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FREQUENCY, CAUSE, AND SIGNIFICANCE OF IRON DEFICIENCY FOR THE CHILDREN OF CENTRAL ASIA

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Abstract

Iron deficiency is the most common global nutritional problem. Among the earliest functions to be affected are those associated with the brain enzymes involved in cognition and behavior and a number of immune mechanisms important for protection against infections. The adverse effects of iron deficiency during infancy on cognition appear to be irreversible. At all ages iron deficiency is intellectually and educationally disadvantageous, independently of ethnicity and of physical and social environment. Where iron deficiency is a public health problem dietary improvement and cereal fortification are recommended, and weekly iron supplementation has been demonstrated to be effective for preventing iron deficiency in vulnerable groups.

Introduction

The most common nutritional deficiency in the world today is that of iron deficiency and its more severe form, iron deficiency anemia. Unfortunately, the countries of Central Asia are not spared, and, as I will discuss in detail, the consequences are serious for the survival, health, and welfare of the populations of the region.

The standard WHO criteria for anemia are shown in Table 1.^{1,2} These criteria serve to indicate that the iron deficiency is sufficiently severe as to interfere with hemoglobin formation. But iron has many other functions that are more sensitive to depletion. Approximately 73% of the body's iron is normally incorporated into hemoglobin and 12% in the storage complexes ferritin and hemosiderin. A very important 15%, however, is incorporated into a variety of other iron-containing compounds of vital importance.

Table 1. WHO CRITERIA FOR THE DEFINITION OF ANEMIA

| Age/Sex Group | Hemoglobin Below | | Hematocrit Below |
|------------------------------|------------------|--------|------------------|
| | g/l | mmol/l | l/l |
| Children 6 months to 5 years | 110 | 6.83 | 0.33 |
| Children 5-11 years | 115 | 7.13 | 0.34 |
| Children 12-14 years | 120 | 7.45 | 0.36 |

| | | | |
|--------------------------------|-----|------|------|
| Non-pregnant women (15+ years) | 120 | 7.45 | 0.36 |
| Pregnant Women * | 110 | 6.83 | 0.33 |
| Men (15+ years) | 130 | 8.07 | 0.39 |

Source: WHO. *Nutritional anaemias*. WHO Technical Report Series No. 405. Geneva: WHO, 1968.

* Severe anemia in pregnancy: Hb levels <70 g/l; very severe anemia: <40 g/l.

The CDC² has developed Hb cut-off points for the definition of anemia, which are based on the mean minus 2 SD of US NHANES II survey. They apply to narrower ranges, and in general, they are between 3 and 5 g/l lower in children and women and in adolescent men. They are 2 g/l higher for older men. Month-by-month values for pregnancy, after the third month, are also 2 and 5 g/l lower except at months 8 and 9, when they are 2 and 4 g/l higher.

Figure 1 shows the stages in the development of iron deficiency from the depletion of iron stores as indicated by low plasma ferritin, interference with biochemical processes indicated by low transferrin saturation, and finally anemia as indicated by low hemoglobin. It has been shown that the proportion of individuals with biochemical iron deficiency is about double those with actual anemia up to 100%.³ Thus, it can be assumed that above 50% of anemia prevalence nearly all of the population is iron deficient. The significance of this is that these subclinical degrees of iron deficiency can interfere with cognitive, immune, and muscle function.

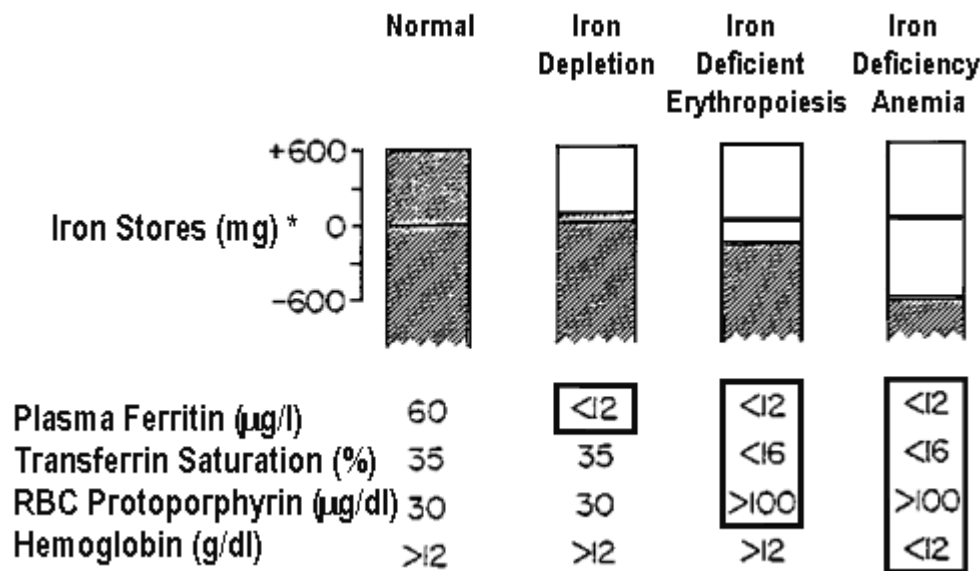


Fig. 1. Biochemical indicators of progressive stages of iron deficiency.

^a Measurements of iron status in relation to body stores (mg). Negative iron stores indicate the amount of iron that must be replaced in circulating red cells before iron reserves can re-accumulate.

Prevalence of Iron Deficiency and Iron Deficiency Anemia in the Region

Figure 2 shows that in the nationally representative 1995 Demographic and Health Survey (DHS) in Kazakhstan, conducted by personnel of the Institute of Nutrition in Almaty, 40% to 50% of women were anemic by the WHO criteria of a hemoglobin value of less than 12 g/dL.⁴ From 8% to 12% of these anemias were moderate to severe. As shown in Figure 3, the situation is even worse for children under 36 months of age, whose anemia rates are from 65% to 75%, with 35% to 45% of

them moderate to severe.

