Estimating the burden of disease attributable to iron deficiency anaemia in South Africa in 2000

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Objectives. To estimate the extent of iron deficiency anaemia (IDA) among children aged 0 - 4 years and pregnant women aged 15 - 49 years, and the burden of disease attributed to IDA in South Africa in 2000.

Design. The comparative risk assessment (CRA) methodology of the World Health Organization (WHO) was followed using local prevalence and burden estimates. IDA prevalence came from re-analysis of the South African Vitamin A Consultative Group study in the case of the children, and from a pooled estimate from several studies in the case of the pregnant women (haemoglobin level < 11 g/dl and ferritin level < 12 µg/l). Monte Carlo simulation-modelling was used for the uncertainty analysis.

Setting. South Africa.

Subjects. Children under 5 years and pregnant women 15 - 49 years.

Outcome measures. Direct sequelae of IDA, maternal and perinatal deaths and disability-adjusted life years (DALYs) from mild mental disability related to IDA.

Results. It is estimated that 5.1% of children and 9 - 12% of pregnant women had IDA and that about 7.3% of perinatal deaths and 4.9% of maternal deaths were attributed to IDA in 2000. Overall, about 174 976 (95% uncertainty interval 150 344 - 203 961) healthy years of life lost (YLLs), or between 0.9% and 1.3% of all DALYs in South Africa in 2000, were attributable to IDA.

Conclusions. This first study in South Africa to quantify the burden from IDA suggests that it is a less serious public health problem in South Africa than in many other developing countries. Nevertheless, this burden is preventable, and the study highlights the need to disseminate the food-based dietary guidelines formulated by the National Department of Health to people who need them and to monitor the impact of the food fortification programme.

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Iron is an essential component of haemoglobin (Hb), required for basic cellular function in all human tissues, particularly muscle, brain and red blood cells.[1] Egg yolk, liver and red meat are excellent dietary sources of iron. Vegetarian sources include cereals, pulses and green leafy vegetables, although the rate of absorption of iron from these foods is lower.[2] Milk from any source contains insufficient amounts of iron, making babies 3 - 6 months of age vulnerable to iron deficiency.

Worldwide, iron deficiency (usually defined as a ferritin level < 12 µg/l) is the most prevalent nutritional deficiency, affecting over 2 billion people. Infants, women of childbearing age and preschool-aged children are particularly affected since iron requirements increase during growth, pregnancy and lactation.[3] Iron deficiency anaemia (IDA) occurs when iron deficiency is sufficiently severe to diminish erythropoiesis, leading to a decrease in the number of red cells in the blood and resulting in development of anaemia (Hb level < 11 g/dl).[4] It is estimated that of children under 5 years of age, 20% in industrialised countries and 39% in non-industrialised countries are anaemic.[3]

Although conditions such as malaria, nutritional deficiencies of folate and vitamin B_{12}, as well as HIV and other chronic diseases can play a role in the causal path of anaemia, the literature suggests that iron deficiency is responsible for about 50% of cases of anaemia in young children and pregnant women in developing countries.[3,4] Schauer and Zlotkin[5] estimated that more than 50% of children under the age of 5 years in developing countries are anaemic, mainly due to a diet that is inadequate in bioavailable iron. The global disease burden distribution of IDA is greatly concentrated in sub-Saharan Africa and Asia.[4]

IDA may lower resistance to infections and has been shown to delay cognitive and psychomotor development in infants, with lasting effects on learning, work productivity, health and growth.[1,3,6] IDA in early childhood can be fatal, it reduces intelligence in mid-childhood, and in the most severe form causes mild mental retardation.[3,6] In pregnant women it increases the risk of a pre-term low-birth-weight delivery, and is a risk factor for maternal and perinatal mortality.[6]

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In South Africa nationally representative data on IDA are scarce. The South African Vitamin A Consultative Group (SAVACG) survey,[7] conducted in 1994 - 1995, is the only national study that included data on the anaemia and iron status of children aged 6 - 71 months. The prevalence of anaemia was 21%. The prevalence of IDA in children was 5% using the bivariate criteria (Hb < 11 g/dl and ferritin < 12 µg/l) and 3% using the trivariate criteria analysis (also including low mean corpuscular volume). Other smaller-scale studies[8-10] done before the SAVACG study showed a higher prevalence of IDA of 10 - 50% in infants and young children. In addition, Oelofse *et al.*[11] found the prevalence of iron deficiency among preschoolers in rural KwaZulu-Natal to be 19.8%, and 18.9% of mothers were iron deficient but not necessarily anaemic. Mayet *et al.*[12] found that 42% of males and 53% of females aged 6 - 74 years in a rural setting in KwaZulu-Natal were anaemic, largely as a result of low iron intake.[11,12] While these studies may have been conducted among vulnerable communities, provincial variations in the prevalence of anaemia range from 10% in KwaZulu-Natal to 34% in Limpopo, suggesting that there are considerable variations in the prevalence of anaemia and IDA.[11-13]

