


Estimating the changing disease burden attributable to iron deficiency in South Africa, 2000, 2006 and 2012

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Background. Worldwide, iron deficiency, and consequent iron-deficiency anaemia, remains the most common nutritional disorder. Iron-deficiency anaemia mostly affects young children and women of reproductive age, especially in Asia and Africa. Iron deficiency may contribute to disability directly or indirectly as a risk factor for other causes of death, and may rarely contribute to death.

Objectives. To estimate the changing burden of disease attributable to iron deficiency in males and females (all ages) for the years 2000, 2006 and 2012 in South Africa (SA).

Methods. The comparative risk assessment methodology developed by the World Health Organization (WHO) and the Global Burden of Diseases, Injuries, and Risk Factors Studies was used to estimate the burden attributable to iron deficiency in SA for the years 2000, 2006 and 2012. We attributed 100% of the estimated iron-deficiency anaemia burden across all age groups by sex to iron deficiency. For maternal conditions, the attributable burden to iron deficiency was calculated using the counterfactual method and applied to all women of reproductive age. The population attributable fraction calculated for these selected health outcomes was then applied to local burden estimates from the Second SA National Burden of Disease Study (SANBD2). Age-standardised rates were calculated using WHO world standard population weights and SA mid-year population estimates.

Results. There was a slight decrease in the prevalence of iron-deficiency anaemia in women of reproductive age from ~11.9% in 2000 to 10.0% in 2012, although the prevalence of anaemia fluctuated over time (25.5% - 33.2%), with a peak in 2006. There has been a gradual decline in the number of deaths from maternal conditions attributable to iron deficiency in SA between 2000 (351 deaths (95% uncertainty interval (UI) 248 - 436)) and 2012 (307 deaths (95% UI 118 - 470)), with a peak in 2006 (452 deaths (95% UI 301 - 589)). Furthermore, our analysis showed a 26% decrease between 2000 and 2012 in the age-standardised burden rates from maternal conditions (truncated to 15 - 49 years) attributable to iron deficiency. Between 2000 and 2012, the age-standardised disability-adjusted life year (DALY) rate from iron-deficiency anaemia attributable to iron deficiency markedly decreased by 33% in males, and increased by 3% in females of all ages. Approximately 1.1 - 1.4% of all DALYs in SA from 2000 to 2012 were attributable to iron deficiency.

Conclusion. Iron-deficiency anaemia prevalence can be markedly reduced if iron deficiency is eliminated. Hence it is essential to encourage, reappraise and strengthen the measures that have been put in place to address iron deficiency, especially in women of reproductive age and children.

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The article in context

Evidence before the study. The first SA Comparative Risk Assessment Study (SACRA1) conducted in 2000 assessed the burden of disease attributable to pregnant women. Pooled estimates from available regional studies showed an anaemia prevalence of 30.4% and iron-deficiency anaemia prevalence of 12.2% among pregnant women aged 15 - 49 years in SA. Furthermore, 0.4% (95% uncertainty interval (UI) 0.2% - 0.6%) of all deaths and 1.1% (95% UI 0.9 - 1.3%) of the total DALYs were attributed to iron deficiency in SACRA1.

Added value of the study. Our study used updated methodology to estimate the burden attributable to iron deficiency for three time points - 2000, 2006 and 2012. We conducted a systematic search of published literature and contacted experts in the field to identify relevant national studies/data sources on iron-deficiency anaemia prevalence in SA and national and regional surveys that included haemoglobin testing. We did not find any national studies on pregnant women (aged 15 - 49 years). We re-analysed the SACRA1 data and cross-walked from pregnant to non-pregnant estimates. This yielded anaemia and iron-deficiency anaemia prevalences of 25.7% and 11.9%, respectively, in women of reproductive age (15 - 49 years). Imputation for participant non-response in the SA National Health and Nutrition Examination Survey (SANHANES) yielded a prevalence of iron-deficiency anaemia of 10% in the same subgroup in 2012. Our study shows

a decline over time in the proportion of maternal deaths attributable to iron deficiency in SA from 38.2% (95% UI 29.0% - 46.1%) in 2000 to 26.6% (95% UI 10.3% - 40.2%) in 2012. Across all three time periods, only 6% - 7% of the burden attributable to iron deficiency was from maternal conditions, with iron-deficiency anaemia accounting for >90% of the DALYs, largely through loss from disability associated with non-fatal outcomes (years lived with disability (YLDs)).

Implications of all available evidence. Iron-deficiency anaemia remains of moderate public health importance for women in SA. Gaps in the implementation of iron supplementation during antenatal visits need to be identified. The recently released updated World Health Organization 2020 guidelines have highlighted the need to address issues around antenatal multiple micronutrient supplementation. In addition, appropriate guidelines for iron supplementation of newborns and children need to be developed. Although there has been a slight decrease in the prevalence of iron-deficiency anaemia in women of reproductive age, the prevalence of overall anaemia, the number of maternal deaths and DALYs attributable to iron deficiency in SA has been changing over time, with a peak in 2006, suggestive of a relationship with untreated HIV/AIDS. An investigation into the relationship between HIV and anaemia and its impact on this population, in addition to the role of antiretroviral therapy and dietary requirements of HIV-positive pregnant women, is needed. Furthermore, locally conducted epidemiological studies would be valuable in providing relative risk and non-fatal burden estimates for more accurate local attributable burden estimation.

