Iron-Deficiency Anemia: Reexamining the Nature and Magnitude of the Public Health Problem

Iron Deficiency and Reduced Work Capacity: A Critical Review of the Research to Determine a Causal Relationship[1,2]

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ABSTRACT The causal relationship between iron deficiency and physical work capacity is evaluated through a systematic review of the research literature, including animal and human studies. Iron deficiency was examined along a continuum from severe iron-deficiency anemia (SIDA) to moderate iron-deficiency anemia (MIDA) to iron deficiency without anemia (IDNA). Work capacity was assessed by aerobic capacity, endurance, energetic efficiency, voluntary activity and work productivity. The 29 research reports examined demonstrated a strong causal effect of SIDA and MIDA on aerobic capacity in animals and humans. The presumed mechanism for this effect is the reduced oxygen transport associated with anemia; tissue iron deficiency may also play a role through reduced cellular oxidative capacity. Endurance capacity was also compromised in SIDA and MIDA, but the strong mediating effects of poor cellular oxidative capacity observed in animals have not been demonstrated in humans. Energetic efficiency was affected at all levels of iron deficiency in humans, in the laboratory and the field. The reduced work productivity observed in field studies is likely due to anemia and reduced oxygen transport. The social and economic consequences of iron-deficiency anemia (IDA) and IDNA have yet to be elucidated. The biological mechanisms for the effect of IDA on work capacity are sufficiently strong to justify interventions to improve iron status as a means of enhancing human capital. This may also extend to the segment of the population experiencing IDNA in whom the effects on work capacity may be more subtle, but the number of individuals thus affected may be considerably more than those experiencing IDA. J. Nutr. 131: 676S–690S, 2001.

KEY WORDS: • *anemia* • *productivity* • *work* • *endurance* • *human capital*

Although the worldwide prevalence of iron-deficiency anemia (IDA)[4] is alarmingly high, its public health significance cannot be judged solely on its prevalence. Significant deleterious consequences of iron deficiency must also be documented in making this judgment. Physical working capacity is one of several areas of human performance that have been widely reported as being impaired by iron deficiency. This paper contributes to this volume's comprehensive review of the functional consequences of IDA, anemia from other causes and iron deficiency without anemiav (IDNA) by examining the evidence for a causal relationship between the various stages of iron deficiency and physical work capacity.

The paper begins with a brief review of the biological functions of iron, which is followed by a discussion of a conceptual framework of causal linkages we developed after reviewing the literature. The next section presents the criteria and rating scale used to determine the validity of causal relationships depicted in the conceptual framework. The literature is then reviewed using the specified criteria. The results of this evaluation are then presented in tabular form followed by an overall evaluation of the findings relative to the objective of establishing whether causal relationships exist. The paper concludes with a discussion of the public health implications of the findings and some directions for further research.

BIOLOGICAL FUNCTION OF IRON IN ENERGY METABOLISM

Iron plays an essential role in oxidative energy production. The portion of iron in the body that transports and uses oxygen in the production of energy is called functional iron (Bothwell et al. 1979). Functional iron is found in hemoglobin (Hb), myoglobin, iron-dependent enzymes and respiratory chain proteins. **Table 1** summarizes their functions in energy production.

Classification of iron deficiency

Iron deficiency is often portrayed as a progressive condition that begins with normal body iron status, which becomes

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[4] Abbreviations: Hb, hemoglobin; IDNA, iron deficiency without anemia; MIDA, moderate iron-deficiency anemia; SIDA, severe iron-deficiency anemia.

TABLE 1

Iron-containing compounds involved in energy production

Name of protein	Functional site	Major biological functions in energy production
Hemoglobin	Red blood cell	Oxygen transport
Myoglobin	Cytoplasm of muscle cells	Facilitate diffusion of oxygen towards the mitochondria
Oxidative enzymes such as dehydrogenase	Mitochondria inner membrane and matrix	Oxidation of substrate (acetyl-CoA) to produce NADH and $FADH_2$
Respiratory chain proteins such as cytochromes	Mitochondria inner membrane	Electron (electrochemical energy) transfer form O_2 molecule to NADH or $FADH_2$

subnormal or depleted because of low dietary iron intake, inadequate intestinal iron absorption or increased iron losses. As this process continues, synthesis of iron-containing proteins, such as Hb, becomes compromised. Finally, when Hb concentration falls below a specified cut-off value, the iron deficiency has progressed to IDA.

For the purpose of this review, iron deficiency will be classified as three levels based on severity. The most severe form of iron deficiency results in anemia, which can be subdivided into two categories. The first is all-cause anemia, which is characterized by low Hb concentration of unspecified etiology. Studies that assessed only Hb status or failed to report other iron status indicators fall under this category. Although most anemia in high prevalence areas is caused by iron deficiency, there are other causes that vary in importance from population to population. Without an independent measure of iron status, it is impossible to determine the relative contributions of iron deficiency to the anemia and to any functional consequences that are affected by iron status independent of anemia. The second category is IDA, which is also characterized by a low Hb concentration. However, only studies that demonstrated iron deficiency using at least one additional iron status indicator such as serum ferritin, transferrin saturation, mean corpuscular volume, erythrocyte protoporphyrin or serum transferrin receptor fall under this category. Depending on the level of Hb, IDA can be classified as severe and moderate. Iron deficiency without anemia is characterized by normal Hb levels and abnormal values for one or several of these indicators of iron status.

Conceptual framework

Figure 1 provides a conceptualization of the important components of this review and the interrelationships that are explored. The figure shows that iron deficiency and anemia are not the same and that the overlap between iron deficiency and anemia is defined as IDA. The different mechanisms through which iron deficiency and anemia affect work capacity are also shown as reduced tissue oxidative capacity and reduced oxygen-carrying capacity. Note that tissue oxidative capacity is affected across all levels of iron deficiency, whereas the oxygen-carrying capacity is affected only at the most severe stages of deficiency when Hb concentration is reduced. In turn, these two impairments affect different aspects of physical performance. Reductions in oxygen-carrying capacity impair aerobic capacity, whereas reductions in tissue oxidative capacity impair endurance and energetic efficiency (Davies et al. 1984). Various work capacity outcomes have been shown to be affected by iron deficiency and anemia. Some (VO_2max) have been studied extensively in animals and humans; others (energetic efficiency) have been less well studied. The choice of an appropriate test of work capacity depends on the severity of iron deficiency and whether anemia is also present.

The diagram also depicts the potential relationships between iron deficiency and societal outcomes such as the quantity and quality of time allocated to various activities related to work, leisure and family responsibilities. Most of the research examines output only in the workplace. Other activities are rarely mentioned, but their relationships to iron status should be mediated by alterations in the ratio of energy expended at work to energy expended outside of work. In other words, as the amount of physiological energy required to complete work-related tasks decreases (because of increased physical fitness and energetic efficiency), individuals are less fatigued and therefore more likely to engage to a greater extent in nonwork-related activities. Consequently, the amount of time and the quality of such activities should increase. The framework also recognizes that iron deficiency may affect cognitive ability and skill acquisition at work, which may affect productivity as well. The following systematic evaluation of the research literature will draw on these biological mechanisms.

CRITERIA FOR LITERATURE EVALUATION

The criteria that will be used to assess causality are derived from a framework presented by Fairchild et al. (1989) for

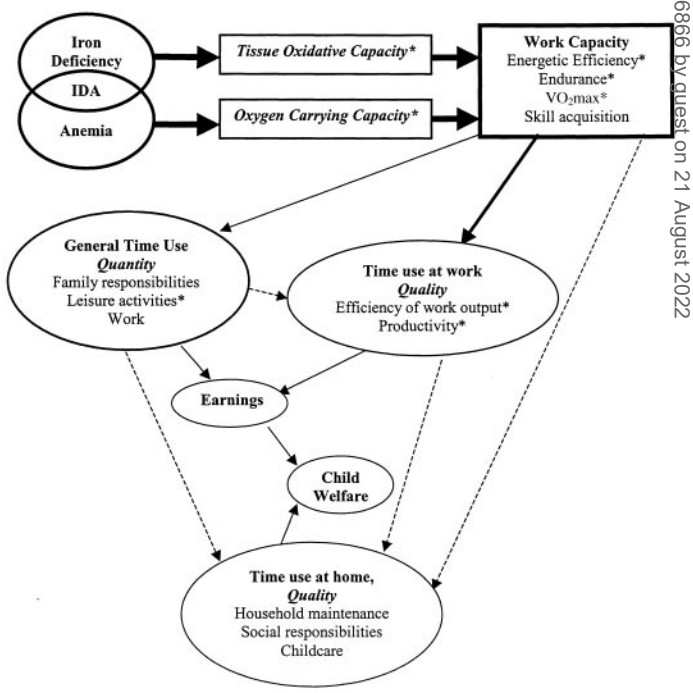

FIGURE 1 Effect of iron deficiency on biological and socioeconomic aspects of work. Outcomes indicated by an asterisk (*) are discussed in this review. IDA = iron deficiency anemia.

