

**Economic
Consequences
of Iron Deficiency**

Jay Ross

and

Susan Horton



Published by the Micronutrient Initiative
PO Box 8500, Ottawa ON Canada K1G 3G9

© Micronutrient Initiative 1998

Canadian Cataloging in Publication Data

Main entry under title:

Economic consequences of iron deficiency

Includes bibliographical references.

ISBN 1-894217-05-5

1. Iron deficiency anemia—Economic aspects. 2. Iron deficiency anemia—Prevention. I. Ross, Jay Sutherland II. Horton, Susan III Micronutrient Initiative (Association).

RC641.7.I7R68 1998

616.3'96

C98-901085-6

The Micronutrient Initiative (MI) was established in 1992 as an international secretariat within the International Development Research Centre (IDRC) in Canada by its principal sponsors: the Canadian International Development Agency, IDRC, the United Nations Children's Fund, the United Nations Development Programme, and the World Bank. MI's mission is to help achieve the goals of the World Summit for Children that relate to the alleviation or elimination of micronutrient deficiencies. It focuses on advocacy, building alliances, the development and transfer of technology, support for national and regional initiatives, capacity building, and the resolution of key operational issues.

MI Publications encourages the widest possible dissemination, for noncommercial research and development purposes, of the information in this publication. The source must be cited in full. Any questions concerning copyright and appropriate use should be referred to the publisher (mi@idrc.ca).

MI endeavours to produce environmentally friendly publications. All paper used is recycled as well as recyclable. All inks and coatings are vegetable based.

Cover photos: Tarik Kassaye, Janice Johnston, and Charton (UNICEF).

Contents

Foreword	iv
Acknowledgments	v
Executive summary	vi
1. Introduction	1
2. Lower future productivity of children	3
2.1 A biological mechanism	3
2.2 Evidence for an effect of iron deficiency on cognitive development in children under 2 years of age	4
2.3 Evidence for an effect of iron deficiency on cognitive development in children 2 years of age and older	9
2.4 Economic implications of cognitive deficits	11
2.5 Productivity effects of iron deficiency in childhood	12
3. Lower current productivity of adults	13
4. Costs of care for low-birth-weight and premature infants	21
5. Costs of maternal mortality and other complications of pregnancy	25
6. Other consequences: growth, immunity, and susceptibility to toxic effects of heavy metals	26
6.1 Growth	26
6.2 Immunity	29
6.3 Susceptibility to toxic effects of heavy metals	29
7. Country examples	30
8. Conclusions	34
References	35

Foreword

In recent years, considerable efforts have been made to eliminate or reduce the prevalence of micronutrient deficiencies around the world. Yet progress in the control of iron deficiency is slow, despite the fact that it is the most prevalent nutritional deficiency worldwide. The high rates of iron deficiency and iron deficiency anemia constitute a public health emergency fully equivalent to an infectious disease epidemic.

Because of the multicausal nature of anemia, the problems of anemia due to iron deficiency and iron deficiency without anemia are among the more complex micronutrient deficiency problems to solve. There is no doubt that iron deficiency deserves much greater attention than it currently receives. The challenge is to justify this attention to policy planners, who are confronted with many competing priorities. One way to do so is to highlight the huge economic costs of the problem as it affects survival, development, and well-being at different points during a person's life. This report was prepared to provide this missing link.

Although all of the functional consequences of iron deficiency are important, this study focuses on the economic costs of iron deficiency due to cognitive losses in young children and productivity losses in adults. Overall, the economic loss is staggering—perhaps several billions of dollars annually. In addition, the dominant effect associated with the cognitive deficits in children clearly provides the justification and indeed points to the urgent need to prevent iron deficiency beginning with children very early in the life cycle.

The Micronutrient Initiative, in collaboration with major international agencies and governments, is committed to developing and disseminating information to highlight both the magnitude and the consequences of iron deficiency and the availability of cost-effective, sustainable solutions to this problem. It is hoped that the findings presented here will assist in this process and accelerate efforts to eliminate the problem around the world.

M.G. Venkatesh Mannar
Executive Director
The Micronutrient Initiative

Acknowledgments

This paper was commissioned by the Micronutrient Initiative (MI) to examine the evidence for a causal relationship between iron deficiency and a variety of functional consequences with economic implications. The effects were then quantified in economic terms. Such information is vital to advocate for appropriate programs to reduce iron deficiency. Jenny Cervinkas, MI, was instrumental in framing the scope of the paper in consultation with Susan Horton. Dr. Horton identified Jay Ross as a collaborator in reviewing the literature on assessing the functional consequences of iron deficiency. The authors thank Jere Haas, who provided valuable comments on an early draft.

The MI is particularly grateful to George Beaton, Jere R. Behrman and Henry M. Levin for constructive and detailed comments that were valuable in shaping and refining the final document. The MI also acknowledges careful reviews by Alan Berg, Janice Johnston, and Venkatesh Mannar.

Janice Johnston coordinated the review process and the production of the final document. The MI acknowledges the assistance of Peggy Robinson for copy editing and Billie MacDonald for cover design.

The work was supported by the MI through a grant from the Canadian International Development Agency.

Executive summary

This paper examines the evidence for a causal relationship between iron deficiency and a variety of functional consequences with economic implications (specifically, motor and mental impairment in children, low work productivity in adults, poor pregnancy outcome, and health effects on children). Although such associations have been well documented in some cases, iron deficiency or anemia may serve simply as an indicator of risk due to other causes, such as a diet poor in other nutrients. We examine in detail the epidemiological evidence for causal relationships. To the extent that we can be confident that iron deficiency does cause a consequence with economic implications, this effect is quantified in economic terms. For the consequences examined, we provide algorithms for estimating the economic losses due to cognitive delays in children, lower productivity among adults, and premature births. Anemia is also an important cause of maternal death in many countries, and although it is possible to estimate the magnitude of this problem we do not attempt to estimate its economic impact. There is some evidence of further economic losses due to the effect of iron deficiency on child growth, immunity, and susceptibility to the toxic effects of heavy metals, but we do not consider it strong enough to permit quantitative estimates. A number of countries are used as examples to illustrate the economic impact of iron deficiency and to argue that the potential benefits from prevention of iron deficiency anemia are great. Our analysis suggests that the median value of productivity losses due to iron deficiency is about US \$4 per capita or 0.9% of gross domestic product (GDP). On a per capita basis, losses are greatest in rich countries, where wages are highest. When calculated as a proportion of GDP, productivity losses are greatest in South Asia, where the prevalence of anemia is highest. The absolute losses in South Asia are estimated at close to US \$5 billion annually. The dominant effect for all countries is the loss associated with cognitive deficits in children.

1. INTRODUCTION

Iron deficiency has earned distinction as the most common nutritional deficiency in the world today. Because iron is important for blood formation, iron deficiency often leads to anemia, defined as a blood hemoglobin level below standard.¹ In a review of studies published up to 1985 it was estimated that 30% of the world's population, or 1.3 billion people, were anemic, 500 million to 600 million of these suffering from iron deficiency anemia (DeMaeyer and Adiels-Tegman 1985). If applied to 1997 global population estimates, these figures suggest that some 600 million to 800 million people now suffer from iron deficiency anemia. Given the magnitude of the problem it is important to know how iron deficiency anemia affects the lives of these individuals.

Many studies document the association of iron deficiency anemia with poor motor and mental performance in children, low work productivity in adults, and poor pregnancy outcome. In considering the effects of iron deficiency, however, it is important to realize that anemia may be only the most visible symptom of a much larger problem. There are many physiological functions of iron, other than its role in hemoglobin synthesis, that might explain the consequences of deficiency. If these other functions are compromised before hemoglobin synthesis is impaired, or before the impairment can be detected as anemia, then the consequences of iron deficiency may extend far beyond the population with iron deficiency anemia. For example, cellular immunity may be compromised by iron deficiency before there are signs of anemia (Macdougall et al. 1975). Evidence for functional consequences of mild deficiency (tissue depletion without anemia) has been harder to obtain, partly because the clinical and laboratory diagnosis of mild deficiency is more difficult and partly because the manifestations of mild deficiency are less severe. Diagnosis of mild deficiency is difficult because of the lack of a sensitive test. The use of several different tests in combination has been recommended (Dallman et al. 1981), but even these may be rendered inaccurate by concurrent infections, altitude, or recent food intake. In spite of these methodological difficulties, it is becoming increasingly clear that iron deficiency without anemia also has important functional consequences with economic implications.

¹Hemoglobin is an iron-containing component of red blood cells that is needed for oxygen transport. Its level in the blood depends on age, sex, and physiological state, so standards vary. The following hemoglobin concentrations are used by the World Health Organization (WHO 1997) to indicate cutoffs below which anemia may be present: children under 6 years, <110 g/L; children 6–11 years, <115 g/L; children 12–14 years, <120 g/L; adult males, <130 g/L; adult females (nonpregnant), <120 g/L; adult females (pregnant), <110 g/L. The population can be divided into four groups depending on the presence or absence of anemia (as indicated by hemoglobin level) and the presence or absence of iron deficiency (as indicated by iron stores). Of concern here is iron deficiency. However, because of the lack of nationally representative data on iron deficiency, the prevalence of anemia is used as a proxy for some of the estimates. This is appropriate when applying coefficients derived from studies of responses to iron supplementation among anemic subjects.

Other common causes of anemia include malaria and intestinal parasitic infections, genetic disorders such as thalassemia and pernicious anemia, and deficiencies of other nutrients such as folate, vitamin A, vitamin C, and protein. Distinguishing among these causes is clearly important for controlling anemia. In southern Malawi, for example, infant anemia was unrelated to maternal hematocrit status but was twice as likely to occur if the placenta had been infected with malaria (Reed et al. 1994). The consequences of anemia may also depend on the cause. For example, Scholl et al. (1992) found that anemia was a risk factor for preterm delivery only if it was accompanied by iron deficiency. In intervention studies addressing anemia that fail to distinguish iron deficiency anemia from other anemias, the impact of therapy on iron deficiency anemia itself may be underestimated. Conversely, if the effects of therapy as determined only from iron deficiency anemia cases are applied to the larger population of all anemic individuals, the population effects would be overestimated. Unfortunately, in most observational studies the cause of anemia is unknown. DeMaeyer and Adiels-Tegman (1985) estimated that iron deficiency accounts for only about 42% of the 1.3 billion cases of anemia worldwide. In a sample of Venezuelan children living below 900 m altitude, 43% of those considered anemic on the basis of hemoglobin values also had ferritin and transferrin saturation values indicative of iron deficiency (Taylor et al. 1993). These estimates suggest that a little less than half of all anemia is due to iron deficiency.

The purpose of this paper is to answer the following questions: To what extent are associations between iron deficiency and functional consequences causal and to what extent is iron status simply a marker for other causal factors? To the extent that the relationships are causal, can the effects be quantified in economic terms? What are the expected economic benefits of improving iron nutrition in specific countries?

The paper does not attempt to undertake a full cost–benefit analysis. Although the losses attributable to iron deficiency anemia can be compared with the costs of supplementation and fortification in current terms, a full cost–benefit analysis requires calculation of the time-path of the costs and benefits. One of us has developed elsewhere (Ross 1997) a methodology for undertaking this calculation for supplementation in adults and applying it to country-level data. Extending this methodology to include the effects discussed in the present paper and applying it to country-level data will be the focus of future work.

Our aim is to propose realistic quantitative estimates of the economic consequences of iron deficiency that can be defended on epidemiological and economic grounds. In the many areas where results are uncertain because of weak or conflicting evidence, we attempt to make unbiased if imprecise judgments of the quantitative relationships at issue. Then, applying these relationships to country-level data, we estimate the economic consequences of iron deficiency in monetary terms.

There are three broad areas in which iron deficiency is considered to have important functional impacts on humans: the cognitive ability of children, the work capacity of adults, and pregnancy

outcome. Although other effects were examined (child growth, immune function, and susceptibility to the toxic effects of heavy metals), there was insufficient consistent evidence to incorporate them into the analysis.

To establish that a causal relationship exists between a risk factor (such as iron deficiency) and an outcome (such as cognitive impairment), a number of conditions must be met. First, there must be an association between the risk factor and the outcome. The stronger and more consistent this association, the more convincing the case for causality. Second, there must be a plausible biological mechanism for the causal relationship (although ignorance of this mechanism does not disprove causality). Third, the cause must come before the outcome. Fourth, there must be no alternative explanation for the association. Much of the work of epidemiological investigation focuses on this last condition, which is usually confirmed by demonstrating a response to therapy. In this review, we apply these standards to the existing literature on the proposed relationships between iron deficiency and functional consequences to assess the strength of the argument for causation in each case.

For relationships that can reasonably be considered causal, the degree of the functional consequence is assessed and, to the extent possible, interpreted in a manner that can be quantified in economic terms.

We examine and quantify four channels of influence in sections 2–5. Section 2 deals with cognitive impairment in childhood and the subsequent effects on adult productivity, section 3 with impaired physical productivity in adults due to current iron deficiency anemia, section 4 with low birth weights and prematurity, and section 5 with the effects of anemia during pregnancy on maternal outcomes. In section 6 we list other channels of influence that cannot yet be quantified but that may be important. In section 7 we illustrate the economic impact of iron deficiency in selected countries using the relationships described in sections 2–5. We present our conclusions in Section 8.