Worldwide, iron-deficiency anaemia remains the most common nutritional disorder, even in high-income countries.^[1-3] Iron-deficiency anaemia is the most severe stage of iron deficiency and the most common type of anaemia.^[4] In 2010, the global anaemia prevalence was 33%, with iron deficiency being the most common cause.^[5,6] Iron-deficiency anaemia mostly affects young children and women of reproductive age, especially in Asia and Africa.^[1,7,8] In Africa, it was estimated that in 2016, 59% of pre-schoolers (children under 5 years old), 46% of pregnant women and 39% of women of reproductive age were anaemic.^[9,10] Iron deficiency is assumed to be the cause of 60% and 50% of anaemia in non-malaria and malaria-infested areas, respectively.^[11] However, a recent meta-analysis of national survey data from 23 low- and middle-income countries showed that 25% and 37% of anaemia in pre-school children and non-pregnant women, respectively, was associated with iron deficiency.^[3] In South Africa (SA), 40% of anaemia reported in women of reproductive age was associated with iron deficiency.^[3]

Iron is required in human tissues at cellular level, and is of critical importance particularly in muscle, brain and red blood cell function.^[7,12] Iron-deficiency anaemia develops when there is a prolonged negative imbalance between iron requirements, iron intake, iron absorption and iron loss from the body, resulting in insufficient production of red blood cells.^[13] Some of the predisposing factors for iron-deficiency anaemia are high iron demands during infant growth and during pregnancy, diets based mainly on staple foods with little or no red meat, fish or poultry, blood loss during menstruation, exposure to infestations that result in blood loss (primarily hookworm and urinary schistosomiasis) and infectious diseases such as HIV.^[6,12,14] Iron deficiency may contribute to death or disability directly or indirectly as a risk factor for other causes of death. Direct sequelae of iron-deficiency anaemia as a result of decreased oxygen delivery to muscles and the brain are cognitive impairment, developmental delays and disability in children, and decreased work productivity due to fatigue in adults. Indirect consequences are an increase in the risk of maternal mortality from, for example, heart failure due to blood loss, and preterm delivery in pregnant women with iron deficiency.^[17,11] Maternal iron deficiency can also result in low iron stores in the newborn, and may progress to iron-deficiency anaemia in infants.^[15] There are various interventions to prevent and correct iron-deficiency anaemia. These include increasing intake of iron-rich foods, iron fortification of staple foods, iron supplementation and infection control measures.^[4] In the context of this article, iron-deficiency risk factor is defined in terms of all causes of anaemia that would respond to iron supplementation, i.e. iron-deficiency anaemia.^[16]

Iron deficiency accounted for 33.7 million disability-adjusted life years (DALYs) (mostly due to disability from iron-deficiency anaemia) and about 60 000 deaths in 2017.^[16] In SA, iron deficiency was estimated to be the 13th leading risk factor for poor health in 2000 out of 17 selected risk factors, accounting for 1.1% of total DALYs.^[17] The 2000 South African Comparative Risk Assessment study (SACRA1) further estimated that 5.1% of children and 9% - 12% of pregnant women in SA had iron-deficiency anaemia, and that 4.9% of maternal deaths and 0.4% of all deaths in SA were attributable to iron deficiency. In this second national study, we updated the SACRA1 data to incorporate improved methods, and the results presented here supersede all previously published SACRA estimates. The aim of this study was to estimate the changing burden of disease attributable to iron deficiency in males and females (all ages) for the years 2000, 2006 and 2012 in SA, as part of a comparative risk assessment (CRA) for the country based on secondary analysis and modelling of available local data.

Methods

We used the standardised CRA methodology developed by the World Health Organization (WHO),^[12,18] and updated the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2017).^[16] We attributed 100% of the estimated iron-deficiency anaemia (the cause) burden (years lived with disability (YLDs) and DALYs) across all age groups by sex to iron deficiency (the risk factor). For the maternal conditions (namely maternal haemorrhage, maternal sepsis, hypertensive disorders of pregnancy, obstructed labour, abortion, indirect maternal causes and other maternal conditions), we calculated the burden attributable to iron deficiency (the risk factor) using CRA methods involving four estimation steps. Firstly, we identified the best estimate of the exposure to iron deficiency in SA. We then identified the counterfactual level of the risk factor exposure, i.e. a theoretical minimum risk exposure level (TMREL). We applied an estimate of the relative risk (RR) of the outcome relative to the TMREL to calculate the potential impact fraction (PIF), which was then applied to estimates of the disease burden assessed for the maternal causes related to this risk factor, i.e. number of deaths, YLDs, years of life lost (YLLs) and DALYs in SA for women of reproductive age. YLLs were calculated for maternal conditions only, as there were no deaths from iron-deficiency anaemia.

Exposure definition

Exposure was defined as peripheral blood haemoglobin (Hb) concentration in g/L for all iron-responsive causes. To quantify the exposure, we used anaemia as an indicator of the presence of iron

deficiency severe enough to affect tissue function, and we defined iron-deficiency anaemia as the simultaneous presence of peripheral blood Hb concentration <110 g/L (pregnant women) or <120 g/L (non-pregnant women), and serum ferritin concentration <15 µg/L.^[19]

Although more specific indicators of functional iron deficiency are available, notably erythrocyte protoporphyrin and serum transferrin receptor, data on the population distribution of those indicators were not available, and the relationship between these indicators and the outcomes of interest was insufficient.^[1]

Exposure levels

A systematic search of the published literature was done to obtain local data on iron-deficiency anaemia prevalence estimates in SA using a comprehensive search strategy. Four databases, PubMed, Scopus, Web of Science and African Index Medicus (Table S1 in the appendix: <https://www.samedical.org/file/1819>) were searched for relevant national studies published between 1997 and 2017, guided by the availability of mortality data for SA from 1997 to 2013. We also searched the SA National Electronic Thesis and Dissertation portal and references of studies already identified. We contacted experts in the field to identify additional relevant national and subnational surveys that completed Hb testing in order to estimate the mean Hb in g/L among women of reproductive age (15 - 49 years of age) and the implied mean Hb among women in the absence of iron deficiency.

