Chapter 3

Iron deficiency anaemia

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Summary

Iron deficiency is a highly prevalent form of undernutrition, affecting around one-fourth of the world's women and children, and is one of the most common causes of anaemia.

We conducted comprehensive reviews of published literature linking iron deficiency to disability and death for four potential outcomes: child mortality, perinatal mortality, maternal mortality and mild mental retardation. For all of these outcomes, the best available data were prospective observational studies in which anaemia or haemoglobin concentration was the risk factor. Data on child mortality were not adequate for this task, although a true risk cannot be precluded by the data. Summary relative risks for perinatal mortality (10 studies), maternal mortality (six studies) and mental retardation (five studies) were estimated using random effects models (both mortality outcomes) or a fixed-effects model (retardation) and weighting individual estimates by the inverse of their within-study variance. For mortality outcomes, the bivariate relations between haemoglobin and death were used. In two studies of perinatal mortality, unadjusted and multivariate adjusted odds ratios were compared to assess the potential degree of bias in the unadjusted associations. For mental retardation, published multivariate adjusted relations between haemoglobin and IQ were used. Global anaemia prevalence data were supplied by the World Health Organization (WHO), and converted to mean haemoglobin concentrations, assuming normal distribution and observed standard deviations from a large number of studies. To estimate the haemoglobin distribution if iron deficiency were corrected, we assumed the prevalence of anaemia in women and children would be reduced by 50%. On average, for the world, this would increase haemoglobin concentration by about 0.45 g/dl (range: 0.0 g/dl to 1.28 g/dl).

The relative risks associated with a 1 g/dl increase in population mean haemoglobin were 0.75 (95% CI 0.62–0.89) for maternal mortality, 0.72 (0.65–0.81) for perinatal mortality and 0.78 (0.70–0.86) for mental retardation. Subgroup analyses suggested that the relative risk for perinatal mortality in malaria-endemic regions, 0.65 (0.56–0.75), was lower than that in regions without endemic *Plasmodium falciparum* malaria, 0.80 (0.73–0.87). These estimates were attenuated by 20% to account for probable bias leading to overestimation of the true relationship. Based on these estimates of iron deficiency anaemia as a risk factor for mortality, iron deficiency is estimated to cause 591 000 perinatal deaths and 115 000 maternal deaths globally. The associated loss of healthy life years amounts to more than 19 million disability-adjusted life years (DALYs) from perinatal causes and more than 3 million from maternal causes. When the direct sequelae of iron deficiency anaemia are added, the total global burden attributed to iron deficiency anaemia amounts to 841 000 deaths and 35 057 000 DALYs.

The available evidence suggests that iron deficiency anaemia contributes substantially to death and disability in the world. The great majority of this disease burden derives from anaemia in pregnancy and early childhood and is borne by women and children in Asia and Africa. The high global prevalence of anaemia and its potentially associated disease burden, as reflected in these estimates, constitute an urgent research agenda. Because these estimates are uncertain in many respects, their most important use may be to motivate public health scientists to provide definitive evidence.

1. Introduction

Iron deficiency is one of the most prevalent nutrient deficiencies in the world, affecting an estimated two billion people (Stoltzfus and Dreyfuss 1998). Young children and pregnant and postpartum women are the most commonly and severely affected because of the high iron demands of infant growth and pregnancy. However, where diets are based mostly on staple foods with little meat intake, or people are exposed to infections that cause blood loss (primarily hookworms and urinary schistosomiasis), iron deficiency may occur throughout the life span. Current WHO/International Nutritional Anemia Consultative Group/United Nations Children's fund/United Nations Children's fund (WHO/INACG/UNICEF) guidelines recommend universal iron and folic acid supplementation of young children and pregnant women where anaemia is highly prevalent (Stoltzfus and Dreyfuss 1998).

Although much is known about iron metabolism, the health consequences of iron deficiency continue to be a subject of research and debate. This is partly because in many regions of the world iron supplements are the standard of care for individuals with anaemia. Most trials of iron supplementation have measured haemoglobin concentra-

tion as the primary outcome. There is a relatively small body of clinical trials of iron repletion to humans with functional iron deficiency (i.e. iron deficiency severe enough to affect erythropoiesis) with pregnancy outcomes or mortality as primary objectives. There is surprisingly little evidence to either support or refute a causal link between iron deficiency and these important adverse health outcomes. As processes like this comparative risk assessment (CRA) bring to light the overall weakness of evidence either supporting or refuting the relationship, new research priorities may emerge.

2. Health outcomes considered

In May 2000, a meeting commissioned by WHO, INACG and the Edna McConnell Clark Foundation systematically reviewed the evidence of a causal relationship between iron deficiency or anaemia and six health outcomes: child mortality, maternal mortality, birth outcomes, morbidity, work productivity and child development. These papers were subsequently published in a supplement to the *Journal of Nutrition* (Beard and Stoltzfus 2001). We began by considering those six outcomes.

Malnutrition (in this case, iron deficiency) may contribute to death and disability through direct sequelae or as a risk factor for death and disability from other causes. The total death and disability attributed to iron deficiency is therefore the sum of its actions as a risk factor and its direct sequelae. The objective of the present paper is to consider iron deficiency as a risk factor for death and disability from other causes.

Of the six outcomes considered above, child mortality, maternal mortality, birth outcomes and morbidity were considered in the framework of iron deficiency as a risk factor. For example, women do not die in childbirth as a direct effect of iron deficiency, but rather die of heart failure due to blood loss, which is made more precipitous by iron deficiency anaemia. Similarly, babies do not die in the perinatal period from iron deficiency, but rather die of other causes, some of which are related to preterm birth, for which maternal iron deficiency is a risk factor. In contrast, decreased work productivity and altered child development (or intelligence) were considered to be direct sequelae of iron deficiency, the assumption being that iron deficiency directly causes decreased oxygen delivery to muscles and the brain.

2.1 Outcomes considered

Child mortality

There is a body of observational evidence linking child mortality to anaemia. However, we could find no published or unpublished studies of reasonably large size that described the relationship between anaemia and cause-specific mortality. Furthermore, nearly all the evidence linking anaemia to overall mortality comes from sub-Saharan Africa or Papua New Guinea, where *P. falciparum* malaria is a major cause of anaemia,

especially severe anaemia, and malaria is also a major cause of mortality. Thus it seemed unjustified to attribute the observed relationship between anaemia and mortality to iron deficiency in this context, or to generalize to other regions of the world. Brabin et al. (2001a) summarized these data and their interpretation. There are no observational studies linking iron deficiency *per se* to child mortality, nor any iron supplementation trials with child mortality as outcome. For these reasons, we were unable to estimate the relationship between iron deficiency and cause-specific child mortality. However, it is important to note that the available evidence does not preclude that relationship.

Maternal mortality

There are a number of observational studies of anaemia and maternal mortality from both Africa and Asia. None of these studies attempted to distinguish iron deficiency anaemia from other causes of anaemia, although several discussed the multiple causes of anaemia within their study population. Where *P. falciparum* malaria is endemic, it is an important cause of anaemia, especially in first pregnancies (Brabin 1983). However, there is no evidence that malarial infection contributes directly to maternal mortality, even in areas where *P. falciparum* is endemic (Brabin et al. 2001b). Thus in contrast to the situation with child mortality, it is less plausible that malaria would confound the observed relationship between anaemia and maternal mortality (as it likely does with anaemia and child mortality). There are no observational studies linking iron deficiency *per se* to maternal mortality, nor are there any iron intervention trials with maternal mortality as outcome. Thus we used the available observational data to estimate the relationship between anaemia and maternal mortality.

Perinatal mortality

There are several observational studies of maternal anaemia and stillbirths, neonatal or perinatal mortality from Africa, Asia, North America, and the United Kingdom of Great Britain and Northern Ireland. None of these studies attempted to distinguish iron deficiency anaemia from other causes linking anaemia. There are no observational studies linking maternal iron deficiency *per se* to perinatal mortality, and the few published iron intervention trials with perinatal morality as outcome are small or poorly designed. As with maternal mortality, we used the available observational data to estimate the anaemia–perinatal mortality relationship.

Low birth weight

We did not consider low birth weight as a separate outcome in these analyses, but rather assumed that the mortality risk and morbidity burden of anaemia-associated low birth weight was subsumed in our estimate of perinatal mortality as outcome. The relationship between iron status and

low birth weight has been examined in several clinical trials, and it has been the subject of two recent systematic reviews (Mahomed 2000a; Rasmussen 2001). Both concluded that causal evidence from trials is lacking. Rasmussen (2001) noted that there was insufficient evidence from these trials either to support or refute the relationship, because most trials conducted in populations with a significant burden of anaemia have suffered from poor research designs. There is however a substantial body of observational data relating pregnancy anaemia to low birth weight, similar to the observational data relating pregnancy anaemia to maternal and perinatal mortality. Scott Poe and Mary Cogswell (personal communication) have recently completed a meta-analysis of these observational studies. They found that pregnancy anaemia assessed in the first two trimesters of pregnancy was significantly associated with preterm birth (but not intrauterine growth retardation), and that the risk of preterm birth increased with increasing severity of anaemia.

2.2 Outcomes considered to be direct sequelae of iron deficiency

Work productivity

There is a substantial body of evidence in animals and humans demonstrating that iron deficiency decreases fitness and aerobic work capacity through mechanisms that include oxygen transport and respiratory efficiency within the muscle (Beard 2001; Haas and Brownlie 2001). This relationship is directly and linearly related to the severity of iron deficiency anaemia. The personal and socioeconomic consequences of this relationship are likely to be real and measurable (Horton and Levin 2001). This consequence of iron deficiency is estimated as a direct sequela of iron deficiency, and is not presented here as a risk factor.

Intelligence or cognitive capacity

There is a growing body of evidence from animal and human studies that supports a causal relationship between iron deficiency anaemia in early childhood and intelligence in mid-childhood (Beard 2001; Grantham-McGregor and Ani 2001). Although this effect of iron deficiency will be considered as a direct sequela of iron deficiency, we used the observational studies of iron deficiency anaemia in early childhood and measures of intelligence in mid-childhood to obtain a quantitative estimate of this relationship. Different investigators used different measures of cognition, learning or intelligence, making it impossible to summarize all the results. We therefore limited the outcome to global measures of intelligence that were either IQ or on the same scale as IQ (i.e. mean of 100 with standard deviation of 15 points). However, all of these studies measured deviations in intelligence within the clinically normal range (i.e. ≥70 points). In terms of the International Statistical Classification of Diseases and Related Health Problems, ninth revision

(ICD-9) classification, disability in this domain is limited to mental retardation, which these studies do not directly address. We have therefore provided an estimate of the effect of early iron deficiency on mental retardation in mid-childhood, making the controversial assumption that the reported association of iron deficiency anaemia and mean IQ does not affect the variance of IQ. Based on this assumption we can estimate the expected increased risk of IQ <70 (i.e. mild mental retardation) associated with shifts in mean IQ.

Morbidity

The bulk of experimental evidence from iron supplementation trials regards morbidity. There is evidence that sufficient iron is essential for immune function (Beard 2001), and also that excess iron may exacerbate some diseases. The evidence from experimental trials does not suggest that iron supplementation reduces morbidity; in some cases it has been associated with increased morbidity, most notably malaria and respiratory infections in malarious areas (Oppenheimer 2001). However, it is most plausible that this excess risk is associated with therapeutic iron supplementation intended to treat iron deficiency; not that iron deficiency itself is beneficial. Those trials that used low-dose oral supplementation in currently recommended dosages found no adverse effect (INACG 1999). Therefore, we did not estimate a morbidity risk associated with iron deficiency; nor does the available evidence support a risk associated with the correction of iron deficiency by currently recommended public health strategies.

To summarize, we have presented estimates of risk relationships for maternal mortality and perinatal mortality. These were based on anaemia as the indicator of iron deficiency, and only a proportion of that risk is therefore attributed to iron deficiency. We have also presented an estimate of the relationship between iron deficiency anaemia, decreased IQ and mental retardation, although we believe it should be interpreted with extreme caution.

3. Nature and definition of the risk factor

Iron is required in all tissues of the body for cellular respiration and many other reduction-oxidation enzyme systems, and has particular functions in muscle, brain and red cells. Critical metabolic functions in these three organs become perturbed at about the same time as animals are depleted of iron (Beard 2001). Anaemia has been used as the hallmark of iron deficiency severe enough to affect tissue function, because red cells are the tissue most amenable to sampling. Although more specific indicators of functional iron deficiency are available, notably erythrocyte protoporphyrin and serum transferrin receptor, there is insufficient data to link those indicators to the health outcomes that fit the construct of this project, namely maternal and perinatal mortality.

It is problematic that all of the available data on maternal and perinatal mortality use anaemia as the indicator, because iron deficiency is not the sole cause of anaemia in most populations. Even within individuals, anaemia may be caused by multiple factors. The available studies do not attempt to separate iron deficiency from anaemia, and there are no good regional estimates of the proportion of anaemia attributable to iron deficiency, although the topic has been discussed and debated (Gillespie and Johnston 1998).

We therefore took the approach of estimating the risk function associated with low haemoglobin, using haemoglobin as a continuous variable. Where studies reported haematocrit instead of haemoglobin, we converted to haemoglobin by dividing haematocrit by 3.