TABLE 2

Criteria for assessing internal validity

Study design	Positive findings	Negative findings
Nonexperimental	Was confounding controlled through . . . 1. Design? 2. Statistics?	Did the study . . . 1. Use sensitive measures? 2. Correctly classify iron status? 3. Control for negative confounders? 4. Have an adequate sample size?
Experimental	1. Did randomization result in comparable groups? 2. If not, were potential confounders controlled?	All of the above, plus: 5. Did treatment improve iron status? 6. Was there a ceiling effect?

testing causality in iron deficiency and behavior research. Three conditions for proving causality are specified, i.e., cause and effect must be associated, temporality must be established such that the cause preceded the effect and potential confounding must be excluded. To examine whether these conditions have been met for various work capacity outcomes studied across the continuum of iron deficiency, the internal validity, plausibility and external validity of individual studies will be evaluated. Internal validity relates to the accuracy of measurements and the ability to separate random errors from treatment effects (Rothman and Greenland 1998). A study with good internal validity allows positive findings to be interpreted as causally related to the experimental treatment (e.g., iron treatment). Conversely, a study with good internal validity and negative findings supports the conclusion that a causal relationship does not exist.

Various forms of bias compromise internal validity; these include selection, information and confounding bias. Selection bias occurs when the relationship between exposure (iron deficiency) and outcome (work performance) differs between those who choose and do not choose to participate in a study. Both selection procedures and other factors that influence participation can lead to selection bias (Rothman and Greenland 1998). Random allocation of treatments can control for this within a study sample, but volunteer subjects may have different reasons for participation that set them apart from the general population being sampled. This form of bias is not relevant for animal studies and is difficult to detect in human studies; therefore, it will be not be applied in this review. Information bias results from differential measurement errors between groups of subjects. This is particularly important when data are collected through subjective assessment techniques such as questionnaires. Because few subjective assessment tools are used in the research being evaluated in this paper, information bias will not be applied. Our discussion will focus on confounding bias that occurs when a factor (measured or unmeasured) influences both iron status and the outcome of interest.

Confounding can either produce artificial treatment effects (false positive results) or mask a true treatment effect (false negative results); therefore, excluding confounding is essential for drawing valid causal inferences. Plausibility, or biological plausibility, refers to the likelihood (nonstatistical) that an observed treatment effect was mediated through the expected biological mechanism. Criteria for establishing plausibility include demonstrating a biological relationship (e.g., change in iron status was related to change in the outcome) and that the biological intermediates in the causal pathway responded as expected. After establishing that a study is internally valid and the observations are biologically plausible, external validity must be evaluated. External validity, or generalizability, is the extent to which findings can be extrapolated to novel situations. The influence of effect modifiers, i.e., factors that alter the effect strength of the causal agent, on external validity will be discussed.

Internal validity

To evaluate internal validity, studies were organized by design (experimental or nonexperimental) and then by findings (positive or negative) because these factors determine the strength of a statement about causality. For example, because group comparability cannot be ensured in nonexperimental studies, assessing possible sources of confounding becomes particularly important. Conversely, for experimental studies, evaluating whether the experimental treatment was effective may be more important. The set of evaluative questions accompanying positive and negative findings also differ. When a study yields positive findings (i.e., authors hypothesis is supported), positive confounding—artificial treatment effects produced by an extraneous factor—must be evaluated. For negative findings, negative confounding—masking of a true treatment effect by an extraneous factor—must be evaluated along with sample size and interactions. Techniques used to evaluate internal validity under these four conditions are described in the next section and are summarized in **Table 2**.

Criteria for positive findings

Experimental studies. Studies that seek to manipulate iron status of the study sample are experimental. These studies generally require that different treatments (e.g., iron supplementation or placebo) be applied to different groups whose subjects are chosen at random. In theory, randomization should ensure group comparability, thereby eliminating confounding. However, randomization is not perfect, especially when sample size is small; therefore, known confounders should be measured and group comparability tested statistically. The internal validity of experimental studies that assessed known confounders, verified group comparability and attempted to control statistically for differences are considered stronger and are given more weight in the causality evaluation process.

Nonexperimental studies. Confounding (positive or negative) is particularly difficult to eliminate in nonexperimental studies because temporality cannot be established and group comparability cannot be ensured. One common approach used to reduce confounding is to match groups (e.g., anemic and nonanemic subjects) on confounding factors. Selection of the control group is the most important factor influencing confounding in cross-sectional studies because it determines the comparability of groups. Confounding can also be controlled

through statistical techniques; however, confounding factors must be identified and measured to apply this technique (i.e., random distribution of confounders cannot be assumed with nonexperimental designs). The internal validity of nonexperimental studies using either of these techniques to control confounding is considered stronger; therefore, such studies are given more weight in the causality evaluation process.

Criteria for negative findings

To draw inferences from negative findings, Fairchild et al. (1998) present six questions that must be answered to verify that the study design was adequate to detect a treatment effect if it existed: *1*) Is the assessment tool sensitive enough to detect a difference? *2*) Was the initial iron status classification correct? *3*) Did iron status improve after treatment? *4*) Are potential confounders masking the treatment effect? 5) Was the sample size adequate to provide sufficient statistical power to detect a difference? 6) Was there a ceiling effect? Questions 1, 4 and 5 are self-explanatory. The others require some explanation. Incorrect classification of subjects at baseline may result in the inclusion of individuals whose iron status is not compromised and therefore will not respond to iron supplementation. Failure to improve iron status after administration of an iron intervention may also occur because of poor subject compliance, inadequate dose or duration of supplementation, and illness or other biological factors that interfere with iron metabolism. The ceiling effect occurs when a subject's margin for improvement is inadequate to detect a change. For example, assessing the influence of iron supplementation on a test of physical performance may not be appropriate for athletes who already perform at a near maximum level on the test. Their margin for improvement may be too small to discern a biologically or statistically meaningful change.

Plausibility

Regardless of study design or findings, biological plausibility should be examined. Assessing plausibility strengthens arguments that support causality when findings are positive and refute causality when findings are negative. In experimental studies, plausibility may be established by demonstrating one or more of the following: subjects whose iron status responded to the iron treatment also responded in the work capacity outcome of interest; a biological correlation is observed such that improvements in iron status are correlated with improvements in the outcome of interest; and intermediates in the causal pathway responded to the iron treatment as expected. In nonexperimental studies, only the second criterion for establishing plausibility is applicable, i.e., a biological correlation is observed. Biological correlation, as defined in this paper, is what Fairchild et al. (1989) and others refer to as a dose-response relationship. The term was purposefully chosen to avoid falsely implying that the studies under evaluation demonstrated a linear relationship between multiple iron doses and changes in the outcome of interest—the true definition of a dose-response. Most studies use a single iron dosage, rendering dose response an inappropriate designation.

External validity

As previously stated, external validity is the extent to which study findings can be extrapolated to novel situations and is influenced by effect modifiers, i.e., factors that alter the strength of the effect of the putative cause on the outcome. For example, given the strict physiological regulation of iron status, one would expect initial iron status to affect response to iron treatment such that more iron-depleted individuals should exhibit the greatest improvements in iron status and physical performance after supplementation. Initial fitness is another potential effect modifier when change in physical performance is the outcome of interest. Because the least-fit individuals have the greatest margin for improvement, they should exhibit the greatest improvement; subjects who are more fit should exhibit proportionately less improvement. Because effect modifiers can greatly alter the conclusions that are drawn from a study (i.e., for whom the results are applicable), they should be evaluated whether the findings are positive or negative. For positive findings, evaluation of effect modifiers may reveal that the observed main effect applies only to a subgroup of the study sample and that the size of the effect in this subgroup was large enough to affect the entire sample distribution. Similarly, for negative findings, a subgroup of the sample may have responded, but the effect was diluted by nonresponders in the total sample. In both cases, evaluation of effect modifiers results in conclusions that differ from the primary analysis.

Causality ratings

Each study included in this review was individually evaluated using the framework presented above (i.e., internal validity, plausibility and external validity). A causality rating was calculated by applying a nine-point scale based on internal validity, external validity and plausibility criteria. Studies receiving a +4 demonstrated that iron deficiency was significantly associated with the outcome of interest, deficiency preceded the observed effects (i.e., an experimental design was used), confounding was excluded (through study design and statistical control) and plausibility was established through one of the methods described earlier. Studies that did not observe a significant main effect (e.g., significant group difference in physical performance after iron therapy) still received +4 if a significant interaction was observed that indicated effect-modification and the other criteria were met. Such findings imply that although a main effect was not observed, the hypothesis was valid for a subgroup of the study sample. Studies receiving +3 met the first three criteria but either did not attempt or failed to demonstrate plausibility. Those receiving +2 demonstrated an association and either established temporality or eliminated confounding. Randomized studies that found no main effect but observed a biological correlation (i.e., the treatment effect was not large enough to be significant) also received +2 if confounding was assessed or controlled. Studies receiving +1 demonstrated only an association and confounding was not adequately eliminated in either an experimental or nonexperimental study. Studies receiving a zero (0) observed a nonsignificant association and the authors did not further explore (e.g., secondary outcome).

Similar but slightly modified criteria were applied to studies that found no association: −1 indicates that a significant association was not observed and additional analyses were not performed (i.e., control for confounding factors). Studies that failed to demonstrate an association, but did control for confounding (by study design or statistically) or had an adequate sample size to show an effect received a −2. Studies receiving −3 met the previous criteria but further investigated and failed to demonstrate a biological relationship between iron status and the outcome. Studies received −4 if each of the previous criteria was met and statistical interactions were investigated (i.e., presence of effect modifiers) but none were identified. For each work capacity outcome, the evidence for a causal rela-

tionship with iron deficiency will be evaluated, beginning with the most severe form of iron deficiency (severe anemia) and continuing through the continuum of deficiency, emphasizing the rationale and specific evidence leading to the rating.