2. LOWER FUTURE PRODUCTIVITY OF CHILDREN

2.1 A biological mechanism

Iron deficiency is thought to influence the future productivity of children primarily through its permanent effects on mental development and cognition and, in turn, on school achievement. The evidence for an effect of iron deficiency on mental development and cognition comes from 1) studies of the role of iron in neural development and the function of the brain, and 2) epidemiological studies of the relationship between anemia and performance on cognitive tests, sometimes in the context of an intervention. The first group of studies is important in establishing the existence of a plausible biological explanation for, and greater understanding of, the observations of the second. For example, evidence from iron-deficient rats suggests a permanent reduction in dopaminergic neurotransmission due to the failure of dopamine receptors

to develop early in life (Ben-Shachar et al. 1986; Yehuda et al. 1986). Because there is no evidence that these problems are mediated by anemia, they might occur at milder levels of deficiency. This possibility is important because if there is a spectrum of debilitation and if nonanemic, iron-deficient children are also affected, then the prevalence of cognitive impairment may be far greater than the prevalence of iron deficiency anemia among infants.

The biological basis for an effect of iron deficiency on the mental and motor development of young children is still a matter of speculation. However, evidence from animal studies (reviewed by Lozoff 1988; Youdim et al. 1989; Beard et al. 1993) permits several conclusions. There are high concentrations of iron in certain similar regions of the brain in rats and humans, which suggests significant roles for iron that could account for its importance in cognition. In the rat, a severe deficiency early in life, but not in adulthood, results in a permanent deficit of brain iron that cannot be corrected with therapy (Dallman et al. 1975). Dopamine is an important neurotransmitter in the brain of both rats and humans, and in rats this compound relies on an iron-dependent receptor to function normally. Unlike the deficit that results from early iron deficiency, which is permanent, loss of dopamine receptor function caused by iron deficiency in adult rats can be reversed by iron therapy. The function of receptors for at least two other neurotransmitters, serotonin and γ -aminobutyric acid, are also compromised in iron-deficient rats, although these systems are less well understood. The amount of a fourth neurotransmitter, norepinephrine, is reduced in the peripheral tissues of iron-deficient rats (Beard et al. 1993). Although these results do not provide conclusive evidence of a direct link between iron deficiency and cognitive effects in humans, they do provide a number of plausible biological mechanisms to support the epidemiological evidence that brain function is compromised in iron deficiency.

2.2 Evidence for an effect of iron deficiency on cognitive development in children under 2 years of age

The standard tests of development in infants, used in virtually all of the studies reviewed here, are the Bayley scales. These scales include both mental and motor development components, each standardized to a mean of 100 and a standard deviation of 16. In addition, the Bayley scales include the Infant Behavior Record, designed to assess the infant's affective state, such as responsiveness to the investigator, attention span, fear, and other behavioural signs that might explain mental or motor test performance. The Bayley scales are not considered an intelligence test but a means of determining the stage of development of the infant relative to age-appropriate standards.

Observational studies of the relationship between iron deficiency anemia and mental test performance are remarkably consistent in finding that infants with moderate iron deficiency anemia have test scores that are 0.5 to 1.5 standard deviations lower than those of infants with sufficient iron stores (see reviews of Lozoff 1988; Pollitt 1993). These differences are large enough to be of great concern, especially given the prevalence of anemia in children in economically deprived settings. Pollitt (1995) has also argued that many of the developmental

effects ascribed to protein-energy malnutrition may in fact be due to iron deficiency, pointing out that these conditions typically coexist. In observational studies, therefore, unless iron status is carefully measured and controlled for, it may confound the relationship between protein-energy malnutrition and cognitive ability. Even in the Guatemala intervention study that demonstrated effects of protein and energy supplementation on cognitive development (Pollitt et al. 1995), the supplements also provided iron, raising the possibility that the additional iron may have at least partly accounted for the observed effect of the supplements.

Many of the observational data referred to here come from baseline assessments in the context of therapeutic trials (Oski and Honig 1978; Lozoff et al. 1982a; Walter et al. 1983; Lozoff et al. 1987; Walter et al. 1989). Part of the association may be confounded by poverty and poor environmental conditions that are also associated with anemia and that may independently influence mental and motor development. However, when such factors are measured and controlled for in regression analyses, iron status generally remains a strong predictor of cognitive development, thus supporting the assumption of causality.

Results from these observational studies are persuasive, but conclusive evidence for the effect of iron deficiency on cognitive development comes from intervention studies. The results of the many iron intervention trials on children up to 26 months of age published to date are summarized in Table 1. The ideal iron supplementation study aims to avert or correct iron deficiency in a group of high-risk infants, while a comparable group receives an identical treatment but without the iron (a placebo). The assignment of the iron therapy or placebo should be random, to help guard against selection bias that might result in the two groups being different in some important way. Finally, both investigators and subjects should be unaware of both the treatment (iron or placebo) and the iron status of the subjects, to guard against possible bias in the assessment of outcomes or the handling of data. The occurrence of cognitive improvements in the treated group relative to the placebo group in such studies establishes a convincing case for a causal effect of iron deficiency on behaviour and cognition. However, because studies that withhold treatment from anemic subjects are hard to justify on ethical grounds, these have generally been restricted to very short periods of placebo-controlled interventions (Oski and Honig 1978; Lozoff et al. 1982a), sometimes followed by a longer period of universal coverage (Lozoff et al. 1987; Walter et al. 1989), or have been conducted in situations where the anticipated benefits of the intervention are uncertain (Moffat et al. 1994).

The short-term placebo-controlled studies have produced mixed results. In a pioneering study in the United States, Oski and Honig (1978) observed a statistically significantly greater increase in mental scores (by 7.5 points or approximately half a standard deviation) in infants given an intramuscular injection of iron relative to infants who received a saline placebo. In a Guatemalan study, there was no effect of daily oral supplementation for 1 week on either motor or mental development scores of anemic infants 6–24 months old (Lozoff et al. 1982a, b). Similarly, a replication of this study in Costa Rica found no effect of iron supplementation (Lozoff et al. 1987).

Only two placebo-controlled studies published to date have described the effects of long-term iron therapy in a population of very young children with iron deficiency anemia (Aukett et al. 1986; Idjradinata and Pollitt 1993). In the first, 31% of 17- to 19-month-old anemic children receiving daily iron supplements but only 12% of those receiving placebo attained the average rate of motor development for children their age over the 60-day intervention period, a difference that was statistically significant ($P < 0.05$) (Aukett et al. 1986). In the second study, done in Indonesia, the mental and motor scores of both treatment and placebo groups improved over the 4-month intervention (Idjradinata and Pollitt 1993). However, in the children receiving daily iron supplements mental scores improved by 19 points more and motor scores by 18 points more (in both cases just over 1 standard deviation) than in the children receiving placebo. These studies provide conclusive evidence for a causal link between iron deficiency and developmental delays that can be corrected by iron therapy. A third placebo-controlled study, performed in Canada, was designed to assess the effect of iron-fortified formula in preventing developmental delays in a sample of neonates at risk for anemia, most of whom who were in fact nonanemic. The infants who received the fortified formula had higher motor development scores at 9 and 12 months (by 4.0 and 6.3 points, respectively) than those who received a standard nonfortified formula, but by 15 months these differences were no longer apparent (Moffat et al. 1994). The lower prevalence and severity of anemia in this population might account for the smaller differences here than in the Indonesian sample (Idjradinata and Pollitt 1993), which included only infants with hemoglobin concentrations less than 105 g/L. This cutoff point is lower than that usually used to define anemia in children under 6 years of age (110 g/L).

What are the functional implications of early developmental delays for the long-term cognitive abilities of these children, and can they be corrected? Answers to these questions remain somewhat speculative, because none of the intervention studies with anemic children had sufficiently long periods of follow-up. Idjradinata and Pollitt (1993), citing Pollitt et al. (1989), warned that mental development scores in infancy do not predict differences in intellectual function in later childhood. Mental development of children as indicated by the Bayley scales is known to be poorly correlated with later intelligence. Motor scores, on the other hand, do predict cognitive test performance not only later in childhood but also at 18 years of age (Pollitt and Gorman 1990), although in the cited study the scores were not attributed to or influenced by iron deficiency. However, if the improvement in motor performance in the Indonesian study is taken as indicative of the magnitude of the motor delay due to iron deficiency, the motor scores in anemic infants could be expected to be reduced by approximately 18 points (or just over 1 standard deviation). Furthermore, since this was the net correction observed in children with anemia from all causes after a placebo-controlled, randomized, double-blind intervention, this reduction can be attributed, with considerable confidence, to iron deficiency anemia. Because the final motor scores were roughly the same as those of the nonanemic children, it appears that the motor impairment was completely reversed by 4 months of therapy.

Failure to reverse the mental and motor effects of anemia in previous placebo-controlled studies may therefore be attributed to the brevity of the therapy offered (Lozoff et al. 1982a; Lozoff et al.

1987; Walter et al. 1989). Longer trials of therapy without placebo controls have also had mixed results. In Costa Rica, oral iron therapy over 90 days had no apparent effect on mental development scores but did appear to improve motor test performance by more than 9 points in anemic children 12–23 months old (Lozoff et al. 1987). In Chile, on the other hand, a similar regimen in 12-month-old infants had no effect on either mental or motor scores (Walter et al. 1989). However, because (for ethical reasons) the comparison groups in both of these trials were nonanemic children and therefore not strictly comparable, and because it is possible that the test performance without therapy might have worsened over this period, these results are inconclusive.

The evidence available satisfies all of the conditions needed to conclude that iron deficiency causes developmental delays and that these can be at least partially reversed by iron therapy. There is a strong association between iron deficiency anemia and cognitive and behavioural test performance that remains even after controlling for a wide variety of potential confounders. This association has been confirmed in numerous studies in a wide variety of situations. Although there is still uncertainty about the biological basis for this effect, the importance of iron in several neurological processes suggests more than one plausible biological mechanism. The timing of iron deficiency relative to the developmental delays is difficult to demonstrate in infants because ethical considerations preclude the experimental induction of iron deficiency. However, given that in observational studies the developmental delays appear at least to accompany the deficiency, there is no evidence to contradict the proposed chronology. Finally, the evidence from therapeutic trials suggests that this relationship is causal and that the observed delays can be corrected.²

2.3 Evidence for an effect of iron deficiency on cognitive development in children 2 years of age and older

In children 2 years of age and older it is possible to measure intelligence with tests such as the Wechsler Intelligence Scales for Children and the Raven Progressive Matrices. It has been shown that iron-deficient children score about half a standard deviation lower on these tests than nondeficient controls (see review by Pollitt 1993). Although this association remains even after statistical adjustment for the effects of socioeconomic status, such adjustment cannot compensate

²In Costa Rica, Lozoff et al. (1991) retested, at 5 years of age, children who had been the subjects of therapeutic trials as infants. Children who had been anemic as infants scored significantly lower on intelligence tests than those who had not been anemic, even though the associated anemia had been entirely corrected and even though the investigators controlled for a variety of potential confounding factors. This result seems to contradict the conclusion that deficits can be corrected. However, not all of the predisposing factors originally contributing to the anemia could have been entirely controlled for. These almost certainly included factors (such as poverty, poor caring practices, or poor health) that might be expected independently to lead to lower performance on intelligence tests later in childhood.

for unrecognized, unmeasured, or imperfectly measured factors. Verification through placebo-controlled interventions is therefore required to establish that the observed associations are causal. In reviewing the results of the several published clinical trials of the effects of iron therapy on cognitive performance and school achievement of children older than 24 months, Pollitt (1993) concluded that iron therapy lasting at least 2 months resulted in major improvements in intelligence quotient (IQ) and that “iron deficiency anemia causes an alteration in cognitive function among preschool and school age children that is reversible following the repletion of iron stores.”

The studies on which this conclusion is based are summarized in Table 2 (Pollitt et al. 1989; Seshadri and Gopaldas 1989; Soemantri 1989; Soewondo et al. 1989). The one study that provides a quantitative estimate of this effect (Seshadri and Gopaldas 1989) suggests a reversible IQ deficit in anemic 5- to 6-year-old Indian boys of 8 points or half a standard deviation. This deficit is similar to the difference in IQ between anemic and nonanemic children in observational studies.

2.4 Economic implications of cognitive deficits

There are a few studies of adults relating cognitive achievement to wages in developing countries. For Colombia, Psacharopoulos and Velez (1992) found that an improvement in cognitive achievement of one standard deviation was associated with a 7–9% increase in hourly earnings, and an improvement in native ability (as measured by Raven’s matrices) of one standard deviation was associated with a 5–7% increase in hourly earnings. Boissiere et al. (1985) examined the effect of cognitive achievement on employees in Nairobi and Dar es Salaam. From their results it can be calculated that an improvement in cognitive score of one standard deviation was associated with a 17% increase in hourly earnings for primary school leavers and a 23% increase for secondary school leavers in Kenya. The corresponding figures for Tanzania were 8% and 13%, respectively. The apparent effect on earnings of an improvement in Raven’s matrices scores of one standard deviation was smaller (increases of 7% in Kenya and 6% in Tanzania) and was only observed for secondary school leavers.

Two other studies in developing countries used more sophisticated econometric techniques to allow for issues of selectivity (the fact that wage workers are not a random sample of all workers) and simultaneity (whereby schooling, cognitive skills, and work experience are determined jointly). For rural Pakistan, Alderman et al. (1996) found that an improvement in cognitive skills of one standard deviation was associated with an increase in wages ranging from 10% (using ordinary least squares) to about 12% (allowing for selectivity and simultaneity). Effects of ability (as measured by Raven’s matrices) were slightly larger but not statistically significant. Finally, Glewwe (1996) found that in Ghana reading and mathematics scores had strong effects on wages: an improvement of one standard deviation in mathematics scores was associated with a 22% increase in wages in the public sector, and a similar improvement in reading scores with a 33% increase in wages in the private sector. Ability effects were not significant on their own, but were so when they interacted with schooling. These studies confirm similar findings for industrial

countries indicating that ability and academic achievement are significantly associated with earnings and income (Hause 1972; Wise 1975; Hauser and Sewell 1986). Although these observational studies do not allow higher earnings to be attributed to better cognitive ability with absolute certainty, the consistency of this evidence across many studies and the biological plausibility of the cause-and-effect argument convince us that this relationship is causal.