Because our task was to estimate the burden due to iron deficiency, the counterfactual (i.e. theoretical minimum) distribution should therefore represent the haemoglobin distribution if iron deficiency were eliminated. We assumed that the change in haemoglobin distribution following a supervised period of iron supplementation was a conservative approximation of the virtual elimination of iron deficiency.[1] By conservative we mean that it is more likely to underestimate the contribution of iron deficiency than to overestimate it, due to problems of noncompliance with supplementation, insufficient dosage, or insufficient duration.

We approached this calculation from two angles. The first approach was to estimate the percentage of anaemia attributable to iron deficiency. Knowing this, we could estimate the shift in the haemoglobin distribution needed to reduce anaemia by that proportion. Beaton recently summarized the per cent reduction in anaemia observed in nine controlled supplementation trials, all conducted in children (Table 3.1). The range of values was wide, 21–85%. Although there is regional diversity in the studies, these data are not sufficient to generate regional estimates. They provide a global average of 51%.

A second and complementary approach was to examine mean changes in haemoglobin attributable to iron supplementation in iron supplementation trials. Sloan et al. (2002) conducted a meta-analysis of haemoglobin response to iron supplementation to pregnant women in randomized controlled trials. Of 70 trials in the literature, 23 met their inclusion criteria, and 15 of those were from developing countries. In studies from developing countries, haemoglobin response was smaller in study samples with higher initial haemoglobin (summarized mean change of 1.13 g/dl in those with initial mean haemoglobin <10.0 g/dl compared to 0.85 g/dl in those with haemoglobin 11.0–11.9 g/dl). However, in studies from developed countries, the initial haemoglobin concentrations were uniformly ≥11.0 g/dl, and the effect size was large (1.17 g/dl). The response to iron supplementation was strongly related to iron dose, with maximum effects observed in the eight studies that provided a daily dose ≥91 mg. In these studies the mean haemoglobin response was around

Table 3.1 Estimated proportion of anaemia attributable to iron deficiency

Site	*Age group*	*Estimated attribution to iron*[a]
Bolivia	School children	84
India (Baroda)	Adolescents	26
India (Bombay)	Adolescents	55
India (Delhi)	Adolescents	41
Indonesia	Adolescents	63
Mali	Adolescents	21
Peru	School children	52
Sri Lanka	Adolescents	36
Viet Nam	Preschool children	85
Average		51

[a] Percentage reduction in anaemia in supplemented group minus per cent age reduction in control group.

Source: Beaton (2002).

1.8 g/dl. This maximal response might be considered the best theoretical basis for predicting the effect of eradicating iron deficiency. However, it is likely that the highest doses were also used in studies of more severely anaemic populations. A case can also be made for using 1.17 as the predicted effect size, as this was the average effect seen in women from developed countries, and very similar to that seen in women from developing countries with initially low haemoglobin (1.10–1.13 g/dl).

An important question for the present exercise is whether the predicted haemoglobin shift should vary by region. Sloan et al. (2002) did not disaggregate their data by global region, and the studies examined by Beaton are too few to disaggregate (see Table 3.1). If significant regional differences exist in the percentage of anaemia attributed to iron deficiency, the iron-attributable portion might be smaller in Africa, where malaria contributes greatly to the burden of anaemia. Therefore iron would logically claim a smaller portion of total anaemia. Shankar recently summarized data from controlled iron supplementation trials conducted in *P. falciparum* malaria-endemic populations, including the haemoglobin response attributable to iron (INACG 1999). Eleven studies were included, nine of them from sub-Saharan Africa (Adam 1997; Fleming et al. 1986; Harvey et al. 1989; Lawless et al. 1994; Menendez et al. 1994, 1997; Murray et al. 1978; Oppenheimer et al. 1986; Smith et al. 1989). The studies included younger and older children, and adults, including pregnant women. The change in haemoglobin attributable to iron supplementation in individual studies ranged from 0.3 to 3.6 g/dl, yielding a weighted average of 1.24 (95% CI 1.16–1.33). Although malaria certainly contributed to anaemia in these populations, it is

remarkable that the haemoglobin response to iron supplementation was similar to that reported by Sloan et al. (2002). Two of the 11 studies in the Shankar analysis were in pregnant women—the subject of analysis by Sloan et al. and the group at risk for the outcomes estimated in this chapter. These two studies from the Shankar analysis both used an iron dose of 60 mg/day, and yield a weighted average haemoglobin response of 0.83 g/dl. These studies were excluded from the analysis by Sloan et al., but are consistent with the haemoglobin responses at the dosage reported by them: 0.41 in studies of doses ≤60 mg/day, and 0.86 in studies of doses 61–90 mg/day.

Thus, the data suggest that iron deficiency is responsible for about 50% of anaemia, and that, where anaemia is prevalent, elimination of iron deficiency results in a change in mean haemoglobin of about 1.17 g/dl or perhaps even higher. The data are lacking in several respects: notably, the studies included in these three meta-analyses did not include non-pregnant adults outside of Africa. From the data at hand, there is no strong basis for altering these values by region. We used both of these lines of evidence to estimate the proportion of the risk associated with anaemia that is attributable to iron deficiency (see section 8).

4. Search strategy

4.1 Maternal mortality

We based our work on the recent systematic review by Brabin et al. (2001b). Because there are no experimental trials of iron deficiency and maternal mortality, we estimated the risk relationship from observational data. As described by Brabin et al. (2001b), several studies from Nigeria have documented extremely high risks of maternal mortality at haemoglobin concentrations <5 g/dl. We decided to limit our description of the haemoglobin-mortality risk relationship to the haemoglobin range of 5–12 g/dl. Values <5 g/dl are rare on a population basis, being more than 2 standard deviations below the mean in even the most severely anaemic communities, and we did not want those data to influence our risk estimates for the common population ranges. Pregnancy haemoglobin values >12 g/dl were excluded because we judged that variation in this high range is mostly unrelated to iron status, and our ultimate objective was to estimate risk associated with iron deficiency. We thus included those studies that reported mortality rates in at least two haemoglobin groups in the range of 5–12 g/dl rates. This excluded three studies: Fullerton and Turner (1962), Johnson and Ojo (1967) and Tasker (1958). We further excluded the study of Chi et al. (1981) from Indonesia, because the haemoglobin categories presented in their Table 5 disagreed with that in the text and we had no basis for determining which was correct. In summary, 10 studies were identified, and six of these were included in the meta-analysis (see Table 3.2 for study descriptions).

Table 3.2 Observational studies of anaemia and maternal mortality

Country (reference)	*Site*	*Period of data collection*	*Selection criteria*	*Time in pregnancy of anaemia assessment*	*Etiologies of anaemia at population level*
India (Konar et al. 1980)	Calcutta	1964–1973	Anaemic and nonanaemic 20–32 weeks pregnant women	Mid-pregnancy	Not discussed
India (Sarin 1995)	Punjab	1990–1994	Population-based survey of pregnant women	Different stages during pregnancies	Iron deficiency anaemia
Indonesia (Chi et al. 1981)	Java (multicentre)	1977–1980	Women admitted for delivery to 12 hospitals	At delivery, upon admission	Not discussed
Malaysia (Llewellyn-Jones 1965)	Kuala Lumpur	1953–1962	Women treated at Maternity Hospital in given time period	Not stated	Iron deficiency anaemia: (i) hookworm; (ii) diet. Megaloblastic anaemia: (i) liver damage in malnutrition (ii) diet-amount of folic acid, haemolytic, normoblastic anaemia
Malaysia (Tasker 1958)	Kuala Lumpur	1952–1958	Women admitted to obstetric unit at General Hospital in Kuala Lumpur	At delivery, upon admission	Iron deficiency and some megaloblastic anaemia
Nigeria (Fullerton and Turner 1962)	Ibadan	1957–1958	Pregnant women with severe anaemia (haematocrit ≤13%) not treated by exchange transfusion	At delivery, upon admission	Haemolytic anaemia—due to malaria
Nigeria (Johnson and Ojo 1967)	Ibadan	1961	20–32 weeks pregnant, anaemic (haematocrit ≤24%) women	20–32 weeks	Haemolysis; folic acid deficiency
Nigeria (Harrison 1975)	Ibadan	1965–1967	Pregnant women with haematocrit ≤26%	Pregnant and puerperal women in hospital	Red cell haemolysis due to malaria, dietary deficiency of folates and haemoglobinopathies
Nigeria (Harrison 1982)	Zaria	1976	Pregnant women who develop anaemia	Mid-pregnancy	Nutritional deficiency of iron and folates, malaria, haemoglobinopathies, blood loss, bacterial infections, and socioeconomic deprivation
Nigeria (Harrison and Rossiter 1985)	Zaria	—	Zaria area pregnant women	At delivery and interval between admission and death	Combined effects of malaria, dietary deficiency of iron and folic acid, sometime blood loss

Country (reference)	*Method of anaemia assessment*	*Maternal mortality definition*	*Level of care*	*Number of deaths/ total sample*	*Reasons for exclusion (see text for details)*
India (Konar et al. 1980)	Haemoglobin level at time of admission, method not stated	Death of any woman dying of any cause while pregnant or within 42 days of term of pregnancy	Eden Hospital, Calcutta (referral hospital for urban and rural population)	637/114 698	
India (Sarin 1995)	Haemoglobin determined by Tallqvist screen for anaemia followed by Sahli acid haematin method for anaemics	Death of pregnant women at delivery according to hospital records (1982–1994)	Referral hospital in area	339/38 565	
Indonesia (Chi et al. 1981)	Haemoglobin at time of admission	Hospital puerperal mortality rate	12 teaching hospitals (urban and rural)	135/36 062	Haemoglobin categories difficult to interpret
Malaysia (Llewellyn-Jones 1965)	Haemoglobin, method not stated	Death at childbirth	Maternity Hospital, Kuala Lumpur	283/73 048	
Malaysia (Tasker 1958)	Haemoglobin determined by Tallqvist screen for anaemia followed by Sahli acid haematin method for anaemics	Death at childbirth	Institute of Medical Research, Kuala Lumpur	132/28 720	Less than two groups with haemoglobin midpoint >5 g/dl

continued

Table 3.2 Observational studies of anaemia and maternal mortality (*continued*)

Country (reference)	*Method of anaemia assessment*	*Maternal mortality definition*	*Level of care*	*Number of deaths/ total sample*	*Reasons for exclusion (see text for details)*
Nigeria (Fullerton and Turner 1962)	Haematocrit	Death at childbirth	University College Hospital, Ibadan	18/92	Less than two groups with haemoglobin midpoint >5 g/dl
Nigeria (Johnson and Ojo 1967)	Microhaematocrit prior to amniocentesis, bone marrow at delivery	Deaths in anaemic and non-anaemic women 20–32 weeks pregnant	University College Hospital, Ibadan	9/234	Less than two groups with haemoglobin midpoint >5 g/dl
Nigeria (Harrison 1975)	Haematocrit	Death in pregnancy, labour or puerperium	University College Hospital, Ibadan	10/401 (excluding group with haematocrit <14%)	
Nigeria (Harrison 1982)	Haemoglobin from capillary sample, method not stated	Death in pregnancy, labour or puerperium	Hospital, Zaria	8/258	
Nigeria (Harrison 1985)	Haematocrit	Deaths during pregnancy and up to 42 days afterward	Hospital access but many home deliveries	121/1 777	

— No data.

Note: Shaded rows indicate excluded studies.

4.2 Perinatal mortality

As with maternal mortality, we estimated the risk relationship from observational studies, using pregnancy or delivery maternal haemoglobin concentration as the risk factor. Published trials of iron supplementation that reported perinatal or neonatal mortality as an outcome were not used as a basis for our risk estimate because the women in the trial were not anaemic (Hemminki and Rimpelä 1991) or because they were small or poorly designed to test the effect of iron (Agarwal et al. 1991; Fleming et al. 1986).

We based our search on the recent systematic reviews of Brabin et al. (2001b), Rasmussen (2001) and Xiong et al. (2000). We added to this one unpublished study by Dreyfuss et al. in which one of us was involved. Xiong et al. described the relationship between pregnancy anaemia and perinatal outcomes in 16 936 women in China. This study is published only as an abstract (Xiong et al. 1996); however, the authors provided the data we needed to include here. In summary, 13 studies were identified and 10 were included in the meta-analysis (see Table 3.3 for study descriptions).

4.3 Child development

We based our work on the recent systematic review by Grantham-McGregor and Ani (2001). We were interested in estimating the risk of continuous decrement in cognitive function or capacity in children who were iron-deficient anaemic in early childhood. Thus we limited our meta-analysis to those studies that identified iron-deficient anaemic and non-anaemic infants and toddlers and then compared their intelligence at age 2–7 years. We further limited the meta-analysis to studies that used standardized tests on a scale of 100 with standard deviation 15 (i.e. IQ tests and the Bayley Mental Development Index). Seven different longitudinal studies were described by Grantham-McGregor and Ani (Table 3.4). The study by Hurtado et al. (1999) was excluded because the outcome measure was placement in special education, rather than a measure of intelligence. Similarly, the study by Dommergues et al. (1989) was excluded because the outcome measure (Brunet-Lezine test) did not meet our criterion for a summarizable outcome. The two longitudinal studies by Lozoff et al. followed the same cohort of children; the data from the 1991 publication were used in this analysis. The two studies of Wasserman et al. also followed the same cohort of children. The data from the 1992 publication were used in this analysis because nearly 40% of the cohort was lost to follow-up by the time of the evaluation of the children at four years of age in the 1994 publication. The five studies that were included in our meta-analysis are described in Table 3.4.