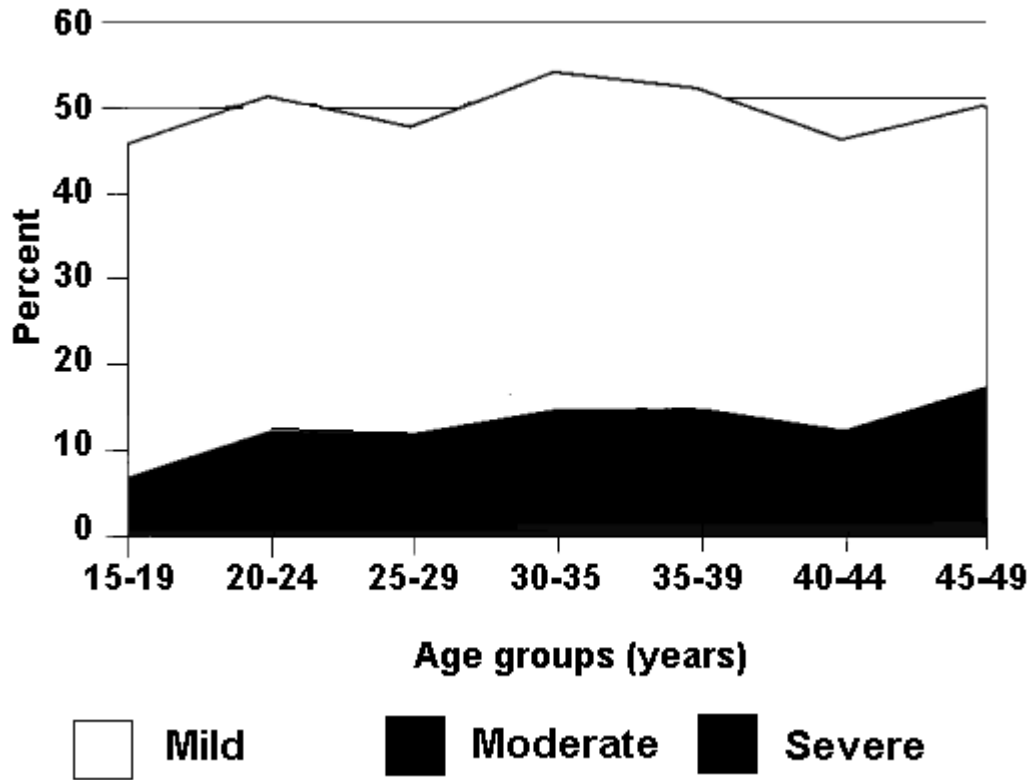


Fig. 2. Percentage of women as having anemia by age group, Kazakhstan, 1995 DHS. Source: UNICEF, CARK Area Office.





Fig. 3. Anemia among children, by age group, Kazakhstan, 1995 DHS. Source: UNICEF, CARK Area Office.

Figure 4 shows the actual distribution of hemoglobin values in women. Women who are pregnant or breastfeeding tend to have lower hemoglobin values than those who are not. As shown in Figure 5, women who are anemic are more likely to have infants who are anemic and who have more severe anemia.

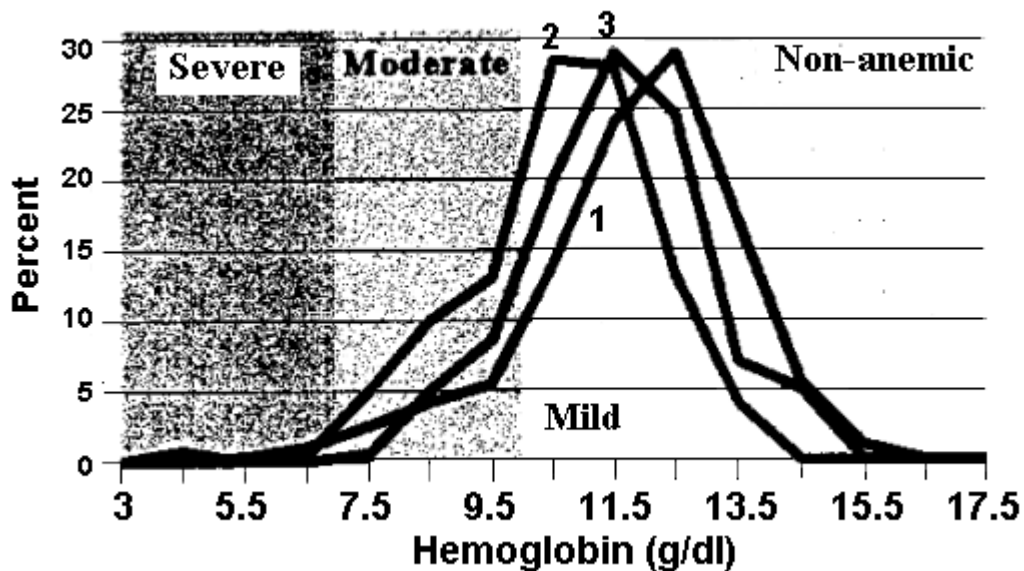
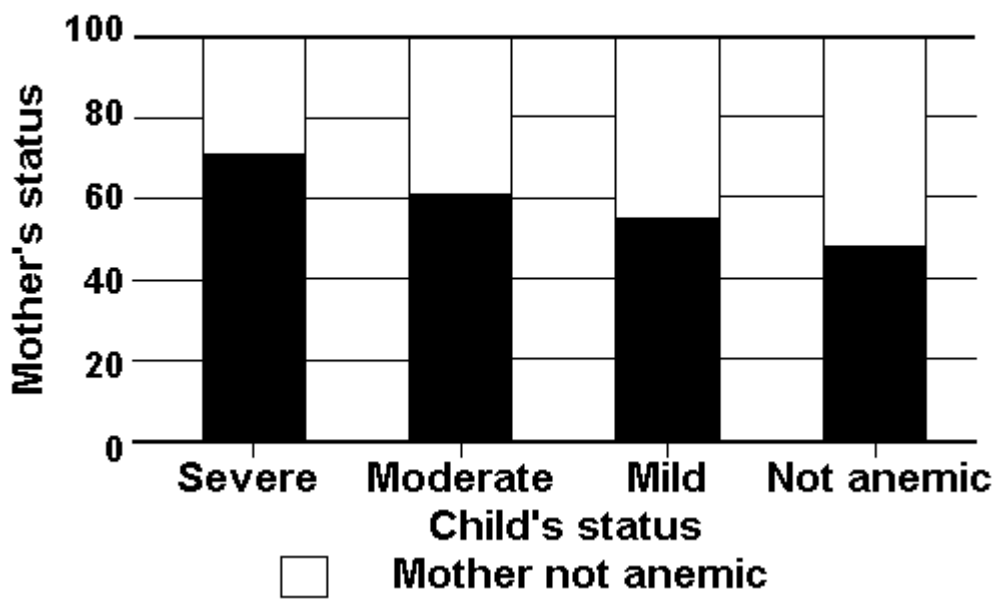


Fig. 4. Distribution of hemoglobin levels among women ages 15-19, Kazakhstan, 1995 DHS. Source: UNICEF, CARK Area Office.