The data sources identified were SACRA1^[17] the National Food Consumption Survey (NFCS) 2005,^[20] and the SA National Health and Nutrition Examination Survey (SANHANES) 2012.^[21] Anaemia and iron-deficiency anaemia prevalence estimates obtained from these studies are summarised in Table S2 in the appendix (<https://www.samedical.org/file/1819>). We did not find any national studies that reported anaemia or iron-deficiency anaemia estimates in pregnant women for the period 2000 - 2012.

SACRA1^[17] pooled estimates from six small studies conducted in pregnant women in SA to derive the overall prevalence of anaemia and the theoretical minimum prevalence of iron-deficiency anaemia, as there were no national studies available at the time. From the pooled prevalence, the mean of the underlying Hb distributions was calculated in the SACRA1 study by assuming a standard deviation (SD) of 1.2 g/L. As this study included only pregnant women, we converted the mean value above to the one that would have been observed in non-pregnant women using a regression equation obtained from the Institute of Health Metrics and Evaluation (Dr Katherine Ballesteros, personal communication):

$$Hb_{\text{pregnant}} = 0.7584 \cdot Hb_{\text{non-pregnant}} + 19.874$$

where Hb_{pregnant} is the mean Hb for pregnant women and $Hb_{\text{non-pregnant}}$ is the mean Hb for non-pregnant women. We then calculated the distribution among all women of reproductive age by assuming a 4% prevalence of women of reproductive age who were pregnant at any point in time.^[22]

For the years 2006 and 2012, we estimated the mean and SD of the distribution of Hb concentration among women of reproductive age from NFCS 2005^[20] and SANHANES 2012^[21] microdata, respectively. We calculated the estimates taking into account the sampling scheme of each survey by using a weighted estimator with robust standard error. Given the low item response rate in SANHANES (32% having donated a blood sample), we used a linear regression model to adjust the estimates for non-response, with geotype (rural v. urban), population group, province, employment status and smoking status as predictors.

Theoretical minimum risk exposure level

The TMREL was defined as the counterfactual Hb distribution that would have been observed among women of reproductive age in the absence of iron deficiency for all iron-responsive causes.^[16] We calculated Hb mean and SD of the TMREL distribution using the same method used for the observed distribution. For the year 2000, we derived the counterfactual distribution of Hb in the absence of iron deficiency from the prevalence estimates in SACRA1, by applying the same cross-walk equation and adjustment for the prevalence of pregnant women. For 2006 and 2012 we used NFCS 2005 and SANHANES 2012 microdata and estimated the TMREL as the distribution among women of reproductive age with anaemia but with normal values of serum ferritin (>15 µg/L). Women with unknown ferritin levels were excluded from the calculation.

Relative risks

The RR estimate used in our analysis was sourced from GBD 2013,^[19] which remained unchanged in GBD 2017.^[16] The RR associated with a 100 g/L increase in population mean Hb level was 1.25 (95% confidence interval (CI) 1.09 - 1.43) for maternal morbidity and mortality.

Population attributable fraction

The PIF, i.e. the proportion by which each of the considered outcomes would be reduced in a given population and in a given year if the exposure to the risk factor in the past was reduced to the counterfactual level of the TMREL, was calculated integrating over the continuous range of the exposure:

$$PIF = \frac{\int_{x=7}^{18} RR_o(x) \cdot P_y(x) \cdot dx - \int_{x=7}^{18} RR_o(x) \cdot PTMREL_y(x) \cdot dx}{\int_{x=7}^{18} RR_o(x) \cdot P_y(x) \cdot dx}$$

Where $RR_o(x)$ is the RR for cause o as a function of the concentration x of Hb, $P_y(x)$ is the observed distribution of Hb in year y and $PTMREL_y(x)$ the counterfactual distribution in the absence of iron deficiency. The integration is extended between 7 and 18 g/L (physiological lower and upper bound). In an exploratory analysis of the SANHANES 2012 data, we considered a normal, a Gamma and a Weibull alternative distribution, and identified the Weibull as the most suitable distribution for Hb. We used the method of moments to recover the scale and shape parameters from the mean and SD (Table S3 in the appendix: <https://www.samedical.org/file/1819>).

Attributable burden and uncertainty analysis

The PIFs were then applied to the burden of disease for maternal conditions (namely maternal haemorrhage, maternal sepsis, hypertensive disorders of pregnancy, obstructed labour, abortion, indirect maternal causes and other maternal conditions) extracted from the burden estimates^[23] for 2000, 2006 and 2012 to calculate the burden attributable to iron deficiency among women of reproductive age. We then added these values together, and to the burden due to iron-deficiency anaemia (which is 100% attributable to iron deficiency) across all ages and for both sexes to obtain the total burden attributable to iron deficiency.

We used Monte Carlo simulation-modelling techniques to present uncertainty ranges around point estimates, reflecting the level of uncertainty in the exposure, the RR functions, the TMREL and the burden of disease. Analyses were conducted with R statistical software v.3.5 (R Core Team, Austria).