In the case of pregnant women there are no national data on the extent of IDA. Studies have reported the prevalence of anaemia in pregnancy to be between 22% and 35% in Durban, 27% and 37% in Johannesburg, and 33% in Gazankulu.[13] A study by Kruger *et al.*[14] observed anaemia in 25% of pregnant and 10% of non-pregnant women in a so-called 'coloured' suburb in the Cape Peninsula. Iron deficiency was observed in 21% of the pregnant and 13% of the non-pregnant women, while the prevalence of IDA (Hb < 11 g/dl and serum ferritin <12 µg/l) was 9% and 7% respectively.[14] A study of women attending antenatal clinics in Durban[15] found that iron deficiency was common among pregnant women, especially women of Indian origin. The prevalence of anaemia in the third trimester of pregnancy was reported at 47% of Indian and 29% of black African women.[15] The prevalence of iron deficiency (serum ferritin < 12 µg/l) in the third trimester of pregnancy was 86% in Indian women and 40% in black African women. However, the prevalence of IDA was not reported. Dannhauser *et al.*[16] reported a 26.2% prevalence of anaemia among pregnant women living in Bloemfontein, and a 20% prevalence of IDA.

As part of a comparative risk assessment (CRA), the aim of this study was to estimate the extent of IDA among children aged 0 - 4 years and pregnant women using the available data, and to quantify the burden of disease from other causes that can be attributed to this form of micronutrient malnutrition in South Africa in 2000.

Methods

It is assumed that iron deficiency contributes to death and disability through direct sequelae as in the Global Burden of Disease Study,[17,18] or as a risk factor for death and disability from other causes. We followed the framework developed by Stoltzfus *et al.*,[3] in which IDA among pregnant women was considered a risk factor for perinatal mortality and maternal mortality (not morbidity). According to the framework, women die of heart failure due to blood loss which is made more precipitous by IDA.[3] Similarly, a baby would die in the perinatal period from causes related to pre-term birth, for which maternal iron deficiency is a risk factor. Decreased work productivity and delayed child development (reduction in intelligence) are considered to be direct sequelae of iron deficiency, the assumption being that iron deficiency directly causes decreased oxygen delivery to muscles and the brain.

The Hb cut-offs used to define anaemia are from Stoltzfus and Dreyfuss[19] and have not changed since the 1990 WHO anaemia database was created. For both children 0 - 4 years and pregnant women an Hb cut-off of 11 g/dl is used to define anaemia in populations living at sea level. Either bivariate (Hb < 11 g/dl + serum ferritin < 12 µg/l) or trivariate (Hb < 11 g/dl + ferritin < 12 µg/l + mean corpuscular volume) criteria can be used to define IDA. For this analysis we used the definition based on bivariate criteria.

The standardised CRA method for estimating population-attributable fractions (PAFs) and attributable burden was used in this study. As has been fully described elsewhere,[1,3,20] attributable burdens were calculated using potential impact fractions, which are multi-level extensions of attributable fractions. As in the global study,[3] the theoretical minimum distribution represents the Hb distribution in the population if iron deficiency was eliminated.

The shift in the mean Hb concentration for children aged 0 - 4 years if iron deficiency was eliminated was estimated by assuming that for a prevalence of anaemia of between 15% and 30%, the Hb is normally distributed,[21] with a standard deviation (SD) of 1.2 g/dl.[3] The shift in mean Hb level is then converted to the shift in the distribution of IQ points using the method described by Stoltzfus and colleagues,[3] so as to estimate the proportion of children with IQ points just above the threshold who would enter the mild mental disability (MMD) range due to IDA. By convention, MMD occurs when the IQ is below 70 points but above 50 points. Intelligence in human populations approximates to a normal distribution with a mean of 100 (95% confidence interval (CI): 98 - 102) and a standard deviation of 15 IQ points.[22,23]

The increase in risk of MMD is estimated from the expected mean change in IQ, by assuming that the mean change represents a shift in the entire distribution of values with no change in the variance of the distribution.[3] For low concentrations of Hb the estimated increase in IQ points associated with a 1 g/dl increase in Hb concentration is 1.73 (95% CI: 1.04 - 2.41).[3] The rate of MMD due to IDA is the difference between the predicted rate of MMD in our population with the Hb distribution shifted downward due to iron deficiency, and the expected rate in the healthy population

