

# Estimating the changing disease burden attributable to raised low-density lipoprotein cholesterol in South Africa for 2000, 2006 and 2012

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**Background.** Low-density lipoprotein cholesterol (LDL-C) is the most important contributor to atherosclerosis, a causal factor for ischaemic heart disease (IHD) and ischaemic stroke. Although raised LDL-C is a key contributor to cardiovascular disease (CVD), the exact attributable disease risk in South Africa (SA) is unknown. The first SA comparative risk assessment (SACRA1) study assessed the attributable burden of raised total cholesterol, and not specifically LDL-C.

**Objectives.** To estimate the national mean serum LDL-C by age, year and sex and to quantify the burden of disease attributable to LDL-C in SA for 2000, 2006 and 2012.

**Methods.** The comparative risk assessment (CRA) method was used. Estimates of the national mean of LDL-C, representing the 3 different years, were derived from 14 small observational studies using a meta-regression model. A theoretical minimum risk exposure level (TMREL) of 0.7 - 1.3 mmol/L was used. LDL-C estimates together with the relative risks from the Global Burden of Disease Study 2017 were used to calculate a potential impact fraction (PIF). This was applied to IHD and ischaemic stroke estimates sourced from the Second National Burden of Disease Study. Attributable deaths, years of life lost, years lived with disability and disability-adjusted life years (DALYs) were calculated. Uncertainty analysis was performed using Monte Carlo simulation.

**Results.** LDL-C declined from 2.74 mmol/L in 2000 to 2.58 mmol/L in 2012 for males, while in females it declined from 3.05 mmol/L in 2000 to 2.91 mmol/L in 2012. The PIFs for LDL-C showed a slight decline over time, owing to the slight decrease in LDL-C levels. Attributable DALYs increased between 2000 ( $n=286\ 712$ ) and 2006 ( $n=315\ 125$ ), but decreased thereafter in 2012 ( $n=270\ 829$ ). Attributable age-standardised death rates declined between 2000 and 2012 in both sexes: in males from 98 per 100 000 members of the population in 2000 to 78 per 100 000 in 2012, and in females from 81 per 100 000 in 2000 to 58 per 100 000 in 2012.

**Conclusions.** Mean LDL-C levels were close to 3 mmol/L, which is the recommended level at which cholesterol-lowering treatment should be initiated for people at low and moderate risk for cardiovascular outcomes. The decreasing trend in the age-standardised attributable burden due to LDL-C is encouraging, but it can be lowered further with the introduction of additional population-based CVD prevention strategies. This study highlights the fact that high LDL-C concentration in relation to the TMREL in SA is responsible for a large proportion of the emerging CVD, and should be targeted by health planners to reduce disease burden.

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**Evidence before the study.** The exact contribution of raised low-density lipoprotein cholesterol (LDL-C) – that is, the attributable disease risk in South Africa (SA) – has not been established. The previous SA comparative risk assessment (SACRA1) study assessed the attributable burden of raised total cholesterol and not specifically LDL-C. This is also the first study to estimate national levels and trends of LDL-C in SA; only a single survey previously measured LDL-C nationally.

**Added value of the study.** This study applied CRA methodology for three time points: 2000, 2006 and 2012. Estimates of the national mean of LDL-C were derived from 14 observational studies using a meta-regression model. A uniform theoretical minimum risk exposure distribution between 0.7 mmol/L and 1.3 mmol/L was used. Epidemiological evidence of the relative risks of ischaemic heart disease and ischaemic stroke from raised LDL-C were drawn from the Global Burden of Disease studies. The present study revealed a decline in LDL-C from 2.74 mmol/L in 2000 to 2.58 mmol/L in 2012 for males, while in females it declined from 3.05 mmol/L in 2000 to 2.91 mmol/L in 2012. The attributable age-standardised rate (ASR) due to raised LDL-C declined between 2000 and 2012 in both sexes: in males from 98 per 100 000 members of the population in 2000 to 78 per 100 000 in 2012, and in females from 81 per 100 000 in 2000 to 58 per 100 000 in 2012.

**Implications of all available evidence.** This study indicates that a substantial part of the cardiovascular mortality and morbidity in SA can be attributed to high LDL-C. If mean population LDL-C values can be lowered further with the introduction of additional population-based CVD prevention strategies, this would likely translate to lower CVD in SA. Regular surveillance of national LDL-C levels is required to guide CVD policies and programmes, and to monitor the impact of such strategies.

Cholesterol, an essential element of cell membrane structure,<sup>[1]</sup> plays a key role in the development of atherosclerosis, which is the accumulation of fatty deposits in the lining of arteries. Subsequent plaque formation and thrombosis leads to blood vessel occlusion and, if the relevant vessels are affected, ischaemic heart disease (IHD) and cerebrovascular disease (stroke).<sup>[1]</sup> Atherosclerosis develops over a lifetime, with the process accelerating in the presence of other cardiovascular disease (CVD) risk factors such as hypertension, smoking, diabetes mellitus and obesity.<sup>[2]</sup> The risk of atherosclerosis and subsequently developing IHD, stroke and other vascular diseases increases with age and, in developing regions such as South Africa (SA), frequently strikes working-age individuals who are family breadwinners. This exacerbates poverty and impacts productivity, which is especially relevant in SA with its struggling economy.

Total cholesterol (TC) consists of three major components: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and very low-density lipoprotein cholesterol (VLDL-C).<sup>[3]</sup> The main contributor to atherosclerosis is LDL-C, and this is the focus of dyslipidaemia management.<sup>[4]</sup> While LDL-C carries most cholesterol from the liver to peripheral tissues, HDL-C, in contrast, removes excess cholesterol from cells and returns it to the liver, thereby playing a protective role in preventing atherosclerosis.<sup>[1,3]</sup>

The need to initiate dyslipidaemia treatment is determined by CVD risk status, which is based on the predicted 10-year risk of developing CVD, calculated using age, gender, smoking status and TC in an algorithm.<sup>[4]</sup> Optimal treatment of dyslipidaemia is vital considering that this can substantially reduce CVD risk. A meta-analysis of statin trials showed that every 1 mmol/L reduction in serum LDL-C levels reduces the risk of major coronary events by 24%, stroke by 15% and the combination of coronary events and stroke by 22%.<sup>[5]</sup>

In SA, stroke and IHD are among the leading causes of death, ranking second and third, respectively, using the age-standardised death rate as a measure.<sup>[6]</sup> This underscores the need to determine the contribution of dyslipidaemia, a key CVD risk factor, to the development of these diseases in the country. Following the comparative risk assessment (CRA) methodology of the World Health Organization (WHO), the first SA CRA study (SACRA1)<sup>[7]</sup> used raised TC to estimate the attributable burden of dyslipidaemia, because of a dearth of population-level studies on LDL-C for 2000, and also for comparison with the WHO estimates, which also used TC as a risk factor.<sup>[3,7]</sup> The analysis was conducted by population group and highlighted a substantial burden attributable to this risk factor, as well as significant differences between population groups, with the age-standardised cholesterol-attributable death rate for black Africans much lower than for other population groups.<sup>[7]</sup>

The shortcoming of this approach, however, was highlighted in a study that showed no change in mean TC levels between 1990 and 2008/2009 in an urban SA population, but a significant rise in LDL-C levels and reduced HDL-C concentrations.<sup>[8]</sup> The focus on LDL-C rather than TC improves the policy relevance of estimates, since LDL-C is the key target for cholesterol-lowering medications: it is the most commonly used biomarker for clinical decision-making.<sup>[9]</sup> This change in focus is reflected in the use of LDL-C instead of TC in the Global Burden of Disease (GBD) Study 2017.<sup>[9]</sup> The GBD study estimated the relative risks (RRs) of developing IHD and ischaemic stroke due to high LDL-C levels. This study showed that high LDL-C levels were among the leading risk factors for all-cause risk-attributable burden in 2017, and that it gained prominence between 1990 and 2017 in low-income settings.