LITERATURE EVALUATION

For clarity of presentation, the literature is organized by primary outcome, study design and level of iron deficiency under investigation. The study outcome categories include aerobic capacity, endurance capacity, energetic efficiency, voluntary activity and economic productivity, which correspond to variables depicted in the conceptual framework. Laboratory studies include randomized experiments conducted on animals (i.e., rats) and either randomized double-blind placebo-controlled trials or unblinded trials in which human subjects were their own controls. Field studies include both randomized trials and nonexperimental studies (i.e., cross-sectional studies) that were not conducted in a laboratory, often using less sophisticated assessment techniques.

Finally, each study was classified by level of iron deficiency under investigation and includes four categories: anemia, severe iron-deficiency anemia (SIDA), moderate iron-deficiency anemia (MIDA) and IDNA. Studies that used Hb as the only indicator of iron status (human field studies) were placed in the "anemia" category. This category represents all-cause anemia and is defined as a Hb concentration <120 g/L. Studies that assessed Hb and at least one other iron status indicator were placed in one of the three other categories. To meet these criteria, iron deficiency had to be demonstrated by using one of the following iron-status indicators: serum iron, transferrin saturation, serum ferritin and serum transferrin receptors. After iron deficiency was established, studies were classified by baseline Hb concentration. SIDA and MIDA were defined as Hb <80 g/L and Hb between 80 and 120 g/L, respectively, and IDNA was defined as iron deficiency with normal Hb (>120 g/L).

Aerobic capacity

Methodology. For both experimental animals and humans, the test of choice to assess aerobic capacity is the maximum oxygen consumption (VO_2max) test (McArdle and Magel 1970). Protocols for the VO_2max test have been standardized and widely used as an indicator of physical (aerobic) fitness. The test is designed to assess oxygen uptake at a point at which the subject has achieved a level of maximum exertion. It is generally conducted on a motorized treadmill or cycle ergometer that can be set to increasing workloads in a stepwise progression so that maximal exertion is achieved in a relatively short time. During the test, cardiac frequency (heart rate), minute volume of oxygen consumed and carbon dioxide produced, and occasionally, metabolic indicators such as blood lactate levels and oxygen content of venous and arterial blood are assessed. Occasionally, a submaximal test protocol is used to predict VO_2max. Most variations of this protocol require oxygen uptake to be measured at several submaximum workloads and a predicted value for VO_2max to be determined by extrapolation to an estimated endpoint reflecting maximum exertion, such as an age-adjusted maximum heart rate.

Alternative assessment techniques have been developed for determining aerobic capacity in the field, where traditional laboratory tests are not practical or even feasible. The most common field-based test is the Harvard Step Test, which measures the heart rate response to one or more fixed workloads achieved by stepping up and down on a step of fixed height. Workloads may be adjusted by varying the cadence or adding weights to be carried while stepping. A decreased heart rate over time to a specific workload indicates improved fitness. The heart rate response has also been assessed using cycle ergometers and treadmills in certain field studies. Aerobic capacity has also been assessed my measuring the maximum workloads achieved on a treadmill or cycle ergometer.

Results from laboratory studies in animals. The animal studies included in **Table 3** that examined the relationship between IDA and aerobic capacity received between +3 and +4 causality ratings because nearly all criteria for testing causality were met and the results were positive and significant. The experimental designs both established temporality (i.e., changes in aerobic capacity followed the experimental treatment) and excluded confounding. Biological plausibility was established by demonstrating a biological correlation between Hb and aerobic capacity such that the severity of anemia was directly proportional to the degree of impairment in aerobic capacity (Davies et al. 1982, Ohira et al. 1981, Perkkio et al. 1985a). As expected, the most severely iron-depleted rats had the lowest aerobic capacity, followed by the moderately anemic rats. Compared with the control rats, both IDA groups had significantly lower aerobic capacity. Perkkio et al. (1985a) illustrated a nonlinear relationship between Hb and aerobic capacity by assessing aerobic capacity at multiple Hb concentrations during depletion. They found that as Hb declined from 140 to 80 g/L, VO_2max declined linearly by 16%, and for Hb values <70 g/L, VO_2max declined at a much greater rate with decreasing Hb. Statistical tests were not performed to assess differences in slopes between decline above and below Hb of 70 g/L. These findings suggest that a threshold Hb level may exist below which aerobic capacity exhibits a precipitous decline.

These studies demonstrate that IDA impairs aerobic capacity; however, the effects of reduced skeletal muscle oxidative capacity (a known correlate of IDA) cannot be separated from the effects of anemia. To address this problem, Davies et al. (1982) tracked improvements in iron status and fitness during iron repletion in rats. After 3 d of iron therapy, both Hb and VO_2max returned to control values, whereas oxidative enzyme concentrations and endurance required 5 d to return to control values. The similar recovery curves exhibited by Hb and VO_2max suggest that Hb is the primary determinant of aerobic capacity. To further investigate the separate effects of anemia (i.e., reduced oxygen-carrying capacity) from mitochondrial impairments (i.e., reduced oxidative enzyme concentrations), Davies and colleagues (1984) assessed aerobic capacity before and after normalizing Hb in IDA rats. Under conditions of anemia, VO_2max values were reduced by 50%. However, normalizing Hb concentrations returned VO_2max to within 15% of control values. These findings provide further evidence that Hb is the primary determinant of aerobic capacity. However, the residual 15% reduction suggests that VO_2max may be impaired by mechanisms not involving Hb; the authors did not investigate this finding. These studies illustrate that both MIDA and SIDA impair aerobic capacity, but only a weak association was observed between IDNA and aerobic capacity.

Results from laboratory studies in humans. Similar to the animal studies, findings from the human studies investigating the relationship between SIDA or MIDA and aerobic capacity provide strong evidence of a causal relationship (**Table 4**). Collectively, the studies presented in Table 4 received high ratings of causality (+3 to +4 points). Confounding was eliminated by the experimental study-designs and confirmation of treatment group comparability. Temporality (change in

TABLE 3

Effects of severe iron-deficiency anemia (SIDA), moderate IDA (MIDA) and ID without anemia (IDNA) on aerobic capacity and endurance capacity in experimental animals[1]

Authors (date)[2]	Treatment	Iron status indicators[3]	Fitness outcome(s)	Other outcome(s)[4]	Results for SIDA rats[3]	Results for MIDA rats[3]
Animal Studies						
Edgerton et al. (1972) [+4]	1. SIDA induced → repletion 2. SIDA and MIDA induced → repletion 3. MIDA induced 4. SIDA induced → repletion	1. Hb 2. Hb 3. Cyto. and Mb[3]	1. Runtime 2. Runtime 3. Runtime 4. na	1. na 2. na 3. na 4. Voluntary activity	1. SIDA < Controls After repletion: NS[5] Hb ∝ Runtime 1. SIDA < MIDA < Controls After repletion: NS Hb ∝ Runtime 2. na 4. SIDA < Controls After repletion: NS Hb ∝ Voluntary activity	1. na 2. Runtime: 40% < Controls After repletion: NS 3. Runtime: MIDA < Controls Mb: MIDA < Controls Cyto: MIDA < Controls Hb and Cyto ∝ Runtime 4. MIDA < Controls After repletion: NS Hb ∝ Voluntary activity
Finch et al. (1976) [+3.5]	1. Equalized Hb at 60 g/L → allowed to ↑ 2. Equalized Hb at 100 g/L 3. IDA induced	1. Hb; sFe 2. Hb; sFe 3. Oxidative Capacity	1. Runtime 2. Runtime 3. na	na[6]	1. Runtime did not ↑ in IDNA rats receiving transfused red cells 2. Run time did not ↑ in rats not receiving Fe 3. Oxidative capacity: IDA < Controls	
Ohira et al. (1981) [+4 SIDA] [+3 MIDA]	SIDA and MIDA induced	Hb; sFe	VO_2max; Exhaustive run	HR; RER; LAC; 2,3-DPG	VO_2max: 45% < Controls Runtime: 62% < Controls HR: NS[6] RER/LAC/2,3-DPG: SIDA > Controls Hb ∝ VO_2max Hb ∝ Runtime	VO_2max: 16% < Controls Runtime: 25% < Controls HR: NS RER/LAC: SIDA > Controls 2,3-DPG: NS Hb ∝ VO_2max Hb ∝ Runtime
Davies et al. (1982) [+4]	SIDA induced → repletion	Hb; oxidatrive Capacity	VO_2max; Exhaustive run (multiple measures during repletion)	RER	VO_2max: SIDA 48% < Baseline Runtime: SIDA 93% < Baseline RER: SIDA 70% > Baseline Repletion gradually increased Hb and Oxidative Capacity Hb repletion ∝ VO_2max repletion Oxidative capacity repletion ∝ runtime repletion	
Koziol et al. (1982) [+3.5]	SIDA and MIDA induced	Hb; Cyto./Mb	Exhaustive run	LAC; HR	Runtime: 82% < Controls HR: >Controls LAC: 130% > Controls Oxidative capacity: <Controls	Runtime: 36% < Controls HR: >Controls LAC: 103% > Controls Oxidative capacity: <Controls
Davies et al. (1984) [+3 SIDA] [0 IDNA]	SIDA induced → TF[7]	Hb; Hct; oxidative Capacity	VO_2max; Exhaustive run	RER; LAC	VO_2max: 48% < Controls After TF: 15% < Controls Runtime: 93% < Controls After TF: 93% < Controls RER: >Controls After TF: NS LAC: >Controls After TF: > Controls	na
Perkkio et al. (1985) [+4]	Range of anemia induced	Hb; Cyto.	VO_2max, Exhaustive run	LAC	VO_2max: SIDA < MIDA < Controls; large declines with Hb < 70 g/L Runtime: SIDA < MIDA < Controls; large declines with Hb 80–100 g/L LAC: SIDA/MIDA > Controls Hb ∝ VO_2max/Endurance Cyto. ∝ VO_2max endurance	
Willis et al. (1990) [+3]	SIDA induced → Fe injection	Hb	Walk duration	na	After injection: 10-fold ↑ walk time	na
Hunt et al. (1994) [+4]	SIDA/MIDA induced	Hb; Liver iron	na	Voluntary activity; Light/Dark cycle activity	Activity: SIDA < MIDA/Controls on all activity measures Light cycle distance traveled: MIDA > SIDA/Controls Dark cycle distance traveled: SIDA < MIDA/Controls Dark cycle vertical movement: SIDA < MIDA/Controls	Activity: MIDA < Controls on 8/12 measures of activity