(2.28%). The disease modelling tool DisMod II[24] was then used to back-calculate the incidence of MMD from the observed prevalence rate, using a relative risk (RR) of total mortality for mental disability of 2 (double that for the total population) and a remission rate of 0. For estimating the disability-adjusted life years (DALYs) due to MMD, this calculated incidence of MMD was introduced into the DALY template MS Excel spreadsheets with duration and age at onset also derived from DisMod II and using the Dutch disability weight for MMD of 0.290.[25]

In the case of pregnant women we similarly used the prevalences of IDA to derive the theoretical minimum prevalence of anaemia, and converted this to a mean Hb level assuming an SD of 1.2 g/dl to estimate the theoretical minimum risk distribution representing the Hb distribution, if iron deficiency were eliminated. The RR estimates for IDA used in these analyses were those published by Stoltzfus *et al*.[3] The odds ratios associated with a 1 g/dl increase in population mean Hb level were 0.80 (95% CI: 0.70 - 0.91) for maternal mortality and 0.72 (95% CI: 0.65 - 0.80) for perinatal mortality (Africa region), and have been adjusted by 20% for confounding factors.[3]

PAFs by cause were calculated in MS Excel using the discrete version of the general potential impact fraction taking into account continuous risk factor disease exposures compared with a theoretical minimum distribution (conferring the lowest possible risk) on a categorical scale:

$$PAF = \frac{\sum_{i=1}^{n} P_i RR_i - \sum_{i=1}^{n} P'_i RR_i}{\sum_{i=1}^{n} P_i RR_i}$$

where n = the number of exposure categories; P_i = the proportion of population in exposure category i; RR_i = the relative risk for exposure category i; and P'_i = the proportion of population in exposure category i in the counterfactual distribution.

The PAFs were then applied to revised burden of disease estimates for South Africa, 2000, for the maternal and perinatal disease categories.[26] DALYs attributed directly to IDA were also included as these estimates include the direct effects of IDA on work productivity, child development and cognition. DALY estimates of IDA in the 0 - 4-year age group were excluded to avoid double counting from the inclusion of the MMD DALYs estimated in this analysis.

Monte Carlo simulation-modelling techniques were used to present uncertainty ranges around point estimates that reflect the main sources of uncertainty in the calculations. @RISK software version 4.5 for Excel[27] was used, which allows multiple recalculations of a spreadsheet, each time choosing a value from distributions defined for input variables. Normal distributions were specified for the prevalence input variables, based on standard errors of the mean Hb values in pregnant women. In order to derive the theoretical minimum distribution for pregnant women, a uniform probability distribution was specified between the upper and lower Hb values corresponding to the minimum and maximum prevalence of anaemia, after subtracting the respective maximum and minimum prevalence of IDA from published studies.

Similarly, to derive uncertainty ranges around the Hb shift in children 0 - 4 years of age (or the difference between the current observed Hb level and the theoretical minimum level if IDA is eliminated), first a uniform probability distribution was specified between the upper and lower Hb values, corresponding to the upper and lower confidence limits of the observed anaemia prevalence. Secondly, a uniform probability distribution was specified between the upper and lower Hb values, corresponding to the minimum and maximum prevalence of anaemia after subtracting the respective maximum and minimum prevalence of IDA from published studies.

For the RR input variables we specified a normal distribution around the logged point estimate and its standard error derived from the published values and their 95% confidence intervals.[3] A uniform probability distribution with a minimum of 98 and a maximum value of 102 was specified for the mean IQ in human populations. A uniform probability distribution was also specified around the estimated increase in IQ points associated with a 1 g/dl increase in Hb, concentration based on the lower and upper limits of the published 95% CI. For each of the output variables (namely attributable burden as a percentage of total burden in South Africa 2000), 95% uncertainty intervals were calculated bounded by the 2.5th and 97.5th percentiles of the 2000 iteration values generated.

Results

Re-analysis of SAVACG data[7] for children 0 - 4 years of age yielded a prevalence of anaemia of 22.6% (95% CI 21.1 - 24.2%) and a prevalence of IDA of 5.1% (95% CI 4.3 - 5.9%). It can therefore be estimated that more than 0.2 million children were affected by this form of iron deficiency in our country in 2000, and that about a quarter of the anaemia in South African children is IDA. This is in contrast to the global study,[3] which estimated that 50% of anaemia is IDA. The theoretical minimum prevalence of anaemia, if iron deficiency were eliminated, would be between 17% and 18%. Assuming a normal distribution with an SD of 1.2 g/dl, the shift in population mean Hb concentration representing the elimination of IDA was 0.22 g/dl (95% uncertainty interval 0.14 - 0.30 g/dl) for children of 0 - 4 years of age.