The exact contribution of raised LDL-C – that is, the attributable disease risk in SA – has not been established. Recently, nationally representative data and several regional studies on LDL-C levels

have become available in SA. This enables the investigation of temporal trends in population LDL-C levels, and the associated risk on cardiovascular outcomes.<sup>[10]</sup> This is important considering that the country is experiencing an epidemiological transition towards non-communicable diseases including CVD,<sup>[11]</sup> and a nutrition transition towards greater intake of fats and processed foods,<sup>[12]</sup> which contribute to dyslipidaemia. Such assessments will provide important guidance for policy and priority setting related to disease prevention in the country.

Therefore, the aim of the present study was to estimate the national mean serum LDL-C by age, year and sex. We also aimed to quantify the burden of disease attributable to LDL-C in persons  $\geq 25$  years by sex and age group in SA for 2000, 2006 and 2012, and to investigate trends over time.

## Methods

The GBD CRA methodology was used, which estimates the disease burden attributable to a risk factor if exposure were shifted to a counterfactual scenario of theoretical minimum risk exposure level (TMREL).<sup>[13]</sup> Attributable burden was estimated by multiplying the potential impact fractions (PIFs) with the total disease burden due to a specific cause. A PIF requires estimates on the level of risk factor exposure and relative risk (RR) of the outcome associated with the risk. It is defined as the proportion by which the outcome would be reduced in a given population and in a given year, if the exposure to a risk factor in the past were reduced to the counterfactual level of the TMREL.

### Exposure variable

The mean population concentration of serum LDL-C was defined as a continuous variable expressed in millimoles per litre of serum (mmol/L) with the standard deviation (SD) used as the measure of variability around the mean. This is estimated by population group because of known correlations with lifestyle, culture and socioeconomic conditions that impact on health and health-related behaviours. The population group classification is based on self-reporting according to the Apartheid-era groups defined by the Population Registration Act of 1950, i.e. black African, coloured, Indian/Asian and white.

### Mean LDL-C and SD

A total of 14 population-based studies<sup>[8,10,14-25]</sup> were identified for inclusion through the extraction of literature on LDL-C in SA from a pan-African systematic review on the prevalence of dyslipidaemia between 1980 and 2017,<sup>[26]</sup> as well as a complementary Medline search and a search of references from identified literature (Table 1). Studies were excluded when they did not report mean serum LDL-C concentrations, participants were on cholesterol-lowering treatment or the sample consisted of participants with familial hypercholesterolaemia, sample size was  $< 100$ , a subclass of LDL-C was measured instead of LDL-C, age was not split into groups or LDL-C was not measured at baseline in prospective cohort studies.

The identified studies were used to estimate mean serum LDL-C and SD by year, age and sex. Only one study from 2012 presented nationally representative estimates of LDL-C in SA.<sup>[10]</sup> Mean serum LDL-C was reported in each study, except three<sup>[14-16]</sup> for which we used the Friedewald equation<sup>[27]</sup> to calculate LDL-C:

$$LDL-C = TC - \left( HDL-C + \frac{TG}{2.2} \right)$$

where *LDL-C* refers to low-density lipoprotein cholesterol, *TC* refers to total cholesterol, *HDL-C* refers to high-density lipoprotein cholesterol and *TG* refers to triglycerides.

**Table 1. Data source of mean LDL-C by location, population group and year of data collection**

Study population	Study design (age range in years)	Year of data collection	n	Method for determining LDL-C
<b>2000</b>				
KwaZulu-Natal (urban, Asian) <sup>[14]</sup>	Household survey (15 - 69)	1985	778	Blood was drawn from fasting samples, and the CHOD-PAP enzymatic method was used to determine serum cholesterol and HDL-C, while TG tests were performed using the GPO-PAP enzymatic colorimetric method. We used the Friedewald equation to determine LDL-C from the HDL-C, TC and TG levels provided in the article.
KwaZulu-Natal (urban, black African) <sup>[15]</sup>	Cross-sectional sample of patients attending a dental clinic (16 - 69)	1986	371	Same method as described above.
KwaZulu-Natal (urban, white) <sup>[16]</sup>	Household survey (15 - 69)	1988	386	Same method as described above.
KwaZulu-Natal (Rural and urban, black African) <sup>[17]</sup>	Household survey (>25)	1989	1 611	TC and HDL-C (after precipitation using phosphotungstate-MgCl) tests were performed on fasting blood samples using the cholesterol esterase oxidase peroxidase method. Serum TG was measured using the lipoprotein lipase glycerokinase peroxidase method. The authors used the Friedewald equation to determine LDL-C.
Western Cape (urban, black African) <sup>[18]</sup>	Cross-sectional study of 7 black residential areas (15 - 64)	1990	986	Plasma TC and HDL-C (after precipitation with heparin/manganese chloride) from non-fasting samples were measured using the CHOD-PAP enzymatic method, while TG tests were performed using the Boehringer Mannheim enzymatic Peridochrom method. The authors used the Friedewald equation to determine LDL-C from the HDL-C, TC and TG levels provided in the paper.
Western Cape (rural, coloured) <sup>[19]</sup>	Household survey (>15)	1996	974	TC and HDL-C (after precipitation using magnesium-dextran sulphate) tests were performed on fasting blood samples using the cholesterol esterase spectrophotometric method. Serum TG was measured using an enzymatic spectrophotometric technique. The authors used the Friedewald equation to determine LDL-C.
Limpopo (rural, black African) <sup>[20]</sup>	Cross-sectional study (>30)	1997	1 360	Analyses were performed on fasting blood samples. No information is provided on the method to determine TC, HDL-C and TG. The authors used the Friedewald equation to determine LDL-C.
<b>2006</b>				
KwaZulu-Natal (urban, Asian) <sup>[25]</sup>	Cross-sectional study (15 - 64)	2007	1 428	Laboratory techniques were used to determine TC, HDL-C and TG analysis. The authors used the Friedewald equation to determine LDL-C.
Western Cape (urban, black African) <sup>[8]</sup>	Cross-sectional study (25 - 74)	2008	1 099	HDL-C was determined from fasting blood samples using cholesterol AE-12 reagent comprising magnesium chloride and phosphotungstic acid. There is no indication how TC and TG were determined. The authors used the Friedewald equation to determine LDL-C.
<b>2012</b>				
National estimate <sup>[10]</sup>	Nationally representative household survey (>15)	2012	5 478	Automated laboratory techniques were used for lipid biomarker analysis, including LDL-C, but no information is provided on the method. There is also no indication whether fasting blood samples were collected.
Gauteng (urban, black African) <sup>[21]</sup>	Cross-sectional study (40 - 60 years)	2012	702	The ADVIA 1800 chemistry system was used to measure TC, HDL-C and TG from fasting blood samples. LDL-C was estimated using the Friedewald formula.
Mpumalanga (rural, black African) <sup>[22]</sup>	Cross-sectional survey (>40)	2015	3 841	Lipid levels (TC, HDL-C, TG and LDL-C) were laboratory tested (Cardiocheck PA Silver version; Indianapolis, Indiana, USA) on fasting blood samples.
North-West (urban, black African and white) <sup>[24]</sup>	Cross-sectional survey (20 - 30)	2015	761	TC, HDL-C and LDL-C were laboratory tested on fasting blood samples but there is no mention of the method that was used.
Limpopo (rural, black African) <sup>[23]</sup>	Cross-sectional survey (18 - 30)	2015	624	Enzymatic assay kits on a Beckman LX20 autoanalyzer (Beckman Coulter, Fullerton, CA) were used to measure TC, HDL-C and TG on fasting blood samples. LDL-C was calculated using the Friedewald formula.