Table 3.3 Observational studies of anaemia and perinatal mortality

Country (reference)	*Site*	*Period of data collection*	*Selection criteria*	*Time in pregnancy of anaemia assessment*	*Etiologies of anaemia*
China (Xiong 1996)	Suzhou	1989–1990	Perinatal care monitoring records	At entry into prental care; about 12 gestational weeks, and again at 32 weeks	Not described
India (Sarin 1995)	Punjab	1990–1994	Population-based survey of pregnant women	Different stages during pregnancies	Iron deficiency anaemia
Kenya (Macgregor 1963)	Mombasa	1957–1961	Patients at Lady Grigg Maternity Hospital	Within 48 hours of onset of labour	Malaria and iron deficiency are discussed
Malaysia (Llewellyn-Jones 1965)	Kuala Lumpur	1953–1962	Women treated in maternity hospital in given time period	Not stated	Iron deficiency anaemia: (i) hookworm; (ii) diet. Megaloblastic anaemia: (i) liver damage in malnutrition; (ii) diet-amount of folic acid, haemolytic, normoblastic anaemia
Malaysia (Tasker 1958)	Kuala Lumpur	1952–1958	Pregnant women with haemoglobin levels <45%	At delivery, upon admission	Iron deficiency and some megaloblastic anaemia
Nepal (Dreyfuss and West 2001)	Sarlahi	1994–1996	Community-based sample of pregnant women enrolled in vitamin A trial	Mid-pregnancy	Iron deficiency, other micronutrient deficiencies, *Plasmodium vivax* malaria, hookworms
Nigeria (Harrison 1975)	Ibadan	1957–1968	Pregnant women with haematocrit ≤26%	At delivery, upon admission	Red cell haemolysis due to malaria, dietary deficiency of folates, and haemoglobinopathies

Nigeria (Johnson and Ojo 1967)	Ibadan	1961	20–32 weeks pregnant, anaemic (haematocrit ≤24%) women	20–32 weeks	Haemolysis; folic acid deficiency
Nigeria (Harrison 1982)	Zaria	1976	Pregnant women who develop anaemia	Mid-pregnancy	Nutritional deficiency of iron and folates, malaria, haemoglobinopathies, blood loss, bacterial infections, and socioeconomic deprivation
Nigeria (Harrison et al. 1985)	Zaria	—	Pregnant women in Zaria area	First attendance at hospital to book for antenatal care or seek emergency care	Malaria, iron deficiency, haemoglobinopathies
Papua New Guinea (Mola et al. 1999)	Port Moresby	1987–1992	Pregnant women booked at antenatal clinics in or around Port Moresby and delivered in Port Moresby General Hospital	Lowest haemoglobin concentration from multiple values, mostly in second half of pregnancy	Malaria, alpha thallasemia, hookworm infection, iron and folate deficiencies
United Kingdom (Murphy et al. 1986)	Cardiff, Wales	1970–1982	All singleton births to South Glamorgan residents (Cardiff Births Study)	At first booking; 70% within first 13 weeks, 24% at 13–19 weeks, 5% at 20–24 weeks	Social disadvantage
USA (Garn et al. 1981)	multicentre	—	National Collaborative Perinatal Project	Lowest haemoglobin concentration in pregnancy from multiple antenatal values	Not described

continued

Table 3.3 Observational studies of anaemia and perinatal mortality (*continued*)

Country (reference)	*Method of anaemia assessment*	*Perinatal mortality definition*	*Level of care*	*Number of events/total sample*	*Reason for exclusion*
China (Xiong 1996)	Not stated	Perinatal mortality	Hospital	209/16 936	
India (Sarin 1995)	Haemoglobin by Sahli acid haematin method	Perinatal mortality	Referral hospital in area	1 529/33 160	
Kenya (Macgregor 1963)	Tallqvist method, confirmed by lab method if <6 g/dl	Stillbirths and neonatal deaths	Maternity hospital	339/3 950	
Malaysia (Llewellyn-Jones 1965)	Haemoglobin, method not stated	"Perinatal loss" (premature and mature stillbirth + neonatal)	Maternity Hospital, Kuala Lumpur	5 109/73 048	
Malaysia (Tasker 1958)	Haemoglobin determined by Tallqvist screen for anaemia followed by Sahli acid haematin method for anaemics	Fetal loss (premature and mature)	Institute of Medical Research, Kuala Lumpur	1 676/26 442	Less than two groups with haemoglobin midpoint >5 g/dl
Nepal (Dreyfuss and West 2001)	Haemoglobin from venous sample, by Hemocue	Neonatal death, i.e. death in first 28 post-natal days	Rural with little access to obstetric care; nearly all deliveries occurred at home	59/1 081	
Nigeria (Harrison 1975)	Haematocrit	Fetal loss	University College Hospital, Ibadan	17/301	

Nigeria (Johnson and Ojo 1967)	Microhaematocrit prior to amniocentesis, bone marrow at delivery	Abortions/immature deliveries, stillbirths and neonatal deaths ("total pregnancy wastage")	University College Hospital, Ibadan	19/145	Less than two groups with haemoglobin midpoint >5 g/dl
Nigeria (Harrison 1982)	Haemoglobin from capillary sample, method not stated	Fetal loss	Hospital, Zaria	36/221	
Nigeria (Harrison et al. 1985)	Haematocrit	Stillbirth and neonatal deaths	General hospital	1 834/18 116 (excluding groups with haemoglobin midpoints <5 g/dl)	
Papua New Guinea (Mola et al. 1999)	Haemoglobin, method not stated	Stillbirths	General hospital	246/13 311 (excluding groups with haemoglobin midpoints >12 g/dl)	
United Kingdom (Murphy et al. 1986)	Haemoglobin, method not stated	Perinatal mortality	Modern United Kingdom health system	4 195/36 466 (excluding group with haemoglobin midpoint >12 g/dl)	
USA (Garn et al. 1981)	Haemoglobin or haematocrit	Fetal death	Modern USA health system	1 196/ >50 000	Numerators and denominators not tabulated for haemoglobin groups

— No data.

Note: Shaded rows indicate excluded studies.

Table 3.4 Longitudinal observational studies of iron deficiency anaemia and child intelligence[a]

Country (reference)	*Sample size*	*Period of follow-up*	*Exclusions*	*Study design*
Chile (de Andraca et al. 1990)	Total = 77. Formerly anaemic = 41. Formerly non-anaemic = 29. All anaemic treated at 12 months	Birth to 5–6 years	BW <2 500 g, chronic ill health, intermediate levels of anaemia	Part of a randomized trial of iron fortification in early infancy, at one year, 25% of the non-fortified group had anaemia. The anaemic children all received 3 months of iron treatment. Selected children re-examined at 5 to 6 years of age
Costa Rica (Lozoff et al. 1991)	163 of 191 children originally evaluated at 12–24 months. 30 had moderate anaemia = Hb ≤10.0 g/dl, ferritin ≤12 mcg, EP >1.77 mcgmol or transferrin ≤10%. 133 comparison group	12 months to 5 years	BW <2.5 kg, multiple pregnancy, complicated births, acute or chronic medical problem	Follow-up at 5 years of Lozoff et al. (1987). The IDA group was initially treated for 3 months to to correct their anaemia. Current evaluators blind to original iron status. All now free of anaemia
Former Yugoslavia (Wasserman et al. 1992)	Children whose mothers were followed up from pregnancy in two areas of Kosovo. Mitrovica = lead exposed. Pristina = nonlead exposed. 541 agreed to participate. 392 (208+184) seen at 24 months	Birth to 24 months	Major CNS defects, chromosomal abnormalities, multiple pregnancy	Follow-up two cohorts from birth measuring serum lead, iron status and developmental indices. Related Hb at each age with DQ at 24 months. Anaemic children treated
Israel (Palti et al. 1983)	Routine health service screen for Hb at 9 months. Tested at 2 years = 873. At 3 years = 388. At 5 years = 239. Hb only measure of iron status	9–10 months to 5 years	Not given	Follow–up of all children from 9–10 months to 2, 3 and 5 years. All with Hb<11 g/dl treated with iron at 9 months for 3 months. At 5 years took a random sample of remaining children
USA (Cantwell 1974)	61 full-term neonates from comparable socioeconomic groups: 29 given IM iron in neonatal period 32 infants developed Fe deficiency anaemia between 6–18 months. (Hb 6.1–9.5g%) without PEM. No details of iron status	Birth to 7 years	Preterm	29 of 61 infants received iron injections (method of assignment not given) and were not anaemic (Hb 11.5–12.9). 32 infants developed IDA. Examined at 6–7 years by examiners blind to the groups

Country (reference)	*Outcome measures*	*Covariates adjusted for*	*Findings*	*Remarks*
Chile (de Andraca et al. 1990)	Stanford-Binet IQ, Illinois psycholinguistic abilities test, psychoeducational abilities test, Bruininks-Osteretsky test of motor proficiency, VMI, neurological exam	Home, maternal depression and stress. Not clear if used in analysis	Hb at 1 year = 10.1 ± 0.7 vs 13.0 ± 0.8. Hb a 15 months = 12.8 ± 0.7 vs 13.0 ± 0.8. Current Hb level not given. Formerly anaemic children performed significantly worse in IQ ($P = 0.02$), psychoeducational abilities ($P < 0.01$), VMI ($P < 0.01$), motor proficiency ($P < 0.01$), language abilities ($P < 0.01$). They were more neurologically immature ($P < 0.01$). Their homes were significantly less stimulating and their mothers were more depressed and less affectionate	
Costa Rica (Lozoff et al. 1991)	Current iron status. WISC test, Woodcock Johnson psychoeducational battery, Goodenough-Harris draw-a-man test, Beery developmental test of VMI, Bruininks-Oseretsky test of motor proficiency	Sex, birth weight, mother's IQ, height and education, breastfeeding, absence of father, home	No current difference in Hb and other measures of iron status. After controlling for covariates, previously anaemic group had lower scores on performance IQ, quantitative and visual matching subtests of the Woodcock Johnson battery, the VMI and the Bruininks-Oseretsky test of motor proficiency. In post hoc analyses, children who were non-anaemic but continued to have iron deficiency after treatment also had significantly lower scores	Good covariate control. Verbal skills less affected
Former Yugoslavia (Wasserman et al. 1992)	Bayley MDI at 6, 12, 18, 24 months with iron and lead status	Ethnic group, home, birth order, BW, sex, maternal IQ, education and age, lead levels	Hb at 6, 12 and 24 months was not significantly associated with MDI at 24 months but Hb at 18 months was significant. Controlling for all covariates, in both	At all ages mothers' education had the most significant effect on DQ

continued

Table 3.4 Longitudinal observational studies of iron deficiency anaemia and child intelligence[a] (*continued*)

Country (reference)	*Outcome measures*	*Covariates adjusted for*	*Findings*	*Remarks*
			Mitrovica and Pristina a change in Hb at 18 months of 2.0 g/dl was associated with a change of 3.4 MDI points ($P = 0.02$). Other indices of iron deficiency not associated with development	
Israel (Palti et al. 1983)	Brunet-Lezine test at 2 years. MILI test (an Israeli intelligence test) at 3 years. Wechsler with Israeli adaptation (WPSSI) at 5 years	Maternal education, father's occupation, BW, sex	When controlling for covariates: Hb at 9 months not significantly associated with DQ at 2 years ($P = 0.105$) and at 3 years ($P = 0.07$) but at 5 years had a significant effect on IQ ($P = 0.02$). At 5 years an increase of 1.0 g/dl of Hb associated with 1.75 change in IQ points	A large number of cognitive tests. Previously anaemic not reported alone
USA (Cantwell 1974)	Neurological examination and Stanford-Binet IQ	None reported	The formerly anaemic group had a higher incidence of "soft signs" e.g. clumsiness with balancing on one foot, in tandem walking, and repetitive hand and foot movement and were more inattentive and hyperactive than the non-anaemic group. IQ scores averaged 98 in the non-anaemic and 92 in the anaemic. No significance levels levels reported	

Key: Hb, haemoglobin; EP, erythrocyte protopophyrin; BW, birth weight; IDA, iron deficiency anaemia; CNS, central nervous system; DQ, developmental quotient; IM, intramuscular; PEM protein–energy malnutrition; VMI, visual-motor integration; MDI, Mental Development Index.

[a] Inclusion criteria: IQ/MDI/General Cognitive Index (GCI) as outcome measure.

Source: Table adapted from Grantham-McGregor and Ani (2001), with permission.