[1] SIDA = Hb < 80 g/L; MIDA = Hb 80–120 g/L; IDNA = normalized Hb.
[2] Causality rankings in brackets.
[3] Abbreviations in this column: Hb, hemoglobin; Cyto, cytochromes; Mb, myoglobin; sFe, serum iron concentration; Hct, hematocrit.
[4] Abbreviations in this column: na, not assessed; HR, heart rate; RER, respiratory exchange ratio; LAC, blood lactate concentration; 2,3-DPG, 2,3-diphosphoglycerate.
[5] NS, not significant.
[6] na, not assessed.
[7] TF, exchange transfusion to normalize Hb concentration.

iron status preceded change in fitness) was also established by study designs. Plausibility was demonstrated through several of the methods previously described, i.e., biological correlation and assessment of causal-pathway mediators. All of the studies demonstrated that changes in Hb resulted in significant changes in VO_2max, which ranged from a 30% decline after

TABLE 4

Effects of severe iron-deficiency anemia (SIDA), moderate IDA (MIDA) and iron deficiency without anemia (IDNA) on aerobic capacity, endurance capacity and work efficiency in humans (laboratory studies)[1]

Authors (date)[1]	Location	Design[2]	Initial iron status[3]	Treatment	Fitness outcome(s)[4]	Other outcome(s)[5]	Iron status results	Confounders	Fitness results
Woodson et al. (1978) [+3.5]	U.S.	Unblinded trial	Hb: 150 g/L	Acute anemia and MIDA induced	VO_2max	HR	*Hb*: 104 g/L	Smokers not excluded	*VO_2max* w/Acute: 23% < Control *VO_2max* w/Established: 27% < Control
Barac-Nieto et al. (1980) [+3.5]	Colombia	Unblinded trial	Hb: 104 g/L	Protein supplements	VO_2max Endurance	HR	*Hb* ↑ to 120 g/L	Anthropometry; not parasites	*VO_2max*: ↑ by 15% *Endurance*: ↓ by 38% *HR*: NS Hb ∝ VO_2max
Celsing et al. (1986) [+3.5 MIDA] [−3 IDNA]	Sweden	Unblinded trial	Hb: 146 g/L SF: 60 μg/L	MIDA induced → transfusion	VO_2max Endurance	HR; LAC; Oxidative Capacity	*Hb*: MIDA: 110 g/L Repleted: 145/gL *SF*: MIDA: 7.3 μg/L Repleted: 9.1 μg/L *Oxidative Capacity* NS changes	na	*VO_2max* MIDA: ↓ by 18% Repleted: NS *Endurance* MIDA: ↓ by 47% Repleted: NS *LAC*: MIDA: ↑ by 42% Repleted: ↑ by 16%
Rowland et al. (1988) [+4]	U.S.	RDBP	Hb > 120 g/L SF < 20 μg/L	975 mg $FeSO_4$ for 4 wk	VO_2max Endurance	HR	*Hb*: NS[7] *SF*: ↑ by 18 μg/L to 26.6 μg/L	Anthropometry; training activity	*VO_2max*: NS *Endurance* (significant) Iron group: ↑ by 33 secs. (3%) Placebo group: ↓ by 40 secs. (4%); HR: NS
Li (1993) [+3 SIDA] [+2.5 MIDA] [−2 IDNA]	China	RDBP	Hb: 114 g/L SF: 9.7 μg/L FEP: 1.01 μmol/L	MIDA: 60 mg Fe for 12 wk SIDA: 120 mg Fe for 12 wk	VO_2max, Energetic efficiency	V_E, HR	*Hb*: ↑ 13 g/L *SF*: 60% greater ↑ in iron vs placebo *FEP*: 48% greater ↓ in iron vs placebo	BC; physical activity; education; work duration	*VO_2max* Total sample: ↑ 5.3% SIDA: ↑ 24% MIDA: NS IDNA: NS *Energetic efficiency (gross)* Total sample: ↑ 5%
Newhouse et al. (1989) [−3.5]	Canada	RDBP	Hb: 130 g/L SF: 12 μg/L TS: 25%	320 mg $FeSO_4$ for 8 wks	Wingate AP VO_2max	na[6]	*SF*: ↑ to 38 μg/L *Hb*: no change *TS*: ↑ to 34%	Anthropometry	*Wingate*: NS *VO_2max*: NS
Lukaski et al. (1991) [−3]	U.S.	Unblinded trial	Hb: 134 g/L Hct: 39% SF: 26 μg/L	MIDA induced → repletion	VO_2max	RER; LAC	*After depletion*: *Hb*: 120 g/L *Hct*: 35% *SF*: 6 μg/L *After repletion*: *Hb*: 126 g/L *Hct*: 36% *SF*: 10 μg/L	Anthropometry	*VO_2max*: NS change *RER*: ↑ by 7% *LAC*: ↑ by 29%
Klingshirn et al. (1992) [−4]	U.S.	RDBP	Hb > 120 g/L SF < 20 μg/L	320 mg $FeSO_4$ for 8 wk	VO_2max Endurance	LAC; RER	*Hb*: NS *SF*: ↑ to 23.44 μg/L	Phys. activity; matched by fitness	*VO_2max*: NS *Endurance*: NS *LAC*: NS, RER: NS
Zhu and Haas (1998) [−3 VO_2max & Endurance] [+4 EE]	U.S.	RDBP	Hb > 120 g/L SF < 20 μg/L	135 mg $FeSO_4$ for 8 wk	VO_2max Endurance EE,	LAC; GLUC;	*Hb*: Iron: NS Placebo: ↓ by 4% *SF*: Iron: ↑ by 23 μg/L Placebo: ↑ by 4 μg/L	Physical activity; anthropometry; dietary iron	*VO_2max*: NS *Endurance*: NS *EE*: Iron group expended 2.0 kJ/min (5%) energy Hb ∝ Post-tx LAC (negative)

[1] Causality rankings in brackets.
[2] Abbreviations in this column: RDBP, randomized double-blind, placebo-controlled trial.
[3] Abbreviations in this column: Hb, hemoglobin; SF; serum ferritin, FEP, free erythrocyte protoporphyrin; TS, transferrin saturation; Hct, hematocrit.
[4] Abbreviations in this column: AP, anaerobic power; EE, energy expenditure during endurance test.
[5] Abbreviations in this column: HR, heart rate; LAC, blood lactate concentration; VE, expiratory volume; RER, respiratory exchange ratio; GLUC, blood glucose concentration.
[6] na, not assessed.
[7] NS, not significant.

experimentally induced anemia to a 24% improvement after 12 wk of iron supplementation (Li et al. 1994, Woodson et al. 1978). Li (1993) demonstrated that improvements in VO_2max were proportional to the severity of initial anemia. Woodson et al. (1978) demonstrated that changes in Hb mediated changes in fitness by removing the Hb effect through statistical controls. Celsing et al. (1986) also demonstrated that Hb mediated reductions in VO_2max by experimentally normalizing Hb, which, again, removed the observed treatment effect.