LDL-C = low-density lipoprotein cholesterol; CHOD-PAP = cholesterol oxidase phenol 4-aminoantipyrine; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; GPO-PAP = glycerol-3-phosphate oxidase-p-aminophenazone; TC = total cholesterol.

This equation can be used to impute LDL-C at the population level when estimates on TC, HDL-C and TG are available.

A fixed-effect generalised additive meta-regression (GAM) model was fitted to the available data separately by sex. The mean LDL-C estimate for each study was used as the outcome, and year of data collection the middle point of the age category (modelled as cubic spline with a single internal knot), with the population group (urban black African, rural black African, white, coloured and Asian) and their interactions as independent variables.

The model was fitted by maximum likelihood, and each data point was weighted according to the inverse variance of the individual estimates. The results were used to predict the mean LDL-C for each age category (25 - 34, 35 - 44, 45 - 54, 55 - 64, ≥65 years), sex and population group by year (Fig. S1 in the appendix: <https://www.samedical.org/file/1840>). A national estimate by age category and sex was calculated as a weighted average of the estimates in each population group, with weights given by the population size in each group.<sup>[28]</sup> Urban/rural proportions in each year were sourced from the World Bank estimates for the whole population of SA, and assumed to be approximately valid also for the black African population group.<sup>[29]</sup>

Uncertainty intervals (UIs) for the national estimates were calculated by simulation. This was done by randomly drawing 10 000 samples from the distribution of the group-specific estimates, calculating their weighted average and considering the 2.5th and 97.5th percentile of the distribution of the results across the replicates as the lower and upper bounds of the 95% UI.

A similar model was fitted to predict the SD of the LDL-C distribution for each age category, sex, and population group by year and to recover national estimates (appendix Table S2: <https://www.samedical.org/file/1840>). The logarithm of the SD was used as the outcome of the GAM, and the results were back-transformed into the natural scale at the end of the procedure.

### Regression dilution correction factors

Measurement of lipids in observational studies is prone to random fluctuations. Therefore, lipid values can be subject to error if based on a single measurement. This effect is known as regression dilution bias. On a single measurement, lipid values tend to be extreme, with a wider distribution than the 'usual' exposure values. There is a 'regression to the mean' of values with repeated measurements whereby values are less extreme. This imprecision is accounted for in the estimates of RR and needs also to be reflected in a narrower distribution around the mean. The extent of regression dilution bias can be quantified using repeated measurement. A meta-analysis of prospective cohort studies obtained a regression dilution factor of 0.64 for LDL-C after repeated measurement at baseline and during duration of follow-up from a total of 44 234 participants.<sup>[30]</sup> This factor was applied to the SD by age and sex to correct for regression dilution bias in this study.

### Theoretical minimum risk exposure level

A theoretical minimum risk exposure distribution uniform between 0.7 mmol/L and 1.3 mmol/L was used. This risk exposure level for LDL-C is based on evidence from a meta-analysis of randomised controlled trials where participants were placed on statin treatment and followed up for cardiovascular events for more than 2 years after trial initiation.<sup>[31]</sup> The trial showed that at very low levels of LDL-C (≤1.3 mmol/L) there was a significant reduction in cardiovascular events (adjusted hazard ratio of 0.81, 95% confidence interval (CI) 0.70 - 0.95), even when compared with low levels (1.94 - 2.58 mmol/L).

### Relative risks

RRs from the GBD 2017 study for ages ≥25 years were used (Table 2).<sup>[27]</sup> Deaths attributable to high LDL-C levels are scarce at younger ages, and therefore the population attributable fraction due to high LDL-C was not considered for estimation in those <25 years. The GBD RRs were considered to be the same for mortality and morbidity outcomes for IHD and ischaemic stroke, and were applied over each year of assessment (2000, 2006 and 2012).

### Related outcomes

IHD (ICD-10 codes I24 - I25) and ischaemic stroke (ICD-10 codes I64 - I65) were used as the disease outcomes for those with high LDL-C levels. These outcomes were also used by the GBD 2017 study, which used the World Cancer Research Fund (WCRF) inclusion criteria for risk-outcome pairs. The WCRF framework uses a grading system based on different levels of evidence to include risk-outcome pairs, i.e. convincing evidence, probable evidence, possible evidence and insufficient evidence. To be included, the risk-outcome pair must meet the grades of convincing evidence or probable evidence.<sup>[27]</sup>

### Potential impact fraction calculation

Customised Excel 2016 (Microsoft Corp., USA) spreadsheets adapted from the SACRA1 study were used to calculate, for each of the two outcomes *o*, age group *a*, sex *s* and year *y*, the population-attributable burden of LDL-C, in terms of PIF:

$$PIF = \frac{\int_{x=0.1}^{10} RR_{obs}(x) \cdot P_{asy}(x) \cdot dx - \int_{x=0.1}^{10} RR_{obs}(x) \cdot PTMREL(x) \cdot dx}{\int_{x=0.1}^{10} RR_{obs}(x) \cdot P_{asy}(x) \cdot dx}$$

where  $RR_{obs}(x) = RR$  for health outcome *o*, age group *a* and sex *s* as a function of the LDL-C level *x*, as reported in Table 1;  $P_{asy}(x)$  = distribution of exposure in age group *a*, sex *s* and year *y*; and  $PTMREL(x)$  = counterfactual distribution of exposure (assumed the same across all age groups, sexes and years) conferring the lowest possible risk.