5. Methods for combining risk estimates from individual studies

5.1 Anaemia and maternal mortality

In each study, maternal mortality data were given in aggregate for each of the ranges. All ranges were converted to haemoglobin by dividing haematocrit values by 3. The midpoint of each range was used as the independent variable. The midpoints were estimated from the information provided in the articles. A logistic regression model was then used to fit the observed data, weighting each haemoglobin midpoint-mortality point by the total number of women in that range. Within each study, an estimate of the risk ratio associated with a one-unit difference in haemoglobin was calculated. These individual estimates were initially combined in a fixed-effects model, weighting individual estimates by the inverse of their within-study variance, to estimate an overall risk ratio. The heterogeneity statistic indicated that individually observed effect sizes varied significantly around the overall fixed-effects model estimate. Dropping the assumption of a fixed-treatment effect, the individual effect sizes were then assumed to be normally distributed and a random-effects combined estimate was calculated using the method of DerSimonian and Laird (1986).

5.2 Anaemia and perinatal mortality

Analyses for perinatal mortality were conducted in a similar manner as that for maternal mortality. The nine studies included in the meta-analysis were sufficiently heterogeneous that a random-effects model was used to generate combined estimates (DerSimonian and Laird 1986).

5.3 Iron deficiency anaemia and child intelligence

The beta coefficients from multivariate regression models associated with a 1 g/dl change in haemoglobin were obtained directly from the original published paper (Palti et al. 1983; Wasserman et al. 1992) or estimated indirectly from means and *P*-values (Cantwell 1974; de Andraca et al. 1990; Lozoff et al. 1991). Standard deviations were obtained directly from the original paper (Wasserman et al. 1992), estimated from *P*-values and beta coefficients (de Andraca et al. 1990; Lozoff et al. 1991; Palti et al. 1983), or estimated by assuming a significance level of 0.05 (Cantwell et al. 1974). As original data were not available, variability in baseline anaemia levels was not considered; rather, baseline mean haemoglobin levels were compared to follow-up IQ scores with standard deviations to estimate individual study regression coefficients. The estimates were combined in a fixed-effects model, weighting studies according to the reciprocal of their within-study variance. A chi-squared test for heterogeneity found no significant between-study variance; thus a random-effects model was not necessary.

6. Results

6.1 Maternal mortality

We computed odd ratios for maternal mortality associated with a 1 g/dl increase in pregnancy haemoglobin. Of the six studies included in our meta-analysis, all had individual study ORs <1.0, and three of those were statistically significant (Table 3.5 and Figure 3.1). The estimated OR from combining data points from all the studies was 0.75, with a CI that clearly excluded unity (0.62–0.89). The studies were not geographically diverse, coming from only three countries (India, Malaysia and Nigeria). However there was not a systematic difference between the risk estimates from the Nigerian vs the Asian studies. Two Nigerian studies had markedly lower ORs than the other four studies; however these two studies carried little weight in the combined OR.

6.2 Perinatal mortality

Ten studies were included in our meta-analysis. The individual ORs for perinatal mortality associated with a 1 g/dl increase in haemoglobin ranged from 0.55 to 0.87 (Table 3.6 and Figure 3.2). Nine of the 10 individual study estimates were statistically different from unity. The estimated OR from the 10 studies combined was 0.72 (95% CI 0.65–0.81).

The nine studies included in the meta-analysis were sufficiently heterogeneous that a random-effects model was used to generate combined estimates. We explored three factors that might explain this heterogeneity; these subgroup analyses are presented in Table 3.7. First, we were liberal in accepting various outcome definitions related to perinatal mortality. Only three of the 10 studies used the correct definition, which includes fetal death after 22 (or 28) weeks' gestation and neonatal mortality in the first seven days of life. Use of the correct definition of

Table 3.5 Individual and combined estimates of odds ratio of maternal death

Country (study)	*Point estimate (OR)*[a]	*95% CI*
India (Konar et al. 1980)	0.61	0.57–0.64
India (Sarin 1995)	0.84	0.81–0.88
Malaysia (Llewellyn-Jones 1965)	0.74	0.69–0.80
Nigeria (Harrison 1975)	0.46	0.15–1.42
Nigeria (Harrison 1982)	0.38	0.14–1.03
Nigeria (Harrison and Rossiter 1985)	0.95	0.83–1.09
Combined	0.75	0.62–0.89

[a] Odds ratio for maternal mortality associated with a 1 g/dl improvement in haemoglobin concentration, in the range of 5–12 g/dl haemoglobin.

Figure 3.1 Individual and combined estimates of odds ratio of maternal death

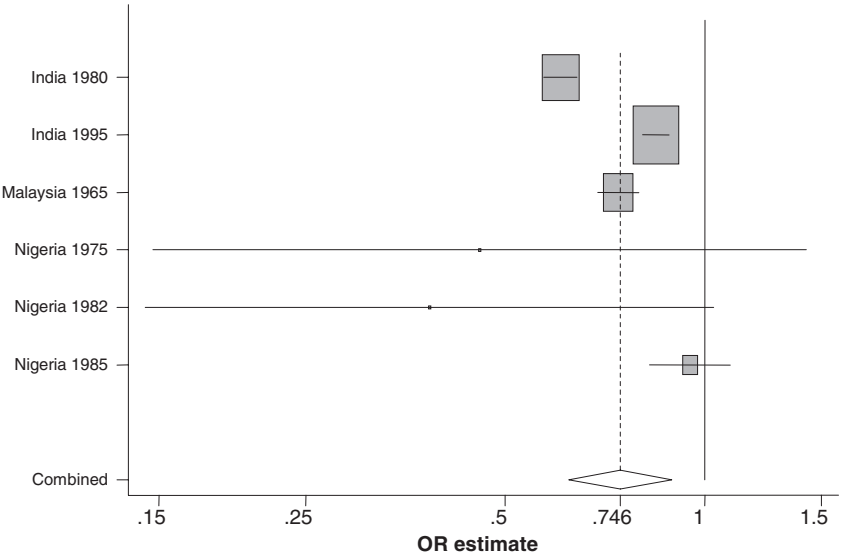


Table 3.6 Individual and combined estimates of odds ratio of perinatal death

Country (study)	*Point estimate (OR)*[a]	*95% CI*
China (Xiong et al. 1996)	0.82	0.66–1.03
India (Sarin 1995)	0.87	0.85–0.89
Kenya (Macgregor 1963)	0.66	0.60–0.73
Malaysia (Llewellyn-Jones 1965)	0.86	0.84–0.89
Nepal (Dreyfuss and West 2001)	0.82	0.70–0.97
Nigeria (Harrison 1975)	0.55	0.33–0.92
Nigeria (Harrison 1982)	0.59	0.45–0.78
Nigeria (Harrison et al. 1985)	0.58	0.55–0.61
Papua New Guinea (Mola et al. 1999)	0.77	0.70–0.85
United Kingdom (Murphy et al. 1986)	0.62	0.57–0.68
Combined[b]	0.72	0.65–0.81

[a] Odds ratio for perinatal mortality associated with a 1 g/dl improvement in haemoglobin concentration, in the range of 5–12 g/dl haemoglobin.

[b] Random effects estimate.

Figure 3.2 Individual and combined estimates of odds ratio of perinatal death

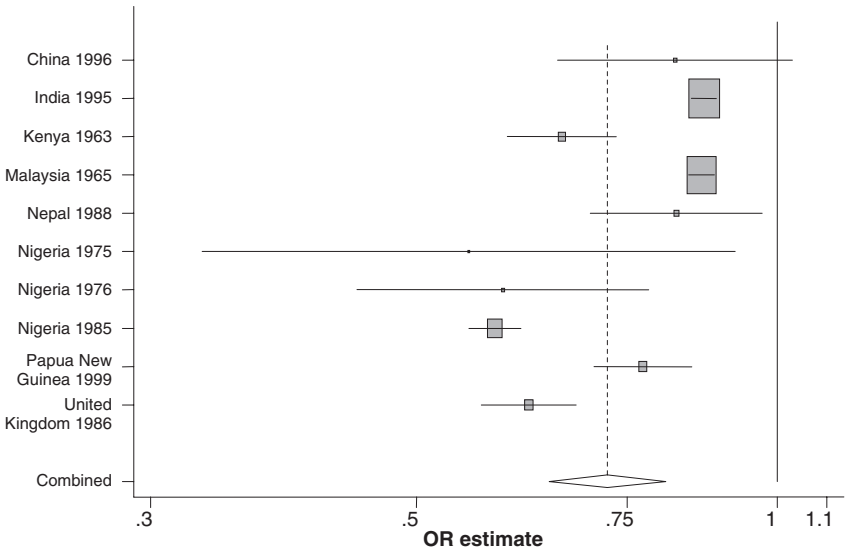


Table 3.7 Subgroup analyses for perinatal mortality

Group of studies (n)	*Point estimate (OR)*	*95% CI*	*% change from overall estimate*
All (10)[a]	0.72	0.65–0.81	
True definition of perinatal mortality (3)[b]	0.76	0.59–0.98	+5.5
Outcome includes some components of perinatal mortality (7)[c]	0.70	0.58–0.84	–2.9
P. falciparum endemic (5)[d]	0.65	0.56–0.75	–10.3
P. falciparum not endemic (5)[e]	0.80	0.73–0.87	+10.8
Haemoglobin assessed at delivery (2)[f]	0.66	0.59–0.73	–8.7
Haemoglobin assessed in early-mid pregnancy (8)[g]	0.74	0.65–0.83	+2.5

[a] Includes all 10 studies in Table 3.6.

[b] China 1996; India 1995; United Kingdom 1986.

[c] Kenya 1963; Malaysia 1965; Nepal 1998, Nigeria 1975, 1976, 1985; Papua New Guinea 1999.

[d] Kenya 1963; Nigeria 1975, 1976, 1985; Papua New Guinea 1999.

[e] China 1996; India 1995; Malaysia 1965; Nepal 1998; United Kingdom 1986.

[f] Kenya 1963; Nigeria 1975.

[g] China 1996; India 1995; Malaysia 1965; Nepal 1998; Nigeria 1976, 1985; Papua New Guinea 1999; United Kingdom 1986.

Table 3.8 Comparison of adjusted and unadjusted odds ratios in two studies of pregnancy anaemia and perinatal mortality

Hb category	*Live births*	*Neonatal deaths*	*Death rate (000s)*	*OR*	*Adjusted OR*
Study: Nepal 1998[a]					
≥11.0 g/dl	330	12	36.4	1.00	1.00
9.0–10.9	534	32	60.6	1.69	1.57
7.0–8.9	176	9	51.1	1.43	1.40
<7.0	41	6	146.3	4.54	4.61
Study: China 1996[b]					
≥10.0 g/dl	15 236	184	12	1.00	1.00
7.0–9.9	1 332	21	16	1.31	1.21
<7.0	159	4	25	2.08	1.81

[a] Adjusted ORs were adjusted for randomized supplement group (i.e. maternal supplementation with vitamin A or beta-carotene during pregnancy; this treatment did not affect neonatal death), primiparity, gestational age at Hb assessment, reported severe illness in late pregnancy, contribution of ≥1 pregnancy to the data set, preterm birth. Source: M. Dreyfuss, personal communication.

[b] Adjusted for maternal age, gestational age, parity, hypertensive disorders of pregnancy, gestational age at enrolment into prenatal care, hospital and maternal education. Source: X. Xiong, personal communication.

perinatal mortality did not significantly change the effect estimate. Second, *P. falciparum* malaria contributes to anaemia in pregnancy and may also affect perinatal mortality. Five of the studies were conducted in populations with endemic *P. falciparum* malaria, and these studies had a combined risk estimate that was substantially further from unity than those studies conducted in populations not heavily exposed to this form of malaria. We concluded that the risk relationship with anaemia is greater in *P. falciparum* malaria-endemic regions. Third, two studies assessed haemoglobin at delivery whereas the other eight assessed haemoglobin earlier in gestation. Xiong et al. (2000) have suggested that anaemia early in pregnancy carries a greater risk of adverse perinatal outcomes; however this inference was based on low birth weight as outcome. We did not find this in our data. In fact, the risk relationship was slightly stronger in the two studies that assessed haemoglobin at delivery. However, those two studies were also in *P. falciparum* malaria-endemic populations, which could bias the analysis.

The ORs presented in Table 3.6 and Figure 3.2 are unadjusted for potential confounding factors. Two of the 10 studies, Nepal 1998 and China 1996, could provide us with both unadjusted and adjusted ORs by haemoglobin category. These are displayed in Table 3.8. In the Nepal study, multivariate adjustment for a number of variables had no effect on the estimated ORs. However, in the China study, in which more

Table 3.9 Final odds ratios and confidence intervals used to generate burden of disease estimates

Outcome	*OR estimate*	*95% CI*
Maternal mortality	0.80	0.70–0.91
Perinatal mortality, Africa	0.72	0.65–0.80
Perinatal mortality, other regions	0.84	0.78–0.90

covariates were measured, multivariate adjustment attenuated the ORs by about 20%.

We have therefore attenuated the ORs for both perinatal and maternal mortality by 20%, as the evidence at hand suggests that the unadjusted estimates may be overestimated to about that degree. The final ORs and confidence intervals used to generate the burden of disease estimates are shown in Table 3.9.

6.3 Child intelligence

Five studies were included in our meta-analysis. The studies were geographically diverse, including Europe, Latin America, the Middle East and North America (the United States of America). However, there were no studies included from Africa or Asia. We estimated the expected change in IQ points associated with a 1 g/dl change in haemoglobin. The individual study estimates ranged from 1.36 to 2.52, and all were statistically different from zero (Table 3.10 and Figure 3.3). The combined estimate was 1.73 points, with a 95% CI of 1.04–2.41. The quality of the studies was high, and all of them provided estimates that were adjusted for multiple covariates.