The estimated decrease in IQ points associated with this downward shift in population mean Hb concentration of 0.22 g/dl was estimated at 0.38 (95% CI: 0.19 - 0.64). Based on this shift, the rate of MMD due to IDA was estimated at 0.14% (95%

uncertainty interval: 0.07 - 0.26%), and represents an incidence of MMD of 0.7 per 1 000 in the 0 - 4-year age group. Using this incidence, an estimated 29 673 DALYs due to MMD were causally attributed to IDA.

Local studies conducted in pregnant women reported a prevalence range of 9 - 12% for IDA,[14-16,28-30] affecting more than 100 000 births in 2000. The prevalence in pregnant women was about double that observed in children. The weighted mean Hb concentration in the community studies was 11.6 g/dl for pregnant women. Assuming a normal distribution with an SD of 1.2 g/dl, this pooled mean indicates a prevalence of anaemia of 30.4%. The predicted Hb shift for pregnant women representing the elimination of iron deficiency was also higher than in children, and was estimated to be around 0.47 g/dl (95% uncertainty interval 0.37 - 0.57 g/dl). Based on this, about 7.3% of perinatal deaths and 4.9% of maternal deaths could be attributed to IDA in pregnant women, amounting to 1 938 perinatal and 100 maternal deaths.

Overall, an estimated 2 038 deaths (95% uncertainty interval 1 292 - 2 914) or 0.4% of all deaths in South Africa in 2000 could be attributed to IDA (Table I). Attributable DALYs were higher, with 174 976 (95% uncertainty interval 150 344 - 203 961) healthy years of life lost (YLLs), or between 0.9% and 1.3% of all DALYs in South Africa in 2000 attributable to IDA. The perinatal burden accounted for 36.7% of all DALYs attributable to IDA, while maternal mortality (1.7%) and MMD (17.0%) accounted for much smaller proportions of the total attributable burden (Fig. 1).

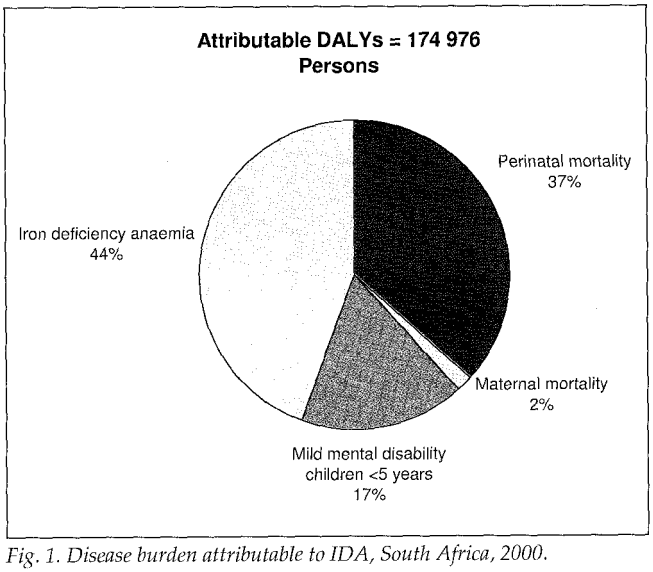

Fig. 1. Disease burden attributable to IDA, South Africa, 2000.

Discussion

The global study[3] found that in total, 0.8 million deaths worldwide (1.5%) are attributable to IDA. Using a comparable method with South African data, the present study indicates that some 2000 deaths (95% uncertainty interval 1 300 - 2 900) could be attributed to IDA, accounting for 0.2 - 0.4% of total deaths in South Africa in the year 2000. The present study estimated that about 7% of perinatal deaths and 5% of maternal deaths were attributed to IDA, while the global study estimated that about 20% of perinatal mortality and 10% of maternal mortality in developing countries is attributable to iron deficiency.[1,3]

There are two possible reasons for the lower proportion of attributable deaths in South Africa. Firstly, the observed IDA prevalence of 9 - 12% in pregnant women, although higher than the 4% estimated for industrialised countries, is much lower than the 20 - 25% estimated for sub-Saharan Africa, South-East Asia and the Western Pacific Regions.[1] The second reason is the high HIV/AIDS burden in South Africa, which has the effect of reducing the relative contribution of other conditions.