TC levels follow a skewed distribution to the right that can best be modelled with a lognormal distribution. The mean and SD of the lognormal distribution within each age-sex group were calculated using the method of moments. For this continuous lognormal risk factor distribution, the PIF was estimated by calculating the integral of the product of the risk factor distribution and the corresponding RR function using the integral function in EpigearXL, an add-on for Excel that performs numerical integration. The lower and upper integration limits (0.1 and 10 mmol/L, respectively) were chosen to represent the range of physiologically plausible values, and encapsulate the conditions of hypobetalipoproteinaemia and familial hypercholesterolaemia for the serum concentration of LDL-C. However, familial hypercholesterolaemia was excluded for consideration owing to its high risk of death from vascular disease compared with age- and sex-matched peers.<sup>[32]</sup>

### Burden estimation

The burden of disease due to LDL-C was calculated by multiplying the PIFs with estimates of deaths, years of life lost (YLLs), years lived with disability (YLDs) and disability-adjusted life years (DALYs) from IHD and ischaemic stroke, by year and sex. These estimates were sourced from the Second SA National Burden of Disease Study (SANBD2).<sup>[6]</sup> The SANBD2 list of causes does not distinguish between the different stroke subtypes; therefore, the proportion of total stroke due to ischaemic stroke was calculated by using the GBD



ratio of ischaemic stroke to total stroke for SA. The proportion of the total burden attributable to LDL-C was also calculated, as was the age-standardised rate (ASR) for deaths and DALYs. To calculate attributable ASRs, we used the mid-year population estimates from Dorrington<sup>[28]</sup> and the WHO standard population.<sup>[33]</sup>

**Uncertainty estimation**

Monte Carlo simulation techniques were used to calculate uncertainty around point estimates using Ersatz software version 1.35 for Excel (Epigear, Australia). Ersatz adds a range of functions to Excel that offer statistical distributions, the ability to draw randomly from these distributions, and repeating calculations multiple times, choosing a different set of random values from predefined distributions of the input variables.

A normal distribution was specified for the mean of the population distribution of the exposure and for the regression dilution factor. For RR estimates we used the Ersatz function ErRelative Risk.<sup>[34]</sup> For the attributable burden and the proportion of attributable burden relative to total burden, 2 000 replicated calculations were used to calculate the 95% UI bounded by the 2.5th and 97.5th percentiles.

**Results**

For males, the estimates of mean serum LDL-C concentrations increased by 14% and 11% in 2000 and 2006, respectively, between the ages of 25 and 64 years, and attenuated by 1% and 2% for those aged ≥65 years in 2000 and 2006, respectively. The patterns were similar in 2012 but peaked in a slightly younger age group (45 - 54 years) and then decreased in the older age groups (Table 3). The pattern for females was slightly different, since mean LDL-C did not attenuate after age 65 in 2000 and 2006 but did so by 2% in 2012. Mean LDL-C values in females >45 years were ≥3 mmol/L in all years. Females across all age groups had higher mean LDL-C levels compared with males for all years.

There was a small decrease in mean LDL-C levels in both sexes, from 2.74 mmol/L in 2000 to 2.58 mmol/L in 2012 for males, and from 3.05 mmol/L in 2000 to 2.91 mmol/L in 2012 for females (Fig. 1).

The attributable ASR for deaths and DALYs declined between 2000 and 2012 in both sexes (Fig. 2). Deaths declined by 21% from 98 per 100 000 population in 2000 to 78/100 000 in 2012 for males, and by 28% from 81/100 000 in 2000 to 58/100 000 in 2012 for females. Between 2000 and 2012, the ASR for DALYs also declined, by 21% from 1 739/100 000 to 1 377/100 000 for males and by 27% from 1 444/100 000 to 1 047/100 000 for females.

Males had a higher death and DALY ASR compared with females across all years. The male to female ratio for deaths and DALY ASRs were similar: 1.20 in 2000 for both deaths and DALYs, 1.27 and 1.24 in 2006 for deaths and DALYs, respectively, and 1.33 and 1.31 in 2012 for deaths and DALYs, respectively.

The pattern of the attributable ASR deaths and DALYs for the ≥50 year age category was similar to the ≥25 year age category. The ASR deaths were 2.2 and 2.3 times higher in the ≥50 year age category for males and females, respectively, ranging between 2000 and 2012 from 215/100 000 to 173/100 000 for males and 188/100 000 to 136/100 000 for females (appendix Fig. S2: <https://www.samedical.org/file/1840>). The ASR DALYs was also higher (2.3 times for males and 2.1 for females) for the ≥50 year age category, ranging between 2000 and 2012 from 3 312/100 000 to 2 700/100 000 for males and 2 961/100 000 to 2 165/100 000 for females.

For males, the attributable deaths peaked in the ≥80 year age group across all years, and was also high between the ages of 50 and 64 years (Fig. 3). IHD was the main contributor across all groups, and there was not much change in pattern across the different years for males.

The attributable deaths for females increased with age, with deaths in the ≥80 year age group being particularly high compared with the other age groups. IHD contributes to most deaths across all age categories, and this pattern was maintained across all years for females.

The contribution of IHD and ischaemic stroke to the attributable DALYs due to high LDL-C is shown by year and cause in Fig. 4. The attributable DALYs increased between 2000 (*n*=286 712) and 2006 (*n*=315 125), and decreased thereafter in 2012 (*n*=270 829). The proportional contribution of IHD and ischaemic stroke remained steady between 2000 and 2012, with IHD contributing about three-quarters of the attributable burden.

The total estimated deaths due to raised LDL-C levels for males was 7 344 (95% UI 6 256 - 8 307) in 2000, 7 977 (95% UI 6 743 - 9 105)

**Table 2. Relative risks by age and disease outcome**

Age group (years)	Ischaemic heart disease		Ischaemic stroke	
	RR	95% CI	RR	95% CI
25 - 29	2.016	1.684 - 2.544	1.670	1.334 - 2.339
30 - 34	2.027	1.768 - 2.354	1.626	1.352 - 2.041
35 - 39	2.038	1.831 - 2.273	1.583	1.342 - 1.849
40 - 44	1.971	1.775 - 2.198	1.518	1.287 - 1.760
45 - 49	1.828	1.676 - 2.004	1.434	1.242 - 1.636
50 - 54	1.685	1.561 - 1.815	1.350	1.212 - 1.514
55 - 59	1.541	1.446 - 1.648	1.265	1.164 - 1.391
60 - 64	1.398	1.306 - 1.494	1.181	1.109 - 1.299
65 - 69	1.254	1.141 - 1.372	1.096	1.043 - 1.223
70 - 74	1.193	1.088 - 1.312	1.062	1.008 - 1.193
75 - 79	1.213	1.124 - 1.321	1.077	1.012 - 1.216
≥80	1.262	1.110 - 1.465	1.116	1.014 - 1.344