Separately for each year, sex, age group and cause, we drew 2 000 random samples from the distributions of the parameters of the exposure distribution, the RR functions, the TMREL and the burden estimates, and we repeated the calculation of the PIF. We used the mean of the distribution of the replicates as the point estimate of the PIF, and the 2.5th and 97.5th percentiles as the bounds of the 95% UI.

In drawing the samples, we assumed a normal distribution for the scale parameter of the Weibull distribution of the exposure and the TMREL (with mean and SD given by the point estimate and its standard error), and a lognormal distribution for the RRs.^[24] For the burden estimates (YLDs and DALYs), we assumed a negative binomial distribution with the same dispersion parameter as in the corresponding estimates from the GBD 2019 study.^[25]

Age-standardised rates were calculated using WHO world standard population weights^[26] and SA mid-year population estimates.^[27]

Results

The prevalence of anaemia in women of reproductive age was estimated at 25.7%, and iron-deficiency anaemia prevalence was 11.9% for the year 2000. Prevalence of anaemia among women of reproductive age in SA between 2000 and 2012 was between 25% and 33%. About 46% of anaemia was

due to iron deficiency in 2000; this decreased to 31.3% in 2006 and increased to 39.2% in 2012. Hence the proportion of anaemia due to iron deficiency was lowest in 2006. Table 1 shows the mean Hb concentration in g/L and estimated prevalence for anaemia and iron-deficiency anaemia for women of reproductive age, and Fig. 1 shows the prevalence of anaemia and iron-deficiency anaemia from all three time periods. Approximately 40% of all anaemia in women of reproductive age in SA was associated with iron deficiency.

The attributable deaths and DALYs are presented in Table 2.

There has been a gradual decline in the proportion of all deaths from maternal conditions attributable to iron deficiency in SA between 2000 and 2012 (38.2% (UI 29.0% - 46.1%) for 2000; and 26.6% (UI 10.3% - 40.2%) for 2012). Furthermore, there has been a decrease from 0.15% (UI 0.10% - 0.18%) to 0.12% (0.05% - 0.19%) in the percentage of all female deaths attributable to iron deficiency in SA between 2000 and 2012. Overall, 351 deaths, accounting for 0.07% of all deaths in SA in 2000, 452 deaths, or 0.07% of all deaths in SA in 2006, and 307 deaths, or 0.06% of all deaths in SA in 2012 were attributed to iron deficiency. All of the attributable deaths were due to maternal conditions in women of reproductive age (Table 2).

The total attributable burden to iron deficiency based on the DALY combining

the health loss from premature mortality and non-fatal outcomes provides a more comprehensive measure of disease burden relative to the number of deaths. From Table 2, it can be seen that the burden is higher in females than males across all three time periods. Fig. 2 shows the age distribution of burden attributable to iron deficiency (the risk factor) by related health outcome for years 2000, 2006 and 2012 for males and females. Attributable burden in males consists entirely of iron-deficiency anaemia (the condition), which is 100% attributable to iron deficiency (the risk factor) (Fig. 2A). The burden in males <15 years old, particularly 5 - 9 years, is considerably higher than in adult ages. Fig. 2B shows the female attributable DALY burden from maternal conditions and iron-deficiency anaemia by age group for the years 2000, 2006 and 2012. High burden of iron-deficiency anaemia for females extended through the adult ages. Attributable DALYs from maternal conditions in females were highest among the 25 - 34 years age group (9 220 DALYs) in 2006.

Fig. 3 shows the iron deficiency age-standardised attributable DALY rate by year. As there were no deaths from iron-deficiency anaemia, the YLD rates are the same as the DALY rates for males. The age-standardised death rate was highest in 2006 (1.7 per 100 000 population), with 452 maternal deaths that were probably due to the impact of HIV/AIDS on maternal mortality over the time period (Table 2).

The age-standardised DALY rates from iron-deficiency anaemia attributable to iron deficiency markedly decreased by 33% over time in males, and increased by 3% in females between 2000 and 2012. Furthermore, our analysis showed a 25.9% decrease between 2000 (1.5 per 100 000) and 2012 (1.1 per 100 000) in the age-standardised death rates from maternal conditions attributable to iron deficiency. The attributable death rate for females was calculated with a restricted numerator since we were looking at women of reproductive age, 15 - 49 years. However, there were deaths in the other age groups not included in this analysis (Table S4 in the appendix: <https://www.samedical.org/file/1819>).

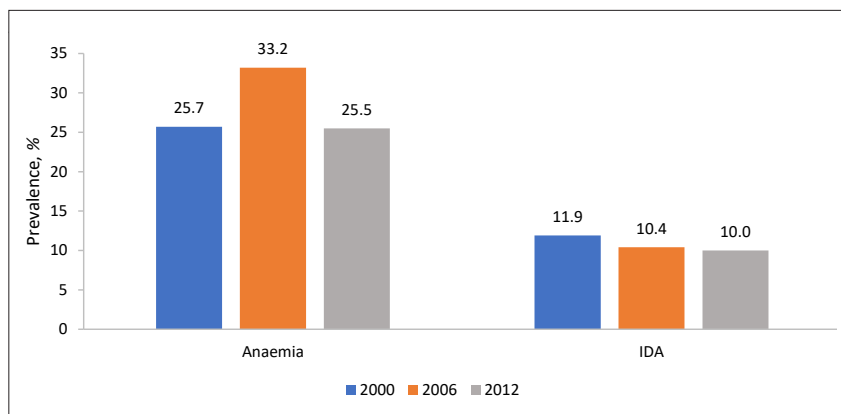


Fig. 1. Prevalence of anaemia and iron-deficiency anaemia among women of reproductive age for 2000, 2006 and 2012.