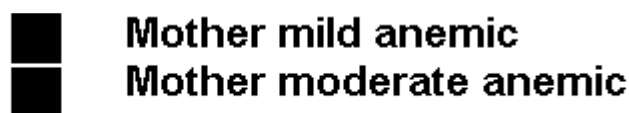


Fig. 5. Effect of mother's anemia status on child's anemia status, Kazakhstan, 1995 DHS. Source: UNICEF, CARK Area Office.

A similar national DHS survey in Uzbekistan in 1996 gave essentially the same results, as shown in Figure 6.⁵ Anemia prevalence ranged around 60%, with over 15% of it moderate to severe. Prevalence rates for young children in Uzbekistan were similar to those in Kazakhstan, with an overall rate of 61.8%, of which 1.2% were severe, 24.6% moderate, and 34.0% mild.

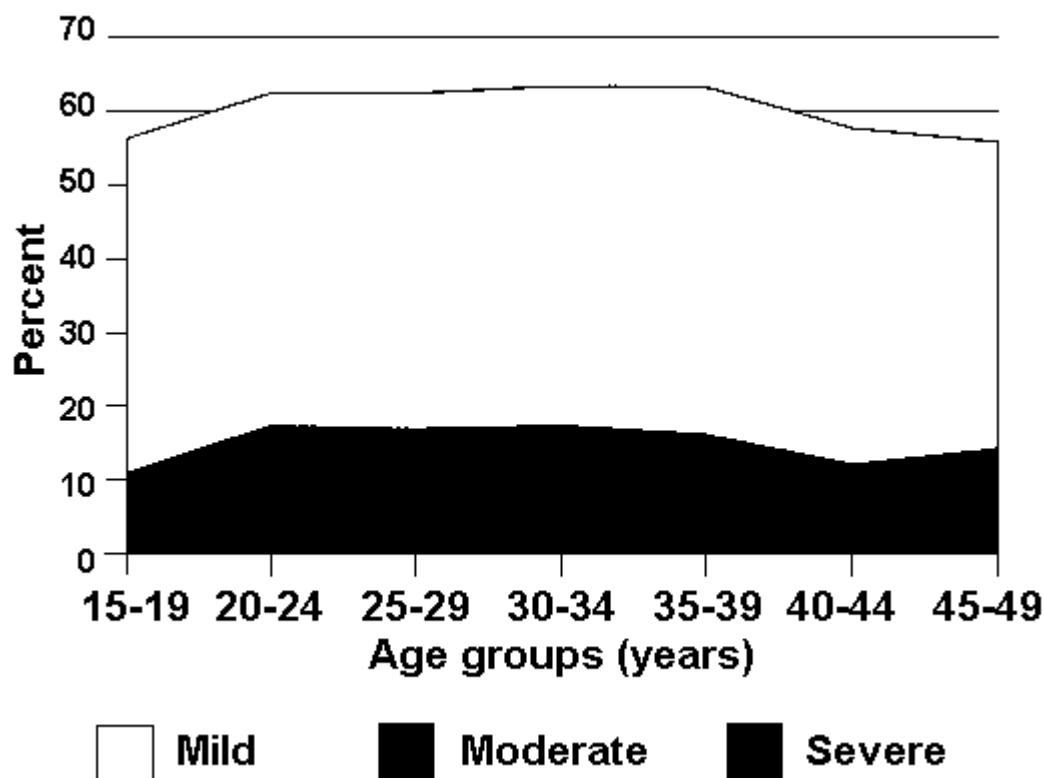


Fig. 6. Percentage of women as having anemia, by age group, Uzbekistan, 1996 DHS. Source: UNICEF, CARK Area Office.

An earlier survey by Crosslink in Karakalpakstan found slightly higher figures in this area.⁶ As shown in Figure 7, the severity of anemia varies by region, with over 50% moderate to severe in Region 1, and still nearly 10% in the capital city, Tashkent. As noted above, the amount of iron deficiency in these populations is approximately double the total amount of anemia.