The global study[8] estimated that 2.4% of DALYs are attributable to IDA, higher than the proportion of attributable deaths. For South Africa, 174 976 (95% uncertainty interval 150 344 - 203 961) healthy YLLs, or between 0.9% and 1.3% of all DALYs, were attributable to IDA. IDA is ranked 13th overall in terms of DALYs compared with 17 risk factors assessed in South Africa, ranking lower than 'underweight' but higher than other forms of micronutrient deficiencies such as vitamin A deficiency. While IDA appears to be of less serious public health importance in South Africa than the rest of sub-Saharan Africa, it is important to acknowledge the geographical

Table I. Disease burden attributable to IDA, South Africa, 2000

Related outcomes	Attributable mortality	Attributable DALYs
Perinatal mortality	1 938	64 254
Maternal mortality	100	3 048
MMD	0	29 673
IDA*	0	78 002
Total attributable burden	**2 038**	**174 976**
95% uncertainty interval	1 292 - 2 914	150 344 - 203 961
% of total burden	**0.4%**	**1.1%**
95% uncertainty interval	0.2 - 0.6%	0.9 - 1.3%

*Direct sequelae attributed directly to iron deficiency in persons 5 years and older (there were no deaths due to IDA).[26]
DALYs = disability-adjusted life years; MMD = mild mental disability; IDA = iron-deficiency anaemia.

differences across the country. In addition, IDA is an important risk factor in children, ranking 4th overall and accounting for 2.3% (1.7 - 3.0%) of all healthy years lost in children aged 0 - 4 years. Since this burden is preventable and amenable to interventions, it is important to identify ways in which this can be reduced.

It should be noted that there is a degree of uncertainty in the results that could not be quantified. One of the limitations of using bivariate analysis is that serum ferritin concentrations could have been increased due to infection, obscuring the presence of iron deficiency.[31] However, this masking is not likely to be substantial in this study since the SAVACG study[7] specifically excluded children with fever. Furthermore, the small community studies[8-10] show higher prevalences in children than reflected in the SAVACG study. It is not clear whether the studies were conducted in atypical settings, or whether the national survey underestimated the extent of the problem. A second contribution to the uncertainty of this estimate is that the data used to determine the prevalence of IDA are dated. The study results are also compromised by the lack of national prevalence data for pregnant women.

Measurement of IDA in population studies remains a challenge. In the community studies in pregnant women only bivariate criteria were used to diagnose IDA, whereas in SAVACG both trivariate and bivariate criteria were used to define IDA in children. Applying the more conservative trivariate criteria to define IDA in the SAVACG data yielded a similar prevalence that falls within the uncertainty range used in this analysis. It is therefore believed that the use of bivariate criteria would not have led to an overestimate of the attributable burden in children in this analysis. However, it would be ideal to be able to use serum transferrin receptor levels as an indicator of iron deficiency.[32]

Stoltzfus *et al.*[3] point out the need for more research in the context of high anaemia prevalence worldwide. They stress that the estimates of decreased IQ and MMD related to IDA presented for children under 5 years of age should also be interpreted with caution.[4] Evidence for the relationship between IDA and maternal and perinatal mortality needs to be researched further, and there is also an urgent need for more consistent data on the association between IDA and mortality as well as mental disability in young children.

Conclusion and recommendations

IDA appears to be of less serious public health importance in South Africa than in the rest of sub-Saharan Africa and some of the other regions in the world. In spite of the need for more recent evidence on the prevalence of IDA, this study suggests that there is a preventable burden resulting from IDA in South Africa. Food-based approaches are needed to direct efforts towards promoting the availability of and access to iron-rich foods. In addition, focus should be placed on the consumption of foods that enhance the absorption or utilisation of iron, such as fruit and vegetables. The challenge remains to ensure that the food-based dietary guidelines developed by the National Department of Health[33] reach the people who need them.

Food fortification is an effective long-term approach to improve the iron status of the population. Following the National Food Consumption Survey of 1999,[34] in which it was found that at least one-third of children have an intake of less than half the recommended levels of important nutrients, legislation has been introduced to enforce the fortification of wheat flour and maize meal. Iron is one of the minerals included in the fortification, and careful assessment of the efficiency and effectiveness of these interventions, as well as of the impact on vulnerable subgroups, is needed.

It is not clear whether iron supplementation for target groups is needed. Further research is recommended to update information on the prevalence of iron deficiency and IDA by age and gender and to identify vulnerable groups. Measures to improve nutrition knowledge and awareness of mothers and health workers may be implemented. Finally, nutrition education and intervention programmes should address iron deficiency with the focus on both dietary quantity and quality of the micronutrient composition. All of these interventions must be monitored for effectiveness.

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