2.5 Productivity effects of iron deficiency in childhood

On the basis of these studies, a reasonable estimate is that a decrease of half a standard deviation in scores for cognitive achievement is associated with a 4% decrease in hourly earnings. This estimate may be conservative, given that it is likely that cognitive achievement has additional indirect effects through greater schooling, and the studies cited controlled for schooling. In turn, a decline of half a standard deviation in adult IQ and cognitive test performance is a reasonable estimate of the effect of iron deficiency anemia in childhood.

We assume that this 4% loss of earnings is also applicable to self-employment earnings, where ability is likely to have if anything a stronger effect on earnings than for wage-earning employees, because the full cost of any productivity decrease is borne by the worker. We conservatively assume that the effect on earnings represents decreased labour productivity, with no effect on the productivity associated with other factors. Hence the loss of per capita productivity due to childhood iron deficiency anemia and a 4% decline in labour productivity is calculated from the following equation:

$$\text{Cog loss} = 4\% \times \text{WS} \times \text{GDP/cap} \times \text{Pr}(\text{child})$$

where

Cog loss = productivity losses due to lower cognitive scores related to childhood iron deficiency anemia

WS = wage share (labour) in GDP (measured at factor cost)

GDP/cap = per capita GDP

Pr(child) = prevalence of anemia in children

(We use the prevalence of anemia rather than iron deficiency anemia because the 0.5 standard deviation improvement in cognitive test scores reported by Seshadri and Gopaldas [1989] was the average observed among treated anemic children, not just among those with iron deficiency anemia.)

By using the current prevalence of childhood anemia to estimate current productivity losses in adults, we make the simplifying assumption that prevalence has remained at the same level over the last several decades. To the extent that prevalence has increased or decreased over this period, this method would over- or underestimate the true current impact of past iron deficiency anemia in childhood.

Example

In Bangladesh, wage share in GDP is assumed to be 40%, per capita GDP is \$220 (US dollars throughout), and prevalence of anemia in children is 73%. Hence, annual loss is calculated as follows:

$$\text{Cog loss} = 0.04 \times 0.40 \times 220 \times 0.73$$

This calculation yields an annual loss of \$2.57 per capita, equivalent to 1.2% of GDP. (See also Table 6 and discussion in section 7.)

3. LOWER CURRENT PRODUCTIVITY OF ADULTS

It has long been observed that the symptoms of iron deficiency anemia include tiredness, lethargy, and fatigue. The biological basis for these effects almost certainly includes the role of hemoglobin as an iron-containing transport protein needed to move oxygen from the lungs to the muscles, the brain and other tissues in the body. Anemic individuals are therefore unable to transport enough oxygen to support strenuous activity of long duration. It is likely that iron deficiency affects several other metabolic systems, such as neurotransmission, formation of myoglobin (needed for oxygen transport and storage within muscles), and formation of cytochromes (essential for the electron transport system in energy metabolism). Evidence of a direct role for these systems in the reduction of physical capacity in iron deficiency is not as clear as that involving anemia directly. However, there is evidence from some physical capacity and productivity studies that functional improvements following therapy are seen before or in the absence of improvements in hemoglobin level (Ohira et al. 1979) and that even nonstrenuous physical activities are affected (Li et al. 1994). These findings suggest that anemia is not the sole mechanism for the effect of iron deficiency on productivity and that subclinical deficiencies also matter.

In their study of physiological responses to exercise in severely (hemoglobin <80 g/L) and moderately (hemoglobin 80–100 g/L) anemic men in Dar es Salaam, Davies et al. (1973) found that anemia was associated with a more rapid heart rate during exercise and a lower ratio of oxygen uptake to cardiac output. Maximum aerobic power in moderate and severe anemia was reduced by 24% and 34%, respectively, relative to nonanemic controls, and heart rate for a given level of oxygen consumption was 26% and 34% higher. However, from this observational study it is difficult to attribute such differences conclusively or exclusively to anemia because other nutritional and health factors associated with anemia could also account for them.

A more informative approach is to examine changes in physical capacity and work productivity in response to iron therapy. Table 3 presents the results of a number of such studies. In a placebo-controlled study in Sri Lanka, Edgerton et al. (1979) examined the effect of a daily iron supplement for 1 month on the weight of tea picked by adult female plantation workers.

Although there was a net mean increase in hemoglobin level of 15 g/L among women receiving the supplement, compared with those consuming the placebo, the net percentage increase in productivity was only 1.2%. However, other evidence suggests that treatment *did* have a significant effect on physical capacity. In a subsample of 8 matched pairs in whom physical activity was mechanically monitored, the increase in daily activity was 80% greater in women receiving iron treatment than in those receiving the placebo, a statistically significant difference. Women whose hemoglobin concentration was below 90 g/L also had a greater productivity response to therapy than women whose hemoglobin level was greater than 110 g/L. After the month-long placebo-controlled trial, all women received therapy for an additional month, which resulted in a net increase in the productivity of the original placebo group. The relatively small productivity response observed in this study may have been due to the lack of economic incentive, which makes this an inappropriate situation in which to test for productivity effects. The authors suggested that a larger productivity effect might have been observed if the women had not also been constrained by peer and supervisor expectations, habit, and the knowledge that any extra tea they picked they then had to carry.

In the same population, a placebo-controlled therapeutic trial tested the effect of iron dextran administered intravenously on hemoglobin level, maximum work load, and heart rate of 6 male and 14 female anemic adults (Ohira et al. 1979). However, the treatment group was significantly more anemic than the placebo group (mean hemoglobin level 66 and 80 g/L, respectively). Within 4 days there was a statistically significant response to iron therapy, in terms of hemoglobin concentration, maximum work load, and heart rate for a fixed work load. None of these measures changed in the placebo group even after 6 days. After 16 days, hemoglobin concentration in the treatment group had increased by 27% and maximum work load by 70%, whereas heart rate for a given work load had declined by 25%. In a comparison of workers with the *same* hemoglobin levels, iron-treated workers had lower heart rates for a given work load than untreated workers, a result that led the authors to conclude that some mechanism other than (or in addition to) anemia explains the effect of iron therapy on heart rate.

Again, in the same population, 10 male and 35 female adult hospital patients were divided into five groups on the basis of their hemoglobin and serum iron levels (Ohira et al. 1981). All received intravenously a quantity of iron dextran calculated to replenish iron stores (30–50 mL). Hemoglobin level, maximum time spent in vigorous exercise on a laboratory treadmill, and heart rate at different work loads were monitored at 2-day intervals for 7 or 8 days. There was a strong association at the outset between physical capacity and hemoglobin levels. Although only slight and statistically insignificant increases in hemoglobin concentration were observed in the anemic subjects over the week following treatment, large increases (46–59%) in the maximal work capacity of these subjects were observed. These were associated with reductions in heart rate both during rest and at different work loads. Subjects with marginal hemoglobin levels but low serum iron also showed gains in work capacity and large reductions in heart rate at different exercise levels, but no hemoglobin response. Nonanemic iron-sufficient subjects showed no response to treatment in terms of either biochemical indices or work capacity. Blood lactate, an

indicator of exercise-induced stress, was more strongly correlated with serum iron than with hemoglobin, suggesting a mechanism at least partly independent of anemia. The short duration of this study and the failure to increase hemoglobin concentration over the course of the week following therapy makes it difficult to predict the longer-term implications of therapy of this kind. However, the large effects observed in iron-deficient nonanemic subjects and in the absence of substantial improvements in hemoglobin concentration suggest that the benefits of iron therapy for work capacity and economic productivity extend beyond the population with iron deficiency anemia.

Further evidence for a negative impact of iron deficiency without anemia on physical capacity comes from a placebo-controlled supplementation trial with iron-deficient *nonanemic* US women (Zhu and Haas 1997). Before supplementation there were differences among the women in their physical capacity, measured as peak oxygen consumption, that were related to their iron stores but not to their hemoglobin levels. Iron supplementation at 135 mg of elemental iron per day for 8 weeks replenished their iron stores and significantly reduced both the level of exertion required and blood lactate levels observed for a given work load (Zhu and Haas 1998). The initial differences in physical capacity and the improvements observed on supplementation suggest an effect of iron deficiency not related to hemoglobin levels or the oxygen transport capacity of the blood.

Basta et al. (1979) conducted a therapeutic placebo-controlled trial to measure the productivity effects of daily iron supplementation in a group of anemic (hemoglobin <130 g/L) and nonanemic male rubber tappers and weeders in Indonesia. Before treatment, there was a strong correlation ($r = 0.56$, $P < 0.001$) between hemoglobin level and income from either weeding or tapping, and the nonanemic workers had Harvard step test scores that were 14.5% higher than those of the anemic workers ($P < 0.001$). Those who received a daily supplement of 100 mg of ferrous sulfate for 60 days experienced a significant increase in hemoglobin level, hematocrit, serum iron, and transferrin saturation compared with initial values and with those of the placebo group. Although Harvard step test scores improved in all groups, the increase was greatest among anemic workers who received the daily iron supplement. The work productivity of anemic tappers who received the supplement was 17% greater than that of anemic tappers who received placebo ($P < 0.05$), a difference similar in magnitude to the baseline productivity difference between the two groups (18.7%, $P < 0.01$). No significant productivity differences were observed between the treated anemic weeders and weeders given placebo, possibly because of the lack of an effective incentive system or the especially large productivity variations among weeders. The authors extrapolated from their results for tappers to estimate a benefit–cost ratio for investment in iron supplementation of 260 : 1. This ratio probably overestimates the true benefit–cost ratio that could be expected in intervention programs because it does not include the cost of screening, delivery, supervision, and the cash incentive offered to increase compliance, nor does it account for the apparent lack of a productivity increase in weeders. This study reinforces a large body of evidence suggesting that work productivity and physical capacity are compromised in people with iron deficiency and that these effects can be rapidly reversed at low cost. It shows clearly that where productivity is limited by reduced physical capacity due to iron deficiency anemia, the

economic benefits are likely to pay for the iron supplementation many times over.

In another study that documented the productivity effects of iron supplementation in anemic workers in a field situation, Li et al. (1994) used a randomized, placebo-controlled, double-blind design to study the effect of 12 weeks of daily ferrous sulfate supplementation on hemoglobin level, iron status, heart rate, energy expenditure, productivity (measured as pay per day), and production efficiency (defined as pay per unit of energy expenditure) of female cotton mill workers in China. Energy expenditure was derived from heart rate, individually calibrated before and after supplementation. The work consisted of operating factory machinery and involved moving the hands and arms while walking along the machines. Productivity was evaluated by pay received, which was based on the quantity and quality of yarn produced. Because quantity was determined primarily by the fixed pace of the machine, large variations in productivity were not expected. Among anemic subjects receiving treatment, hemoglobin level increased (from 114 to 127 g/L, $P < 0.001$), as did other indices of iron status; these indicators remained unchanged in the placebo group. Treatment resulted in a significant decrease (by 4.6%) in heart rate at work. The reduction in heart rate was strongly correlated with the increase in hemoglobin level ($r = 0.60$, $P < 0.001$). Productivity increased by 5% and production efficiency by 17% in women receiving iron, whereas there was virtually no change in either measure in women receiving placebo. These benefits are surprisingly large considering the light nature of the work performed. Even larger productivity effects would be expected in activities requiring greater exertion or in situations where pay is more closely tied to physical effort.

The largest functional impact of iron therapy here is the increased production efficiency due to the reduction in energy expenditure combined with an increase in productivity. This benefit is not due to a higher aerobic potential, because energy expenditure actually decreased, nor can it be entirely due to the change in cardiovascular efficiency, because it is not correlated with the change in heart rate. A plausible explanation, as the authors suggested in their report, is that iron deficiency has effects on energy metabolism not directly related to oxygen transport. These results are important because they suggest a significant economic impact of iron deficiency on physical tasks that involve a low level of exertion.

Supporting evidence was reported in a study of female loom operators in Indonesia (Scholz et al. 1997). Although the operation of the looms was not strenuous, anemic women had lower work output than nonanemic women. The authors found a strong relationship between hemoglobin level and productivity even after controlling for a variety of potentially confounding factors, such as education, age, other indicators of nutritional status, and work experience. Each reduction of one standard deviation in hemoglobin level (13.3 g/L) was associated with a reduction in productivity of 3.6%. The authors speculated that the productivity effects might be explained as the effects of anemia on the women's alertness and therefore their ability to detect and correct problems with the looms quickly.

Support for the hypothesized effect on cognition of iron deficiency without anemia comes from a

study of adolescent girls in the United States (Bruner et al. 1996). Girls with normal hemoglobin levels but low serum ferritin concentrations ($<12 \mu\text{g/L}$) received either a supplement of ferrous sulfate (260 mg of elemental iron) or a placebo daily for 8 weeks. A battery of cognitive tests administered before and after the period of therapy revealed that girls receiving iron performed better on a verbal learning test relative to girls receiving placebo, but not on three other tests of attention and cognition.