RR = relative risk; CI = confidence interval. Source: Global Burden of Disease Study 2017.<sup>[27]</sup>

**Table 3. Estimates of mean serum LDL-C (mmol/L) for South Africa by age, sex and year**

Sex	Parameter	Age group (years)				
		25 - 34	35 - 44	45 - 54	55 - 64	≥65
<b>2000</b>						
Male						
	Mean	2.56	2.76	2.89	2.92	2.89
	SD	0.94	1.04	1.10	1.07	1.02
Female						
	Mean	2.73	3.01	3.23	3.37	3.44
	SD	0.86	0.98	1.07	1.11	1.15
<b>2006</b>						
Male						
	Mean	2.50	2.70	2.79	2.78	2.71
	SD	0.85	0.99	1.06	1.04	0.97
Female						
	Mean	2.71	2.97	3.14	3.23	3.22
	SD	0.81	0.95	1.05	1.07	1.08
<b>2012</b>						
Male						
	Mean	2.46	2.65	2.71	2.64	2.53
	SD	0.78	0.97	1.08	1.05	0.99
Female						
	Mean	2.69	2.95	3.08	3.07	3.02
	SD	0.77	0.96	1.07	1.09	1.09

LDL-C = low-density lipoprotein cholesterol; SD = standard deviation.

Table 4. Burden attributable to raised low-density lipoprotein cholesterol in the SA population aged ≥25 years by sex for 2000, 2006 and 2012

Disease outcome	Males			Female			Persons		
	AF (%)	Deaths, n	DALYs	AF (%)	Deaths, n	DALYs	AF (%)	Deaths, n	DALYs
<b>2000</b>									
IHD	47	5 912	115 253	49	5 686	103 297	48	11 598	218 551
Ischaemic stroke	23	1 431	26 686	25	2 457	41 475	24	3 889	68 162
<b>Total</b>	-	<b>7 344</b>	<b>141 940</b>	-	<b>8 143</b>	<b>144 773</b>	-	<b>15 487</b>	<b>286 712</b>
95% UI	-	6 256 - 8 307	124 444 - 156 590	-	6 472 - 9 585	122 951 - 163 479	-	12 795 - 17 832	248 611 - 319 959
% of total burden	-	<b>2.76</b>	<b>1.47</b>	-	<b>3.42</b>	<b>1.54</b>	-	<b>3.07</b>	<b>1.50</b>
95% UI	-	2.35 - 3.12	1.29 - 1.62	-	2.71 - 4.02	1.31 - 1.74	-	2.53 - 3.53	1.30 - 1.68
<b>2006</b>									
IHD	44	6 510	128 271	47	6 121	114 451	45	12 632	242 722
Ischaemic stroke	22	1 467	27 182	23	2 628	45 222	22	4 095	72 404
<b>Total</b>	-	<b>7 977</b>	<b>155 453</b>	-	<b>8 749</b>	<b>159 672</b>	-	<b>16 727</b>	<b>315 125</b>
95% UI	-	6 743 - 9 105	135 366 - 173 116	-	6 983 - 10 292	136 292 - 180 685	-	13 841 - 19 365	273 284 - 352 169
% of total burden	-	<b>2.32</b>	<b>1.27</b>	-	<b>2.62</b>	<b>1.23</b>	-	<b>2.47</b>	<b>1.25</b>
95% UI	-	1.97 - 2.65	1.10 - 1.41	-	2.09 - 3.08	1.05 - 1.39	-	2.04 - 2.86	1.08 - 1.40
<b>2012</b>									
IHD	42	5 479	110 328	44	5 094	94 997	43	10 573	205 325
Ischaemic stroke	19	1 316	24 216	21	2 441	41 289	20	3 757	65 504
<b>Total</b>	-	<b>6 795</b>	<b>134 544</b>	-	<b>7 536</b>	<b>136 286</b>	-	<b>14 330</b>	<b>270 829</b>
95% UI	-	5 589 - 7 850	114 622 - 151 090	-	5 666 - 9 106	112 499 - 156 501	-	11 407 - 16 865	228 353 - 306 266
% of total burden	-	<b>2.46</b>	<b>1.33</b>	-	<b>2.98</b>	<b>1.30</b>	-	<b>2.71</b>	<b>1.32</b>
95% UI	-	2.02 - 2.84	1.13 - 1.49	-	2.24 - 3.61	1.08 - 1.50	-	2.16 - 3.19	1.11 - 1.49

DALYs = disability-adjusted life-years; PAF = population attributable fraction calculated by adding attributable deaths across ages ≥25 years divided by total deaths; IHD = ischaemic heart disease; UI = uncertainty interval.

in 2006 and 6 795 (95% UI 5 589 - 7 850) in 2012 (Table 4). IHD contributed to most of the attributable deaths across all years in both males (>80%) and females (>68%) (Table 3). The attributable DALYs due to IHD and ischaemic stroke followed a similar pattern to the deaths, with IHD contributing to a larger proportion of attributable DALYs in males (>81%) than females (>70%) across all years. Total attributable deaths for females were higher across all years, and followed a similar pattern to that of males.

Similar to the deaths, the total attributable DALYs due to raised LDL-C were highest in 2006 at 155 453 (95% UI 135 366 - 173 116) and 159 672 (95% UI 136 292 - 180 685) DALYs for males and females, respectively, and lowest in 2012 at 134 544 (95% UI 114 622 - 151 090) and 136 286 (95% UI 112 499 - 156 501) for males and females, respectively. For males the proportion of all deaths attributable to LDL-C was lowest in 2006 at 2.32% (95% UI 1.97% - 2.65%) and highest in 2000 at 2.76% (95% UI 2.35% - 3.12%). The pattern was similar for females, at 2.62% (95% UI 2.09% - 3.08%) in 2006, and 3.42% (95% UI 2.71% - 4.02%) in 2000. For DALYs, the attributable burden due to LDL-C was highest in 2000 at 1.47% (95% UI 1.29 - 1.62) and 1.54% (95% UI 1.31% - 1.74%) for males and females, respectively, while it was lowest in 2006 at 1.27% (95% UI 1.10% - 1.41%) and 1.23% (95% UI 1.05% - 1.39%) for males and females, respectively.

## Discussion

This is the first study to estimate national levels and trends of LDL-C in SA by pooling data from 14 studies to provide a best estimate: only a single survey previously measured LDL-C nationally.<sup>[10]</sup> In comparison with the SACRA1 study, the method was enhanced in this study by using more local population data and focusing on LDL-C rather than TC, since LDL-C is the preferred biomarker for clinical decision-making. Using these data, the burden of disease attributable to LDL-C was estimated over three time points and by sex.

