Iron Deficiency and Reduced Work Capacity: A Critical Review of the Research to Determine a Causal Relationship¹,²

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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)³ 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 anemia (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.

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

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Iron deficiency and whether anemia is also present. An appropriate test of work capacity depends on the severity of energetic efficiency have been less well studied. The choice of been studied extensively in animals and humans; others (en-

<table>
<thead>
<tr>
<th>Name of protein</th>
<th>Functional site</th>
<th>Major biological functions in energy production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>Red blood cell</td>
<td>Oxygen transport</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>Cytoplasm of muscle cells</td>
<td>Facilitate diffusion of oxygen towards the mitochondria</td>
</tr>
<tr>
<td>Oxidative enzymes such as dehydrogenase</td>
<td>Mitochondria inner membrane and matrix</td>
<td>Oxidation of substrate (acetyl-CoA) to produce NADH and FADH$_2$</td>
</tr>
<tr>
<td>Respiratory chain proteins such as cytochromes</td>
<td>Mitochondria inner membrane</td>
<td>Electron (electrochemical energy) transfer form O$_2$  molecule to NADH or FADH$_2$</td>
</tr>
</tbody>
</table>

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 non-work-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...
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. 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 1 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 a 1 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 +1 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 (VO2max) test (McArdle and Magel 1970). Protocols for the VO2max 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 increase 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 VO2max. Most variations of this protocol require oxygen uptake to be measured at several submaximum workloads and a predicted value for VO2max 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 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, VO2max declined linearly by 16%, and for Hb values <70 g/L, VO2max 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 VO2max 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 VO2max 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, VO2max values were reduced by 50%, however, normalizing Hb concentrations returned VO2max 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 VO2max 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
The methods previously described, i.e., biological correlation of iron status preceded changes in fitness was also established by Finch et al., Davies et al., Hunt et al., Willis et al., and Perkkio et al. This correlation was further supported by the work of Koziol et al. and Perkkio et al., who showed that changes in Hb resulted in significant changes in VO2max, heart rate, RER, oxidative capacity, and lactate concentration. These changes were observed in both SID A and MIDA induced anemia conditions and were normalized after repletion.

Iron status preceded changes 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 VO2max, which ranged from a 30% decline after

### Table 3

<table>
<thead>
<tr>
<th>Animal Studies</th>
<th>Treatment</th>
<th>Iron status indicators</th>
<th>Fitness outcome(s)</th>
<th>Other outcome(s)</th>
<th>Results for SIDA rats</th>
<th>Results for MIDA rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koziol et al. [1982]</td>
<td>SIDA induced → repletion</td>
<td>1. Hb; Cyto.Mb</td>
<td>Runtime</td>
<td>1. na</td>
<td>1. SIDA &lt; Controls After repletion: NS</td>
<td>1. na</td>
</tr>
<tr>
<td>Davies et al. [1982]</td>
<td>SIDA induced → repletion</td>
<td>1. Hb; oxidative Capacity</td>
<td>VO2max; Exhaustive run</td>
<td>RER; LAC; 2,3-DPG</td>
<td>VO2max: 45% &lt; Controls</td>
<td>VO2max: 16% &lt; Controls</td>
</tr>
<tr>
<td>Davies et al. [1984]</td>
<td>SIDA induced → TF7</td>
<td>1. Hb; Hct; oxidative Capacity</td>
<td>VO2max; Exhaustive run</td>
<td>RER; LAC</td>
<td>VO2max: SIDA 48% &lt; Baseline</td>
<td>VO2max: SIDA/MIDA 48% &lt; Baseline</td>
</tr>
<tr>
<td>Perkkio et al. [1985]</td>
<td>Range of anemia induced</td>
<td>1. Hb; Cyto.</td>
<td>VO2max; Exhaustive run</td>
<td>LAC</td>
<td>VO2max: SIDA &lt; MIDA &lt; Controls; large declines with Hb &lt; 70 g/L</td>
<td>VO2max: SIDA &lt; MIDA &lt; Controls; large declines with Hb 80–100 g/L</td>
</tr>
<tr>
<td>Willis et al. [1990]</td>
<td>SIDA induced → Fe injection</td>
<td>1. Hb</td>
<td>Walk duration</td>
<td>na</td>
<td>VO2max &gt; MIDA/Controls</td>
<td>VO2max &gt; MIDA/Controls</td>
</tr>
<tr>
<td>Hunt et al. [1994]</td>
<td>SIDA/MIDA induced</td>
<td>1. Hb; Liver iron</td>
<td>na</td>
<td>Voluntary activity; Light/Dark cycle activity</td>
<td>Activity: SIDA &lt; MIDA/Controls on all activity measures</td>
<td>Activity: MIDA &lt; Controls on 8/12 measures of activity</td>
</tr>
</tbody>
</table>

1 SID A = 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.
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 VO2max 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 VO2max by experimentally normalizing Hb, which, again, removed the observed treatment effect.