Table 1. Prevalence of anaemia and iron-deficiency anaemia among women of reproductive age in South Africa

Year	Age group (years)	Key parameters			
		Anaemia prevalence (%)	Mean (SD) Hb concentration in g/L	Iron-deficiency anaemia prevalence (%)	Proportion of anaemia due to iron deficiency (%)*
2000 ^[17]	15 - 49	25.7	12.7 (1.26)	11.9	46.3
2006 ^[20]	16 - 49	33.2	12.5 (1.55)	10.4	31.3
2012 ^[21]	16 - 35	25.5	12.9 (1.53)	10.0	39.2

SD = standard deviation; Hb = haemoglobin.

*The proportion of anaemia due to iron deficiency = anaemia prevalence ÷ iron deficiency anaemia prevalence; see Table S2 in appendix (<https://www.samedical.org/file/1819>) for data sources used.

Table 2. Disease burden attributable to iron deficiency in females, males and total persons in South Africa for 2000, 2006 and 2012

	Males			Females		Total persons	
	Attributable deaths, <i>n</i>	Attributable DALYs, <i>n</i>	AF (%) ^a	Attributable deaths, <i>n</i>	Attributable DALYs, <i>n</i>	Attributable deaths, <i>n</i>	DALYs, <i>n</i>
2000							
Maternal conditions (15 - 49 years)	-	-	38.2	351	16 011	351	16 011
Iron-deficiency anaemia (all ages)	-	108 478	100.0	-	136 031	-	244 509
Total burden (all ages)[†]	-	108 478	-	351	152 042	351	260 520
95% UI	-	(86 803 - 133 396)	-	(248 - 436)	(128 479 - 178 187)	(248 - 436)	(227 568 - 296 039)
% of total burden	-	1.12	-	0.15	1.62	0.07	1.36
95% UI	-	(0.90 - 1.38)	-	(0.10 - 0.18)	(1.37 - 1.89)	(0.05 - 0.09)	(1.19 - 1.55)
Iron-deficiency anaemia (children under 5 years)	-	30 041	100.0	-	29 770	-	59 812
% of total burden in children <5 years	-	1.68	-	-	1.81	-	1.75
95% UI	-	(1.09 - 2.41)	-	(0 - 0)	(1.21 - 2.54)	(0-0)	(1.31 - 2.24)
2006							
Maternal conditions (15 - 49 years)	-	-	28.5	452	19 242	452	19 242
Iron-deficiency anaemia (all ages)	-	112 753	100.0	-	149 067	-	261 820
Total burden (all ages)[†]	-	112 753	-	452	168 310	452	281 063
95% UI	-	(91 888 - 135 655)	-	(301 - 589)	(145 167 - 194 111)	(301 - 589)	(249 410 - 315 637)
% of total burden	-	0.92	-	0.14	1.30	0.07	1.11
95% UI	-	(0.75 - 1.11)	-	(0.09 - 0.18)	(1.12 - 1.50)	(0.04 - 0.09)	(0.99-1.25)
Iron-deficiency anaemia (children under 5 years)	-	29 648	100.0	-	29 694	-	59 342
% of total burden in children under 5 years	-	1.38	-	-	1.54	-	1.45
95% UI	-	(0.94 - 1.88)	-	-	(1.07 - 2.11)	-	(1.13 - 1.82)
2012							
Maternal conditions (15 - 49 years)	-	-	26.6	307	13 889	307	13 889
Iron-deficiency anaemia (all ages)	-	75 581	100.0	-	150 182	-	225 763
Total burden (all ages)[†]	-	75 581	-	307	164 070	307	239 652
95% UI	-	(58 878 - 95 431)	-	(118 - 470)	(141 045 - 188 800)	(118 - 470)	(210 474 - 270 930)
% of total burden	-	0.75	-	0.12	1.57	0.06	1.16
95% UI	-	(0.58 - 0.94)	-	(0.05 - 0.19)	(1.35 - 1.80)	(0.02 - 0.09)	(1.02 - 1.32)
Iron-deficiency anaemia (children under 5 years)	-	20 012	100.0	-	29 761	-	49 773
% of total burden in children under 5 years	-	1.51	-	-	2.42	-	1.95
95% UI	-	(1.01 - 2.12)	-	-	(1.69 - 3.24)	-	(1.50 - 2.44)

DALYs = disability-adjusted life years; AF = attributable fraction based on the numbers of attributable deaths; UI = uncertainty interval
^a100% of iron-deficiency anaemia is attributable to iron deficiency.
[†]Denominator is deaths and DALYs for all ages.

The DALY burden attributable to iron deficiency by health outcomes for 2000, 2006 and 2012 is presented in Fig. 4. Maternal conditions accounted for about 6% - 7% of the attributable burden, with iron-deficiency anaemia accounting for the rest across all three time periods.

In children, the burden attributable to iron deficiency consists entirely of the iron-deficiency anaemia burden, which is 100% attributable to this risk factor (Table 2). There has been a reduction in the attributable

age-specific DALY rates over time in under-5 children, and there were no significant differences between males and females (Fig. 5).