In his review of a number of published and unpublished studies on the relationship between hemoglobin level and manual work output, Levin (1986) estimated that for each 1% increase in hemoglobin level (for example, from 100 to 101 g/L) among anemic subjects, manual work output increases by 1–2%. The studies reviewed here and summarized in Table 3 corroborate this estimate and suggest that it does not apply only to anemic individuals undertaking heavy manual labour. The rapid and substantial increase in physical capacity following short-term supplementation without an increase in hemoglobin level (Ohira et al. 1981), the improvements in physical capacity following replenishment of iron stores in nonanemic individuals (Zhu and Haas 1998), and the improvements in productivity and production efficiency in less physically demanding light work (Scholz et al. 1997; Li et al. 1994) suggest that benefits might be seen in a range of individuals and situations that extend beyond the anemic population and include nonstrenuous labour.

To be conservative, we assume that iron therapy in anemic adults is associated with a 5% increase in labour productivity in all blue-collar work except heavy manual labour. For heavy manual labour, we assume that the increase in productivity is 17%, in keeping with the productivity increase observed in iron-supplemented Indonesian rubber tappers (Basta et al. 1979) and the 1–2% increase in productivity with each 1% increase in hemoglobin level observed among anemic workers (Levin 1986).³ Losses associated with iron deficiency are therefore assumed to comprise a 5% loss for all blue-collar workers and an additional 12% loss for blue-collar workers engaging in heavy manual labour. To calculate the output loss associated with lower productivity in heavy manual labour, we assume that manual labour accounts for half of the output of agriculture and construction but none of the output of other industries (such as manufacturing, utilities, services, commerce). We further assume that output in construction is 15% of that in agriculture, because disaggregated data on output are less readily available for construction. Note that the productivity loss we use is more conservative than that of Levin et al. (1994), who assumed a 20% productivity impairment for all adult wage employees, which is

³We say this is “in keeping” with Levin’s 1–2% elasticity relating hemoglobin level to productivity because a 17% increase in productivity for a group of anemic individuals with a mean hemoglobin concentration of, say, 100 g/L would imply an improvement of 8.5–17 g/L (to between 108.5 and 117 g/L), an increase in keeping with those observed in therapeutic trials. We refrain from linking the productivity increase directly to the hemoglobin increase because such calculations would imply a direct causal relationship between hemoglobin level and productivity, but, as we argue elsewhere, productivity increases may not necessarily occur through an increase in hemoglobin concentration.

almost certainly an overestimate.

Hence the per capita effect of adult anemia (through lower physical productivity of adults) is estimated from the following expression:

$$[5\% \times WS \times BC \text{ Share} \times GDP/cap \times Pr(\text{adult})] + [12\% \times WS \times HML \times GDP/cap \times Pr(\text{adult})]$$

where:

WS = wage share in GDP (measured at factor cost)

BC Share = share of blue-collar employment in total employment (share of output attributable to blue-collar workers in GDP would be preferable but is not available)

GDP/cap = per capita GDP

Pr(adult) = prevalence of anemia in adults (weighted average of male and female rates, using relative shares in labour force as weights)

(We use the prevalence of anemia rather than iron deficiency anemia because the estimates of the consequences of iron deficiency anemia from Basta et al. [1979] represent the average response to therapy in anemic workers rather than only those with confirmed iron deficiency anemia.)

HML = heavy manual labour share in GDP (measured as 50% of the value of output in agriculture and construction)

Thus, combining the effects of childhood anemia on cognitive achievement (from the previous section) with those of adult anemia on physical productivity requires some assumption about the degree of overlap of the cognitive and physical productivity effects. We assume conservatively that all anemic adults were anemic as children and that the cognitive and physical productivity effects overlap completely. Hence, we calculate the cognitive effects (based on a 4% decrease in productivity for all workers [Cog loss]) and to this add a 1% decrease for blue-collar workers only (5% total decrease in productivity for blue-collar workers [BC loss]) and a further 12% decrease for blue-collar workers performing heavy manual labour (17% total decrease in productivity for heavy manual labour [HML loss]).

Hence, total productivity loss due to iron deficiency anemia is estimated from the following:

$$\begin{aligned} & \text{Cog loss} + \text{BC loss} + \text{HML loss} \\ &= [0.04 \times WS \times GDP/cap \times Pr(\text{child})] \\ &+ [0.01 \times WS \times BC \text{ Share} \times GDP/cap \times Pr(\text{adult})] \\ &+ [0.12 \times WS \times HML \times GDP/cap \times Pr(\text{adult})] \end{aligned}$$

Example

For Bangladesh we have already calculated that the cognitive loss represents \$2.57 per capita or 1.2% of GDP (see section 2.5). For this country the share of blue-collar work in GDP is taken as 70% and the prevalence of anemia in adults as 65.9% (based on a prevalence of 74% for women and 60% for men and a female share of the labour force of 42%). As before, the wage share is 40% and per capita GDP is \$220. Thus the *additional* loss of productivity in blue-collar work (BC loss) can be calculated as follows:

$$\begin{aligned} & 0.01 \times \text{WS} \times \text{BC Share} \times \text{GDP/cap} \times \text{Pr(adult)} \\ & = 0.01 \times 0.4 \times 0.70 \times \$220 \times 0.659 \end{aligned}$$

This calculation yields \$0.41 per capita, which amounts to 0.2% of GDP.

A further loss is expected in heavy manual labour, which is a subset of blue-collar work. The share of heavy manual labour in GDP is estimated as 57.5% of the share of agriculture in GDP (assuming that half of the labour in agriculture and construction is heavy labour, and that the size of the construction sector is 15% that of the agriculture sector). In Bangladesh, the share of agriculture in GDP is 30%. Thus, the additional loss in heavy manual labour (HML loss) is:

$$\begin{aligned} & 0.12 \times \text{WS} \times \text{HML} \times \text{GDP/cap} \times \text{Pr(adult)} \\ & = 0.12 \times 0.40 \times (0.575 \times 0.3) \times \$220 \times 0.659 \end{aligned}$$

This calculation yields \$1.20 per capita, which amounts to 0.5% of GDP.

Thus, the total loss due to cognitive impairment, lower productivity in blue-collar work, and lower productivity in heavy manual labour in Bangladesh can be calculated as follows:

$$\begin{aligned} & \text{Cog loss} + \text{BC loss} + \text{HML loss} \\ & = \$2.57 + \$0.41 + \$1.20 \end{aligned}$$

Thus the total loss is \$4.18 per capita or 1.9% of GDP (see also Table 6 and discussion in section 7).

4. COSTS OF CARE FOR LOW-BIRTH-WEIGHT AND PREMATURE INFANTS

The prevalence of anemia is highest among pregnant women, reaching close to 90% in some communities. This is unfortunate, because anemia during pregnancy is thought to contribute to poor birth outcomes, including prematurity and low birth weight. These conditions in turn contribute to infant morbidity and mortality. This is part of the justification for the recommendation in many countries that all pregnant women receive daily supplements of iron and folate. The evidence reviewed in this section suggests that the association between anemia and birth weight is due mainly to an effect of iron deficiency anemia on prematurity. We offer an

algorithm to calculate the economic consequences of this effect but because of a lack of adequate data, no country-level examples can be provided.

Several observational studies have noted associations between anemia in pregnancy and poor birth outcomes (MacGregor 1963; Murphy et al. 1986; Mavalankar et al. 1992). In the largest of these, Murphy et al. (1986) reported a greater prevalence of both low birth weight and prematurity, by approximately 2 percentage points, among women with a predelivery hemoglobin level below 104 g/L than among those with hemoglobin level in the range of 104–132 g/L. However, because it is virtually impossible to control for other aspects of the environment, illness (especially exposure to malaria during pregnancy), and diet, which may simultaneously contribute to both anemia and poor birth outcome, these studies are inconclusive.

Although some randomized trials of iron supplementation in pregnancy have examined the impact on birth outcomes (Fleming et al. 1974; Fleming et al. 1986; Menendez et al. 1994), none of them found statistically significant differences in birth weights or rates of low birth weight between treatment and control groups. However, the first of these studies (Fleming et al. 1974) was conducted on a small sample of 73 Australian mothers with a mean hemoglobin level of 127 g/L, a level that suggests the women were not at risk. In the second study (Fleming et al. 1986), which involved a group of Nigerian mothers, the sample size was larger (200) but because all the women were experiencing pregnancy for the first time, they too may have been at relatively low risk for iron deficiency (although at higher risk for anemia because of malaria). In the third study (Menendez et al. 1994), conducted in the Gambia, the prevalence of low birth weight in the overall sample of 450 singleton births was only 4.2%, lower than in most developed countries. Although the mean hemoglobin level of these women was only 100 g/L, they were not at higher risk of delivering low-birth-weight infants. Thus, although there is some suggestive evidence from observational studies that anemia is related to low birth weight, this association has not yet been shown to be consistent or causal.

Anemia has also been associated with a higher risk of prematurity, on the basis of observational data concerning differences in hematocrit between preterm and term deliveries (Lieberman et al. 1988). However, this interpretation has been questioned on the grounds that hematocrit rises during the last trimester and that this increase at least partially explains the differences observed (Klebanoff et al. 1989). Using hematocrit values recorded earlier in gestation, from the Collaborative Perinatal Project, Klebanoff et al. (1989) found only a very weak association between anemia and the risk of preterm delivery and only for hematocrit measured before the 30th week of gestation. Later in gestation there was actually a statistically *lower* risk of prematurity among African American women with hematocrit levels <0.34 .

In a prospective study of 826 low-income pregnant women in New Jersey, there was a weak but statistically insignificant association between anemia on entry to the study (at 16.7 weeks gestational age, on average) and the risk of prematurity, after the authors statistically controlled for factors that might confound this relationship (Scholl et al. 1992). However, for the small

number of women with both anemia *and* iron deficiency (only 3.5% of the sample and only 12.5% of the anemic women), the risk of delivering prematurely was 2.7 times greater than for nonanemic women. The effect of iron deficiency on low birth weight was similarly large, but all of this effect could be attributed to preterm delivery, because there was no effect on the risk of delivering an infant small for gestational age. Although this was not an intervention trial, the investigators' ability to adjust statistically for a wide variety of potential confounders (maternal age, parity, prior low-birth-weight or preterm delivery, education, gestation at time of blood sampling, smoking, and prepregnancy body mass index) is enough to persuade us that the relationships observed were causal.

The economic consequences of this greater prematurity depend on the prevailing rate of prematurity in the population, the rate of iron deficiency anemia, and the costs of caring for the premature infant over and above the costs of caring for an infant delivered at term. An expression⁴ for the proportion of prematurity attributable to iron deficiency anemia (the population-attributable risk, PAR) is the following:

$$\frac{\text{Pr} \times (\text{RR} - 1)}{1 + [\text{Pr} \times (\text{RR} - 1)]}$$

where Pr is the prevalence of iron deficiency anemia and RR is the relative risk (2.7) of preterm delivery among women with iron deficiency anemia. PAR multiplied by the number of preterm births in the whole population yields the number of such births due to iron deficiency anemia. Note that whereas the algorithms that relate iron deficiency anemia to economic productivity use the prevalence of anemia, this formula uses the prevalence of iron deficiency anemia itself.

The economic cost of prematurity includes the cost of extra care required (both from the health care system and from the family) and the cost of "replacement" (food, care, and health care services needed by the mother for an earlier or subsequent pregnancy) when the poor birth outcome results in death. There may also be long-term developmental consequences of both low birth weight and prematurity that have economic implications for the individual, the household, and the community. Data on the costs of prematurity in developing countries are scarce. For developed countries, Stevenson et al. (1996) found that the cost of neonatal care for infants weighing less than 2000 g at birth was 13 times that for control newborns weighing over 2500 g and that the higher costs associated with greater use of health care facilities persisted until at least age 8. Fangman et al. (1994) found that the costs of birth at 35 and 36 weeks gestational age were 18 and 5 times, respectively, that of full-term birth. Thus, a conservative assumption would be that premature and low-birth-weight births in developing countries cost 10 times as much as control births. Even if the initial costs of hospital care were not this high for preterm infants, these babies are more likely to require additional medical care in infancy. However, we do not have data for developing countries on such care.

⁴From Kleinbaum et al. (1982).

Hence, additional costs of care associated with iron deficiency anemia in pregnant women could be calculated from the following expression:

$$\text{MULT} \times \text{PAR} \times \text{LBIRTHS} \times \text{PRPEM} \times \text{DELCOST}$$

where

MULT = the proportionate increase in delivery costs for premature infants

PAR = population-attributable risk (defined above)

LBIRTHS = annual number of live births

PRPEM = proportion of live births at gestational age <37 weeks

DELCOST = cost per delivery (averaged for births at home with trained attendant and births in health care facilities)

These data are generally not available on a country basis. Although estimates of the proportion of low-birth-weight infants are often available, there is generally no distinction between low birth weight due to prematurity and that due to fetal growth retardation. And although for some countries there are estimates of the prevalence of anemia in pregnancy, the proportion due to iron deficiency anemia is not generally known. Finally, delivery costs are not usually reported and would need to be studied for individual countries, as would the higher costs associated with prematurity.

Although the mechanisms are not well understood, anemia during pregnancy may increase the risk of infant mortality independent of its effects on birth weight and gestational age. In a study of 54 000 pregnancies in England, Murphy et al. (1986) found that perinatal mortality rates associated with low hemoglobin levels (<104 g/L) in pregnant women were 1.077 to 1.357 times higher than those associated with higher hemoglobin levels. The economic implications of perinatal mortality are not clear. These would mainly include the costs of care for the ill infant before death and the costs of “replacement.” However, because anemic mothers often suffer from other health and nutrition problems, it is not certain that the higher perinatal death rate associated with anemia can be entirely attributed to low hemoglobin levels or to iron deficiency alone. Until this relationship can be quantified with greater confidence we cannot offer an algorithm to calculate its effect.