Two types of studies were conducted to investigate this

### TABLE 4

<table>
<thead>
<tr>
<th>Authors (date)</th>
<th>Location</th>
<th>Design</th>
<th>Initial iron status</th>
<th>Treatment</th>
<th>Fitness outcome(s)</th>
<th>Other outcome(s)</th>
<th>Iron status results</th>
<th>Confounders</th>
<th>Fitness results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodson et al. (1978)</td>
<td>U.S.</td>
<td>Unblinded trial</td>
<td>Hb: 150 g/L</td>
<td>Acute anemia and MIDA induced</td>
<td>VO2max</td>
<td>HR</td>
<td>Hb: 104 g/L</td>
<td>Smokers not excluded</td>
<td>VO2max w/Acute: 23% &lt; Control</td>
</tr>
<tr>
<td>Barac-Nieto et al. (1980)</td>
<td>U.S.</td>
<td>Unblinded trial</td>
<td>Hb: 104 g/L</td>
<td>Protein supplements</td>
<td>VO2max Endurance</td>
<td>HR</td>
<td>Hb ↑ to 120 g/L</td>
<td>Anthropometry; not parasites</td>
<td>VO2max ↑ by 17%</td>
</tr>
<tr>
<td>Celsing et al. (1986)</td>
<td>Sweden</td>
<td>Unblinded trial</td>
<td>Hb: 146 g/L</td>
<td>MIDA induced → transfusion</td>
<td>VO2max Endurance</td>
<td>HR, LAC, Oxidative Capacity</td>
<td>Hb: 110 g/L</td>
<td>MIDA: 110 g/L</td>
<td>Repleted: 145 g/L SF: 7.3 μg/L</td>
</tr>
<tr>
<td>Zhu and Haas (1998)</td>
<td>U.S.</td>
<td>RDBP</td>
<td>Hb &gt; 120 g/L</td>
<td>Wingate AP</td>
<td>VO2max</td>
<td>TS</td>
<td>Hb ↑ to 13 g/L</td>
<td>Anthropometry; training activity</td>
<td>VO2max ↑ by 16%</td>
</tr>
<tr>
<td>Newhouse et al. (1989)</td>
<td>Canada</td>
<td>RDBP</td>
<td>Hb: 130 g/L</td>
<td>MIDA induced → repletion</td>
<td>VO2max</td>
<td>HR</td>
<td>Hb: 13 g/L</td>
<td>BC: Physical activity; education; work duration</td>
<td>VO2max ↑ by 33%</td>
</tr>
<tr>
<td>Lukasik et al. (1991)</td>
<td>U.S.</td>
<td>Unblinded trial</td>
<td>Hb: 134 g/L</td>
<td>Wingate AP</td>
<td>VO2max</td>
<td>TS</td>
<td>Hb: 13 g/L</td>
<td>Anthropometry</td>
<td>VO2max ↑ by 23%</td>
</tr>
<tr>
<td>Klinghism et al. (1992)</td>
<td>U.S.</td>
<td>RDBP</td>
<td>Hb &gt; 120 g/L</td>
<td>MIDA induced → repletion</td>
<td>VO2max Endurance</td>
<td>LAC, RER</td>
<td>Hb: 120 g/L</td>
<td>Phys. activity; matched by fitness</td>
<td>VO2max ↑ by 23%</td>
</tr>
<tr>
<td>Zhu and Haas (1998)</td>
<td>U.S.</td>
<td>RDBP</td>
<td>Hb &gt; 120 g/L</td>
<td>MIDA induced → repletion</td>
<td>VO2max Endurance</td>
<td>EE</td>
<td>Hb: 120 g/L</td>
<td>Physical activity; anthroplometric efficiency; dietary iron</td>
<td>VO2max ↑ by 23%</td>
</tr>
</tbody>
</table>

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.
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\textsubscript{2max}. IDNA does not affect aerobic capacity because of the strong dependency of VO\textsubscript{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 rankings 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 injection 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. 1982).
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, but pedal speed is allowed to vary at the subject’s discretion.

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$_2$max 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$_2$max, 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 which 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 VO2 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 became 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
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 during shorter, more physically demanding tasks may be easier to assess than during long, less physically demanding tasks.

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 weeder 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 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 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 1998b). This greater energy cost to perform the same work compared with a noniron-deficient individual (Zhu and Haas 1998b). This greater increased productivity, 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 as 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.

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LITERATURE CITED


Hinton, P. S., Giordano, C., Brownlie, T. & Haas, J. D. (1983) The motivation and neurotransmitter is an in-...
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**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 there are some reasonable assumptions. Strongly and was linked to the change in hemoglobin as well.

**Dr. Stoltzfus:** 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. 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.

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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 based just on cognition. You could speak about the quality of life of the child.