Discussion

In 2012, 94% of the burden attributable to iron deficiency was due to disability caused by iron-deficiency anaemia, with a large part of the burden experienced among children <15 years old and women of reproductive age. A similar pattern was also found for the earlier

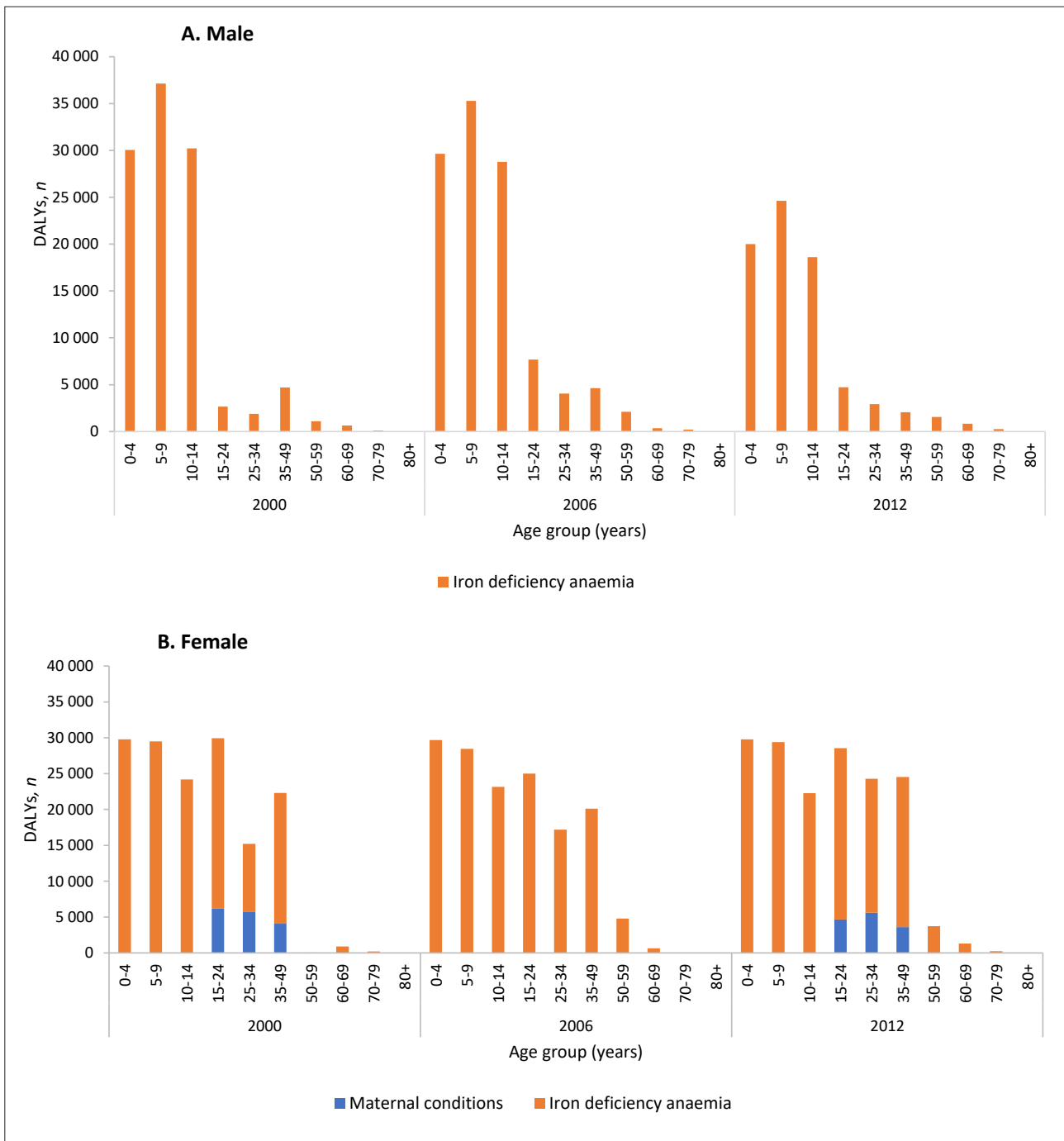


Fig. 2. Disability-adjusted life years (DALYs) attributable to iron deficiency by age, related health outcome and time period for (A) males and (B) females. Maternal conditions only reported for women of reproductive age (aged 15 - 49 years).

years. Compared with the level of the attributable burden in 2000, the age-standardised DALY rate increased slightly in 2006, and then declined in 2012, for both males and females.

Although there has been a slight decrease in the prevalence of iron deficiency anaemia in women of reproductive age, from about 11.9% in 2000 to 10.0% in 2012, the prevalence of overall anaemia in SA has changed over time (25.5% - 33.2%), with a peak in 2006. This increase in anaemia is possibly due to other causes such as HIV infection.^[3] Our anaemia prevalence estimates among women of reproductive age are similar to those reported in a local study by Sibeko *et al.*^[28] in 2004, conducted in a community health clinic in a Cape Town peri-urban settlement, and the South Africa Demographic and Health Survey

(SADHS) 2016,^[22] which reported prevalences of anaemia of 32% and 33.3%, respectively. Furthermore, it is estimated that ~40% (38.9%) of all anaemia in women of reproductive age in SA is associated with iron deficiency. Hence, if iron deficiency is eliminated, there will be a 40% reduction in the prevalence of anaemia among females aged 15 - 49 years in SA. This is similar to what was reported in the meta-analysis of national survey data from low- and middle-income countries by Petry *et al.*^[3] SACRA1^[17] reported an anaemia and iron deficiency anaemia prevalence of 30.4% and 12.2% respectively in pregnant females for SA in 2000.

