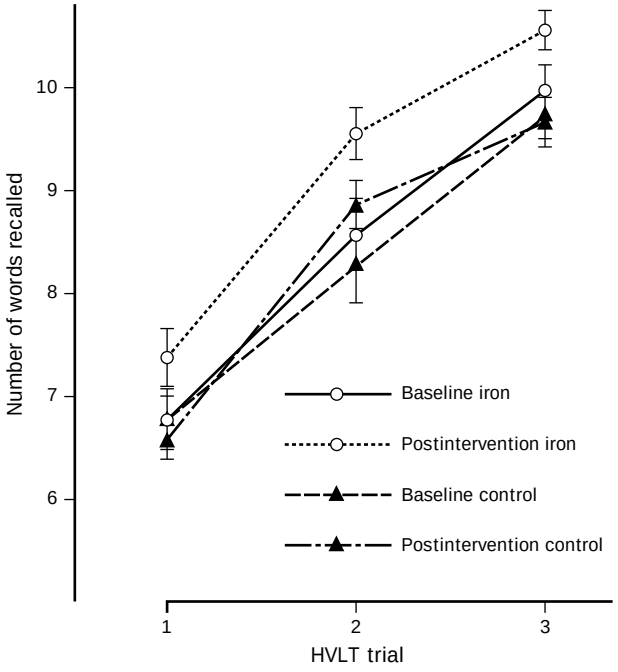

Figure 2: **HVLT learning curves**
Mean (SE) by group, session (baseline or postintervention), and trial (three free recall trials per test) at baseline and postintervention.

asked to guess whether they had taken iron or placebo: 21 (62%) girls in the treatment group and 14 (45%) in the control group correctly guessed their group assignment (p=0·18). Regression analysis did not show any association between cognitive performance and which intervention girls thought they had received. Overall, both groups reported the same frequency of side-effects: abdominal pain (26%), constipation (4%), diarrhoea (6%), headache (20%), nausea (19%). However, significantly more iron-treated girls reported changes in stool colour than girls in the control group (22 [65%] *vs* 3 [10%], p<0·001). Data on subjective behaviour changes were divided into two groups (more/better or same/less/worse) for analytical purposes because of the small number of participants. We found no significant differences in energy, mood, or attention; a few more girls who took iron reported slightly more improvement in memory than girls in the control group (7 [21%] *vs* 3 [10%], p=0·20).

Discussion

The findings suggest that, even in the absence of anaemia, iron supplementation improves some aspects of cognitive functioning in iron-deficient adolescent girls. The positive effect of iron supplementation on verbal learning and memory was shown in both the per-protocol and intention-to-treat analyses. Our findings in adolescent girls accord with previous research on infants and toddlers in whom iron deficiency had a negative effect on language development.[25] Although all features of cognition are important, verbal learning and memory are particularly important in terms of academic performance.

The effect of iron therapy on learning, shown by the increased HVLT scores of the treatment group, raises questions about the overall effects of iron deficiency on cognition. Although there was a significant difference between groups in total HVLT scores, the difference across trials did not achieve significance. This finding may have been due to the small number of participants, because our study was designed to detect significant changes on total cognitive test scores rather than subtest or trial scores. Although causal mechanisms by which iron deficiency may alter brain function have not been thoroughly defined, various theories have been proposed. Animal models show that iron deficiency is associated with changes in: neurotransmitter synthesis, uptake, and degradation; mitochondrial function; brain iron deposition; protein synthesis; and oxidation-reduction and electron transport.[26] Little clinical research to validate such animal models has been done. However, one study[27] showed an association between ferritin concentrations and electroencephalographic asymmetry, and another[28] observed changes in urinary catecholamines in iron deficient infants, which returned to normal after iron therapy. Clearly, the association between iron status and cognition is complex, and further research is needed.

Our study focused on the effects of iron deficiency in the absence of anaemia in a cohort of adolescent girls. More than 6% of girls developed iron-deficiency anaemia during the study. By definition, none of these girls was anaemic at the start of the intervention. However, in the treatment group, iron therapy increased mean haemoglobin concentrations and mean cell volume, whereas in the control group there was a mean decrease in haemoglobin concentration, which suggests that some girls did have a degree of biochemical iron deficiency.

The methodological limitations of our study need to be considered. Ferritin was the only measure of iron status in the study. Primary statistical analysis was by group assignment rather than changes in serum ferritin, because serrum ferritin concentrations can increase secondary to infection or inflammation. A linear correlation was also seen between iron status and cognitive function. By contrast, Fordy and Benton[29] measured ferritin concentrations in young men and women and found no association between low iron status and psychological functioning. One possible explanation for these conflicting findings is that the effect of iron deficiency on cognitive function may be subtle. We did not assess whether there were any baseline differences in cognitive functioning between normal and iron-deficient adolescents.

Iron treatment had no effect on the three measures of attention. Previous studies have shown that iron deficiency has a detrimental effect on attention, but it is not clear why our study did not detect this effect. Perhaps the measures we used were not sensitive enough to detect changes in attention. For example, mean baseline scores on the BTA were at or near 100% of the possible test score in both groups; this ceiling effect may have limited the ability of the BTA to detect any changes in attention between the groups. We assessed the effects of iron supplementation only on standardised cognitive tests; further research is needed to assess whether such cognitive effects are limited to neuropsychological measures or are also evident in academic performance.

Although iron fortification of formulas and cereals has improved the iron status of infants and toddlers, young women remain at high risk of iron deficiency and anaemia—the prevalence of iron deficiency in this population was more than 15%. This study suggests that, even in the absence of anaemia, iron supplementation improves verbal learning and memory among adolescent

girls, which suggests that further investigations of the non-haematological effects of iron deficiency are warranted.

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