The relevant disease outcome for this analysis would be mild mental retardation, defined as IQ <70, or more than 2 standard deviations below the expected population mean of 100. The increase in risk of mental retardation can be estimated from the expected mean change in IQ if one assumes that the mean change represents a shift in the entire distribution of values with no change in variance of the distribution. These calculations are displayed in Table 3.10. The resultant relative risk associated with a 1 g/dl increment in haemoglobin concentration is 0.78. The relative risk estimates associated with the upper and lower confidence limits of the estimated change in IQ are 0.70 and 0.86, respectively (Table 3.11).

7. Description of malnutrition tables

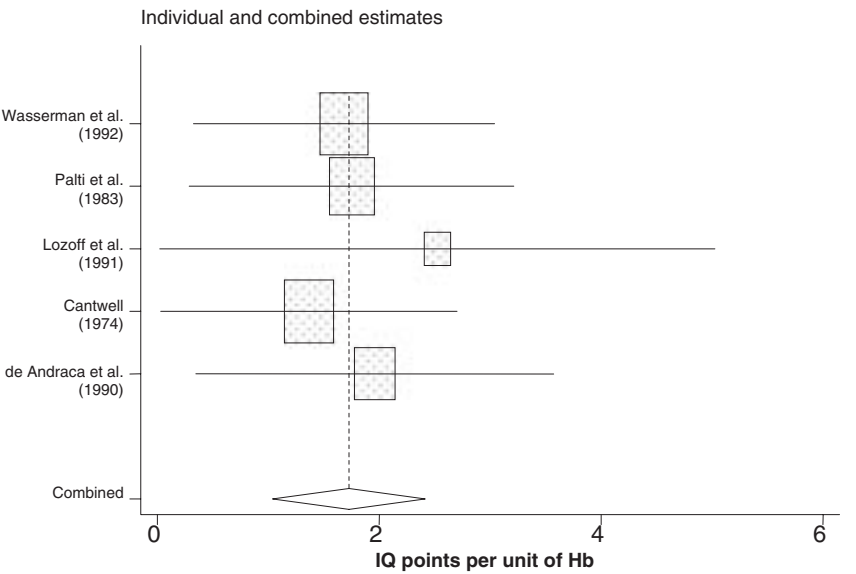
To describe the distribution of low haemoglobin by region we used the anaemia prevalence data that were published in the 1990 Global Burden

Table 3.10 Individual and combined estimates of the expected difference in IQ points per unit (g/dl) of haemoglobin

Study	*Point estimate (IQ points)*[a]	*95% CI*
Wasserman et al. (1992)	1.68	0.32–3.04
Palti et al. (1983)	1.75	0.29–3.21
Lozoff et al. (1991)	2.52	0.02–5.02
Cantwell (1974)	1.36	0.03–2.70
de Andraca et al. (1990)	1.96	0.35–3.57
Combined	1.73	1.04–2.41

[a] Estimated increase in IQ associated with a 1 g/dl increase in haemoglobin concentration.

Figure 3.3 Individual and combined estimates of IQ point difference associated with haemoglobin levels in infancy



of Disease (GBD) books (Murray and Lopez 1996a, 1996b). This database is currently being revised and updated, but the complete new data will not be available within the time frame of this project. We applied the following steps: (i) converted the prevalence data from the GBD 1990 regions to the subregions[2] used currently; (ii) converted data on prevalence of anaemia into mean haemoglobin values; and (iii) estimated the

Table 3.11 Predicted risks and relative risks of mental retardation, based on combined estimate of difference in mean IQ points in Table 3.10

	Point estimate	*Lower bound*	*Upper bound*
Expected rate of mental retardation in a healthy population[a]	2.3%		
Estimated average decrement in IQ per 1 g/dl decrement in haemoglobin[b]	1.73 points	1.04 points	2.41 points
Predicted rate of mental retardation in population with haemoglobin distribution shifted 1 g/dl downward due to iron deficiency[c]	2.94%	2.68%	3.29%
Predicted relative risk of mental retardation associated with 1 g/dl increment in haemoglobin[d]	0.78	0.86	0.70

[a] Assumes mean IQ of 100, with SD = 15.

[b] From Table 3.10.

[c] Assumes shift in mean given in row 2 with constant SD = 15.

[d] Point estimate in row 1 divided by percentages in row 3.

counterfactual haemoglobin distribution, representing the elimination of iron deficiency.

The anaemia database that we used was based on surveys conducted prior to 1990. Global monitoring of anaemia trends suggests that the prevalence of anaemia in the world has not decreased in the past decade (UNICEF 1998). However, the representativeness and reliability of these data (in terms of sample sizes) are less than we would hope for. Table 3.12 summarizes the numbers of country surveys included in the available data set, and the conversion from previous regions to the subregions used in the present analysis. Data for EUR-B and EUR-C are especially scarce. In the case of SEAR-D, the previous data source included only one country, India, but several surveys contributed to the country estimate.

Nationally representative anaemia data from the United States are available that are more recent than the data in the 1990 WHO database, and demonstrate lower anaemia prevalences (Looker et al. 1997). So as not to overestimate the burden of anaemia in economically developed regions, we used these data from the United States for three subregions, AMR-A, EUR-A and WPR-A. The haemoglobin cut-offs used to define anaemia globally have not changed since the 1990 database was created (Table 3.13). The resulting anaemia prevalence estimates are given in Table 3.14.

The second step was to convert the prevalence of anaemia to a mean haemoglobin value. We assumed all haemoglobin distributions to be approximately normal (Yip et al. 1996). We then needed to make

Table 3.12 Conversion of anaemia prevalence data from GBD 1990 regions to subregions

Subregion	*Previous (GBD 1990) region used as data source*	*Number of countries contributing surveys to regional estimate*
AFR-D	Sub-Saharan Africa	16
AFR-E	Sub-Saharan Africa	16
AMR-A	[a]	
AMR-B	Latin America and Caribbean	21
AMR-D	Latin America and Caribbean	21
EMR-B	Middle Eastern Crescent	6
EMR-D	Middle Eastern Crescent	6
EUR-A	[a]	
EUR-B	Former Soviet Economy	1
EUR-C	Former Soviet Economy	1
SEAR-B	Other Asia and islands	8
SEAR-D	India	1
WPR-A	[a]	
WPR-B	Other Asia and islands	8

[a] For these subregions, recent nationally representative data from the USA were used (Looker et al. 1997).

Table 3.13 Haemoglobin cut-offs to define anaemia in populations living at sea level

Population group	*Haemoglobin cut-off (g/l)*
Children 0–4 years	110
Children 6–14 years	120
Non-pregnant women	120
Pregnant women	110
Men	130

Source: Stoltzfus and Dreyfuss (1998).

assumptions about the standard deviation of the distributions. The standard deviation of haemoglobin in a population depends on at least two factors. The first factor is the proportion of individuals who are at their homeostatic haemoglobin concentration (i.e. non-anaemics). There is a certain amount of variability in haemoglobin that is set by individual characteristics, including genetics. This would be represented by the standard deviation in a population with no anaemia. Added to this "inherent" variability is the variability associated with non-physiologic states,

Table 3.14 Estimated anaemia prevalence by subregion, sex and age

		Age group (years)							
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	60.0	52.0	28.0	28.0	28.0	47.0	47.0	47.0
	Female	60.0	52.0	41.0	41.0	41.0	47.0	47.0	47.0
AFR-E	Male	60.0	52.0	28.0	28.0	28.0	47.0	47.0	47.0
	Female	60.0	52.0	41.0	41.0	41.0	47.0	47.0	47.0
AMR-A	Male	6.5	5.0	5.0	5.0	5.0	6.0	7.0	7.0
	Female	6.5	5.0	8.0	8.0	8.0	7.0	7.0	7.0
AMR-B	Male	46.0	24.0	11.0	11.0	11.0	18.0	18.0	18.0
	Female	46.0	24.0	23.0	23.0	23.0	18.0	18.0	18.0
AMR-D	Male	46.0	24.0	11.0	11.0	11.0	18.0	18.0	18.0
	Female	46.0	24.0	23.0	23.0	23.0	18.0	18.0	18.0
EMR-B	Male	63.0	39.0	17.0	17.0	17.0	25.0	25.0	25.0
	Female	63.0	39.0	44.0	44.0	44.0	25.0	25.0	25.0
EMR-D	Male	63.0	39.0	17.0	17.0	17.0	25.0	25.0	25.0
	Female	63.0	39.0	44.0	44.0	44.0	25.0	25.0	25.0
EUR-A	Male	6.5	5.0	5.0	5.0	5.0	6.0	7.0	7.0
	Female	6.5	5.0	8.0	8.0	8.0	7.0	7.0	7.0
EUR-B	Male	22.0	20.0	5.0	5.0	5.0	12.0	12.0	12.0
	Female	22.0	20.0	10.0	10.0	10.0	12.0	12.0	12.0
EUR-C	Male	22.0	20.0	5.0	5.0	5.0	12.0	12.0	12.0
	Female	22.0	20.0	10.0	10.0	10.0	12.0	12.0	12.0
SEAR-B	Male	49.0	33.0	32.0	32.0	32.0	48.0	48.0	48.0
	Female	49.0	33.0	49.0	49.0	49.0	48.0	48.0	48.0
SEAR-D	Male	66.0	65.0	36.0	36.0	36.0	65.0	65.0	65.0
	Female	66.0	65.0	60.0	60.0	60.0	65.0	65.0	65.0
WPR-A	Male	6.5	5.0	5.0	5.0	5.0	6.0	7.0	7.0
	Female	6.5	5.0	8.0	8.0	8.0	7.0	7.0	7.0
WPR-B	Male	49.0	33.0	32.0	32.0	32.0	48.0	48.0	48.0
	Female	49.0	33.0	49.0	49.0	49.0	48.0	48.0	48.0

including iron deficiency. Thus it is logical to expect the standard deviation of haemoglobin to be higher in populations with more anaemia compared to those with infrequent anaemia. The second factor is the precision of the haemoglobin assay, with greater precision yielding smaller observed standard deviations.

The variation in haemoglobin standard deviations is illustrated in Table 3.15, which relates the prevalence of anaemia to the standard deviation, using data from a draft version of the updated (but still incomplete) anaemia database for the WHO African and Eastern Mediterranean Regions (B. de Benoist, personal communication) and data from the most recent national health and nutrition examination survey in the United States, after excluding iron-deficient individuals. The standard deviations from the data from the United States are significantly smaller,

Table 3.15 Standard deviations of haemoglobin values

	Africa and EMRO surveys[a]	*USA NHANES III data*[b]
Prevalence of anaemia	>50%	<5%
Standard deviation (g/dl)		
Children 0–4 years	1.45	0.75
Children 5–14 years	1.58	0.85
Non-pregnant women	1.66	0.91
Men	1.60	0.97

EMRO WHO Eastern Mediterranean Region.

[a] B. de Benoist, personal communication. Values are weighted averages from available country surveys.

[b] From Looker et al. (1997), Table 2.

Table 3.16 Standard deviations used to convert anaemia prevalence to mean haemoglobin

Anaemia prevalence	*Standard deviation of haemoglobin*
<15%	1.0 g/dl
15–30%	1.2 g/dl
>30%	1.5 g/dl

probably due to both of the factors discussed above. Namely, the proportion of anaemic individuals in this United States sample was very low, and the haemoglobin assessment method (venous blood collection, laboratory-based assay with rigorous quality control) was more precise than most field-based studies in developing countries.

Based on these considerations, we assumed certain standard deviations based on the anaemia prevalence of each population group. These are given in Table 3.16.

Knowing the proportion below a certain haemoglobin cut-off (i.e. prevalence of anaemia in a population) and the standard deviation of the normal distribution, we estimated the mean haemoglobin associated with the current prevalence of anaemia (Snedecor et al. 1980). These values are given in Table 3.17.