The population attributable fraction for maternal conditions attributable to iron deficiency in SA has declined over time from

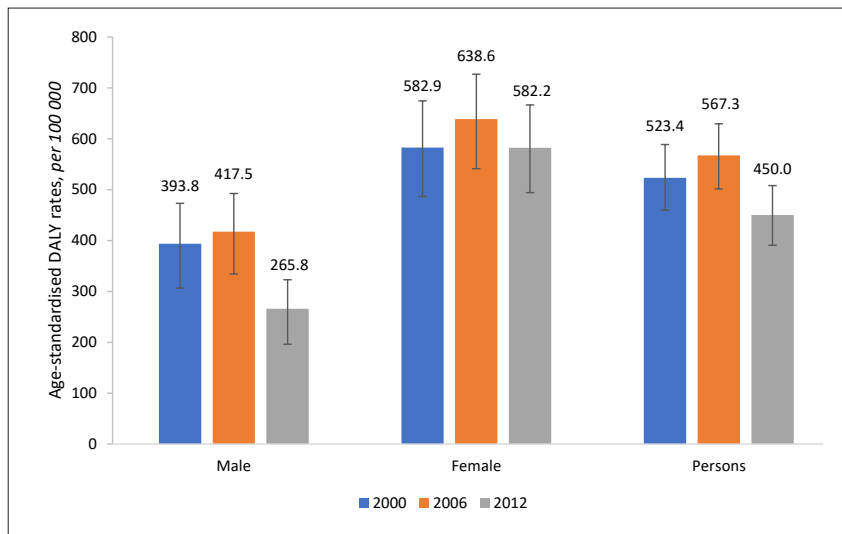


Fig. 3. Age-standardised disability-adjusted life year (DALY) rates (per 100 000) of total burden attributable to iron deficiency in all ages for 2000, 2006 and 2012.

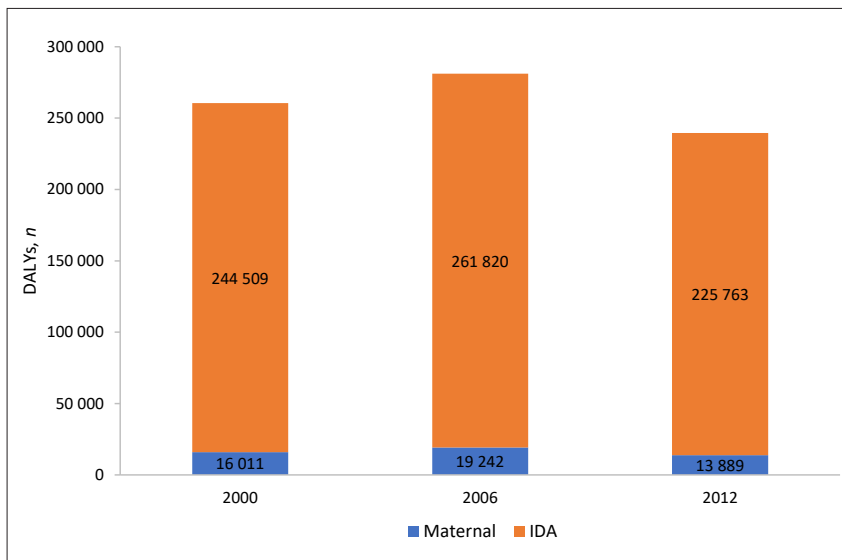


Fig. 4. Disability-adjusted life year (DALY) burden attributable to iron deficiency by health outcome for 2000, 2006 and 2012.

38.2% (95% UI 29.0 - 46.1%) in 2000 to 26.6% (95% UI 10.3 - 40.2%) in 2012. However, these estimates are higher than the GBD 2017 estimates of 27.2% (95% CI 10.6 - 43.9) in 2000 to 23.7% (95% CI 9.3 - 37.9%) in 2012,^[16] although they show a similar trend. Although our revised estimates of attributable deaths for 2000 (351 maternal deaths and 0.2% of all deaths) are higher than those estimated in SACRA1, they are similar to those estimated by the GBD 2017 study (392 maternal deaths (0.1% of all deaths) were attributable to iron deficiency for the year 2000 in SA). Overall, we observed a decline in the total deaths attributable to iron deficiency over time, but a peak in maternal deaths was observed in 2006. This peak in maternal deaths from iron deficiency in 2006 could possibly be

due to untreated HIV/AIDS. A report on confidential enquiries into maternal deaths in SA^[29] has reported a decrease in maternal deaths related to HIV/AIDS and obstetric haemorrhage over time. There were no deaths due to iron-deficiency anaemia in all ages, including children aged under 5 years in SA.

Globally, an estimated 1.2% of total DALYs (0.5% - 0.6% of total DALYs in SA from 2000 to 2012) are attributable to iron deficiency.^[24] Findings from our analysis show slightly higher estimates (1.1% - 1.4%) of attributable DALY burden in SA from 2000 to 2012. This is similar to the estimates (0.9% - 1.3%) reported in SACRA1. Globally, iron deficiency was the leading risk factor in the 10 - 24-year-olds, with an estimated 3.0% (2.3 - 3.8%) of DALYs attributable to

iron deficiency.^[24] In the current study, iron deficiency accounted for about 1.8% - 2.0% of total attributable DALYs in SA between 2000 and 2012 in children aged under 5 years.