Cost savings to the health care system can be compared with the costs of supplementation. Levin et al. (1994) have estimated the latter at \$2 per pregnancy. This represents the cost of the daily iron tablets but excludes the costs of delivering them to the pregnant women and educating the women as to the importance of compliance. Cost and impact data for iron supplementation in the field are scarce. Although the costs of distribution are low if primary health care facilities and reasonable antenatal care exist, there are substantial problems with compliance (Gillespie 1998). Thus, the cost of shifting one pregnant woman from anemic to nonanemic status may be

considerably higher than the cost of the supplement alone. Determining these costs is a priority area for future study.

5. COSTS OF MATERNAL MORTALITY AND OTHER COMPLICATIONS OF PREGNANCY

Maternal mortality remains a devastating problem in many developing countries. Worldwide, it is estimated that 600 000 women die each year because of problems related to pregnancy and childbirth. Severe anemia may cause death directly, and even mild anemia may increase the probability that hemorrhage or exhaustion will be fatal. By reducing physical stamina and increasing fatigue, anemia may also prevent mothers from seeking and obtaining medical care during pregnancy or an obstetric emergency. Precise estimates of the contribution of anemia to maternal mortality are not available. In any particular situation the contribution of anemia to maternal deaths will be a function of the prevalence and severity of anemia and of the availability of obstetric services, especially life-saving procedures for obstetric emergencies, such as transfusion and cesarean section. For many countries there are national-level estimates of anemia prevalence, sometimes disaggregated by severity level, but information on services is less often available. The availability of these services should be taken into account before attributable risk estimates are indiscriminately applied in specific situations. Nevertheless, a rough estimate of attributable risk is provided by a review of mainly hospital-based studies in Africa and Asia. These studies suggest that about 20% of maternal deaths in Africa and about 23% of those in Asia can be attributed to anemia, as summarized in Table 4 (Ross and Thomas 1996). If the Asian estimate is applied to India, it can be calculated that in 1997 alone, over 31 000 maternal deaths in that country were due to anemia,⁵ although not all of these would have been attributable to iron deficiency.

The human and economic cost of a maternal death is enormous, both to the family and to the community. Even when the mother does not die, there is a cost, borne by the family and the health care system, of the morbidity associated with anemia in pregnancy. If anemia contributes to medical emergencies, the need for transfusions, more expensive procedures, and longer stays in hospital, then there are additional economic costs. Anemic mothers who are referred to a higher level in the health care system because of anemia detected in pregnancy consume more expensive services, often at significant additional cost to the household. This is especially true

Table 4: Risks (%) of maternal mortality attributable to anemia, hemorrhage, and other causes.

⁵The maternal mortality ratio has been reported as 570 per hundred thousand live births (UNICEF 1998), and the number of births in 1997 was about 24.5 million. The number of maternal deaths attributable to anemia is therefore estimated as $570 \times 245 \times 0.226$ or 31 561.

Region	Anemia (direct)	Hemorrhage	Other ^a	Total anemia ^b
Africa	7.6	21.0	71.4	20.0
Asia	10.8	19.2	70.0	22.6

Source: Ross and Thomas 1996.

^a 100 – (anemia + hemorrhage).

^b The total risk attributable to anemia is calculated as the deaths directly attributable to anemia plus 25% of the deaths due to hemorrhage and 10% of deaths due to other causes (total = anemia [direct] + [hemorrhage × 0.25] + [other × 0.10]).

when such services are not available in the mother's own community and the household must bear the cost of travel and her absence from economic activities. Unfortunately, data on these costs are extremely difficult to obtain for developing countries and depend to a large extent on the degree of access to and quality of health care services.

6. OTHER CONSEQUENCES: GROWTH, IMMUNITY, AND SUSCEPTIBILITY TO TOXIC EFFECTS OF HEAVY METALS

6.1 Growth

Iron is needed for a variety of physiological functions, apart from oxygen transport, that are necessary for growth. Iron deficiency has also been associated with reduced appetite, although the mechanism for this effect is not understood. There are reasons to believe that iron deficiency anemia retards growth, but there is little evidence that iron therapy alone in anemic children results in faster growth. Perhaps this is because iron is rarely the most limiting nutrient or when it is and the deficiency is corrected, other deficiencies (of protein, energy, or zinc, for example) soon become limiting.

The results of published trials of the effects of iron therapy on the growth of children are presented in Table 5. In the United Kingdom, Aukett et al. (1986) gave ninety-seven 17- to 19-month-old anemic children (hemoglobin 80–110 g/L) a daily dose of 24 mg of iron with vitamin C or vitamin C alone for 2 months. Over the study period, iron-treated children showed faster weight gains than those receiving vitamin C alone (10.4 and 6.3 g/day, respectively). Also, children whose hemoglobin concentration increased by at least 20 g/L had faster weight gains than those with a smaller hemoglobin response. The functional implications of the higher rate of growth in the treatment group are difficult to estimate because of the short duration of follow-up. If the response observed in the treated children represents catch-up growth, a stronger response would be expected for interventions in children with lower weight-for-age z-scores than was the case here (–0.14 in the treatment group) and where severely anemic children (hemoglobin < 80 g/L) were not excluded.

Anemic Indonesian preschool children receiving 30 mg of iron per day (81 mg ferrous sulfate) together with vitamin C for 2 months also grew more quickly in length than a control group receiving just vitamin C (Angeles et al. 1993). There was no difference between the groups in their rate of weight gain, even though all of the children had low initial weight-for-age z-scores (between -2 and -3). The authors attributed the faster linear growth of children taking iron to their lower incidence of illness. Neither the duration of illness nor energy intake was measurably affected by treatment.

Also in Indonesia, Chwang et al. (1988) randomly allocated anemic and nonanemic school children aged 8–14 years to receive either an oral iron supplement (2 mg/kg daily) or a placebo for 12 weeks. All children with stool samples positive for helminths were treated with pyrantel pamoate before the treatment began. After treatment, the anemic children who received iron had higher hemoglobin concentrations (and other hematological indices), lower morbidity (as measured by an index of severity and duration of illness), and faster gains in weight, height, and arm circumference than the anemic children who received placebo. No effects of iron supplementation were observed in the nonanemic subjects. The net improvements in iron-treated anemic children relative to those receiving placebo were 0.11, 0.07, and 0.13 z-scores for weight, height, and arm circumference, respectively.

From their study of the effects of iron supplementation on Kenyan school children, Lawless et al. (1994) reported faster growth in both weight and height in children taking 150 mg of ferrous sulfate daily for 3 months than in children consuming a placebo. An appetite test given to all children before and after that study suggested that those in the iron-treated group were eating more, a result verified by the subjective reports of the children.

From the studies summarized above and in Table 5, it is not possible to determine whether growth improvements continue beyond the 2- or 3-month period of supplementation or whether the gains attributed to therapy are maintained. The extent of the long-term growth benefit from therapy under different conditions is therefore unknown. In Indonesian preschoolers, therapy improved linear growth but not weight gain (Angeles et al. 1993), whereas in school-age children in Kenya, the weight benefit was much greater than the 3-month improvement in linear growth (Lawless et al. 1994). Adding to this confusion is a report from Indonesia that preschool children without anemia and with adequate iron stores gained 200 g *less* weight over 4 months of iron therapy than a similar group of children given a placebo (Idjradinata et al. 1994). At this time, therefore, although there is evidence of important effects of supplementation on child growth in some situations, there is not enough evidence to allow identification of those situations beforehand or prediction of the size or even the direction of the growth impact with any precision.

For readers able to quantify the growth effect in specific situations, some guidance on the economic implications may be useful. The economic consequences of growth failure are uncertain but probably include reduced future productivity of the stunted child as an adult. None of the work relating stunting to physical capacity and productivity has distinguished between different nutritional and other causes. Evidence for the relationship between malnutrition and productivity comes from an extensive literature spanning several fields, including nutrition,

physiology, economics, and history, reviewed recently by Martorell (1996). The underlying mechanism for the relationship between nutrition and productivity is not well understood but may be due to effects on internal organ systems and physiological functions, with height simply serving as a marker for these less visible effects. Although quantitative estimates of the height–productivity relationship are rare, a study in the Philippines found that wages earned by sugarcane workers were higher by 1.38% for every 1% increase in height (Haddad and Bouis 1991), and another study of rural wage workers in Pakistan found a 0.3% increase in wages associated with each 1% increase in height (Alderman et al. 1996). These coefficients could be used to estimate the future productivity effects of childhood stunting, assuming that current height deficits of stunted children are maintained through to adulthood. This assumption is based on the observation that, although there may be some potential for catch-up growth, in practice this rarely occurs.

6.2 Immunity

Although some investigators have documented associations between iron deficiency and indicators of impaired cell-mediated immunity (Macdougall et al. 1975; Thibault et al. 1993), efforts to demonstrate functional improvements following supplementation (Thibault et al. 1993) or fortification (Walter et al. 1997) have failed. Indeed, there is evidence suggesting that iron supplementation actually promotes some kinds of infection (Murray et al. 1978; Oppenheimer et al. 1986). The relationship between anemia and infection is complicated by the inhibition of red cell production during infection, which might contribute to anemia. The association between anemia and infection might also be explained without invoking a causal relationship. For example, iron deficiency often coexists with deficiencies of other nutrients, such as protein or zinc, that may have a more direct influence on immunity. Because of these uncertainties, this relationship and its economic consequences cannot be quantified at present.

6.3 Susceptibility to toxic effects of heavy metals

Iron deficiency may lead to increased absorption of toxic metals from the gut or transport across the blood–brain barrier and other membranes, thus increasing susceptibility to environmental contaminants. Intestinal absorption of lead in rats increases during iron deficiency (Six and Goyer 1972), possibly because of competition between lead and iron for binding sites (Kochen and Greener 1975). The “highest acceptable level” of lead in the blood, as defined by the Centers for Disease Control and Prevention, is 25 $\mu\text{g/dL}$, but there is evidence that much lower levels may lead to impaired cognitive development in children (Bellinger et al. 1991), which would vastly increase the number of children considered at risk. This is a problem of potentially huge dimensions in the rapidly growing urban areas of developing countries, where high rates of iron deficiency among children coincide with high levels of environmental lead contamination due to increasing use of leaded fuel for vehicular transport. Unfortunately, little is known about the magnitude of this problem or its consequences either for blood lead levels or for cognitive development.

A number of studies have linked blood lead levels in children to cognitive function. However, it is difficult to isolate and quantify the contribution of iron deficiency to this problem because both iron deficiency and lead are known to affect cognitive development and, furthermore, although the presence of lead may cause iron deficiency, iron deficiency may also exacerbate the toxic effects of lead. Ruff et al. (1996) found that at 2 years of age, iron-deficient children responded less well to treatment for elevated blood lead levels. Furthermore, in children with adequate iron stores, there was a strong relationship between reductions in blood lead and improvements in cognitive test scores. This relationship was not observed in children with iron deficiency. This study provides important evidence for an interaction in children between iron deficiency and lead that has implications for mental development. However, it remains to be shown that iron deficiency actually contributes to the elevation of blood lead or to the effect of lead on mental development.

7. COUNTRY EXAMPLES

Table 6 presents the results of calculations of the labour productivity effects of iron deficiency (obtained with the methodology described in sections 2 and 3) for selected countries.⁶ These results suggest that in dollar terms, productivity losses are greater in richer countries, because we have assumed a constant percentage loss of productivity. This is only partially offset by the facts that iron deficiency anemia is lower in richer countries and that blue-collar work and heavy manual labour are less important in these countries. The dominant effect for all countries is the loss associated with cognitive effects on children. Whereas it is possible to argue that the losses in heavy manual labour are possibly overestimates in countries with a labour surplus, this is less likely to be the case for losses associated with cognitive skills.

The results suggest that these losses are large, with a median value of about \$4 per capita or 0.9% of GDP. They range from \$0.95 per capita in Tanzania, where anemia rates are in the medium range and wages are low, to \$51.72 per capita in Oman, where anemia rates are lower but wages are relatively high. For almost all countries, the cognitive losses in children are more than half of the total. When results are expressed as a percentage of GDP, the losses are highest in the poorest countries, where both anemia rates and heavy manual labour are highest. The losses are 1.90% of GDP in Bangladesh, 1.27% in India, and 1.20% in Malawi (the Malawi estimates underestimate the true value, because there are no data on adult anemia, and hence adult productivity losses have been excluded). Even in richer countries with lower rates of

⁶Note that for most countries in Table 6, there are no data on the prevalence of anemia among adult males. For these countries we have conservatively assumed that the prevalence of anemia among men is zero. If, alternatively, we assume that the prevalence among men is 85% that among women (the average for countries for which there are data), the total calculated losses for countries for which male prevalence data are missing would be 19.5% higher. Similarly, because there are no anemia prevalence data for either men or women in Ghana and Malawi, the estimated losses for those countries do not include the effect of current iron deficiency anemia on economic productivity.

anemia, the losses are significant (for example, 0.44% of GDP in Egypt). In absolute dollar terms, the losses in South Asia are staggering: almost half a billion dollars annually in each of Bangladesh and Pakistan and \$3.8 billion in India. In South Asia as a whole (including Nepal and Sri Lanka) losses probably exceed \$5 billion annually — as much as the government health budget, according to the World Bank (1993).

The available evidence on costs and benefits indicates that investment in iron fortification would probably be extremely attractive from a cost–benefit standpoint. We have not undertaken a formal cost–benefit analysis. To do so requires modelling the costs and benefits over time, a topic for future study. For illustrative purposes, the recurrent costs of fortifying flour with iron are extremely modest. Levin et al. (1994) gave the annual costs as \$0.20 per capita, although this would be higher if more expensive but more bioavailable sources of iron were used. Combs et al. (1994) gave the costs of fortifying wheat flour with ferrous fumarate (which is preferable to reduced iron) as \$0.72/metric ton. Issues related to the cost and feasibility of fortification are addressed by Lotfi et al. (1996).