Two types of studies were conducted to investigate this

TABLE 5

Effect of severe iron-deficiency anemia (SIDA), moderate IDA (MIDA) and iron deficiency without anemia (IDNA) on physical performance in humans (field studies)

Authors (year)[1]	Location	Subjects	Age (*y*)	Initial iron status[2]	Design[3]	Treatment	Fitness outcome(s)[4]	Other outcome(s)[5]	Confounder[6]	Iron status results	Fitness results
Davies et al. (1973) [+3]	Africa	Male factory workers	17–40	*Hb*: Controls: 145 g/L MIDA: 92 g/L SIDA: 30 g/L	XS	None	VO_2max	HR	Age, weight, height, job-matched	na[7]	*VO_2max*: Controls: 2.88 L/min[2] MIDA: 2.20 L/min SIDA: 1.90 L/min *HR*: SIDA > MIDA > Control
Gardner et al. (1975) [+4 SIDA] [+2 MIDA]	Venezuela	Male/female	17–46	*Hb*: Controls: 139 g/L Iron: 77 g/L Placebo: 81 g/L	RDBP	Fe-dextran; saline injection for 80 d	HR during a step-test	Grip strength; LAC	Iron group received Hookworm treatment; BC	*Hb* ↑ in the iron group (men & women)	*HR response to Iron*: Men: ↓ by 27% Women: ↓ by 19% *Grip response to iron*: Men/Women: NS[8] *LAC*: Iron < Placebo
Gardner et al. (1977) [+3 SIDA] [+2.5 MIDA]	Sri Lanka	Female tea pickers	22–65	Hb: 60–160 g/L sFe: 30–136 μg/L	XS	None	Timed treadmill test; HR during a treadmill test	LAC	BC	na	Hb ∝ HR Hb ∝ Work time Hb ∝ Reaching Peak HR Hb ∝ LAC (negative)
Ohira et al. (1978) [+3]	Sri Lanka	Tea estate workers (male/female)	21–65	Hb: 35 g/L	XS	Transfusion and Fe-dextran	HR during treadmill test	None	Parasitic infection treatment	*Hb*: ↑ by 48% to 68 g/L	*HR* ~ 25% lower in iron treated subjects
Ohira et al. (1979) [+4]	Sri Lanka	Not reported	21–72	*Hb*: Iron: 66 g/L Placebo: 80 g/L *sFe*: Iron: 51 μg/L Placebo: 67 μg/L	RDBP	30–50 mL iron dextran i.v. (4× over 16 d)	Maximum workload on a treadmill test	HR	None	*Hb* ↑ by 27% in 16 d	*Workload:* ↑ from 2.6 km/h to 5.6 km/h *HR*: significantly ↓ at a given workload *LAC*: significantly increased after treatment
Edgerton et al. (1981) [+1 SIDA] [+3 MIDA]	Sri Lanka	Tea estate workers and hospitalized anemics	Mean Age: 34–39	*Hb*: HSA: 35 g/L HMA: 56 g/L TMA: 63 g/L TN: 138 g/L	Unblind trial	Transfusion for HSA/HMA subjects	Maximum workload on a treadmill test	HR; LAC	None	*Hb* ↑ by ~ 53% (35 to 58 g/L)	Hb ∝ Workload Hb ∝ HR (negative) LAC: significantly ↓ in TN

[1] Causality rankings in brackets.
[2] Abbreviations in this column: Hb, hemoglobin; sFe, serum iron concentration; Hct, hematocrit; HAS, hospitalized severely anemic; HMA, hospitalized moderately anemic; TMA, tea estate moderately anemic; TN, tea estate normal.
[3] Abbreviations in this column: XS, cross-sectional; RDBP, randomized double-blind, placebo-controlled trial.
[4] Abbreviations in this column: HR, heart rate.
[5] Abbreviations in this column: HR, heart rate; LAC, blood lactate concentration.
[6] Abbreviations in this column: BC, body composition.
[7] na, not assessed.
[8] NS, not significant.

relationship between IDNA and aerobic capacity, i.e., studies examining aerobic capacity after inducing iron deficiency in nonanemic subjects and those examining aerobic capacity among subjects already iron deficient but not anemic. Regardless of the approach, none of the studies found that iron deficiency impaired aerobic capacity if anemia was not present (Celsing et al. 1986, Klingshirn et al. 1992, Li 1993, Lukaski et al. 1991, Newhouse et al. 1989, Zhu and Haas 1998b). Although these studies were well designed, the proposed biological mechanism by which iron deficiency in the absence of low Hb could affect aerobic capacity was not addressed explicitly in any of the studies. Reduced oxidative capacity was an implied mechanism in studies that assessed indicators of skeletal muscle oxidation; however, plausibility was not addressed by any of the studies (i.e., correlation between oxidative capacity and aerobic capacity or change in iron status and change in oxidative capacity was not assessed) (Celsing et al. 1986, Newhouse et al. 1989).

In summary, evidence from the laboratory studies suggest that both severe and moderate IDA impair aerobic capacity, which can be corrected by increasing Hb concentration. Impairments are proportional to the severity of deficiency and range from roughly 10 to 50% reductions in VO_2max. IDNA does not affect aerobic capacity because of the strong dependency of VO_2max on oxygen transport (Hb), which is not impaired in nonanemic subjects.

Field studies. The field studies that examined the effect of anemia and IDA on aerobic capacity provide further evidence of a strong causal relationship (**Table 5**). The causality ratings are lower in these studies compared with the experimental laboratory studies because of the inability of field studies to control certain study conditions.

All of the studies listed in Table 5 received causality ratings in the range of +2.5 to +4. These studies observed strong positive associations between IDA and impairments in aerobic capacity and demonstrated plausibility through biological correlation. Four of the studies observed response to improved iron status induced by blood transfusion or intravenous injections of iron dextran. Two of the studies using randomized double-blind placebo controls reported increases in various measures of aerobic capacity (Gardner et al. 1975, Ohira et al. 1979). Two of the cross-sectional studies, which reported positive relationships between Hb and aerobic capacity, controlled for major confounding but could not establish temporality (Davies et al. 1973, Gardner et al. 1977). Another study was an unblinded experiment in which aerobic capacity was assessed from the maximum workload achieved during a graded treadmill test after subjects were transfused (Edgerton

et al. 1981). Although able to establish temporality, possible confounding from expectation effects could not be controlled. Although all of these studies measured Hb, none measured iron status using currently accepted indicators. Reduced aerobic capacity can be attributed to iron deficiency only in studies that actually observed improvements in Hb after iron treatment.

Although most of these studies cannot independently demonstrate that iron deficiency causes impairments in aerobic capacity, they corroborate the findings of the laboratory studies. They are also particularly encouraging because they show that the effects of iron deficiency can be demonstrated in a field setting.

Endurance capacity

Methodology. Endurance is defined as the maximum length of time an individual can sustain a given workload. Physiologically, it depends on both oxygen delivery and oxygen use capacities of the working muscle. After the discovery in animal models that the effects of reduced oxygen transport and reduced oxidative capacity can be separated by careful selection of the appropriate test of physical performance (Davies et al. 1984), more researchers began investigating the effects of iron deficiency on endurance capacity.

Two major types of endurance test protocols are used to assess the effects of iron deficiency, with and without anemia, on endurance. The first type uses a graded exercise protocol in which exercise intensity is progressively increased at fixed intervals of long duration until the subjects cannot keep up with the workload (Matter et al. 1987, Rowland et al. 1987). This protocol tests the work capacity near maximal exertion, which is energized mainly by anaerobic glycolysis rather than aerobic oxidation.

The second type of endurance protocol measures time to exhaustion at a fixed submaximal exercise intensity (Celsing et al. 1986, Klingshirn et al. 1992, LaManca and Haymes 1993, Rowland et al. 1987). The level of the fixed work load is important to the interpretation of the results relative to iron status. Endurance at a high work load that is above the anaerobic threshold will depend heavily on anaerobic glycolysis, whereas tests at work levels below the threshold will depend more on aerobic processes. The choice of endurance test often is dictated by the time constraints for testing. Tests at high work loads progress to exhaustion quickly, whereas those at lower work loads may require several hours for indicators of exhaustion to be observed. Because subject motivation in longer tests often limits the ability to observe true muscle exhaustion, most studies of iron deficiency and endurance use tests of high work load. This limits the interpretation of the effects of iron deficiency on aerobic processes that may be more limited by tissue iron status than by oxygen transport. An alternative approach used by Zhu and Haas (1998b) and Hinton et al. (2000) to assess endurance is a test of fixed submaximal work on a cycle ergometer in which resistance and absolute number of revolutions (distance traveled) are fixed, but pedal speed is allowed to vary at the subject's discretion. This simulates a race in which subjects can set their own pace, and improvements over time are assessed by the reduction in time to complete the time trial. Test conditions such as distance to be traveled and resistance can be set so that the length of the test is sufficient to reflect endurance and not anaerobic capacity. For studies of tissue iron deficiency, the test duration should be long enough to test oxidative capacity of different energy substrates that reflect the efficiency of substrate use during prolonged work.

Laboratory studies in animals. Evaluation of the animal studies investigating the relationship between iron status and endurance capacity revealed strong evidence for causality across the continuum of iron deficiency (Table 3). All of the studies observed a significant association between iron status and endurance capacity. Moreover, all used experimental designs that eliminated confounding and established temporality. Variation in causality rating depended on how well plausibility was assessed and demonstrated. Only three studies assessed and successfully demonstrated plausibility. Edgerton et al. (1972 and 1977) demonstrated that run time to exhaustion was significantly correlated with Hb concentration and that reductions in endurance were proportional to declines in oxidative capacity (Edgerton et al. 1972). Ohira et al. (1981) also observed a significant correlation between endurance capacity and Hb ($r = 0.85$). Perkkio et al. (1985b) not only demonstrated that endurance capacity was correlated with cytochrome c concentration, but that the relationship became stronger as the concentrations declined. This observation supports the hypothesis that reduced oxidative capacity mediates impairments in endurance that accompany iron deficiency. Davies et al. (1982 and 1984) made significant contributions toward understanding the relationship between iron deficiency and physical performance by separating the effects of anemia and reduced oxidative capacity. In the first study, they demonstrated that normalizing Hb did not restore endurance to control levels. In the second study, fitness capacity and iron status were tracked during iron repletion. They observed that Hb and VO_2max followed a similar recovery pattern, whereas oxidative capacity and endurance followed their own recovery pattern. This suggests that reduced oxidative capacity mediates the effects of iron status on endurance.