Our study findings were based on analysis of available data, which were sparse, and the study has limitations. Few nationally representative estimates of anaemia and iron-deficiency anaemia were available, and there were no national estimates of iron-deficiency anaemia in pregnant women. Response rates in the SANHANES^[21] survey were extremely low and unequal across geographic and socioeconomic strata. Overall, valid Hb measurements were available for 32% of the eligible women of reproductive age who consented to giving a blood sample, while in only 27% of cases valid measurement of both Hb and ferritin were available. Response rates were significantly higher in rural formal areas (farms), at 47.1%, compared with 28.8% in urban formal areas. Whites (with a response rates of 11.2%) and Indians (16.7%) were greatly under-represented, and more unemployed women of reproductive age were represented than those employed. While the estimates were statistically adjusted to recalibrate the results to the total population based on sociodemographic variables, with this level of non-response we cannot exclude the presence in our results of significant residual bias. Furthermore, none of the included surveys adjusted for altitude and inflammation when reporting Hb and ferritin, respectively. This could result in underestimation of anaemia and iron-deficiency prevalence.

RR and non-fatal burden estimates were sourced from the GBD studies.^[16,19] Locally conducted epidemiological studies would be valuable in providing these estimates for more accurate local attributable burden estimation.

Of the 17 risk factors assessed in the SACRA1 study, iron deficiency was ranked 13th overall in terms of DALYs. Of the 18 risk factors assessed in the current CRA study, iron deficiency remained 13th overall in terms of DALYs and 18th overall for deaths, in 2012.^[30] Iron-deficiency anaemia remains of moderate public health importance (20% - 39.9%) for women and mild public health importance for men (5% - 19.9%) as reported in previous studies^[17,22] in SA.

There are guidelines in place in SA to address iron deficiency in pregnant women via iron supplementation.^[31] The 2016 SADHS^[22] reported that high proportions of women received iron supplementation during antenatal care for their last live

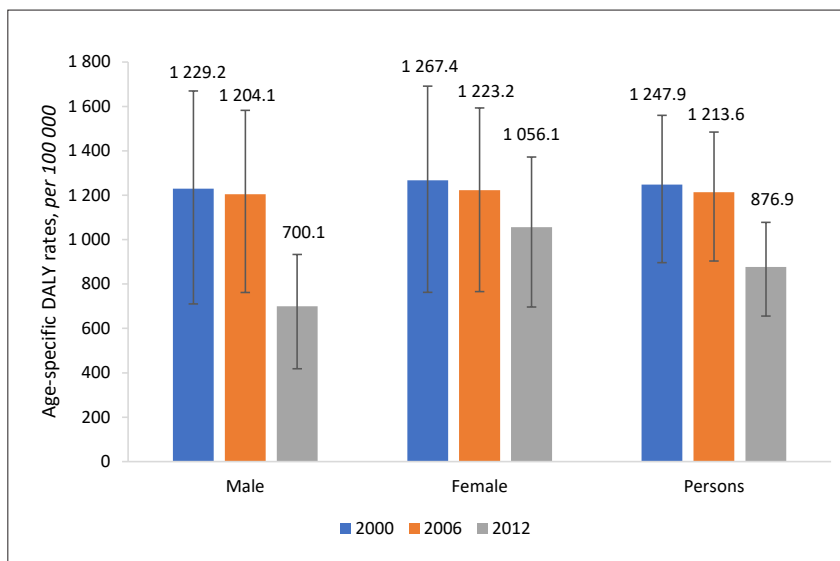


Fig. 5. Iron-deficiency attributable disability-adjusted life year (DALY) rates in children under 5 years for 2000, 2006 and 2012.

birth (90%). It is important to identify any gaps in this programme to further reduce the impact on maternal conditions. The recent WHO 2020 guidelines^[32] on multiple micronutrient supplementation (MMS) should be considered as part of antenatal care. In addition, there are currently no national guidelines/policies on iron supplementation in infants (except low-birthweight and preterm infants).^[33-35] Furthermore, there are very sparse data on anaemia and iron-deficiency prevalence in young infants (<6 months old). Interventions such as food fortification are not likely to have as much impact on younger infants as exclusive breastfeeding, formula feeding and iron supplementation (particularly in preterm and low-birthweight infants with low iron stores).^[15,36] Owing to the effect of inflammation on iron status,^[13] any underlying inflammation should be managed appropriately when implementing iron supplementation programmes. Furthermore, other non-nutritional interventions, such as delayed umbilical cord clamping, are also important to increase iron stores of infants by allowing more blood to be transferred to the newborn, and consequently preventing iron-deficiency anaemia in early infancy.^[15,36,37]

Conclusion

Iron-deficiency anaemia prevalence can be markedly reduced if iron deficiency is eliminated. Hence it is essential to encourage, reappraise and strengthen the measures that have been put in place to address iron deficiency, including food fortification and the iron supplementation

programme for infants >6 months of age and women of reproductive age. More research is needed to evaluate the performance and implementation of current policies (such as the updated WHO guidelines on MMS), so as to provide evidence on areas for improvement in these interventions. In addition, iron supplementation in young infants (<6 months of age) requires attention and policy direction. More research is also needed in the area of iron deficiency and iron-deficiency anaemia in children <6 months of age to guide these policies. Furthermore, the reported increase in anaemia prevalence in pregnant women that could possibly be due to other causes such as HIV infection, and its impact on this population, needs to be evaluated, including the role of antiretroviral therapy and dietary requirements of HIV-positive pregnant females.

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Conflicts of interest. None.

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