However, the cost of iron fortification very much depends on logistics. It is about 10 times more costly to fortify whole grains (such as rice) than to fortify flour. Although the calculations in Levin et al. (1994) do not take account of the costs of equipment for fortification, these are generally not significant, unless processing is done on a very small scale. Obviously, fortification will not benefit rural communities — the populations most often affected by iron deficiency — if grain is produced and consumed locally without centrally processing. However, for those communities that can be reached by fortification, this is an option well worth considering.

Supplementation is generally more expensive than fortification, but even so it is relatively inexpensive, about \$2 per pregnancy (Levin et al. 1994). However, in spite of promising results in efficacy trials, the effectiveness of large-scale supplementation programs has not been good because of problems with distribution and compliance (Sloan et al. 1992; Gillespie 1998). Improving these factors through better supervision and communication will increase the cost per individual whose anemia is reduced or eliminated. This is an area where field data are needed.

These estimates include only the effects on market production. Various estimates put the value of home production at 19% of household cash income or 16% of household “full income” in the Philippines (Quizon 1978), 66% of pretax family income in the United States (Gronau 1977), and 70% of worldwide GDP as measured conventionally (UNDP 1995). If the productivity effects of iron deficiency anemia on nonmarket production were included, the benefits of iron fortification would be much greater.

8. CONCLUSIONS

In this paper we have tried to calculate and substantiate some of the economic losses due to iron deficiency. These include the cognitive losses due to childhood iron deficiency (section 2) and the losses due to lower productivity among adults in manual occupations (section 3). Of these, the cognitive losses are greater and more pervasive, although they have been less widely recognized in previous literature. We have also provided a method for calculating the economic costs incurred in terms of additional medical expenses associated with increased prematurity, but the data to do the calculations are lacking (section 4). Another social cost is the estimated 20% and 23% of maternal deaths in Africa and Asia, respectively, that are attributable to maternal anemia; there has been no attempt to attach an economic value to this loss (section 5). Finally, there may be other important effects, such as lower growth and hence lower productivity, impaired immunity, and increased susceptibility to the toxic effects of heavy metals, areas where the extent of the effects is more speculative (section 6). Country examples suggest that the median value of per capita productivity losses is about \$4 and the median loss as a percentage of GDP 0.9% (section 7). The absolute dollar value of the losses is particularly high in South Asia, close to \$5 billion annually. These calculations suggest that if iron fortification and supplementation are effectively implemented, they could be highly cost-effective investments in developing countries.

Table 1. Effects of iron therapy on cognitive and behavioural development in children up to 26 months of age.

Source	Location	Age (months)	Study design	Iron treatment		<i>n</i>	Definition of IDA ^b	Test	Effect of treatment	
				Dose	Period (d ^a)				On IDA children	On IDNA children
Lozoff et al. (1982a, b), Lozoff et al. (1985)	Guatemala	6–24	Randomized, placebo-controlled, double-blind	10 mg/kg daily as ferrous ascorbate in two oral doses	6–8	28 IDA 40 nonanemic	Hb 105 g/L	Bayley scales	None	<i>na</i>
Lozoff et al. (1987)	Costa Rica	12–23	Randomized, placebo-controlled, double-blind	10 mg/kg daily as ferrous ascorbate in two oral doses <i>or</i> intramuscular injection	7	97 IDA 94 nonanemic	Hb 105 g/L	Bayley scales	Mental: none ($P > 0.69$) Motor: none ($P > 0.80$)	No difference from IS at baseline
Lozoff et al. (1987)	Costa Rica	12–23	Pre–post comparison with nonanemic controls	6 mg/kg daily as ferrous ascorbate in two oral doses <i>or</i> intramuscular injection	90	17 IDA (moderate) 90 IDA (mild) or nonanemic	Hb 105 g/L	Bayley scales	Mental: none ($P = 0.76$) Motor: 9.3 points ($P = 0.007$)	No difference from IS at baseline
Walter et al. (1983)	Chile	15	Pre–post comparison with nonanemic controls	3–4 mg/kg daily as ferrous sulfate (oral)	11	10 IDA 12 IDNA 15 IS	Hb < 110 g/L	Bayley scales	Mental: 10 points ($P < 0.01$) Motor: none	For 6 nonanemic children with ≥ 2 abnormal indices, mental: 10 points ($P < 0.01$)
Walter et al. (1989)	Chile	12	Randomized, placebo-controlled, double-blind	15 mg three times daily as ferrous sulfate (oral)	10	39 anemic 127 IDNA 30 IS	Hb < 110 g/L + 2 abnormal biochemical measures	Bayley scales	Mental: 1.9 points ^c (NS) Motor: 1.6 points ^c (NS)	Mental: 0.2 points ^c (NS) Motor: 0.2 points ^c (NS)

Walter et al. (1989)	Chile	12	Pre-post comparison with nonanemic controls	15 mg three times daily as ferrous sulfate (oral)	90	39 anemic 127 IDNA 30 IS	Hb < 110 g/L + 2 abnormal biochemical measures	Bayley scales	Mental: -0.2 points (NS) Motor: 1.9 points (NS)	Mental: 0.3 points (NS) Motor: 0.2 points (NS)
----------------------	-------	----	---	---	----	--------------------------------	---	---------------	--	---

(continued)

Table 1 concluded.

Source	Location	Age (months)	Study design	Iron treatment		<i>n</i>	Definition of IDA ^b	Test	Effect of treatment	
				Dose	Period (d ^a)				On IDA children	On IDNA children
Aukett et al. (1986)	United Kingdom	17–19	Randomized, placebo-controlled, double-blind	24 mg daily as ferrous sulfate (oral; parent administered at home)	60	110 anemic	80–100 g/L	Denver test	More attained average rate of development: 31% treatment and 12% control (<i>P</i> < 0.05)	<i>na</i>
Oski and Honig (1978)	United States	12–26	Randomized, placebo-controlled, double-blind	Intramuscular injection, dose calculated to replenish stores	5–8	24 IDA	Hb < 105g/L MCV 73 μm ³ SI 50 μg/dL TS 12%	Bayley scales	Mental: 7.5 points ^c (<i>P</i> = 0.01) Motor: 6.8 points ^c (<i>P</i> = 0.10)	<i>na</i>
Oski et al. (1983)	United States	9–12	Pre–post comparison	50-mg intramuscular injection as iron dextran	7	18 IDNA 20 non-deficient	IDNA: Hb 110 g/L FEP > 30 μg/dL (0.53 μmol/L)	Bayley scales	<i>na</i>	Mental: 15.7 points ^c
Idjradinata and Pollitt (1993)	Indonesia	12–18	Randomized, placebo-controlled, double-blind	3 mg/kg daily as ferrous sulfate (oral)	120	47 IDA 28 IDNA 44 IS	Hb 105 g/L SF 12 μg/L TS 10%	Bayley scales	Mental: 18.8 points ^c (<i>P</i> < 0.001) Motor: 18.4 points ^c (<i>P</i> < 0.001)	None
Moffat et al. (1994)	Canada	Neonates	Randomized, placebo-controlled, double-blind	Iron-fortified formula (12.8 mg/L)	6, 9, 12, 15 months	225, 204, 186, 154 at each time of assessment, respectively	<i>na</i>	Bayley scales	Mental: none Motor: 4.0 points at 9 months, 6.3 points at 12 months (<i>P</i> < 0.001), none at 6 and 15 months (<i>P</i> > 0.05)	Results include mostly nonanemic children (90% at 15 months)

Note: IDA, iron-deficient, anemic; IDNA, iron-deficient, nonanemic; Hb, hemoglobin concentration; *na*, not applicable; IS, iron sufficient; NS, not statistically significant; MCV, mean corpuscular volume; SI, serum iron; TS, transferrin saturation; FEP, free erythrocyte protoporphyrin; SF, serum ferritin.

^a Except where indicated otherwise.

^b In some cases hemoglobin alone was used as a proxy indicator of iron deficiency anemia, which could lead to an overestimation of actual prevalence of iron deficiency anemia by up to 60% (see page 2).

^c Adjusted for response in controls receiving placebo.

Table 2. Effects of iron therapy on cognitive and behavioural development in older children.

Source	Location	Age (years)	Study design	Iron treatment		<i>n</i>	Definition of IDA	Test	Effect of treatment	
				Dose	Period				On IDA children	On IDNA children
Seshadri and Gopaldas (1989)	India	5–6	Randomized, placebo-controlled, double-blind	40 mg daily + deworming and folate; control, deworming only	60 d	14 matched pairs	Hb < 105 g/L	WISC	Verbal 5 points ^a Performance 11 points ^a Total 8 points ^a	<i>na</i>
Soemantri (1989)	Indonesia	8–11	Randomized, placebo-controlled, double-blind	2 mg/kg daily + deworming	12 weeks	58 IDA 72 IS	Hb < 110 g/L TS < 12%	RCPM, EAT	Marked improvement in EAT scores but not in RCPM	<i>na</i>
Soewando et al. (1989)	Indonesia	Preschool (mean 4.5)	Randomized, placebo-controlled, double-blind	50 mg daily	8 weeks	49 IDA 57 IDNA 70 IS	Hb < 110 g/L + 2 additional abnormal indices	Discrimination learning, oddity learning	Improvements in discrimination and oddity learning	Not reported
Pollitt et al. (1989)	Thailand	9–11	Randomized, placebo-controlled, double-blind	2 mg/kg daily for 2 weeks, then 4 mg/kg daily for 14 weeks + deworming; control, deworming only	16 weeks	101 IDA 47 IDNA 1210 IS	Hb < 120 g/L + 2 additional abnormal indices	RCPM, EAT	None	None

Note: IDA, iron-deficient; anemic, IDNA, iron-deficient, nonanemic; Hb, hemoglobin concentration; WISC, Wechsler Intelligence Scale for Children; *na*, not applicable; IS, iron sufficient; TS, transferrin saturation; RCPM, Raven Colored Progressive Matrices; EAT, educational achievement test.

^a Adjusted for response in controls receiving placebo.

Table 3. Effects of iron therapy on physical capacity and work productivity in adults.

Source	Location	Subjects	Age (years)	Study design	Iron treatment		<i>n</i>	Definition of IDA ^a	Outcome measure	Effect of treatment	
					Dose	Period (d)				On iron status	On productivity
Edgerton et al. (1979)	Sri Lanka	Female tea pickers	20–60	Placebo-controlled	200 mg daily as ferrous sulfate	30	199	<i>na</i> (no Hb eligibility criteria)	Hb, weight of tea picked per day	Net increase in Hb, by 15 g/L (13.9%) ($P < 0.05$)	Mean net increase in tea picked of 1.2% (NS)
Ohira et al. (1979)	Sri Lanka	Hospital patients	21–72	Placebo-controlled	Single IV infusion of 30–50 mL iron dextran	3, 4, 8, 12, 16	20	“Hematological test”	Hb, maximum work load, heart rate response to exercise	Increase in Hb from 66 to 84 g/L (27%) at 16 d	Increase in maximum work load by about 70%; reduction in heart rate for a given work load by about 25%
Ohira et al. (1981)	Sri Lanka	Hospital patients	Group means 40–55	Pre–post comparison with nonanemic controls	Single IV infusion of 30–50 mL iron dextran	7–8	11 anemic 12 marginal 22 normal	Marginal: Hb < 130 g/L Low: Hb < 100 g/L SI < 44 µg/dL	Hb, maximum exercise time, heart rate response to exercise	Slight increase in Hb in anemic groups (NS)	Increase in maximum exercise time by 46–59% in anemic groups, reduction in heart rate during heavy work by ~20% in anemic and low serum iron groups
Basta et al. (1979)	Indonesia	Male rubber plantation workers	16–40	Placebo-controlled, double-blind	100 mg daily as ferrous sulfate	60	152 anemic, 150 nonanemic	Hematocrit < 38%	HST, labour productivity	Significant improvement in Hb (and 4 other indices) over initial values and placebo controls	No effect on HST, 17% increase in weight of latex collected, no effect on weeding productivity

(continued)

Table 3 concluded.

Source	Location	Subjects	Age (years)	Study design	Iron treatment		<i>n</i>	Definition of IDA ^a	Outcome measure	Effect of treatment	
					Dose	Period (d)				On iron status	On productivity
Li et al. (1994)	China	Female textile factory workers	19–44	Placebo-controlled, double-blind	60 or 120 mg daily	84	80	Hb < 120 g/L and <i>either</i> SF < 12 µg/L or FEP > 0.62 µmol/L	Heart rate, productivity, production efficiency (pay/energy expenditure)	Significant improvement in Hb (from 114 to 127 g/L) (<i>P</i> < 0.001), SF, FEP	4.6% decrease in heart rate at work, 5% increase in productivity, 17% increase in production efficiency
Zhu and Haas (1998)	United States	Active healthy females	19–36	Placebo-controlled, double-blind	135 mg daily	56	43	Hb > 120g/L and SF < 16 µg/L	Level of exertion for a fixed work load	Significant increase in SF concentration relative to baseline and placebo group (<i>P</i> < 0.005); decrease in SF receptor relative to placebo (<i>P</i> < 0.05)	5.1% lower exertion (as % of maximum oxygen consumption) after controlling for baseline levels (<i>P</i> = 0.016)

Note: IDA, iron deficiency anemia; *na*, not applicable; Hb, hemoglobin concentration; NS, not statistically significant; IV, intravenous; SI, serum iron; HST, Harvard step test; SF, serum ferritin; FEP, free erythrocyte protoporphyrin.