Laboratory studies in humans. Human studies that measured endurance capacity are summarized in Table 4. Similar to findings from the animal studies, Celsing et al. (1986) demonstrated that MIDA significantly reduced endurance capacity by 47%. Conversely, studies evaluating the effect of iron deficiency without anemia on endurance capacity failed to replicate animal study findings. The average causality rating is −1.75. Of the four studies reviewed, only Rowland et al. (1988) observed a significant effect of improving iron status on endurance. The discrepancy between the animal and human studies may be attributable to several factors. First, in most of the human studies, endurance was tested at ≥80% VO_2max, which was likely to be well above the anaerobic threshold of most subjects. At this high level of exertion, subjects would be relying on noniron-dependent oxidative ATP production pathways. A second possible explanation for the discrepancy relates to demonstration of tissue-iron sufficiency. As depicted in the conceptual framework, impairments in endurance capacity should be mediated through reductions in tissue-level oxidative capacity. Consequently, iron deficiency without anemia should lead to reduced endurance capacity only if tissue iron status is compromised. Only one human study (Hinton et al. 2000), using serum transferrin receptors as the indicator of tissue status, has successfully demonstrated tissue iron deficiency effects on endurance. In this study, all subjects experienced 4 wk of aerobic training while being supplemented with iron. With this study design, it is impossible to distinguish the independent effect of tissue iron improvement from the training effect.

Energetic efficiency

Methodology. Energetic efficiency is defined as the amount of physiological energy required to perform a given

amount of external work. Energy expenditure is usually assessed by indirect calorimetry that converts oxygen uptake and carbon dioxide production to energy by standard equations (Weir 1949). External work is assessed simultaneously by the physical work performed on either a cycle ergometer or treadmill, usually reported in watts. Various expressions of the relationship between subject energy expenditure and work output are commonly used to reflect gross, net or delta efficiency (Gaesser and Brooks 1975). In field studies, energetic efficiency can be assessed by estimating energy expenditure and measuring practical items of output. Energy expenditure is estimated from minute-by-minute heart rate monitoring and applying a regression equation. Work output may be assessed by measuring the quantity of items produced, such as weight of sugar cane cut, tea picked or earth moved in a fixed period of observation when total energy expenditure is also assessed. Wages earned have been occasionally used to assess the output in productivity studies when wages depend on production output. This construct is particularly important because it represents an important link between the biological outcomes (e.g., aerobic capacity or energy expenditure) and societal outcomes (e.g., productivity or time allocation) of iron deficiency.

Laboratory studies. We found only three laboratory studies that investigated the effect of iron deficiency on energetic efficiency using an iron supplementation design (Table 4). A case-control study without intervention (Zhu and Haas 1997) reported no difference between groups in delta efficiency, which is the slope of the regression of VO_2 on work output at different work levels on a cycle ergometer. Zhu and Haas (1998b) conducted a randomized trial on marginally iron-deficient women and found that 8 wk of iron supplementation significantly reduced (5.1%) the total amount of energy expended during a fixed-distance cycle ergometer test of ~30 min. The researchers demonstrated a significant relationship between serum ferritin and energetic efficiency after controlling for confounding through design and statistical analyses and made a strong argument for plausibility through biological correlation. In a randomized placebo-controlled study of iron-deficient Chinese female cotton mill workers, Li (1993) reported a significant 5% increase in both gross and net energetic efficiencies over five workloads on a cycle ergometer. This analysis did not separate anemic from nonanemic subjects. These two experimental studies clearly suggest that iron deficiency impairs energetic efficiency, and the effects may be seen even when anemia is not present.

Field studies. We found only one study conducted in the field that specifically investigated the effect of iron deficiency on energetic efficiency. Li et al. (1994) extended the laboratory study of Li (1993) described above to observe average heart rate and estimated energy expenditure in the workplace. After 12 wk of iron supplementation, they observed a significant decrease in heart rate in the iron-treated compared with the placebo-treated group. The amount of time spent at work did not change or differ between groups and only a modest nonsignificant increase in wages was reported. However, the earnings per unit of energy expended over 8 h of work were significantly improved in the iron-supplemented group compared with the placebo group, resulting in a 17% increase in production efficiency. Furthermore, the iron-supplemented group reported an increase in time engaged in leisure activities as well as an increase in energy expended during those activities.

Voluntary activity

Methodology. Voluntary activity is assessed through activity wheels in animal studies and through time-allocation questionnaires and heart rate monitoring in human studies. Iron deficiency may affect voluntary activity by contributing to fatigue during the conduct of nondiscretionary activities such as those found in the workplace. Iron-deficient individuals who experience fatigue would consequently devote less time to strenuous voluntary activities or spend more time in voluntary sedentary activities, including sleep.

Laboratory studies. Both animal studies that evaluated the relationship between iron deficiency (all levels) and voluntary activity received high causality ratings. Edgerton et al. (1972) and Hunt et al. (1994) both showed significant reductions in voluntary activity after inducing iron deficiency in rats. Greater reductions in activity were seen as iron deficiency become more severe, but repletion in the study by Edgerton and colleagues did not result in increased activity. We were not able to locate any laboratory studies of voluntary activity in human subjects, although several field studies were identified.

Field study. Edgerton et al. (1979) observed that iron supplementation significantly increased voluntary activity in Sri Lankan female tea plantation workers. Findings from this study, combined with the results from the previously cited study of female cotton factory workers (Li et al. 1994) and the animal research, provide compelling evidence for an effect of iron deficiency on important aspects of behavior. These findings are particularly interesting for two reasons. First, they link the physical performance outcomes (e.g., aerobic capacity, endurance or fatigue) to the societal outcomes (e.g., time allocation, child care or social participation) depicted in the conceptual framework. (Fig. 1). Second, significant effects were observable across all levels of iron deficiency, from IDA to IDNA. This may have important implications given the extremely high prevalence of iron deficiency worldwide.

Economic productivity

Methodology. Productivity has typically been measured in jobs that involve producing some commodity or object that can be easily quantified over a specified time. Those studies identified in the literature were all conducted in developing countries. They include studies of tea pickers, rubber tappers, cotton or jute mill workers, and cigarette rollers. The ability to measure production output is a real advantage in studies of economic productivity, especially if earnings are based on amount produced. However, not all of these jobs have similar financial incentives for production. In some cases, the technology places limitations on production rate. One can also question whether these types of jobs represent the types of work encountered by most people living in underdeveloped areas, thus limiting extrapolation of results beyond a small set of similar occupations.

Field studies. Studies evaluating the effects of iron deficiency on economic productivity received a collective causality rating below the ratings of studies with measured biological outcomes (**Table 6**). All of the studies investigated the effect of anemia (all-cause or IDA) on productivity. We did not find any studies that evaluated the effect of IDNA on economic productivity. The causality ratings tended to be lower than ratings for other outcomes for several reasons. First, productivity is influenced by a host of factors other than iron status, which may obscure the effects of iron deficiency. For example, motivation is rarely assessed in studies of this nature but can

TABLE 6

Effect of SIDA, MIDA, and IDNA on work capacity and economic return (field studies)

Authors (year)	Location	Subjects	*n*	Age (*y*)	Initial iron status[2]	Design[3]	Treatment	Outcome(s)[4]	Confounder[5]	Effects of treatment[2,4]
Edgerton et al. (1979) [+4 Vol. activity] [+1 Productivity]	Sri Lanka	Female tea estate workers	1. 199 2. 18	20–60	Hb: 102–114 g/L	RDBP	1. 200 mg $FeSO_4$ for 1 month 2. 200 mg $FeSO_4$ for 3 wks	Weight of tea picked; Voluntary activity; HR during daily activity	Matched by initial Hb and initial productivity	1. *Hb*: net ↑ of 15 g/L (14%) *Tea picked* ↑ by 1.2% (NS)[6] Low Hb associated with lower productivity over yr 2. *Voluntary Activity*: Iron > placebo (40–80%) 3. *HR*: significant among a subgroup
Basta et al. (1979) [+3]	Indonesia	Male rubber plantation workers	302	16–40	Hb: <90 to >150 g/L (other outcomes: sFe; TS)	RDBP	100 mg $FeSO_4$	HST, Income of rubber tappers; Earth excavated by weeders	Dietary intake; morbidity	*Iron*: All iron status indicators significantly improved *Morbidity*: ↓ in both groups, but more among iron group *HST*: Iron group ↑; greatest among most depleted at baseline *Productivity*: Iron > Placebo (weeder/tappers)
Li et al. (1994) [+3 PE] [−1 Productivity]	China	Female cotton mill workers	80	19–44	*Hb*: Iron: 114 g/L Placebo: 115 g/L *SF*: Iron: 9.7 μg/L Placebo: 10.6 μg/L *FEP*: Iron: 1.01 μmol/L Placebo: 0.93 μmol/L	RDBP	MIDA: 60 mg Fe for 12 wk SIDA: 120 mg Fe for 12 wk	Productivity; HR at work; EE; EEW, EEL, PE	BC; physical activity; education; work duration.	*Hb*: Iron: ↑ by 13 g/L (11%) *SF*: 60% greater ↑ among iron group *FEP*: 48% greater ↓ among iron group *HR*: ↓ 5% at work *EEW*: ↓ by 11% *EEL*: ↑ by 7% *Productivity (absolute)*: NS *PE*: ↑ by 17% Hb ∝ HR at work ($r = -0.60$) Hb ∝ PE ($r = 0.58$)
Scholz et al. (1997) [+2.5]	Indonesia	Female jute mill workers	100	16–>30	Hb: <100 to >120 g/L	XS	None	% of overall jute output; VO_2max	Education; BC; work experience; sleep	Hb ∝ VO_2max (NS) Hb ∝ Work output *Work output* significantly ↓ among women w/Hb < 110 g/L
Untoro et al. (1998) [+2.5]	Indonesia	Female cigarette factory workers	230	>18	*Hb*: <120 g/L: 40% >120 g/L: 60%	XS	None	Cigarettes rolled/d	BC, work experience; marital status; education	*Productivity*: 4.9% ↓ among anemic subjects Hb ∝ Productivity ($r = 0.14$)