The age-standardised attributable deaths and DALYs due to LDL-C dropped between 2006 and 2012, which coincided with a decline in ASRs of IHD deaths (from 149/100 000 population in 2006 to 119/100 000 in 2012) and ischaemic stroke deaths (from 100/100 000 population in 2006 to 91/100 000 in 2012) for people aged >25 years.<sup>[6]</sup> There are other risk factors that contribute to IHD and ischaemic stroke, hence the drop in ASRs attributable to LDL-C should be interpreted with caution. In contrast, the global attributable ASR due to LDL-C remained stable at 54/100 000

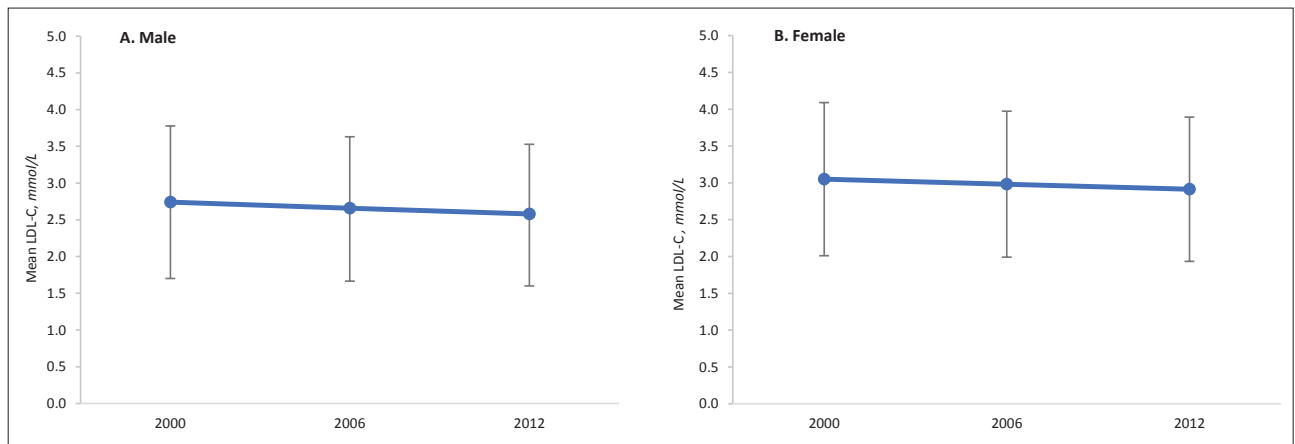


Fig. 1. Mean serum low-density lipoprotein cholesterol (LDL-C) trend for (A) male and (B) female age  $\geq 25$  years between 2000 and 2012. (Error bars = lower and upper uncertainty bounds.)

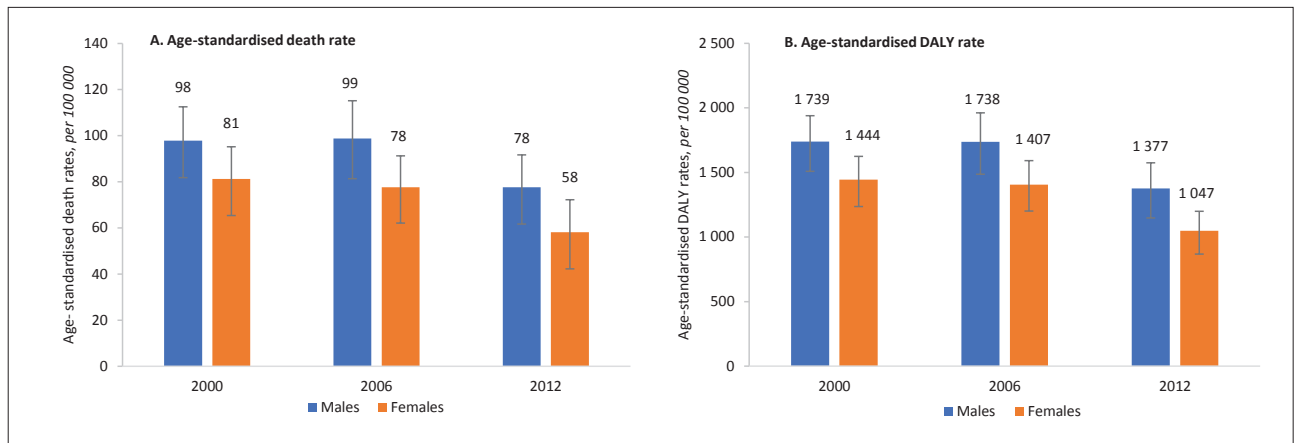


Fig. 2. Age-standardised (A) death and (B) disability-adjusted life year (DALY) rates attributable to low-density lipoprotein cholesterol for South African adults age  $\geq 25$  years by sex in 2000, 2006 and 2012. (Error bars = lower and upper uncertainty bounds.)

population between 2000 and 2012.<sup>[35]</sup> This stable pattern was also shown for the age-standardised attributable DALY rate.<sup>[35]</sup> Although the patterns differed between the two studies, the age-standardised attributable deaths in the GBD study and the present study are not directly comparable because different population standards were used. This might imply a need for serial national data on LDL-C to better understand the patterns found in SA.

Despite the decrease in age-standardised attributable deaths in SA, a sizeable burden due to LDL-C remained in 2012. The proportion of total deaths and DALYs due to LDL-C increased between 2006 and 2012, but was still lower than in 2000. This was likely influenced by the contribution of HIV/AIDS to the total deaths in SA. HIV/AIDS was a significant contributor to mortality in the mid-1990s and peaked in 2006,<sup>[6,36]</sup> but tapered off thereafter following the introduction of antiretroviral drugs.<sup>[6,36]</sup> The pattern found in this study does not mimic that of the GBD 2017 study. In the latter, the proportion of total GBD deaths and DALYs attributable to high LDL-C increased steadily between 2000 and 2012, from 6.5% to 7.3% for deaths and 3.0% to 3.5% for DALYs.<sup>[35]</sup>

Apart from a decreased ASR for cardiovascular deaths, the decrease in the attributable death and DALY ASRs is also partly explained by a small but steady decline in the PIF between 2000 and 2012, which in turn is driven by a decline in LDL-C over the same period. The decline in LDL-C in both men and women was surprising considering the rise in urbanisation with ensuing overnutrition and increases in obesity in the country.<sup>[12,37]</sup> However,

there has been a concerted effort by the SA government to improve the health of the nation by enacting legislation to restrict the trans-fatty acid content in foods to a maximum of 2 g per 100 g of oil or fat.<sup>[38]</sup> The qualitative composition of high saturated and trans-fatty acid intake in dietary fats influences the risk of CVDs such as IHD and stroke.<sup>[39]</sup>

The benefits of population-level interventions to improve national health have been demonstrated in Mauritius, among other countries.<sup>[40]</sup> Although the SA legislation was implemented only in 2011, this is a lengthy process with discussions involving many stakeholders, which would have raised media attention and awareness among the public many years prior to 2011. This may have influenced South Africans to reduce their intake of foods high in unhealthy fats prior to the introduction of the legislation, and contributed to the decreasing trend in LDL-C levels. In a study in the USA, which reported a slight decrease in mean LDL-C level over two decades, the authors also suggested that a decrease in trans-fatty acid consumption was a likely contributor.<sup>[41]</sup>