We then estimated the theoretical-minimum-risk distribution, representing the haemoglobin distribution if iron deficiency were eliminated. Assuming that 50% of anaemia in the world is attributable to iron deficiency (see section 3), we divided the current anaemia prevalences by 2. Because anaemia cut-offs are defined as the 5th percentile of a normative reference distribution (i.e. the distribution of individuals known to

Table 3.17 Estimated mean haemoglobin values (g/dl) by subregion, sex and age in 2000

		Age group (years)							
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	10.62	11.67	13.70	13.70	13.70	13.11	13.11	13.11
	Female	10.62	11.67	12.34	12.34	12.34	12.11	12.11	12.11
AFR-E	Male	10.62	11.67	13.70	13.70	13.70	13.11	13.11	13.11
	Female	10.62	11.67	12.34	12.34	12.34	12.11	12.11	12.11
AMR-A	Male	12.51	13.39	14.64	14.64	14.64	14.55	14.55	14.55
	Female	12.51	13.39	13.41	13.41	13.41	13.48	13.48	13.48
AMR-B	Male	11.15	12.60	14.47	14.47	14.47	14.10	14.10	14.10
	Female	11.15	12.60	12.89	12.89	12.89	13.10	13.10	13.10
AMR-D	Male	11.15	12.60	14.47	14.47	14.47	14.10	14.10	14.10
	Female	11.15	12.60	12.89	12.89	12.89	13.10	13.10	13.10
EMR-B	Male	10.50	12.17	14.14	14.14	14.14	13.81	13.81	13.81
	Female	10.50	12.17	12.23	12.23	12.23	12.81	12.81	12.81
EMR-D	Male	10.50	12.17	14.14	14.14	14.14	13.81	13.81	13.81
	Female	10.50	12.17	12.23	12.23	12.23	12.81	12.81	12.81
EUR-A	Male	12.51	13.39	14.64	14.64	14.64	14.55	14.55	14.55
	Female	12.51	13.39	13.41	13.41	13.41	13.48	13.48	13.48
EUR-B	Male	11.93	12.76	14.64	14.64	14.64	14.41	14.41	14.41
	Female	11.93	12.76	13.28	13.28	13.28	13.41	13.41	13.41
EUR-C	Male	11.93	12.76	14.64	14.64	14.64	14.41	14.41	14.41
	Female	11.93	12.76	13.28	13.28	13.28	13.41	13.41	13.41
SEAR-B	Male	11.04	12.41	13.70	13.70	13.70	13.08	13.08	13.08
	Female	11.04	12.41	12.04	12.04	12.04	12.08	12.08	12.08
SEAR-D	Male	10.38	11.17	13.54	13.54	13.54	12.42	12.42	12.42
	Female	10.38	11.17	11.62	11.62	11.62	11.42	11.42	11.42
WPR-A	Male	12.51	13.39	14.64	14.64	14.64	14.55	14.55	14.55
	Female	12.51	13.39	13.41	13.41	13.41	13.48	13.48	13.48
WPR-B	Male	11.04	12.41	13.70	13.70	13.70	13.08	13.08	13.08
	Female	11.04	12.41	12.04	12.04	12.04	12.08	12.08	12.08

be free of disease), we set the minimum prevalence of anaemia in all world subregions to be 5.0%. We assumed a normal distribution, and applied the standard deviations in Table 3.15. This yields values in Table 3.18.

To check the plausibility of this theoretical minimum distribution, we examined the shift in population mean haemoglobin concentration from current reality to the theoretical minimum, representing the eradication of iron deficiency. These shifts are summarized in Table 3.19.

The predicted shifts in mean haemoglobin ranged from 0.0, in young adult men in affluent subregions, to 1.28 g/dl in children in SEAR-D. The predicted haemoglobin shift for young children in AFR was 1.17, which is consistent with the evidence from iron supplementation trials in the

Table 3.18 Estimated mean haemoglobin (g/dl) values if iron deficiency were eliminated (theoretical minimum distribution), by subregion, sex and age

		Age group (years)							
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*
AFR-D	Male	11.79	12.52	14.08	14.08	14.08	13.87	13.87	13.87
	Female	11.79	12.52	12.99	12.99	12.99	12.87	12.87	12.87
AFR-E	Male	11.79	12.52	14.08	14.08	14.08	13.87	13.87	13.87
	Female	11.79	12.52	12.99	12.99	12.99	12.87	12.87	12.87
AMR-A	Male	12.58	13.39	14.64	14.64	14.64	14.60	14.55	14.55
	Female	12.58	13.39	13.51	13.51	13.51	13.55	13.55	13.55
AMR-B	Male	11.89	12.92	14.60	14.60	14.60	14.34	14.34	14.34
	Female	11.89	12.92	13.20	13.20	13.20	13.34	13.34	13.34
AMR-D	Male	11.89	12.92	14.60	14.60	14.60	14.34	14.34	14.34
	Female	11.89	12.92	13.20	13.20	13.20	13.34	13.34	13.34
EMR-B	Male	11.72	12.78	14.37	14.37	14.37	14.15	14.15	14.15
	Female	11.72	12.78	12.93	12.93	12.93	13.15	13.15	13.15
EMR-D	Male	11.72	12.78	14.37	14.37	14.37	14.15	14.15	14.15
	Female	11.72	12.78	12.93	12.93	12.93	13.15	13.15	13.15
EUR-A	Male	12.58	13.39	14.64	14.64	14.64	14.60	14.55	14.55
	Female	12.58	13.39	13.51	13.51	13.51	13.55	13.55	13.55
EUR-B	Male	12.23	13.03	14.96	14.96	14.96	14.55	14.55	14.55
	Female	12.23	13.03	13.64	13.64	13.64	13.55	13.55	13.55
EUR-C	Male	12.23	13.03	14.96	14.96	14.96	14.55	14.55	14.55
	Female	12.23	13.03	13.64	13.64	13.64	13.55	13.55	13.55
SEAR-B	Male	11.83	12.92	14.19	14.19	14.19	13.85	13.85	13.85
	Female	11.83	12.92	12.83	12.83	12.83	12.85	12.85	12.85
SEAR-D	Male	11.66	12.43	14.10	14.10	14.10	13.68	13.68	13.68
	Female	11.66	12.43	12.79	12.79	12.79	12.68	12.68	12.68
WPR-A	Male	12.58	13.39	14.64	14.64	14.64	14.60	14.55	14.55
	Female	12.58	13.39	13.51	13.51	13.51	13.55	13.55	13.55
WPR-B	Male	11.83	12.92	14.19	14.19	14.19	13.85	13.85	13.85
	Female	11.83	12.92	12.83	12.83	12.83	12.85	12.85	12.85

P. falciparum-endemic populations (1.24, 95% CI 1.16–1.33, see section 3). The predicted haemoglobin shifts for women of reproductive age range from 0.11 to 1.17 g/dl. These estimates were somewhat lower than the average haemoglobin response of pregnant women to iron supplementation (0.85 to 1.17 g/dl), and were substantially lower than the haemoglobin responses in women provided iron doses of ≥90 mg/day (i.e. 1.8 g/dl) estimated by Sloan et al. (2002).

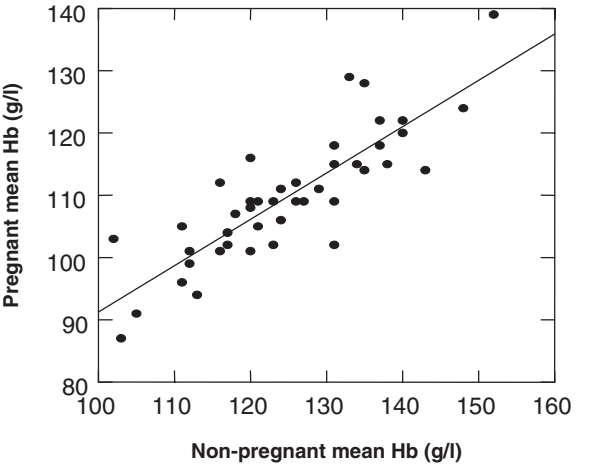
We are thus faced with some uncertainty about how to estimate the haemoglobin shift that would occur if iron deficiency were eliminated. Basing our estimates on a 50% reduction in anaemia yields a smaller shift than we would obtain if we assumed that the responses of pregnant women to maximal daily iron doses in the trials summarized by Sloan

Table 3.19 Shifts in mean haemoglobin (g/dl) from 2000 estimates (Table 3.17) if iron deficiency were eliminated (Table 3.18)

		Age group (years)								
Subregion	*Sex*	*0–4*	*5–14*	*15–29*	*30–44*	*45–59*	*60–69*	*70–79*	*≥80*	*Row means*
AFR-D	Male	1.17	0.85	0.38	0.38	0.38	0.75	0.75	0.75	0.68
	Female	1.17	0.85	0.65	0.65	0.65	0.75	0.75	0.75	0.78
AFR-E	Male	1.17	0.85	0.38	0.38	0.38	0.75	0.75	0.75	0.68
	Female	1.17	0.85	0.65	0.65	0.65	0.75	0.75	0.75	0.78
AMR-A	Male	0.06	0.00	0.00	0.00	0.00	0.04	0.08	0.08	0.03
	Female	0.06	0.00	0.11	0.11	0.11	0.08	0.08	0.08	0.08
AMR-B	Male	0.74	0.33	0.13	0.13	0.13	0.24	0.24	0.24	0.27
	Female	0.74	0.33	0.31	0.31	0.31	0.24	0.24	0.24	0.34
AMR-D	Male	0.74	0.33	0.13	0.13	0.13	0.24	0.24	0.24	0.27
	Female	0.74	0.33	0.31	0.31	0.31	0.24	0.24	0.24	0.34
EMR-B	Male	1.22	0.61	0.23	0.23	0.23	0.34	0.34	0.34	0.44
	Female	1.22	0.61	0.70	0.70	0.70	0.34	0.34	0.34	0.62
EMR-D	Male	1.22	0.61	0.23	0.23	0.23	0.34	0.34	0.34	0.44
	Female	1.22	0.61	0.70	0.70	0.70	0.34	0.34	0.34	0.62
EUR-A	Male	0.06	0.00	0.00	0.00	0.00	0.04	0.08	0.08	0.03
	Female	0.06	0.00	0.11	0.11	0.11	0.08	0.08	0.08	0.08
EUR-B	Male	0.30	0.27	0.32	0.32	0.32	0.14	0.14	0.14	0.24
	Female	0.30	0.27	0.36	0.36	0.36	0.14	0.14	0.14	0.26
EUR-C	Male	0.30	0.27	0.32	0.32	0.32	0.14	0.14	0.14	0.24
	Female	0.30	0.27	0.36	0.36	0.36	0.14	0.14	0.14	0.26
SEAR-B	Male	0.79	0.51	0.49	0.49	0.49	0.77	0.77	0.77	0.64
	Female	0.79	0.51	0.79	0.79	0.79	0.77	0.77	0.77	0.75
SEAR-D	Male	1.28	1.26	0.56	0.56	0.56	1.26	1.26	1.26	1.00
	Female	1.28	1.26	1.17	1.17	1.17	1.26	1.26	1.26	1.23
WPR-A	Male	0.06	0.00	0.00	0.00	0.00	0.04	0.08	0.08	0.03
	Female	0.06	0.00	0.11	0.11	0.11	0.08	0.08	0.08	0.08
WPR-B	Male	0.79	0.51	0.49	0.49	0.49	0.77	0.77	0.77	0.64
	Female	0.79	0.51	0.79	0.79	0.79	0.77	0.77	0.77	0.75
Column means		0.71	0.46	0.38	0.38	0.38	0.43	0.43	0.43	0.45

et al. (2002) represented the true effect. We used the 50% reduction in anaemia for two reasons. First, it yields more conservative estimates for the overall burden of disease attributable to iron deficiency. Second, we expect that the responses seen in iron supplementation trials are not representative of all women in the region in which they were conducted. Researchers frequently select study populations that are unusual in their potential to respond to an intervention; in this case populations that are more anaemic than the average population. Therefore it is reasonable to expect that data from randomized trials would overestimate global or regional average effects.

Figure 3.4 Relationship between mean haemoglobin values in pregnant and non-pregnant women within populations



Note: $n = 43$ surveys, $r = 0.84$, $P < 0.001$.

Source: Data from WHO (B. de Benoist, personal communication).

A final consideration is that these global tables report values for all women in the reproductive age ranges, whereas the risks of perinatal and maternal mortality apply uniquely to pregnancy anaemia. Population surveys that include both pregnant and non-pregnant women demonstrate a strong linear correlation between the haemoglobin values in these two population subgroups, as shown in Figure 3.4. Across the range of haemoglobin for women in Table 3.17, the difference between haemoglobin values in non-pregnant and pregnant states is nearly constant (range: 1.39 g/dl to 1.34 g/dl). The haemoglobin cut-off used to define anaemia is also lower in pregnancy. The WHO cut-off, for simplicity, is 1.0 g/dl lower in pregnancy. However, the physiologic haemodilution of pregnancy reduces the haemoglobin concentration by 1.5 g/dl in mid-pregnancy (Institute of Medicine 1990), when many pregnancy values are obtained in field surveys. Thus we can expect the prevalence of true anaemia to be approximately the same in pregnant and non-pregnant women. Because pregnant women are more iron-deficient than non-pregnant women, there is reason to believe that the iron-attributable fraction of anaemia would be higher in pregnancy than in other states. However, lacking firm data on this relationship, we have made the conservative assumption that the anaemia prevalence and predicted haemoglobin shift associated with the elimination of iron deficiency are the same for pregnant women as non-pregnant women.

8. Burden of disease estimates

The estimated deaths and DALYs attributable to iron deficiency are shown in Tables 3.20 and 3.21. Those attributed to iron deficiency as a risk factor for perinatal and maternal conditions are shown separately from those attributed directly to iron deficiency anaemia. For perinatal and maternal conditions, only mortality (as opposed to morbidity) from maternal conditions was attributed to iron deficiency. In the absence of any data on anaemia and morbidity related to childbirth or the puerperium, we assumed that such a relationship did not exist. As discussed earlier, the effects of iron deficiency anaemia on work productivity and child development and cognition are included in the direct attributions to iron deficiency anaemia (i.e. in the iron deficiency anaemia columns). These direct estimates are updated from the 1990 GBD (Murray et al. 1996a, 1996b), using 2000 demographic statistics, but otherwise the same methods.