[1] Causality rankings in brackets.
[2] Abbreviations in this column: Hb, hemoglobin; sFe, serum iron concentration; TS, transferrin saturation; SF, serum ferritin; FEP, free erythrocyte protoporphyrin.
[3] Abbreviations in this column: RDBP, randomized double-blind placebo-controlled trial; XS, cross-sectional.
[4] Abbreviations in this column: HR, heart rate; HST, Harvard step test; EE, energy expenditure; EEW, energy expenditure at work; EEL, energy expenditure at leisure; PE, production efficiency calculated as days wages/EEW.
[5] Abbreviations in this column: BC, body composition.
[6] NS, not significant.

dramatically affect productivity. Production incentives have important effects on motivation. Second, the type of labor determines the mechanism by which iron affects productivity. Physically strenuous work requires high aerobic capacity and would be impaired by anemia. Less strenuous work might require better endurance and be impaired by iron deficiency regardless of whether anemia is present. The type of labor not only affects the mechanism by which iron affects productivity but, by extension, the feasibility of discerning a significant effect. Similar to laboratory measurements, impaired productivity during shorter, more physically demanding tasks may be easier to assess than during long, less physically demanding tests in which motivation and other physiological compensatory mechanisms may interfere.

The strongest evidence for an effect of IDA on productivity comes from the study of Basta et al. (1979) of male rubber tree tappers and weeders in Indonesia, in which the output of iron-supplemented anemic tappers was 17% higher than anemic tappers receiving a placebo. Another placebo-controlled field study of female tea pickers in Sri Lanka (Edgerton et al. 1979) found only small effects from a 30-d supplementation therapy on the daily weight of tea picked, possibly because of a lack of incentives for these workers. However, mechanical monitoring of physical activity of a smaller matched sample in this study showed very significant increases in daily physical activity for those receiving the supplement. This suggests that when institutional or technological factors (e.g., the inflexibility of assembly line work or fixed hourly wages) constrain the ability or motivation of subjects to increase their output on the job, increased iron intake may nevertheless have substantial benefits for individual or household welfare through increased time or productivity in other activities, including child care or self-employment activities.

The study of Chinese female cotton mill workers by Li et al. (1994) points in a similar direction. Although the women in the study were paid for the quantity and quality that each produced (meaning there was a modest incentive problem), productivity increases were constrained by the fixed pace of the machines so that increases among women receiving a 12-wk daily iron supplement were small (~5%). However,

there were much larger (17%) increases in production efficiency or output relative to energy expenditure. Another important conclusion of the study, particularly relevant to industrializing countries, is that iron deficiency can affect energy expenditure and productivity even in nonstrenuous physical occupations (such as factory work). This is the conclusion as well of two nonexperimental studies from Indonesia by Scholz et al. (1997) and Untoro et al. (1998), which showed a reduced productivity in different types of anemic female factory workers.

DISCUSSION

The evidence is clearly the strongest for IDA causing reductions in aerobic work capacity. The animal and human studies consistently find that aerobic capacity is significantly reduced with SIDA and MIDA. Conversely, despite strong study designs, there is no evidence that IDNA reduces aerobic capacity. The human studies investigating this relationship do not explicitly specify the proposed biological mechanism under investigation. Although Hb was specifically eliminated as a causal agent (by sampling or transfusion), reduced oxidative capacity (reduced oxidative enzymes) is the apparent proposed mechanism for reduced performance in IDNA. However, none of the human studies adequately measured oxidative capacity or assessed its relationship with aerobic capacity. This particular relationship parallels an ongoing debate concerning whether VO_2max is exclusively limited by oxygen delivery (central limitation argument) or whether oxygen use plays a role (peripheral limitation argument) (Wagner 1996). It is difficult to separate the two mechanisms when conducting research on human subjects. Of particular difficulty is distinguishing individuals with IDNA from those with IDA whose Hb is around the anemia cut-off values commonly used. The field studies examining aerobic capacity observed similar results, i.e., anemia or IDA impaired aerobic capacity. None of the field studies investigated IDNA and aerobic capacity. However, given the evidence from laboratory studies for no effect, it is unlikely that effects could be documented under less controlled field conditions.

The evidence clearly suggests that SIDA and MIDA also impair endurance capacity, but this is based almost exclusively on studies of experimental animals. All of the animal studies induced anemia and then normalized Hb to test the independent effects of reduced oxidative capacity on endurance. The few human studies either enrolled marginally iron-deficient subjects or induced some level of iron deficiency and then normalized Hb. Without directly assessing tissue iron status or oxidative capacity, neither of these approaches ensures tissue iron depletion in subjects. Studies enrolling subjects with IDNA used Hb and serum ferritin for screening, which is not an accurate indicator of tissue iron status (Zhu and Haas 1998a). Newhouse et al. (1989) sampled iron-depleted women and assessed tissue iron status from muscle biopsies, but methodological problems and uneven sampling between the iron and placebo groups precluded drawing conclusions from the data. Celsing et al. (1986) induced anemia and assessed oxidative enzyme concentrations and found they were unchanged by the depletion process. This provided a plausible explanation for their negative findings, i.e., the biological intermediate was not affected, therefore, endurance was not affected. In future research on iron deficiency and endurance, tissue iron depletion should be verified, perhaps with measures such as the serum transferrin receptor.

Isolating the effects of iron deficiency or IDA on endurance in humans is limited by the test protocols to assess endurance. Test of long duration (several hours) are required to achieve exhaustion with work fueled by aerobic oxidation. However, subject motivation becomes a deciding factor in completing these tests. Shorter tests must expose the subjects to higher workloads, which then require them to perform above the threshold at which aerobic metabolic processes are replaced by anaerobic ones. In everyday experience, almost all human work is performed below this threshold (below ~60–65% of VO_2max) so that performance on these short-duration high intensity endurance tests have limited practical importance, except perhaps for athletes. Moreover, the role of iron is likely to be very different in the control of aerobic compared with anaerobic metabolism.

The evidence from both animal and human studies suggests that a strong causal relationship exists between all levels of iron deficiency (IDA and IDNA) and voluntary physical activity. However, only three animal studies and one human study have been conducted. Moreover, assessment tools for measuring voluntary activity have not been standardized, which is important for comparing studies. These studies should provide a foundation for future research investigating the economic and noneconomic consequences of iron deficiency, especially if these findings can be reproduced in subjects with IDNA.

The practical significance of iron deficiency is of particular importance to public health. Research on economic effects of anemia has been motivated in part by attempts to impart practical significance to this problem. Future research should consider that extrapolation of the findings from laboratory research to economic and social effects is not a direct process. A 15–20% reduction in VO_2max or a 10% reduction in endurance time does not translate into an equal reduction in economic productivity. The limited research in IDA and productivity suggest that many factors influence productivity. Although individual motivation is known to be important in endurance testing, its effects on economic productivity have not been adequately addressed in studies of iron deficiency and IDA.

As illustrated in the conceptual framework in Figure 1, the potential for iron deficiency to affect society goes beyond its effects on economic productivity. Iron deficiency, especially when it results in anemia, reduces VO_2max and by extension, reduces endurance. Individuals with low endurance cannot sustain moderate-to-heavy physical labor to the extent seen in those with better endurance. There is even evidence that low levels of physical activity such as those seen in cotton factories in China (Li et al. 1994) are performed at higher energy costs if women experienced IDA. Laboratory tests show that even in nonanemic women, iron deficiency accounts for a 5% greater energy cost to perform the same work compared with a noniron-deficient individual (Zhu and Haas 1998b). This greater metabolic cost of work should render the iron-deficient individual more fatigued at the end of a work day compared with a noniron-deficient individual who performed the same amount of physical work. Even if the iron deficiency does not result in a reduced amount of work performed, the higher cost of performing that work leaves the iron-deficient person less able to engage fully in nonworkplace responsibilities, such as child care, household maintenance, and participation in social and leisure activities. No research has addressed these far-reaching implications of the well-documented effects of IDA on work capacity.

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DISCUSSION

Participants: Lozoff, Haas, Beaton, Horton, Allen, Grantham-McGregor, Stoltzfus, Beard, Lynch, Schultink, Cogswell, Sazawal, Pelletier, Rasmussen, Pollitt

Dr. Lozoff: The issue of motivation to work and other mechanisms for work differences might tie into neurotransmitter systems again. I would be interested in your thoughts on how the data you reviewed, which is very persuasive, would show in a child.

Dr. Haas: The motivation and neurotransmitter is an interesting idea. A lot goes into why people will perform. I had not thought of that link but certainly it is an issue that could be considered.