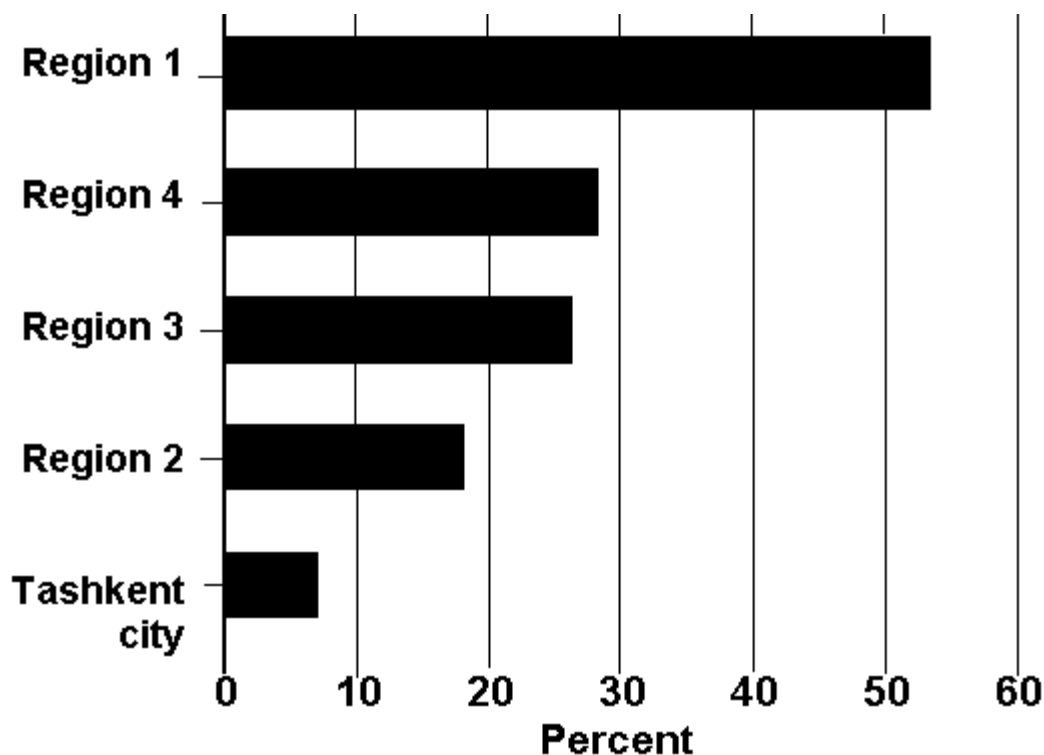


Fig. 7. Moderate and severe anemia among children 0-36 months, Uzbekistan, 1996 DHS. Source: UNICEF, CARK Area Office.

There are no comprehensive survey data for the other Central Asian countries, but more limited studies indicate that the prevalence rates are similar. At this meeting, the Director of Research of the Pediatric Institute of Azerbaijan reported on recent survey findings of 47% anemia among children in local villages and 69% among those in refugee camps, 24% of them moderate or severe (Dr. Guliyev Nasib Jafar Oglu, personal communication, 1997).

The seriousness of iron deficiency anemia can be understood from WHO data, indicating global rates in developing countries to be 51% for children 0 to 4 years of age, 46% for school-age children, 42% for women, and 26% for men.⁷ Even in the United States, the NHANES II survey found an overall 7% prevalence of actual anemia in women 15 to 44 years of age, but with the highest burden in minority and poverty groups.⁸ As described below, several of the studies indicating reduced performance of iron-deficient children and adolescents were in the U.S. population.

Causes of Iron Deficiency Anemia in the Central Asian Region

Such high anemia prevalence rates in Central Asia were not anticipated, especially since anemia was not reported as a public health problem when the countries were part of the former Soviet Union. In 1993, a study by the Republican Research Center of Maternal and Child Health in Kazakhstan found that anemia rates for pregnant women had increased more than six times in 13 years -- from 6.6% in 1979-1980, up to 40.2% in 1993. At that time, UNICEF also learned from the Kazakhstan Nutrition Institute studies that consumption of fruits, vegetables, and meats had significantly decreased between 1990 and 1993, thereby reducing both sources of heme and non-heme iron and enhancers of iron absorption.

Some have found it hard to believe that iron deficiency was the cause and sought other possibilities, citing the tradition of meat consumption. The low ferritin values reported in the Crosslink study, however, leave no doubt that iron deficiency is the main causative factor in most cases.⁶ The role of hemoglobinopathies has been questioned, but these were found in only 0.14% of the Karakalpakstan sample. Moreover, there is no evidence that the parasitic infections that cause iron losses in developing country populations—hookworm, schistosomiasis, and malaria—contribute significantly to anemia in this region.

The answer is to be found in the poor availability of iron in the diet due to a combination of factors. The most important is the high proportion of iron coming from vegetable sources high in iron-binding phytates. In addition, tea consumption with meals is almost universal, and the tannins in tea also inhibit iron absorption. While meat consumption is nearly universal, it is not currently high enough in the lower socioeconomic groups to supply sufficient heme iron. Heme iron is not only much better absorbed, but also improves the absorption of vegetable iron. The other major dietary factor is the relatively low intake of ascorbic acid that can enhance iron absorption by counteracting the effect of inhibitors. While the vitamin C intake is high enough to prevent scurvy, it is not high enough to improve the absorption of iron significantly.

A recent paper reporting on dietary iron intakes in the Soviet Union incorporated an algorithm for calculating iron availability, taking into account the above factors.⁹ It concluded that they were deficient in available iron, even though gross iron intakes appeared to be satisfactory. It is the high iron requirements of children for growth and of pregnant women for the formation of new tissue that make them particularly vulnerable. Lactation is also a time of nutritional stress, and the menstrual blood losses of women of reproductive age are severely skewed. Thus, many women have much higher losses than would be predicted from figures for average menstrual blood losses.

Pesticide contamination is often cited in countries of the region as the cause of the anemia. There is no experimental evidence for this, and the occurrence of equally severe anemia in populations in which pesticides are not known to be a problem makes it unlikely that they play a significant role.

Consequences of Iron Deficiency Anemia

Given the high frequency of iron deficiency anemia in women and children of the countries represented at this meeting, there should be great concern for its damaging consequences for individuals and their societies. Iron deficiency anemia has long been associated with weakness and tiredness. It is now recognized that even mild-to-moderate iron deficiency without anemia has adverse consequences.¹⁰ These include impaired cognitive performance, decreased physical capacity and work performance, reduced growth of children, lowered immune status, and increased morbidity from infections in all age groups. Severe iron deficiency anemia also impairs maintenance of body temperature.