The total burden of death and disability attributable to iron deficiency is higher than the 1990 estimate. This is due to differences in the risk estimates, not the prevalence estimates, which remain unchanged. The inclusion of iron deficiency anaemia as a risk factor for perinatal mortality is new, and contributes substantially to estimated deaths and DALYs lost. Furthermore, in the 1990 estimate, deaths from iron defi-

Table 3.20 Deaths from perinatal conditions, maternal conditions and iron deficiency anaemia, attributable to iron deficiency, by subregion

Subregion	*Perinatal causes (000s)*	*Maternal causes (000s)*	*Iron deficiency anaemia (000s)*	*Total (000s)*
AFR-D	97	20	8	125
AFR-E	103	29	13	145
AMR-A	1	0	3	4
AMR-B	17	2	7	26
AMR-D	3	1	3	7
EMR-B	4	1	1	6
EMR-D	56	14	9	79
EUR-A	1	0	3	4
EUR-B	4	0	2	6
EUR-C	2	0	1	3
SEAR-B	16	5	13	34
SEAR-D	222	38	66	326
WPR-A	0	0	0	0
WPR-B	63	5	5	73
World	591	115	135	841

Table 3.21 DALYs from perinatal conditions, maternal conditions and iron deficiency anaemia, attributable to iron deficiency, by subregion

Subregion	*Perinatal causes (000s)*	*Maternal causes (000s)*	*Iron deficiency anaemia (000s)*	*Total (000s)*
AFR-D	3237	614	934	4785
AFR-E	3442	881	1033	5356
AMR-A	47	2	430	479
AMR-B	561	59	291	911
AMR-D	102	36	201	339
EMR-B	149	22	344	515
EMR-D	1882	418	895	3195
EUR-A	29	1	269	299
EUR-B	145	6	286	437
EUR-C	61	4	205	675
SEAR-B	545	148	835	1528
SEAR-D	7428	1114	3955	12497
WPR-A	6	0	105	111
WPR-B	2101	145	2092	4338
World	19736	3448	11873	35057

ciency anaemia were included only as "direct" deaths due to severe and very severe anaemia. The increased maternal mortality from iron deficiency anaemia as an underlying risk factor is newly included in these estimates.

It is apparent that while the death and especially the disability *directly* attributable to iron deficiency anaemia is large, death and disability attributable to iron deficiency anaemia acting as a *risk factor* for perinatal and maternal causes is much larger. Because of the great numbers of perinatal deaths globally, perinatal causes account for 70% of the total deaths and 56% of the total DALYs attributable to iron deficiency anaemia. Numbers of maternal deaths, while very high, are much lower than perinatal deaths. Therefore the absolute contribution of maternal causes to the totals is smaller, namely 10% of DALYs and 14% of deaths. The relative contribution of maternal and perinatal causes to the total DALYs lost is largest where death rates are high (e.g. 80% in SEAR-D compared to only 25% in EUR-A). Indeed, as expected, the contribution of iron deficiency anaemia to maternal deaths is zero in AMR-A, EUR-A and WPR-A, where maternal mortality rates are very low.

When examined by region, the global burden of iron deficiency anaemia and its consequences are most heavily borne by those in South-East Asia and Africa. For maternal causes, 43% and 37% of the mater-

nal deaths (and DALYs) attributed to iron deficiency anaemia occur in Africa (AFR-D and AFR-E combined) and South-East Asia (SEAR-B and SEAR-D combined), respectively. For perinatal causes, the relative burden in the two regions is reversed, but they still suffer the greatest toll, with 34% of the iron deficiency-related perinatal deaths (and DALYs lost) in Africa and 40% in South-East Asia. WPR-B and EMR-D also bear a large burden of iron deficiency-related perinatal deaths, with approximately 10% of the global total in each of these two subregions.

9. Expected changes in the prevalence of iron deficiency anaemia

Based on the trends observed over the past 20 years there is no reason to expect anaemia or iron deficiency anaemia prevalence to decrease in the coming decade. The United Nations Subcommittee on Nutrition (ACC/SCN) reviewed trends in data from the 1970s and 1980s (ACC/SCN 1992). Iron density in the diet was decreasing during this period for every global region except the Near East and North Africa. Furthermore, trends in anaemia from 1977 to 1987 were increasing in the two regions where the problem is most severe: south Asia, and sub-Saharan Africa. In 1990, the World Summit for Children set goals for reducing malnutrition, sickness and death in children that included a goal to reduce iron deficiency anaemia by one-third by the year 2000. A progress report in 1995 (UNICEF 1995) stated:

> Very few countries have so far taken nation-scale action to eliminate iron deficiency anaemia. . . . No mid-decade target was established for progress against anaemia; but the goal . . . is unlikely to be met without a significant acceleration of effort over the next six years.

This needed acceleration of effort did not take place. A more recent progress report (WHO 2000) concluded the following:

> Unfortunately, there has been *little appreciable change* over the last two decades in the high worldwide prevalence of iron deficiency anaemia. Few active programmes in both developed and developing countries have succeeded in reducing iron deficiency and anaemia. Important factors contributing to the lack of progress include failure to recognize the causes of iron deficiency and anaemia, lack of political commitment to control it, inadequate planning of control programmes, insufficient mobilization and training of health staff, and insufficient community involvement in solving the problem.

Thus the evidence strongly suggests that under a "business-as-usual" scenario, the prevalence of iron deficiency anaemia will not decrease over the next decade. We hope that the new estimates of the burden of disease attributed to iron deficiency will result in a significant deviation from business-as-usual.

10. Discussion

Our analysis of the relationship between pregnancy anaemia and maternal mortality differed from that of the recent analysis by Brabin et al. (2001b), although we drew upon the same published studies. The salient difference is that we began by estimating the mortality–haemoglobin relationship within each study (expressed as an OR per g/dl increment in haemoglobin), and then used meta-analytic techniques to obtain a weighted average of those ORs. Restricting the analysis to observations between 5 and 12 g/dl haemoglobin, the risk increased with decreasing haemoglobin within each study.

As noted previously, there are no trials of iron supplementation with maternal mortality as outcome. Furthermore, because of cost and ethical considerations, we will likely have to continue to rely on observational data to refine these estimates. However, better observational data are badly needed. The currently available data are generally quite old, are predominantly from Asia (India and Malaysia) and are not controlled for many potentially confounding or modifying factors.

This analysis differs from most previous statements about anaemia and maternal mortality by positing a continuous relationship between haemoglobin concentration and mortality risk. INACG issued the following statement about severe anaemia and death in childbirth (1989):

> At 6.0 g/dl, evidence of circulatory decompensation becomes apparent. Women experience breathlessness and increased cardiac output at rest. At this stage, added stress from labor . . . can result in maternal death. Without effective treatment, maternal death from anemic heart failure . . . is likely with a haemoglobin concentration of 4.0 g/dl. Even a blood loss of 100 ml can cause circulatory shock and death.

A more recent summary statement (Stoltzfus 2001), based on the systematic review of Brabin et al. (2001b) also concluded that "A significant body of causal evidence exists for . . . severe anaemia and maternal mortality" but that "causal evidence is lacking or contradictory for . . . mild-moderate anaemia and maternal mortality" (Table 1). However, considering that death from cardiovascular causes is a function of blood volume, blood loss, cardiac fitness and haemoglobin concentration, it seems plausible that the relationship between haemoglobin concentration and maternal death would be continuous in nature, although not necessarily linear. Indeed the relationship as we have modelled it in this analysis is log-linear, with risk increasing exponentially with decreasing haemoglobin concentration.

We are not aware of another systematic analysis of the observational data linking pregnancy anaemia to perinatal mortality. The risk estimates from geographically diverse studies were remarkably consistent, and we believe provided the best evidence available for our purpose. Rasmussen (2001) identified four controlled iron supplementation trials that reported perinatal deaths as an outcome. All four studies had major

design concerns (low rates of follow-up or lack of anaemic individuals enrolled in the trial), and all were of insufficient sample size to draw clear conclusions. Rasmussen did not draw any firm conclusion from these data.

One relatively large trial was recently completed in rural Nepal, where the incidence of pregnancy anaemia and perinatal mortality are both high. This trial has only been reported in abstract form (Christian et al. 2002) and also was not sufficiently large to draw clear conclusions about perinatal mortality. However, it represents the strongest randomized trial evidence to date, because it was placebo-controlled and had high follow-up rates. In this trial, all women were provided anthelminthic treatment and vitamin A supplements. Women supplemented with 60 mg iron and 400 μg folic acid had 20% (95% CI 0.55–1.17) lower incidence of perinatal mortality than the placebo group (P. Christian, personal communication). This point estimate is larger than the per cent reduction we estimated in this analysis (i.e. 16%, 95% CI 10–22%). However, the trial also included several additional treatment arms, including one group that received folic acid without iron. The folic acid-supplemented group also had lower perinatal mortality rates than the placebo group, a reduction of 11% (95% CI 0.63–1.26). Micronutrient supplementation began after the first trimester of pregnancy, and therefore these reductions cannot be attributed to the demonstrated effects of folic acid in preventing neural tube defects. Although neither of these reductions is statistically significant, they are important public health findings. If we accept these point estimates as the best available estimates from trial data, we conclude that our perinatal risk estimates are in accord with the benefits seen with effective iron-folic acid supplementation, but that a large part of the benefit may in fact be attributable to the folic acid.

The biological mechanisms linking iron deficiency anaemia (or anaemia from any cause) to perinatal mortality remain to be elucidated. One possible pathway is through preterm delivery. Recent reviews of clinical trial evidence have found the evidence inconclusive in support of a role for iron supplementation in preventing preterm birth or low birth weight (Mahomed 2000b; Rasmussen 2001). However, the evidence for or against is remarkably weak, and does not rule out a causal relationship (Stoltzfus 2001). Scott Poe and Mary Cogswell (personal communication) have recently completed a meta-analysis of the observational evidence relating pregnancy anaemia to low birth weight, intrauterine growth retardation and preterm birth. They found that pregnancy anaemia assessed in the first two trimesters of pregnancy was more strongly associated with preterm birth than intrauterine growth retardation or low birth weight, and that the risk of preterm birth increased with increasing severity of anaemia. Thus, while controlled trial evidence is lacking, the observational evidence suggests that preterm birth is one plausible mechanism for the anaemia-related risk of perinatal mortality.

If we accept preterm birth as a plausible causal pathway, the question remains as to how iron deficiency anaemia causes preterm birth. Allen suggested three possible mechanisms (Allen 2001). Iron deficiency anaemia might activate a hormonal stress response, might increase oxidative stress or might increase the risk of maternal infections. Further research is needed to elucidate these mechanisms or to suggest alternative ones.

While preterm birth may be considered the leading hypothesis to explain the link between maternal anaemia and perinatal mortality, it is not the only hypothesis that should be pursued. If these above proposed mechanisms exist, it is plausible that they cause adverse effects on the fetus that go beyond preterm birth, for example by impairing the neonatal immune system, endocrine function, temperature regulation, or other systems critical to a successful transition from intra to extrauterine life. Additionally, the adverse effects of maternal anaemia on the mother's function and well-being may also increase risks to her neonate through her decreased capacity to actively care for and breastfeed the infant (Henly et al. 1995). In the extreme case, maternal death associated with anaemia would increase the neonate's risk of death.

We included here an estimate of the continuous relationship between iron deficiency anaemia in early childhood and later intelligence, even though this relationship is included in the direct disability score attributed to iron deficiency anaemia. The possible biological mechanisms underlying this relationship are the subject of a large body of ongoing research in animals and children (e.g. see Beard 2001). To date, two published placebo-controlled randomized trials have measured the effect of longer-term (i.e. >2 months) iron supplementation on cognitive development of young children in samples that included anaemic children (Idjradinata and Pollitt 1993; Stoltzfus et al. 2001). Both trials found significant benefits in the iron-supplemented group. In Indonesia (Idjradinata and Pollitt 1993), the positive effect was measured on the Bayley Scales of Infant Development, while in Zanzibar (Stoltzfus et al. 2001), parental reports of motor and language milestones were used. These trials support a causal link between iron deficiency anaemia and child development that is at least partly preventable with early treatment.

The major difficulty has been quantifying this relationship in meaningful epidemiological and socioeconomic terms, especially in the sociocultural contexts in which iron deficiency anaemia is most prevalent. Our estimated OR is an attempt to put the relationship in epidemiological terms. This estimate relies on the assumption that a mean shift in IQ can be converted into increased risk of mild mental retardation, assuming that the entire IQ distribution was shifted equally. To our knowledge there has been only one published report of the relationship between early childhood anaemia and mild mental retardation as a dichotomous outcome (as opposed to intelligence or developmental scores as continuous outcomes). Hurtado et al. (1999) assessed the association between

haemoglobin concentration of children in the United States enrolled in the Special Supplemental Program for Women, Infants, and Children, a programme of the U.S. Government that provides food supplements to low-income pregnant women and their young children (Hurtado et al. 1999). After adjusting for several important covariates, the OR for mild or moderate mental retardation at school age remained significant in their model, which treated haemoglobin concentration as a continuous risk factor (as did ours). This finding supports the plausibility of our assumption that the association between mean cognitive scores and anaemia is associated with increased risks of mild mental retardation. However, it is only a single observational study, and we believe our estimate should be interpreted with extreme caution.