The decrease in mean LDL-C between 2000 and 2012 did not necessarily confer a lower risk for CVD because this study did not estimate the change in LDL-C subparticles, which are differentially atherogenic. Some LDL-C subparticles e.g. small dense low-density lipoprotein (sdLDL), are more atherogenic, and confer a greater risk for CVD.<sup>[42]</sup> However, a breakdown of studies by subparticles was beyond the scope of this study. LDL-C levels are influenced by many factors, including exercise, obesity, smoking, use of drugs such as

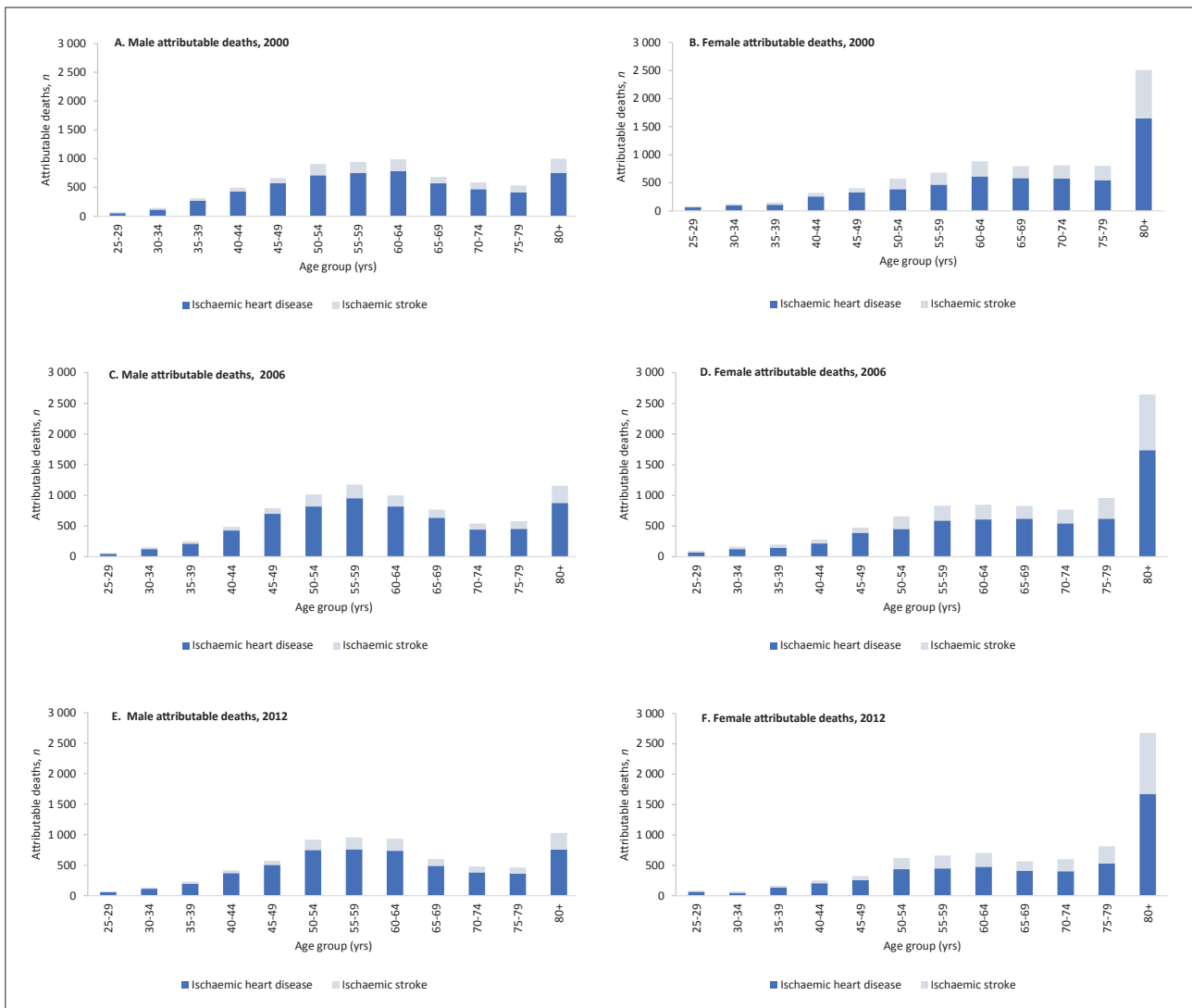


Fig. 3. Attributable deaths for (A) male and (B) female for 2000, (C) male and (D) female for 2006 and (E) male and (F) female for 2012.

antiretrovirals and HIV status,<sup>[36,43,44]</sup> and further research is needed to explore their contributions to the trends found in this study.

The SACRA1 study reported population level differences in TC levels<sup>[7]</sup> with higher mean TC levels and higher prevalence estimates of TC >5 mmol/L in whites (90%), Asians (87%) and coloureds (82%) compared with black Africans (24%). This suggests lower levels of urbanisation and ‘westernised’ lifestyles among black Africans compared with the other population groups at the time. Our study was unable to assess population level trends due to the paucity of data by population group. For instance, LDL-C levels were reported in only 3 studies with white, 2 with coloured and 3 with Asian population groups (appendix Table S1: <https://www.samedical.org/file/1840>). A population group analysis would have been useful to determine any changes compared with SACRA1.

Although LDL-C levels have decreased slightly between 2000 and 2012, the estimated mean levels – especially in females – were close to 3 mmol/L across the period of analysis. This is the recommended level for initiating cholesterol-lowering treatment in people at low and moderate risk for cardiovascular outcomes.<sup>[4]</sup> This suggests that more needs to be done to encourage the downward trend, with a steeper drop in LDL-C levels. The mean LDL-C concentration in this study from SA, a middle-income country, was comparable with that reported in the Prospective Urban Rural Epidemiology (PURE)

study<sup>[45]</sup> for middle-income countries, especially for females. The latter study reported higher LDL-C levels of 3.3 mmol/L in high-income countries and 3.2 mmol/L in low-income countries, but 3.0 mmol/L in middle-income countries.