Effect of Iron Deficiency on Cognitive Performance

The most serious pediatric effect of iron deficiency anemia is that in infancy it interferes with brain development at a critical time, to produce defects that cannot subsequently be reversed by correcting the anemia. Figure 8 shows the difference in Bailey test performance between anemic and non-anemic infants in Guatemala.^{11,12} These studies were repeated in Costa Rica with similar results, as shown in Figure 9, but they went further and examined the same children after they had entered

school at age seven.¹³ Those who had been anemic as infants still had poorer performance on appropriate cognitive tests even when they were no longer anemic. This could not be explained by any of a comprehensive set of socioeconomic factors. Results in Chile were similar.¹⁴⁻¹⁶

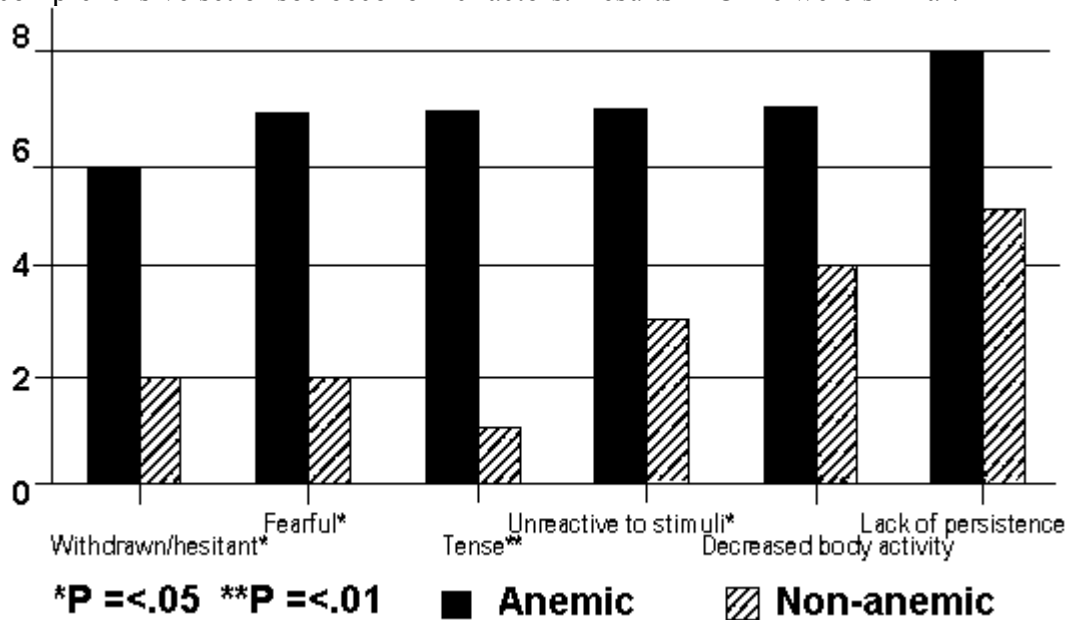


Fig. 8. Effects of iron deficiency anemia on Bailey test performance in Guatemalan infants. Sources:

Lozoff B, Brittenham G, Viteri F et al. Behavioral abnormalities in infants with iron deficiency anemia. In: Pollitt E, Leibel RL, editors. *Iron Deficiency: Brain Biochemistry and Behavior*. New York: Raven Press, 1982 (pp. 183-194)

Lozoff B. Methodologic issues in studying behavioral effects of infant iron-deficiency anemia. *Am J Clin Nutr*, 1989;50:641-654.

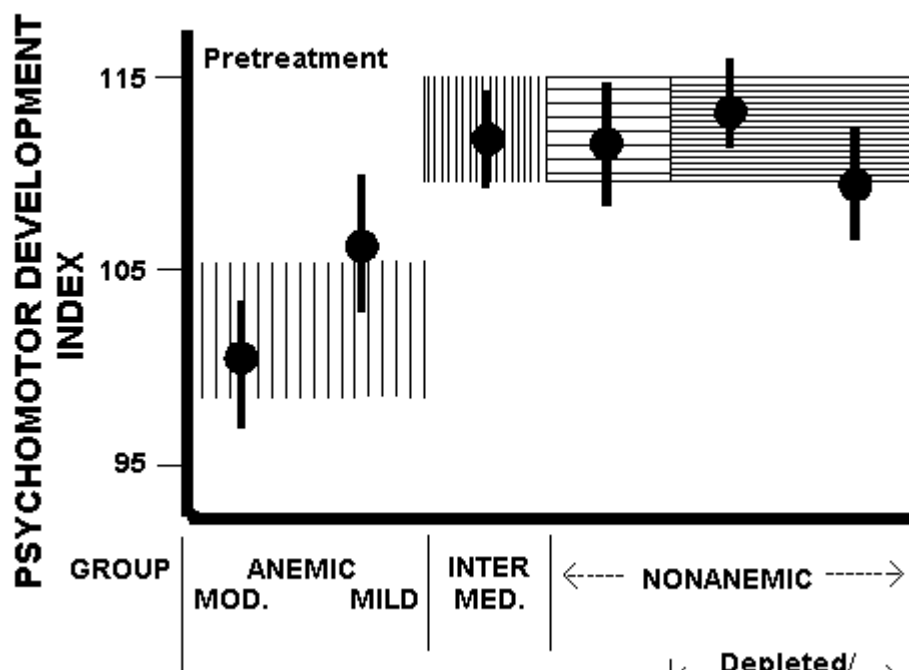




Fig. 9. Psychomotor development scores at different levels of iron deficiency: Costa Rican infants. Source: Lozoff B, Jimenez E, Wolf AW. Long term developmental outcome of infants with iron deficiency. *New Engl J Med.* 1991;325:687-695.

In the pioneering observations of Pollitt with children 3-6 years of age in Cambridge, Massachusetts, who were iron deficient but not anemic, the effect of iron deficiency on some cognitive tests was significant but reversible with iron supplementation.¹⁷ When Pollitt repeated this study in Guatemala where many of the children in the same age group were actually anemic, adverse effects of anemia on cognitive performance were still reversible, as shown in Figure 10.