In summary, the available evidence suggests that iron deficiency anaemia contributes substantially to death and disability in the world. The great majority of this disease burden is in Africa and Asia and derives from anaemia in pregnancy and early childhood. This evidence is based on critical assumptions, most importantly, that the observed prospective relationships are causal in nature, and that the relationships analysed using anaemia as the risk factor pertain equally to iron deficiency anaemia as one particular form of anaemia.

The high global prevalence of anaemia and its potentially associated disease burden, as reflected in these estimates, constitute an urgent agenda for both research and action. First, we must clarify the assumptions above, the first and foremost of these being causality, and refine these estimates with stronger evidence. Because these estimates are uncertain in many respects, their most important use may be to motivate public health scientists to provide definitive causal evidence. Second, we must establish ways to effectively reduce iron deficiency anaemia to prevent these apparent consequences. We hope these new estimates of the burden of disease due to iron deficiency will motivate these actions.

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Notes

1 We recognize that iron supplementation is not the only means of shifting the haemoglobin distribution, but randomized trials of iron supplementation provide the best estimate of the distribution if dietary iron deficiency were nearly eliminated.

2 See preface for an explanation of this term.

References

ACC/SCN (1992) *Second report on the world nutrition situation. Vol. 1: Global and regional results*. The United Nations Subcommittee on Nutrition, ACC/SCN, Geneva.

Adam Z (1997) *Iron supplementation and malaria: a randomized, placebo-controlled field trial in rural Ethiopia* [Dissertation]. London School of Hygiene and Tropical Medicine, London.

Agarwal KN, Agarwal DK, Mishra KP (1991) Impact of anaemia prophylaxis in pregnancy on maternal haemoglobin, serum ferritin and birth weight. *Indian Journal of Medical Research*, **94**:277–280.

Allen LH (2001) Biological mechanisms that might underlie iron's effects on fetal growth and preterm birth. *Journal of Nutrition*, **131**:S581–589.

Beard JL (2001) Iron biology in immune function, muscle metabolism and neuronal functioning. *Journal of Nutrition*, **131**:S568–580.

Beard JL, Stoltzfus R, eds. (2001) Iron-deficiency anaemia: reexamining the nature and magnitude of the public health problem. Proceedings of the WHO-INACG Conference, Belmont, MD, USA, 2000. *Journal of Nutrition*, **131**:2S-II.

Beaton GH (2002) Functional outcomes of iron deficiency and iron deficiency in pregnancy and beyond. (Proceedings of the INACG Symposium, February 15–26, 2001 in Hanoi, Viet Nam) Hanoi.

Brabin BJ, Hakimi M, Pelletier D (2001b) An analysis of anaemia and pregnancy-related maternal mortality. *Journal of Nutrition*, **131**:S604–614.

Brabin BJ, Premji Z, Verhoeff F (2001a) An analysis of anaemia and child mortality. *Journal of Nutrition*, **131**:S636–645.

Brabin BJ (1983) An analysis of malaria in pregnancy in Africa. *Bulletin of World Health Organization*, **61**:1005–1016.

Cantwell RJ (1974) The long term neurological sequelae of anaemia in infancy. *Pediatric Research*, **342**:68.

Chi I-C, Agoestina T, Harbin J (1981) Maternal mortality at twelve teaching hospitals in Indonesian epidemiologic analysis. *International Journal of Gynaecology and Obstetrics*, **19**:259–266.

Christian P, West KP Jr, Khatry SK, LeClerq SC, Kimbrough-Pradhan E, Katz J (2002) The effect of maternal micronutrient supplementation on fetal loss and infant mortality in rural Nepal: a randomized trial. *FASEB Journal*, **16**:A748.

de Andraca I, Walter T, Castillo M, Pino P, Rivera P, Cobo C (1990) *Iron deficiency anaemia and its effects upon psychological development at pre-school age: a longitudinal study*. Nestlé Foundation, Lausanne.

DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Controlled Clinical Trials*, **7**:177–188.

Dommergues MP, Archambeaud B, Ducot Y et al. (1989) Carence en fer et tests de developpement psychomoteur: etude longitudinale entre l'age de 10 mois et l'age de 4 ans. [Iron deficiency and psychomotor development tests: longitudinal study between 10 months and 4 years of age.] *Archives Francaises de Pediatrie*, **46**:487–490.

Dreyfuss ML, Shrestha JB, Khatry SK et al. (1996) Relationship between iron status and helminth infection among pregnant women in Nepal. *FASEB Journal*, **10**:A730.

Fleming AF, Ghatoura GB, Harrison KA, Briggs ND, Dunn DT (1986) The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Annals of Tropical Medicine and Parasitology*, **80**:211–233.

Fullerton WT, Turner AG (1962) Exchange transfusion in treatment of severe anaemia in pregnancy. *The Lancet*, **1**:75–78.

Garn SM, Ridella SA, Petzold AS, Falkner F (1981) Maternal hematologic levels and pregnancy outcomes. *Seminars in Perinatology*, **5**:155–162.

Gillespie S, Johnston JL (1998) *Expert consultation on anaemia determinants and interventions*. Micronutrient Initiative, Ottawa, ON.

Grantham-McGregor S, Ani C (2001) A review of studies on the effect of iron deficiency on cognitive development in children. *Journal of Nutrition*, **131**:S649–666.

Haas JD, Brownlie T (2001) Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *Journal of Nutrition*, **131**:S676–690.

Harrison KA, Lister UG, Rossiter CE, Chong H (1985) Perinatal mortality. *British Journal of Obstetrics and Gynaecology*, **5**:86–99.

Harrison KA, Rossiter CE (1985) Maternal mortality. *British Journal of Obstetrics and Gynaecology*, **5**:100–115.

Harrison KA (1975) Maternal mortality in anaemia in pregnancy. *West Africa Medical Journal*, 27–31.

Harrison KA (1982) Anaemia, malaria, and sickle cell disease. *Clinics in Obstetrics and Gynaecology*, **9**:445–477.

Harvey PWJ, Heywood PF, Nesheim MC et al. (1989) The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. *American Journal of Tropical Medicine and Hygiene*, **40**:12–18.

Hemminki E, Rimpelä U (1991) A randomized comparison of routine versus selective iron supplementation during pregnancy. *Journal of the American College of Nutrition*, **10**:3–10.

Henly SJ, Anderson CM, Avery MD, Hills-Bonczyk SG, Potter S, Duckett LJ (1995) Anaemia and insufficient milk in first-time mothers. *Birth*, **22**:86–92.

Horton S, Levin C (2001) Commentary on "Evidence that iron deficiency anaemia causes reduced work capacity". *Journal of Nutrition*, **131**: S691–696.

Hurtado EK, Claussen AH, Scott KG (1999) Early childhood anaemia and mild or moderate mental retardation. *American Journal of Clinical Nutrition*, **69**:115–119.

Idjradinata P, Pollitt E (1993) Reversal of developmental delays in iron-deficient anaemic infants treated with iron. *The Lancet*, **341**:1–4.

INACG (1989) *Guidelines for the control of maternal nutritional anaemia*. International Nutritional Anemia Consultative Group. International Life Sciences Institute (ILSI), Washington, DC.

INACG (1999) *Safety of iron supplementation programs in malaria-endemic regions*. ILSI, Washington, DC.

Institute of Medicine (1990) *Nutrition during pregnancy*. National Academy Press, Washington, DC.

Johnson JWC, Ojo OA (1967) Amniotic fluid oxygen tensions in severe maternal anaemia. *American Journal of Obstetrics and Gynecology*, **97**:499–506.

Konar M, Sikdar K, Basak S, Lahiri D (1980) Maternal Mortality. *Journal of the Indian Medical Association*, **75**:45–51.

Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM (1994) Iron supplementation improves appetite and growth in anaemic Kenyan primary school children. *Journal of Nutrition*, **124**:645–654.

Llewellyn-Jones D (1965) Severe anaemia in pregnancy. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, **5**:191–197.

Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL (1997) Prevalence of iron deficiency in the United States. *Journal of the American Medical Association*, **277**:973–976.

Lozoff B, Jimenez E, Wolf AW (1991) Long-term developmental outcome of infants with iron deficiency. *New England Journal of Medicine*, **325**:687–694.

Macgregor MW (1963) Maternal anaemia as a factor in prematurity and perinatal mortality. *Scottish Medical Journal*, **8**:134–140.

Mahomed K (2000a) Iron supplementation in pregnancy. *Cochrane Database System Reviews*, (2):CD000117.

Mahomed K (2000b) Iron and folate supplementation in pregnancy. *Cochrane Database System Reviews*, (2):CD001135.

Menendez C, Kahigwa E, Hirt R et al. (1997) Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *The Lancet*, **350**: 844–850.

Menendez C, Todd J, Alonso PL et al. (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**:590–593.

Mola G, Permezel M, Amoa AB, Klufio CA (1999) Anaemia and perinatal outcome in Port Moresby. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, **39**:31–34.

Murphy JF, O'Riordan J, Newcombe RG, Coles EC, Pearson JF (1986) Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *The Lancet*, **1**:992–994.

Murray CJ, Lopez AD, eds. (1996a) *The global burden of disease a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Global Burden of Disease and Injury, Vol 1. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray CJ, Lopez AD, eds. (1996b) *Global health statistics*: *a compendium of incidence, prevalence and mortality estimates for over 200 conditions*. Global Burden of Disease and Injury, Vol 2. Harvard School of Public Health on behalf of WHO, Cambridge, MA.

Murray MJ, Murray AB, Murray NJ, Murray MB (1978) The effect of iron status of Nigerian mothers on that of their infants at birth and 6 months, and on the concentration of Fe in breast milk. *British Journal of Nutrition*, **39**:627–630.

Oppenheimer SJ (2001) Iron and its relation to immunity and infectious disease. *Journal of Nutrition*, **131**:S616–635.

Oppenheimer SJ, Macfarlane SB, Moody JB, Bunari O, Hendrickse RG (1986) Effect of iron prophylaxis on morbidity due to infectious disease: report on clinical studies in Papua New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **80**:596–602.

Palti H, Pevsner B, Adler B (1983) Does anaemia in infancy affect achievement on developmental and intelligence tests? *Human Biology*, **55**:183–194.

Rasmussen KM (2001) Is there a causal relationship between iron deficiency or iron-deficiency anaemia and weight at birth, length of gestation and perinatal mortality? *Journal of Nutrition*, **131**:S590–603.

Sarin AR (1995) Severe anaemia of pregnancy, recent experience. *International Journal of Gynaecology and Obstetrics,* **50**:S45–49.

Sloan NL, Jordan E, Winikoff B (2002) Effects of iron supplementation on maternal hematologic status in pregnancy. *American Journal of Public Health*, **92**:288–293.

Smith AW, Hendrickse RG, Harrison C, Hayes RJ, Greenwood BM (1989) The effects on malaria of treatment of iron-deficiency anaemia with oral iron in Gambian children. *Annals of Tropical Paediatrics*, **9**:17–23.

Snedecor GW, Cochran WG (1980) *Statistical Methods*. Iowa State University Press, Ames.

Stoltzfus RJ (2001) Iron-deficiency anaemia: reexamining the nature and magnitude of the public health problem. Summary: implications for research and programs. *Journal of Nutrition*, **131**:S697–700.

Stoltzfus RJ, Dreyfuss ML (1998) *Guidelines for the use of iron supplements to prevent and treat iron deficiency anaemia*. ILSI Press, Washington, DC.

Stoltzfus RJ, Kvalsvig JD, Chwaya HM et al. (2001) Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study. *British Medical Journal*, **323**:1389–1393.

Tasker PWG (1958) Anaemia in pregnancy. A five year appraisal. *Medical Journal of Malayasia*, **8**:3–8.

UNICEF (1995) *The state of the world's children 1995*. Oxford University Press, Oxford.

UNICEF (1998) *The state of the world's children 1998*. Oxford University Press, Oxford.

Wasserman G, Graziano JH, Factor-Litvak P et al. (1992) Independent effects of lead exposure and iron deficiency anaemia on developmental outcome at age 2 years. *Journal of Pediatrics*, **121**:695–703.

WHO (2000) *Nutrition for health and development. A global agenda for combating malnutrition. A progress report*. (WHO/NHD/00.6). World Health Organization, Geneva.

Xiong X (1996) *Anaemia during pregnancy and birth outcomes: new data from China & a meta-analysis* [Dissertation]. Université Libre de Bruxelles Health Science Library, Brussels.

Xiong X, Buekens P, Alexander S, Demianczuk N, Wollast E (2000) Anaemia during pregnancy and birth outcome: a meta-analysis. *American Journal of Perinatology*, **17**:137–46.

Xiong X, Buekens P, Alexander S, Wollast E (1996) The relationship between anaemia during pregnancy and birth outcomes. *Archives of Public Health*, **53**:S136.

Yip R, Stoltzfus RJ, Simmons WK (1996) Assessment of the prevalence and the nature of iron deficiency for populations: the utility of comparing haemoglobin distributions. In: *Iron nutrition in health and disease*. Hallberg L, ed. John Libby & Co., London.