Further, this study showed higher PIFs for raised LDL-C in younger adults and in women (appendix Fig. S3: <https://www.samedical.org/file/1840>), which contrasts with the lower CVD risk usually assigned to younger individuals and to premenopausal women. For example, a high 10-year CVD risk ( $\geq 20\%$ ), estimated using the Framingham risk equation, was more than twofold higher in men (13.0%) compared with women (6.1%) in a SA study.<sup>[46]</sup> This is a function of the equations that assign greater weight to men while, in women, lower scores are unable to adequately ensure that individual women are at low risk. This suggests a potential re-evaluation, in the SA population, of the weights allocated to age and sex in the current equations used to predict the 10-year risk of developing CVD. Further, the commonly used Framingham risk equation includes TC and HDL-C levels, and not LDL-C estimates nor its subparticles, which may differentially affect the risk score. Moreover, all CVD risk factors, particularly physical inactivity and stress, which are high in SA populations, are not included in these risk equations. In younger individuals and in women, medical and lifestyle history, markers of preclinical disease, etc. should



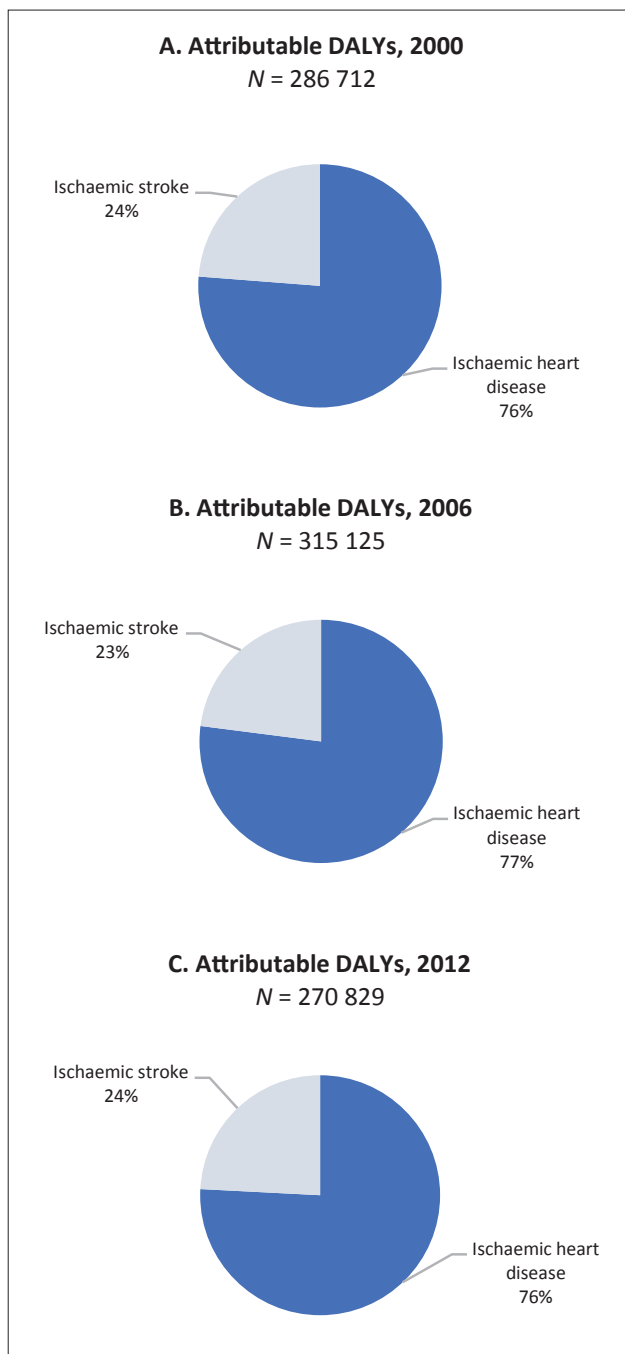


Fig. 4. Attributable disability-adjusted life years (DALYs) due to raised low-density lipoprotein cholesterol by cause, for (A) 2000, (B) 2006 and (C) 2012.

be assessed. Further research, ideally in longitudinal studies, is needed to clearly identify the contributors to high CVD risk in SA. SA could adopt something similar to the systematic coronary risk estimation approach, which estimates the 10-year risk of a first fatal atherosclerotic event and thus allows for recalibration with changes in the cardiovascular mortality trend.<sup>[47]</sup> However, much investigation is required before this can be done. For the purpose of this study it will have to be assumed that risk assessment is applicable simplistically and equally to all population groups.

The persistent high attributable burden due to LDL-C highlights the need for more intense population-based intervention measures to reduce LDL-C levels. These may include nationwide nutrition education programmes, collaboration with the food industry to

improve labelling that would enable consumers to make informed healthier choices as well as stimulate product reformulation, and additional legislation including the cheaper pricing of healthy compared with unhealthy alternatives. Additionally, risk factors such as smoking, obesity, hypertension and diabetes must also be addressed to reduce the CVD burden.

The limitations of this study include the sparsity of data to estimate the mean LDL-C concentrations for three different time periods. The estimates were not aggregated by population group, which showed markedly different mean TC levels in the SACRA1 study. This study did not estimate the prevalence of LDL-C >3 mmol/L, which is the treatment threshold in individuals with low and moderate cardiovascular risk; the difference in CVD risk attributable to LDL-C by this cut-off point could then have been determined. However, the benefit of estimating LDL-C as a continuous variable is that it allows the estimation of cardiovascular risk with every 1 mmol/L increase in serum LDL-C above the theoretical minimum risk exposure. Although sLDL is more atherogenic and a better predictor of CVD than LDL-C, there are very few population-based studies that have assessed sLDL owing to a historical lack of homogenous assays, and this component could not be evaluated.<sup>[42]</sup> The GBD RRs are based on pooled analysis from studies in Asia and Europe, which does not necessarily represent the risk of cardiovascular outcomes in low- and middle-income sub-Saharan African countries such as SA. Although studies on familial hypercholesterolaemia were excluded from our meta-analysis, it is a substantial public health problem, as demonstrated by the global call to action for familial hypercholesterolaemia.<sup>[48]</sup> The study by Oelofse *et al.*<sup>[18]</sup> did not use fasting blood samples to estimate lipid levels, which may have resulted in incorrect estimates.

### Conclusion

This study indicates that a substantial amount of the cardiovascular mortality and morbidity in SA can be attributed to high LDL-C. The decreasing trend in the age-standardised attributable burden due to high LDL-C between 2006 and 2012 is encouraging, but should be interpreted with caution since numerous risk factors contribute to CVD. Nevertheless, the PIFs for LDL-C did show a slight decline over time, due to the slight decrease in LDL-C levels. If mean population LDL-C values can be lowered further with the introduction of additional population-based CVD prevention strategies, this would likely translate to lower CVD in SA. Regular surveillance of national LDL-C levels is required to guide CVD policies and programmes, and to monitor the impact of such strategies.

**Declaration.** Disclaimer: The population group classification is based on self-reporting according to Apartheid-era groups defined by the Population Registration Act of 1950, i.e. black African, coloured, Indian/Asian and white. This classification is used as it has important correlates of lifestyle, culture and socioeconomic conditions that impact on health and health-related behaviours. The authors do not subscribe to this classification for any other purpose.

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**Author contributions.** Conceived and designed the study: IN, RP, DB, VPvW. Analysed the data: IN, AC. Prepared data for analysis: IN, AC. Interrogated and interpreted results: IN, AC, NP, RP, DB, VPvW. Drafted manuscript: IN, NP, AC, BN, RP, DB, VPvW. Critical review of manuscript for important intellectual content: IN, NP, AC, BN, RP, DB, VPvW. Senior authors: DB, VPvW, RP. Agree to final version: All.

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