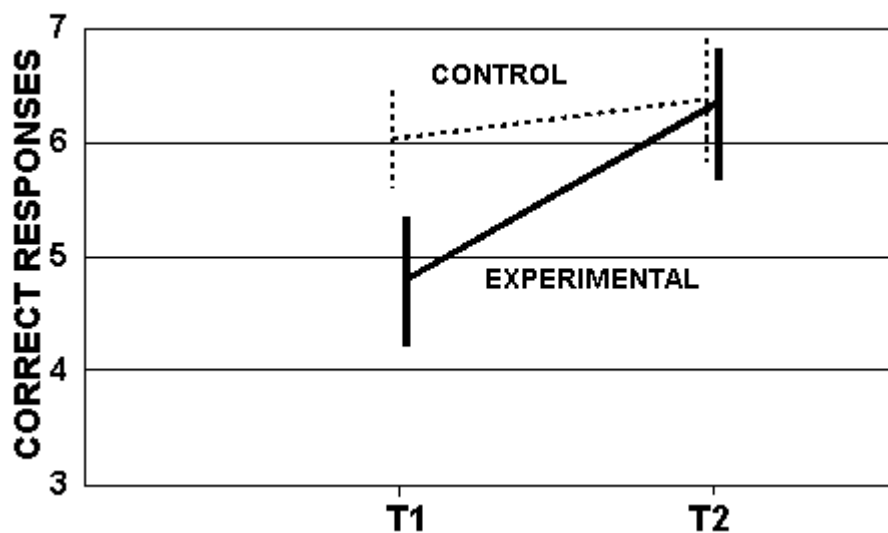
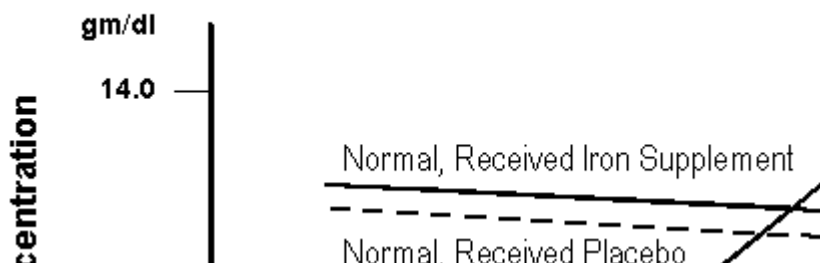


Fig. 10. Performance of control and experimental groups of 3- to 6-year-old children in Guatemala on oddity learning tasks before (T₁) and after (T₂) administration of oral iron; means and standard errors. Source: Pollitt E, Viteri F, Saco-Pollitt C et al. Behavioral effects of iron deficiency anemia in children. In: Pollitt E, Leibel RL, eds. *Iron Deficiency: Brain Biochemistry and Behavior*. New York: Raven Press, 1982 (pp. 195-208).

In a study in rural school children near Semarang, Indonesia, whose iron deficiency was relatively mild, complete recovery of hemoglobin in the anemic group with iron supplementation is shown in Figure 11a. There was some improvement in aptitude test scores, but it fell far short of catch-up with non-anemic children (Figure 11b).¹⁸ Two other studies near Bandung, Indonesia, obtained similar results.^{19,20} In Egypt, there was some improvement in cognitive test performance in preschool and school children showing a hematological response to iron supplementation.²¹



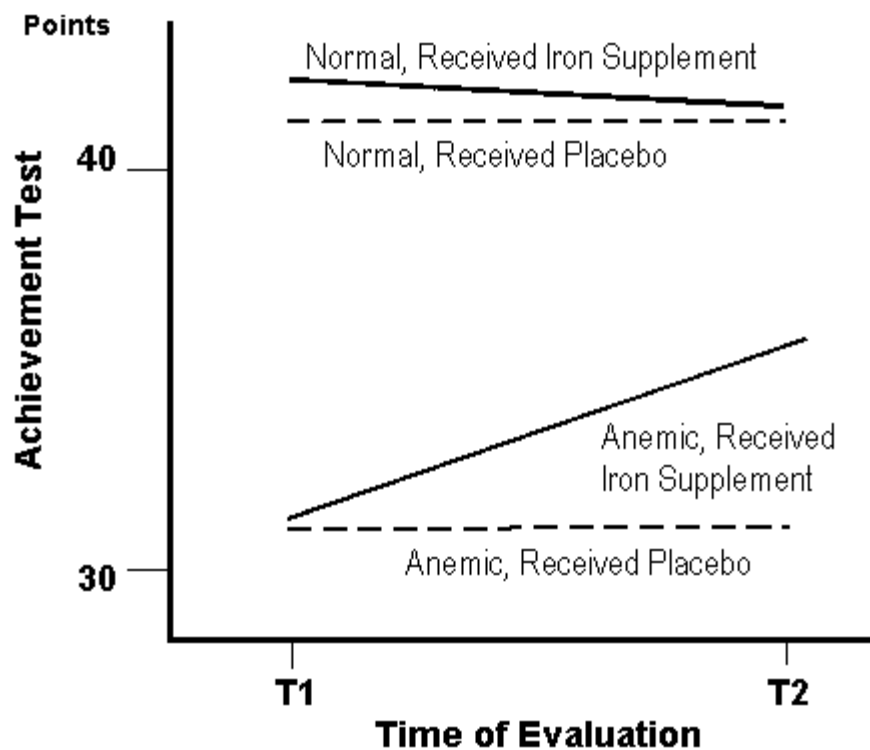
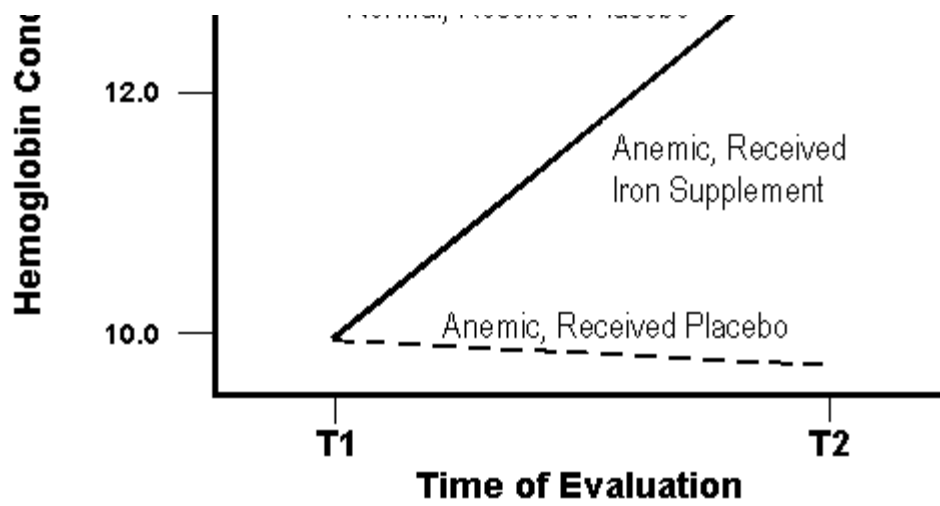


Fig. 11a (top) and 11b. Iron-deficient school children before and after 12 weeks of iron supplementation: Indonesia. Source: Soemantri AG. Preliminary findings on iron supplementation and learning achievement of rural Indonesian children. *Am J Clin Nutr.* 1989;50(suppl. 3):698-702.