^a In some cases hemoglobin alone was used as a proxy indicator of iron deficiency anemia, which could lead to an overestimation of actual prevalence of iron deficiency anemia by up to 60% (see page 2).

Table 5. Effects of iron therapy on child growth.

Source	Location	Age (years)	Study design	Iron treatment		<i>n</i>	Definition of IDA ^a	Outcome measure	Effect of treatment on IDA children	Net improvement in z-score ^b
				Dose	Period (d)					
Aukett et al. (1986)	United Kingdom	1.5 ^c	Randomized, placebo-controlled, double-blind	24 mg daily as ferrous sulfate (oral; parent administered at home)	60	97 anemic	Hb 80–110 g/L	Weight gain	Faster weight gain over 2 months Treatment: 10.4 g/d Placebo: 6.3 g/d (<i>P</i> < 0.001)	Weight: 0.205 Height: <i>na</i>
Chwang et al. (1988)	Indonesia	8.2–13.5	Randomized, placebo-controlled, double-blind	2 mg/kg daily	84	78 anemic 41 non-anemic	Hb 80–110 g/L TS > 20%	Weight, height, and AC gain	Faster weight, height and AC gain over 12 weeks	Weight: 0.11 Height: 0.07 AC: 0.13
Angeles et al. (1993)	Indonesia	2–5	Randomized, placebo-controlled	30 mg Fe and 20 mg vitamin C daily + deworming; control, vitamin C + deworming	60	76 anemic	Hb < 110g/L SF < 12 µg/L WFA -2 to -3 z-scores	Weight and height gain	Faster height gain over 2 months Treatment: 2.7 cm Placebo: 1.5 cm (<i>P</i> < 0.001) Weight: NS	Weight: NS Height: 0.312

Lawless et al. (1994)	Kenya	6–11	Randomized, placebo-controlled, double-blind	150 mg daily as ferrous sulfate (sustained-release capsules)	98	87 (76% anemic)	Hb 80–110 g/L	Weight and height gain	<p>Faster height gain over 14 weeks</p> <p>Treatment: 1.4 cm Placebo: 1.1 cm ($P < 0.01$)</p> <p>Faster weight gain over 14 weeks Treatment: 1.6 kg Placebo: 0.7 kg ($P < 0.001$)</p>	<p>Weight: 0.243</p> <p>Height: 0.051</p>
-----------------------	-------	------	--	--	----	-----------------	---------------	------------------------	---	---

Note: IDA, iron-deficient, anemic; Hb, hemoglobin concentration; *na*, not applicable; TS, transferrin saturation; AC, arm circumference; SF, serum ferritin; WFA, weight for age; NS, not statistically significant.

^a In some cases hemoglobin alone was used as a proxy indicator of iron deficiency anemia, which could lead to an overestimation of actual prevalence of iron deficiency anemia by up to 60% (see page 2).

^b Adjusted for response in controls receiving placebo.

^c 17–19 months.

Table 6. Economic consequences of iron deficiency anemia for selected countries.

Country	Pr(child) (%)	Pr(male) ^a (%)	Pr(fem) (%)	F labforce (%)	Ag share (%)	BC share (%)	GDP/cap (\$)	Cog loss (\$/capita)	BC loss (\$/capita)	HML loss (\$/capita)	Total loss		
											As \$/capita	As million \$	As % of GDP
Bangladesh	73	60	74	42	30	70	220	2.57	0.42	1.20	4.19	495	1.90
India	66	<i>nd</i>	59	32	30	70	320	3.38	0.17	0.50	4.05	3761	1.27
Nepal	<i>nd</i>	<i>nd</i>	<i>nd</i>	40	44	70	200	—	—	—	—	—	—
Pakistan	47	<i>nd</i>	37	28	25	70	430	3.23	0.12	0.31	3.67	499	0.85
Ghana	25	<i>nd</i>	<i>nd</i>	51	46	70	410	1.64	—	—	1.64	28	0.40
Malawi	75	<i>nd</i>	<i>nd</i>	54	21	70	170	2.04	—	—	2.04	20	1.20
Mali	28	33	27	51	42	70	250	1.12	0.31	0.87	2.30	9	0.92
South Africa	24	42	52	37	5	50	3040	11.67	13.33	1.92	26.92	1116	0.89
Tanzania	25	15	15	49	57	70	140	0.56	0.06	0.33	0.95	28	0.68
Egypt	25.2	<i>nd</i>	17	30	20	60	720	2.90	0.09	0.20	3.19	198	0.44
Oman	60	14	32	13	3	50	5140	49.34	1.68	0.70	51.72	114	1.01
Yemen	<i>nd</i>	<i>nd</i>	<i>nd</i>	26	<i>nd</i>	70	280	—	—	—	—	—	—
Bolivia	35	<i>nd</i>	16	37	24	60	770	4.31	0.11	0.30	4.72	35	0.61
Honduras	17.5	<i>nd</i>	14.3	28	20	70	600	1.68	0.07	0.13	1.88	11	0.31
Nicaragua	28	<i>nd</i>	36	36	33	70	340	1.52	0.28	0.40	2.20	24	0.65

^aFor most countries there are no data on the prevalence of anemia among adult males. For these countries the prevalence of anemia among men has been assumed to be zero. If, alternatively, the prevalence among men is assumed to be 85% that among women (the average for countries for which data are available), this would add an average of 19.5% to the total calculated losses for countries for which prevalence among men is missing. Similarly, because there are no anemia prevalence data for either men or women for Ghana and Malawi, the estimated losses for these countries do not include the effect of current iron deficiency anemia on economic productivity.

nd, no data; —, no estimate because of lack of data.

(continued)

Table 6 concluded.

Pr(child), prevalence of anemia in children (source: Micronutrient Initiative [MI] web page, www.idrc.ca/mi)

Pr(male), prevalence of anemia in adult males (source: MI web page, www.idrc.ca/mi)

Pr(fem), prevalence of anemia in adult females (nonpregnant, nonlactating) (source: MI web page, www.idrc.ca/mi)

F labforce, % of labour force that was female in 1994 (percentage of labour force is used rather than percentage of marketed output produced by women, because the latter is not available) (source: World Bank [1996])

Ag share, % share of agriculture in GDP in 1994 (source: World Bank [1996])

BC share, % share of blue-collar work in total employment (it would be preferable to use percentage of output attributable to blue-collar workers, but this is not available) (source: interpolated from ILO [1996]; figures used were 70% for low-income countries, 60% for lower-middle-income countries including Egypt, and 50% for upper-middle-income countries)

GDP/cap, per capita GDP (source: World Bank [1996])

Cog loss, productivity loss due to cognitive losses in childhood: $\text{Pr}(\text{child}) \times 0.04 \times \text{Wage share} \times \text{GDP/cap}$, where Wage share in GDP is taken as 40% on the basis of national accounts data for various countries, various years (data on individual countries not readily available); 0.04 represents assumed 4% productivity loss associated with decrease of 0.5 standard deviation in cognitive scores.

BC loss, additional productivity loss associated with lower physical productivity of anemic adults in blue-collar occupations: $\{[\text{Pr}(\text{fem}) \times \text{F labforce}] + [\text{Pr}(\text{male}) \times (100 - \text{F labforce})]\} \times \text{BC share} \times 0.01 \times \text{WS}$, where 0.01 represents the additional loss (5% – 4%) associated with blue-collar work. For countries where Pr(fem) or Pr(male) is greater than Pr(child), an additional amount is added to account for the 4% loss not already attributed to the cognitive effects of childhood anemia.

HML loss, additional productivity loss associated with lower physical productivity in heavy manual labour: $\{[\text{Pr}(\text{fem}) \times \text{F labforce}] + [\text{Pr}(\text{male}) \times (100 - \text{F labforce})]\} \times (0.12 \times \text{Wage share}) \times (0.575 \times \text{Ag share})$, where 0.12 represents the additional loss (17% – 5%) associated with heavy manual labour and the expression $0.575 \times \text{Ag share}$ assumes that 50% of agricultural and construction work is heavy manual labour and also that construction is 15% of agriculture share of GDP (source: World Bank [1996])

Total loss, total value of per capita productivity loss: Cog loss + BC loss + HML loss, expressed both as 1994 US dollars (per capita and overall) and as percentage of per capita GDP.

References

- Alderman, H.; Behrman, J.R.; Ross, D.R.; Sabot, R. 1996. The returns to endogenous human capital in Pakistan's rural wage labour market. *Oxford Bulletin of Economics and Statistics*, 58, 29–55.
- Angeles, I.T.; Schultink, W.J.; Matulesi, P.; Gross, R.; Sastroamidjojo, S. 1993. Decreased rate of stunting among anemic Indonesian preschool children through iron supplementation. *American Journal of Clinical Nutrition*, 58(3), 339–342.
- Aukett, M.A.; Parks, Y.A.; Scott, P.H.; Wharton, B.A. 1986. Treatment with iron increases weight gain and psychomotor development. *Archives of Disease in Childhood*, 61(9), 849–857.
- Basta, S.S.; Soekirman; Karyadi, D.; Scrimshaw, N.S. 1979. Iron deficiency anemia and the productivity of adult males in Indonesia. *American Journal of Clinical Nutrition*, 32(4), 916–925.
- Beard, J.L.; Connor, J.R.; Jones, B.C. 1993. Brain iron: location and function. *Progress in Food and Nutrition Science*, 17, 183–221.
- Bellinger, D.; Sloman, J.; Leviton, A.; Rabinowitz, M; Needleman, H.L.; Waternaux, C. 1991. Low-level lead exposure and children's cognitive function in the preschool years. *Pediatrics*, 87(2), 219–227.
- Ben-Shachar, D.; Ashkenazi, R.; Youdim, M.B.H. 1986. Long-term consequence of early iron-deficiency on dopaminergic neurotransmission in rats. *International Journal of Developmental Neuroscience*, 4(1), 81–88.
- Boissiere, M.; Knight, J.B.; Sabot, R.H. 1985. Earnings, schooling, ability, and cognitive skills. *American Economic Review*, 75, 1016–1030.
- Bruner, A.B.; Joffe, A.; Duggan, A.K.; Casella, J.F.; Brandt, J. 1996. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet*, 348(9033), 992–996.
- Chwang, L.C.; Soemantri, A.G.; Pollitt, E. 1988. Iron supplementation and physical growth of rural Indonesian children. *American Journal of Clinical Nutrition*, 47(3), 496–501.
- Combs, G.F.; Dexter, R.B.; Horton, S.; Buescher, R. 1994. Micronutrient fortification and enrichment of PL480 commodities: recommendations for improvement. John Snow Inc. Opportunities for Micronutrient Interventions (OMNI), Arlington, VA, USA.
- Dallman, P.R.; Reeves, J.D.; Driggers, D.A.; Lo, E.Y. 1981. Diagnosis of iron deficiency: the limitations of laboratory tests in predicting response to iron treatment in 1-year-old infants. *Journal of Pediatrics*, 99(3), 376–381.
- Dallman, P.R.; Siimes, M.A.; Manies, E.C. 1975. Brain iron: persistent deficiency following short-term iron deprivation in the young rat. *British Journal of Haematology*, 31(2), 209–215.
- Davies, C.T.M.; Chukweumeka, A.C.; Van Haaren, J.P.M. 1973. Iron-deficiency anaemia: its effect on maximum aerobic power and responses to exercise in African males aged 17–40 years. *Clinical Science*, 44(6), 555–562.
- DeMaeyer, E.M.; Adiels-Tegman, M. 1985. The prevalence of anemia in the world. *World Health Statistics Quarterly – Rapport Trimestriel de Statistiques Sanitaires Mondiales*, 38(3), 302–316.
- Edgerton, V.R.; Gardner, G.W.; Ohira, Y.; Gunawardena, K.A.; Senewiratne, B. 1979. Iron-deficiency anaemia and its effect on worker productivity and activity patterns. *British Medical Journal*, 2(6204), 1546–1549.
- Fangman, J.J.; Mark, P.M.; Pratt, L.; Conway, K.K.; Healey, M.L.; Oswald, J.W.; Uden, D.L. 1994. Prematurity prevention programs: an analysis of successes and failures. *American Journal of Obstetrics and Gynecology*, 170(3), 744–750.
- Fleming, A.F.; Ghatoura, G.B.; Harrison, K.A.; Briggs, N.D.; Dunn, D.T. 1986. The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Annals of Tropical Medicine and Parasitology*, 80(2), 211–233.
- Fleming, A.F.; Martin, J.D.; Hahnel, R.; Westlake, A.J. 1974. Effects of iron and folic acid antenatal supplements on maternal haematology and fetal wellbeing. *Medical Journal of Australia*, 2(12), 429–436.