There is virtually no work on children, especially young children. Some have looked at nutritional status in early life and then the effect on such things as VO_2max at, I think it was 16 y of age. We also observed this in Guatemala. It is very difficult to administer any of these laboratory tests to children under age 7 y. We have done some work with 7-, 8- and 9-y-old children but not in the context of anemia. So, there is no research on children. There is nothing on adolescents who are anemic, to my knowledge.

I think the question of what is going on in children is important. It is not so much work productivity. Some of them do enter the work force but they do other things related to their normal everyday life. The point that I really wanted to make is that the effect of anemia may be measurable in productivity but it has to be viewed much more widely than that—in terms of how it affects what adults do, and what children do in everyday life that makes their life important to

them. There is no reason why children who are iron-deficient anemic and have reduced work capacity should be viewed any differently from adults who are iron-deficient anemic and have reduced work capacities. They may have different things that are important in their lives but they may both be compromised by their reduced ability to do physical work.

Dr. Beaton: Dr. Horton, when you have a research recommendation, you ask yourself what is the weakest link in the argument chain and is there any way of trying to address that link. Where is the biggest chunk of learning going to come, in terms of your calculations?

Dr. Horton: I think the big assumptions are about productivity and I do not have a good feel for how much of a range to put on those. I think the rest of it is reasonable and I am more concerned about the cognitive effects, which is why I do the physical ones separately and then the cognitive. I think the physical ones are reasonably strong. Now that there are some effectiveness studies for fortification, I am thinking about leaping still further into the unknown and actually comparing interventions. If you can fortify flour in Venezuela for 12 cents per person and show an effect on anemia and iron status, I would like to relate that to the kinds of work we have done.

Dr. Allen: Dr. Horton, if I understand rightly, you have included effect on cognitive performance of adults in your calculations. Dr. Grantham-McGregor did not discuss this and I know there are hardly any studies on iron and cognition in adults, but it seems like a big vacuum.

Dr. Horton: What I have assumed is that some minimal amount of cognitive effects from children persist through to adulthood that are on the order of 4% of productivity of adults, based on the studies of the link between wages and cognition in adults. It would be extremely useful to quantify that.

Dr. Allen: I kept thinking through about the child development discussion—if you have an anemic mother, you might have a stronger chance of having an anemic child. Throughout this discussion, we are ignoring the ways that iron deficiency in adults might influence all of this.

Dr. Grantham-McGregor: The point that we do not know what anemia does for cognition in adults is very well taken.

Dr. Horton: What I am assuming is something a bit different. I am assuming iron therapy in children can improve cognition, then interlink with schooling, and then affect adult wages.

Dr. Stoltzfus: There is an interesting body of literature that has come out of the renal disease studies where they have anemia, and in the past decade there have been a lot of controlled trials with erythropoietin. Those are not being conducted any more because erythropoietin is very effective in improving their hemoglobins. Many of those trials included quality-of-life assessments. It made me wonder why we do not do that more. For example, very few studies of pregnancy anemia have really made a serious effort to assess women's subjective quality of life or the problems they report having. So I was interested to see this cohesive body of literature and standardized tools being used to look at quality of life in relation to anemia. There are really large effects that are seen in outcomes such as energy, emotional reactions and social isolation. In another study, social functioning reacted very strongly and was linked to the change in hemoglobin as well.

Dr. Beard: The confounder here is that these are all dialysis patients. They are in a dialysis unit and they are getting rid of uremia. All sorts of things are going on with them clinically that make them feel a lot better, not just correcting the anemia.

Dr. Stoltzfus: Still, these quality-of-life scales exist. Why not try them?

Dr. Lynch: I think most clinicians would say the advent of Epogen has made a huge difference in quality of life in renal patients.

Dr. Schultink: Two remarks. First, Dr. Horton's calculations of effect in terms of finance, however fuzzy and full of assumptions they may be, are extremely important. It is very powerful to have this type of data to convince governments or program planners to do something about this. If we can improve them by improving the assumptions or the data quality, that would be very good.

Also, in the past couple of years I was involved in three studies on work productivity. They were observational studies. We used a cutoff point for anemia, all-cause anemia, of 120 g/L. We found an association showing that the reduction in work output was anywhere from 4% to 5%. They were in cigarette rollers and in women working in textile factories. We could correct for all kinds of confounders. So, it is not only in heavy physical labor that anemia affects. It is also not only in anemia with hemoglobin values below 90 g/L that it has an effect. I think that is extremely important to realize this.

Dr. Cogswell: My understanding is that the U.S. Public Health Service Task Force does not recommend universal anemia screening of women of reproductive age in the United States because they found that there is not enough evidence for the effect of iron deficiency on functional outcomes in this age group in the United States. They only recommend screening for high-risk groups. It is imperative that we have data in developed countries that look at quality-of-life measures in relation to anemia and iron deficiency.

Dr. Sazawal: From your presentation, Dr. Horton, I gathered that the total cost per person, was $2 per person per year. This is the estimate in economic cost because of anemia, is it?

Dr. Horton: That is a conservative estimate, yes.

Dr. Sazawal: If you talk in terms of supplementation costs and then look at cost-benefit ratios, although we seem to feel that these are huge costs, whenever I have tried to estimate the costs of supplement for a child—that does not include the delivery mechanism or anything else and probably includes no profits—it is usually more like about $10–15 per year, and that is for a child. Does your calculation mean that it will only be cost effective if we are doing selective supplementation? If you assumed a universal supplementation to prevent anemia, then it is not cost effective.

Dr. Horton: You are exactly right. You can do selective supplementation or you can do universal fortification, and I think that is cost effective. There may be other approaches, diet based or whatever, in the long run.

Dr. Sazawal: Then basically we are saying that supplementation is not a cost-effective approach.

Dr. Horton: Hardly anyone is going to advocate universal supplementation for a population. I do not think that makes sense.

Dr. Pelletier: I would like to go back to Dr. Lozoff's first comment about the possible link to neurotransmitters or other things that might feed into motivation. We need to ask ourselves what it is that causes people to voluntarily back off, perhaps at the mild stage of iron deficiency or iron deficiency anemia. Dr. Schultink's study, where he is finding effects with cigarette rollers and so on, even though physically these are trivial tasks—easy for me to say, I do not roll cigarettes all day—but relatively speaking, they are nowhere near the endurance tests and VO_2max tests. Maybe it is the motivational thing that is working in there.

Dr. Schultink: What is important here are things such as concentration and dexterity. This is something where, with the heavy physical labor, it is the mechanisms going through

oxygen transport. With milder activities you have to look at other things. For example, in this textile factory they have to pay great attention to how the machines are rolling. Often, things go off track and they have to stop the machines immediately. If they wait too long, then it is a big mess and it takes a lot of time to clear it up. That is the type of thing that might play a role with milder levels of anemia.

Dr. Beard: That supports what Dr. Lozoff is suggesting. It is an older literature that comes from the Israeli research groups and then our own more recent studies with drugs that are specific, such as cocaine or drugs that affect the dopaminergic system. There is some neurobiology that could potentially explain it.

Dr. Lozoff: I came across a small study in juvenile primates where they had sequential hemoglobin in an iron-deprivation design. The first behavior that changed was a decrease in running and playing. This occurred at hematocrits around 0.31, or mild anemia. We have to pay attention to this.

Dr. Haas: The voluntary physical activities would be really interesting to study. There are a few animal studies with anemia that have looked at it, and only one human study that I found that did that. The study I alluded to in China was interesting. It also dealt with women who were working at a fairly low level of work in cotton factories. If you look at their heart rates, which were monitored during the workdays, they were only working at heart rates of 90–95 beats per minute. So, they are not doing heavy work. Women who were receiving iron supplement for 12 wk showed a reduced heart rate doing the same amount of work of only about 5 beats/min, which they translate into ~10% reduced energy expenditure. They averaged an extra 30 min/d doing things that they had not done before, such as working in the kitchen and going shopping. These were young women and not many of them had family responsibilities.

Dr. Pelletier: This gets back to the quality-of-life kinds of issues.

Dr. Lozoff: The concept of compensatory mechanisms—how much the body can compensate at a cost, and then, when it starts to fall apart—is a really useful way of asking the questions.

Dr. Haas: I would like to know what the iron effects are on productivity and what the resultant energy savings are for some of these other activities. We talked about the voluntary activities in terms of the extra 30 min of shopping time. I think much more important, especially for women who have families, is what they do when they return to the households and they have household responsibilities, much of which is associated with child care. Do they spend more time with their children? Is the quality of that time improved? Do you see that in terms of improved growth and development of the children?

Dr. Grantham-McGregor: Half an hour a day playing with your baby can have an enormous effect on child development.

Dr. Stoltzfus: There is another interesting report in the literature. Maternal anemia is significantly associated with insufficient milk syndrome in low-income American women. It suggests, again, that we need to cast our nets wider.

Dr. Lynch: Quality-of-life issues are not something that I have really thought about before, but I think they are very important. Until recently, for example, for patients with cancer it was assumed that anemia was fine. You have this bad disease and you might as well be anemic and it does not make a lot of difference. There are many articles now showing that Epogen has made a huge difference to the well-being of these people. Some of them, of course, are in a much lower hemoglobin range. Certainly that would be true of the renal patients. It is not true of all of the oncology patients. Many of them are in the 90–100 g/L, and the use of Epogen has made a big difference to their well-being.

Dr. Pollitt: I was thinking about this issue of quality of life. If we were to look at the evidence on children in different developmental domains, I think that the evidence that we would have would be much stronger than what we have had based just on cognition. You could speak about the quality of life of the child.