A study of anemic school children in Thailand showed poorer performance on the Raven Progressive Matrices used to measure IQ, on the Thai language test, and on a mathematics test. It is noteworthy that even children who were iron-depleted without anemia had significantly lower scores on the Thai language test than did iron-replete children. None of these differences was corrected by iron supplementation.²²

Four separate studies in India have explored the impact of iron supplementation on school children.

The first investigated iron-folate supplementation for 60 days on cognition in 94 boys and girls aged 5 to 8 years.²³ Scores improved markedly in the anemic group compared with non-anemic controls. The second involved the same design for 14 pairs of anemic 5- to 6-year-olds with one of each pair receiving the supplement and showing significant cognitive benefit. The third study compared the effect of doses of 30 and 40 mg of elemental iron and a placebo on a number of tests of cognitive function in schoolboys 8 to 15 years old. Both doses improved recent memory, attention, auditory memory, auditory sequencing, visual-motor coordination, and visual perception. The fourth study investigated the impact of a prophylactic dose of 60 mg of elemental iron per day, or a placebo, for 60 days, twice in a school year on underprivileged girls aged 8 to 15 years. Attention, memory, and concentration were improved by the iron supplementation. The conclusion from these studies was that iron supplementation would improve the scholastic performance of similar children in India's public schools.

A recent study in the United States showed that iron-deficient teenage girls in Pennsylvania had retarded reaction time and other test performance that improved with iron supplementation.²⁴ In a 1990 study of 9- to 10-year-old school children in a rural community in greater Zagreb, Croatia, the variables that best explained the variation in results on a "Revised Beta Examination Test" were transferrin saturation, body height, and vitamin C blood levels (R. Buzina, personal communication, 1995). The latter would also be associated with better absorption of iron. Transferrin saturation, a more sensitive indicator of iron deficiency anemia than hemoglobin, was also a predictor of Wechsler test scores. It is noteworthy that 67% of the children were adequately nourished and 20% were overweight or obese. Only 14% were slightly undernourished.

It can be concluded that iron deficiency in infancy is likely to result in permanent neurological damage that cannot be corrected later by iron supplementation. These children will have delayed psychomotor development, and when they reach school age, they will have poorer performance on tests of language skills, motor skills, and coordination, equivalent to a 5-to-10 point deficit in IQ. After infancy, iron deficiency anemia is also associated with adverse cognitive effects, but in older children and adults these appear to be reversible. The effects of iron deficiency on cognition are independent of ethnicity and physical and social environment.

Mechanisms of Iron Effects

As already mentioned, a very important 15% of body iron is incorporated into a variety of iron-containing compounds of metabolic importance. The heme compounds include myoglobin, cytochromes, catalases, and peroxidases. The non-heme compounds include NADH and succinic dehydrogenases; xanthine, aldehyde, and alphasglycerophosphate oxidases; phenylalanine hydroxylase; and ribonucleotide reductase. Alphasglycerophosphate oxidase, for example, shuttles electrons across the mitochondrial membrane. Also important are the iron dependent enzymes: lipid peroxidase, proline and lysine hydroxylase, and a large number of others. It is not surprising, therefore, that a deficiency of iron would have a variety of consequences, of which reduced hemoglobin synthesis is a relatively later phenomenon.

Cognitive: There is no direct evidence from human studies for the mechanism of the effect of iron deficiency on neurological function. Iron, however, is known to be concentrated in specific regions of the human brain. Work in Israel with rats indicates that iron deficiency at an early age results in irreversible damage to developing dopamine neurons²⁵ and learning ability of rats.²⁶ The decreased number of dopamine D₂ receptors causes a selective diminution of central dopamine neurotransmission.^{27,28} The result is a modification of dopamine-dependent behaviors and reactions,

the most important of which is a reduction in learning processes, a deficit that persists in adult rats.²⁹ It is postulated that, also in children, interference with iron metabolism at an early age can result in irreversible damage to developing dopamine neurons.

Immune Function: A number of different immune mechanisms are affected by iron deficiency.

Chandra³⁰ has demonstrated in Indian children that the mitogenic response of the lymphocytes, the capacity for respiratory bursts necessary for killing ingested organisms, and the number of intracellular bacteria in lymphocytes exposed in culture are related to transferrin saturation (Figure 12). There is also extensive evidence³¹⁻³³ for a direct relationship between iron status and plasma T-lymphocyte concentrations. Impaired delayed cutaneous hypersensitivity to a number of ubiquitous antigens has also been described in iron-deficient children in India^{32,33} and Kenya.