- Gillespie, S. 1998. Major issues in the control of iron deficiency. Micronutrient Initiative, Ottawa, ON, Canada. 104 pp.
- Glewwe, P. 1996. The relevance of standard estimates of rates of return to schooling for education policy: a critical assessment. *Journal of Development Economics*, 51, 267–290.
- Gronau, R. 1977. Home production — a forgotten industry. National Bureau of Economic Research and Hebrew University. Draft. Mimeo.
- Haddad, L.J.; Bouis, H.E. 1991. The impact of nutritional status on agricultural productivity: wage evidence from the Philippines. *Oxford Bulletin of Economics and Statistics*, 53, 45–68.
- Hause, J.C. 1972. Earnings profile, ability and schooling. *Journal of Political Economy*, 80(supplement), 108–138.
- Hauser, R.M.; Sewell, W.H. 1986. Family effects in simple models of education, occupational status and earnings: findings from the Wisconsin and Kalamazoo studies. *Journal of Labor Economics*, 4, 83–115.
- Idjradinata, P.; Pollitt, E. 1993. Reversal of developmental delays in iron-deficient anaemic infants treated with iron. *Lancet*, 341(8836), 1–4.
- Idjradinata, P.; Watkins, W.E.; Pollitt, E. 1994. Adverse effect of iron supplementation on weight gain of iron-replete young children. *Lancet*, 343(8908), 1252–1254.
- ILO (International Labour Office). 1996. *International yearbook of labour statistics*. ILO, Geneva, Switzerland.
- Klebanoff, M.A.; Shiono, P.H.; Berendes, H.W.; Rhoads, G.G. 1989. Facts and artifacts about anemia and preterm delivery. *Journal of the American Medical Association*, 262(4), 511–515.
- Kleinbaum, D.G.; Kupper, L.L.; Morgenstern, H. 1982. *Epidemiologic research: principles and quantitative methods*. Van Nostrand Reinhold, New York, NY, USA. p. 161.
- Kochen, J.; Greener, Y. 1975. Interaction of ferritin with lead and cadmium. *Pediatric Research*, 9, 323. Abstract.
- Lawless, J.W.; Latham, M.C.; Stephenson, L.S.; Kinoti, S.N.; Pertet, A.M. 1994. Iron supplementation improves appetite and growth in anemic Kenyan primary school children. *Journal of Nutrition*, 124(5), 645–654.
- Levin, H.M. 1986. A benefit–cost analysis of nutritional programs for anaemia reduction. *Research Observer*, 1, 219–246.
- Levin, H.M.; Pollitt, E.; Galloway, R.; McGuire, J. 1994. Micronutrient deficiency disorders (chapter 19). *In* Jamison, D.T.; Mosley, W.H., eds., *Disease control priorities in developing countries*. Oxford University Press, New York, NY, USA. pp. 421–451.
- Li, R.; Chen, X.; Yan, H.; Deurenberg, P.; Garby, L.; Hautvast, J.G. 1994. Functional consequences of iron supplementation in iron-deficient female cotton mill workers in Beijing, China. *American Journal of Clinical Nutrition*, 59(4), 908–913.
- Lieberman, E.; Ryan, K.J.; Monson, R.R.; Schoenbaum, S.C. 1988. Association of maternal hematocrit with premature labor. *American Journal of Obstetrics and Gynecology*, 159(1), 107–114.
- Lotfi, M.; Mannar, M.G.V.; Merx, R.H.J.M.; Heuvel, P.N. 1996. *Micronutrient fortification of foods: current practices, research and opportunities*. Micronutrient Initiative, Ottawa, ON, Canada, and International Agriculture Centre, Wageningen, The Netherlands.
- Lozoff, B. 1988. Behavioral alterations of iron deficiency. *Advances in Pediatrics*, 35, 331–359.
- Lozoff, B.; Brittenham, G.M.; Viteri, F.E.; Wolf, A.W.; Urrutia, J.J. 1982a. The effects of short-term oral iron therapy on developmental deficits in iron-deficient anemic infants. *Journal of Pediatrics*, 100(3), 351–357.
- 1982b. Developmental deficits in iron-deficient infants: effects of age and severity of iron lack. *Journal of Pediatrics*, 101(6), 948–952.
- Lozoff, B.; Brittenham, G.M.; Wolf, A.W.; McClish, D.K.; Kuhnert, P.M.; Jimenez, E.; Jimenez, R.; Mora, L.A.; Gomez, I.; Krauskoph, D. 1987. Iron deficiency anemia and iron therapy effects on infant developmental test performance. *Pediatrics*, 79(6), 981–995.
- Lozoff, B.; Jimenez, E.; Wolf, A.W. 1991. Long-term developmental outcome of infants with iron deficiency. *New England Journal of Medicine*, 325(10), 687–694.

- Lozoff, B.; Wolf, A.W.; Urrutia, J.J.; Viteri, F.E. 1985. Abnormal behavior and low developmental test scores in iron-deficient anemic infants. *Journal of Developmental and Behavioral Pediatrics*, 6(2), 69–75.
- Macdougall, L.G.; Anderson, R.; McNab, G.M.; Katz, J. 1975. The immune response in iron-deficient children: impaired cellular defense mechanisms with altered humoral components. *Journal of Pediatrics*, 86(6), 833–843.
- MacGregor, M. 1963. Maternal anemia as a factor in prematurity and perinatal mortality. *Scottish Medical Journal*, 8, 134–140.
- Martorell, R. 1996. The role of nutrition in economic development. *Nutrition Reviews*, 54(4 Part 2), S66–S71.
- Mavalankar, D.V.; Gray, R.H.; Trivedi, C.R. 1992. Risk factors for preterm and term low birthweight in Ahmedabad, India. *International Journal of Epidemiology*, 21(2), 263–272.
- Menendez, C.; Todd, J.; Alonso, P.L.; Francis, N.; Lulat, S.; Ceesay, S.; M’Boge, B.; Greenwood, B.M. 1994. The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 88(5), 590–593.
- Moffatt, M.E.; Longstaffe, S.; Besant, J.; Dureski, C. 1994. Prevention of iron deficiency and psychomotor decline in high-risk infants through use of iron-fortified infant formula: a randomized clinical trial. *Journal of Pediatrics*, 125(4), 527–534.
- Murphy, J.F.; O’Riordan, J.; Newcombe, R.G.; Coles, E.C.; Pearson, J.F. 1986. Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet*, 1(8488), 992–995.
- Murray, M.J.; Murray, A.B.; Murray, M.B.; Murray, C.J. 1978. The adverse effect of iron repletion on the course of certain infections. *British Medical Journal*, 2(6145), 1113–1115.
- Ohira, Y.; Edgerton, V.R.; Gardner, G.W.; Gunawardena, K.A.; Senewiratne, B.; Ikawa, S. 1981. Work capacity after iron treatment as a function of hemoglobin and iron deficiency. *Journal of Nutritional Science and Vitaminology*, 27(2), 87–96.
- Ohira, Y.; Edgerton, V.R.; Gardner, G.W.; Senewiratne, B.; Barnard, R.J.; Simpson, D.R. 1979. Work capacity, heart rate and blood lactate responses to iron treatment. *British Journal of Haematology*, 41(3), 365–372.
- Oppenheimer, S.J.; Gibson, F.G.; Macfarlane, S.B.; Moody, J.B.; Harrison, C.; Spencer, A.; Bunari, O. 1986. Iron supplementation increases prevalence and effects of malaria: report on clinical studies in Papua New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 80(4), 603–612.
- Oski, F.A.; Honig, A.S. 1978. The effects of therapy on the developmental scores of iron-deficient infants. *Journal of Pediatrics*, 92(1), 21–25.
- Oski, F.A.; Honig, A.S.; Helu, B.; Howantiz, P. 1983. Effect of iron therapy on behavior performance in nonanemic, iron-deficient infants. *Pediatrics*, 71(6), 877–880.
- Pollitt, E. 1993. Iron deficiency and cognitive function. *Annual Review of Nutrition*, 13, 521–537.
- 1995. Functional significance of the covariance between protein energy malnutrition and iron deficiency anemia. *Journal of Nutrition*, 125 (8 Supplement), 2272S–2277S.
- Pollitt, E.; Gorman, K. 1990. Long term developmental implications of motor maturation and physical activity in infancy in a nutritionally at risk population. In Schürch, B.; Scrimshaw, N.S., eds., *Activity, energy expenditure and energy requirements of infants and children*. International Dietary Energy Consultative Group, Lausanne, Switzerland. pp. 279–296.
- Pollitt, E.; Gorman, K.S.; Engle, P.L.; Rivera, J.A.; Martorell, R. 1995. Nutrition in early life and the fulfillment of intellectual potential. *Journal of Nutrition*, 125 (4 Supplement), 1111S–1118S.
- Pollitt, E.; Hathirat, P.; Kotchabhakdi, N.J.; Missell, L.; Valyasevi, A. 1989. Iron deficiency and educational achievement in Thailand. *American Journal of Clinical Nutrition*, 50 (3 Supplement), 687–697.
- Psacharopoulos, G.; Velez, E. 1992. Schooling, ability and earnings in Colombia, 1988. *Economic Development and Cultural Change*, 40, 629–643.
- Quizon, E.K. 1978. Time allocation and home production. *Philippine Economics Journal*, 17, 185–202.

- Reed, S.C.; Wirima, J.J.; Steketee, R.W. 1994. Risk factors for anemia in young children in rural Malawi. *American Journal of Tropical Medicine and Hygiene*, 51(2), 170–174.
- Ross, J. 1997. PROFILES guidelines: calculating the effects of malnutrition on economic productivity and survival. Academy for Educational Development, Washington, DC, USA. Mimeo. 31 pp.
- Ross, J.S.; Thomas, E.L. 1996. Iron deficiency anemia and maternal mortality. Academy for Educational Development, Washington, DC, USA. PROFILES 3 Working Notes Series, No. 3. 14 pp.
- Ruff, H.A.; Markowitz, M.E.; Bijur, P.E.; Rosen, J.F. 1996. Relationships among blood lead levels, iron deficiency, and cognitive development in two-year-old children. *Environmental Health Perspectives*, 104(2), 180–185.
- Scholl, T.O.; Hediger, M.L.; Fischer, R.L.; Shearer, J.W. 1992. Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. *American Journal of Clinical Nutrition*, 55(5), 985–988.
- Scholz, B.D.; Gross, R.; Schultink, W.; Sastroamidjojo, S. 1997. Anaemia is associated with reduced productivity of women workers even in less-physically-strenuous tasks. *British Journal of Nutrition*, 77(1), 47–57.
- Seshadri, S.; Gopaldas, T. 1989. Impact of iron supplementation on cognitive functions in preschool and school-aged children: the Indian experience. *American Journal of Clinical Nutrition*, 50 (3 Supplement), 675–686.
- Six, K.M.; Goyer, R.A. 1972. The influence of iron deficiency on tissue content and toxicity of ingested lead in the rat. *Journal of Laboratory and Clinical Medicine*, 79(1), 128–136.
- Sloan, N.L.; Jordan, E.A.; Winikoff, B. 1992. Does iron supplementation make a difference? John Snow Inc., Arlington, VA, USA. MotherCare Working Paper No. 15. Mimeo. 50 pp.
- Soemantri, A.G. 1989. Preliminary findings on iron supplementation and learning achievement of rural Indonesian children. *American Journal of Clinical Nutrition*, 50 (3 Supplement), 698–702.
- Soewondo, S.; Husaini, M.; Pollitt, E. 1989. Effects of iron deficiency on attention and learning processes on preschool children: Bandung, Indonesia. *American Journal of Clinical Nutrition*, 50 (3 Supplement), 667–674.
- Stevenson, R.C.; McCabe, C.J.; Pharoah, P.O.; Cooke, R.W. 1996. Cost of care for a geographically determined population of low birthweight infants to age 8–9 years. I. Children without disability. *Archives of Disease in Childhood, Fetal and Neonatal Edition*, 74(2), F114–F117.
- Taylor, P.G.; Martinez-Torres, C.; Méndez-Castellano, H.; Bosch, V.; Leets, I.; Tropper, E.; Layrisse, M. 1993. The relationship between iron deficiency and anemia in Venezuelan children. *American Journal of Clinical Nutrition*, 58(2), 215–218.
- Thibault, H.; Galan, P.; Selz, F.; Preziosi, P.; Olivier, C.; Badoual, J.; Hercberg, S. 1993. The immune response in iron-deficient young children: effect of iron supplementation on cell-mediated immunity. *European Journal of Pediatrics*, 152(2), 120–124.
- UNDP (United Nations Development Programme). 1995. Human development report 1995. UNDP, New York, NY, USA. 230 pp.
- UNICEF (United Nations Children's Fund). 1998. The state of the world's children 1998. Oxford University Press, New York, NY, USA. 131 pp.
- Walter, T.; De Andraca, I.; Chadud, P.; Perales, C.G. 1989. Iron deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics*, 84(1), 7–17.
- Walter, T.; Kovalskys, J.; Stekel, A. 1983. Effect of mild iron deficiency on infant mental development scores. *Journal of Pediatrics*, 102(4), 519–522.
- Walter, T.; Olivares, M.; Pizarro, F.; Muñoz, C. 1997. Iron, anemia and infection. *Nutrition Reviews*, 55, 111–124.
- WHO (World Health Organization). 1997. Iron deficiency: indicators for assessment and strategies for prevention. WHO, Geneva. WHO/NUT/96.12.
- Wise, D.A. 1975. Academic achievement and job performance. *American Economic Review*, 65, 350–366.
- World Bank. 1993. World development report 1993. World Bank, Washington, DC, USA. 329 pp.

- 1996. World development report 1996. World Bank, Washington, DC, USA. 241 pp.
- Yehuda, S.; Youdim, M.B.H.; Mostofsky, D.I. 1986. Brain iron-deficiency causes reduced learning capacity in rats. *Pharmacology, Biochemistry and Behavior*, 25(1), 141–144.
- Youdim, M.B.; Ben-Shachar, D.; Yehuda, S. 1989. Putative biological mechanisms of the effect of iron deficiency on brain biochemistry and behavior. *American Journal of Clinical Nutrition*, 50 (3 Supplement), 607–617.
- Zhu, Y.I.; Haas, J.D. 1997. Iron depletion without anemia and physical performance in young women. *American Journal of Clinical Nutrition*, 66(2), 334–341.
- 1998. Altered metabolic response in iron-depleted nonanemic young women during a 15-km time trial. *Journal of Applied Physiology*, 84(5), 1768–1775.