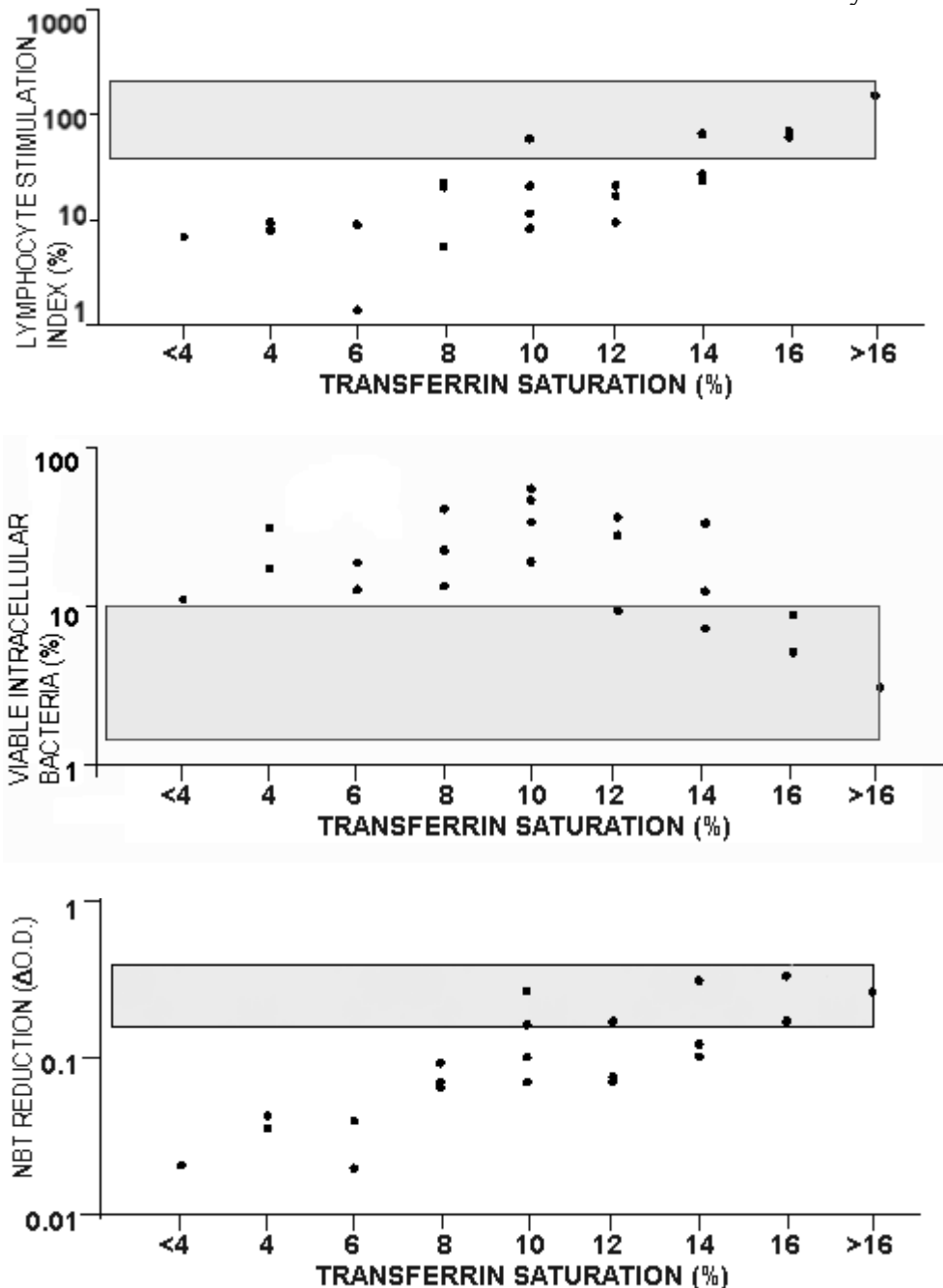


Fig. 12a (top), 12b (middle), and 12c. Lymphocyte proliferation (top), intracellular bactericidal capacity of neutrophils (middle), and quantitative nitroblue tetrazolium test, related to serum transferrin saturation: children in India. Shaded areas represent the means and ranges of values obtained in iron-replete controls. Source: Chandra RK, Newberne PM. *Nutrition, Immunity, and Infection: Mechanisms of Interactions*. New York: Plenum, 1977.

Physical Capacity: The physical performance of severely anemic agricultural workers is not improved by blood transfusion³⁴ but recovers in about ten days with iron supplementation before there has been time for a hemoglobin response. This suggests that iron-dependent muscle enzymes responsible for energy transfer respond more rapidly.

Are There Contraindications to Iron Supplementation?

Iron is essential for the replication of microorganisms, and one of our body's natural defenses to infection is the ability to withhold iron from invading organisms. Normally, this is the function of serum transferrin augmented by lactoferrin released by leukocytes. With severe malnutrition, normal host immune mechanisms are severely compromised. Under these circumstances, it has been observed among Somalia refugees^{35,36} and children with kwashiorkor³⁷ that parenteral iron can result in overwhelming infection. This is not the case with supplementation. Even with daily supplementation, the dose is sufficiently small that the existing transferrin and lactoferrin is sufficient to bind free iron so that the organisms cannot utilize it. Wherever morbidity has been measured in daily supplementation programs, at a level of 60 mg of iron there has been a decrease in diarrheal and respiratory disease. With weekly iron supplementation there is even less reason for concern.

Another consideration has been the danger to persons carrying genes for hemochromatosis. The downregulation of iron absorption is very effective, even when the diet is rich in heme iron and of a composition that favors absorption. The development of iron overload from dietary iron intake or supplementation at an appropriate level, therefore, is highly unlikely in normal individuals. About 1 to 5 individuals per 1000, depending on the population, however, is homozygous for a gene that blocks this downregulation and can lead to the liver disease, hemochromatosis.³⁸ Males express the disease ten times more often than females because they have less systematic iron loss. The heterozygotes do not appear to be affected. It is a rare clinical problem and should not be used as a reason for not preventing iron deficiency in the other 99.5% to 99.9% of a population. When detected, fortunately, the condition is easily and effectively treated by periodic blood donations.

Prevention by Weekly Iron Supplementation

Finally, I would like to describe a recent breakthrough that can contribute importantly to the conquest of iron deficiency. Daily iron supplementation has been and remains the standard and effective means of treating iron deficiency anemia. As a preventive measure, however, it has encountered serious problems of compliance because of adverse side effects and has been too costly to sustain without continuing international assistance. Four years ago, studies in rats indicated that, after the first day of oral iron supplementation, absorption of iron drops rapidly.³⁹ It was postulated that sufficient iron might be absorbed from a weekly dose for the correction of mild-to-moderate anemia and development of adequate iron stores in a reasonable period of time.

Ten studies in which the taking of each supplement is supervised have now been completed in women and children in Bolivia, China, Guatemala, Indonesia, Malaysia, and the United States.⁴⁰ The

results indicate that at an appropriate dosage and with assured compliance, hemoglobin levels are the same after two to three months with both daily and weekly regimens unless there are complicating factors, such as malaria. The potential logistic and financial advantages of a weekly supplement compared with a daily one are obvious. The challenge is to demonstrate the practicality of large-scale weekly programs with sustainable mechanisms to ensure adequate compliance.

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