Implications of scaling up cardiovascular disease treatment in South Africa: a microsimulation and cost-effectiveness analysis

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Summary

Background Cardiovascular diseases and their risk factors—particularly hypertension, dyslipidaemia, and diabetes—have become an increasing concern for middle-income countries. Using newly available, nationally representative data, we assessed how cardiovascular risk factors are distributed across subpopulations within South Africa and identified which cardiovascular treatments should be prioritised.

Methods We created a demographically representative simulated population for South Africa and used data from 17 743 respondents aged 15 years or older of the 2012 South African National Health and Nutrition Examination Survey (SANHANES) to assign information on cardiovascular risk factors to each member of the simulated population. We created a microsimulation model to estimate the health and economic implications of two globally recognised treatment recommendations: WHO's package of essential non-communicable disease interventions (PEN) and South Africa's Primary Care 101 (SA PC 101) guidelines. The primary outcome was total disability-adjusted life-years (DALYs) averted through treatment of all cardiovascular disease or microvascular type 2 diabetes complications per 1000 population. We compared outcomes at the aspirational level of achieving access to treatment among 70% of the population.

Findings Based on the SANHANES data, South Africans had a high prevalence of hypertension (24·8%), dyslipidaemia (17·5%), and diabetes (15·3%). Prevalence was disproportionately high and treatment low among male, black, and poor populations. Our simulated population experienced a burden of 40·0 DALYs (95% CI 29·5–52·0) per 1000 population per year from cardiovascular disease or type 2 diabetes complications at current treatment levels, which lowered to 32·9 DALYs (24·4–44·7) under WHO PEN implementation and to 32·5 (24·4–44·8) under SA PC 101 implementation. Under both guidelines, there were increases in blood pressure treatment (4·2 percentage points under WHO PEN vs 12·6 percentage points under SA PC 101), lipid treatment (16·0 vs 14·9), and glucose control medications (1·2 vs 0·6). The incremental cost-effectiveness of implementing SA PC 101 over current treatment would be a saving of US$24 902 (95% CI 14 666–62 579) per DALY averted compared with a saving of $17 587 (1840–42 589) under WHO PEN guidelines.

Interpretation Cardiovascular risk factors are common and disproportionate among disadvantaged populations in South Africa. Treatment with blood pressure agents and statins might need greater prioritisation than blood glucose therapies, which contrasts with observed treatment levels despite a lower monthly cost of blood pressure or statin treatment than of sulfonylurea or insulin treatment.

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Introduction

Cardiovascular diseases and their risk factors—particularly hypertension, dyslipidaemia, and diabetes—have become an increasing concern in middle-income countries.[1] Overall prevalence and mortality statistics for cardiovascular disease have been estimated since 1990 through imputation methods, providing a broad sense of the rising burden of disease at the country level[1] and the expected economic consequences of non-communicable diseases,[2] but detailed, nationally representative surveys of cardiovascular disease risk factors have only recently been completed. These surveys provide data to answer crucial questions

such as the extent to which lower-income populations are affected compared with higher-income populations who might be less in need of public health sector interventions; which strategies and interventions (eg, blood pressure, lipid, or diabetes glucose management) are highest priorities given the distribution of disease and avertable complications; and what level of health-care system budgeting might be necessary and cost-effective to scale up management. Despite these questions being posed,[3–5] few studies have aimed to assess the implications of interventions for countries using real-population survey data rather than imputed aggregate country-wide averages.

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Research in context

Evidence before this study
We searched PubMed on July 10, 2018, for the search terms "cardiovascular disease", "blood pressure", "lipid", "diabetes" AND "low-income", "middle income", or "low- and middle-income". Articles were restricted to English language original research papers published since 2000. Cardiovascular disease is becoming more prevalent in middle-income countries. Prior studies have identified key unanswered questions for public health and clinical practice: the extent to which lower-income populations in middle-income countries are affected compared with higher-income populations who might be less in need of public health sector interventions; which strategies and interventions (eg, blood pressure treatment, lipid treatment, or diabetes glucose management) are the highest priorities given the distribution of disease and avertable complications; and what level of health-care system budgeting might be necessary and the most cost-effective for scaling up of treatment. Few studies have aimed to assess the implications of interventions for countries using real-population survey data rather than imputed aggregate country-wide averages.

Added value of this study
We used nationally representative survey data from South Africa and a microsimulation model to estimate rates of cardiovascular and diabetes-related microvascular disease across demographic

groups and to explore how implementation of available guidelines for cardiovascular risk factor control would affect the burden of cardiovascular disease and associated costs in the South African population. We found that high blood pressure, dyslipidaemia, and diabetes were prevalent across demographic groups, with low treatment levels (particularly for lipid treatment) among male, black African, and poor populations. Microsimulation results suggested that treatment with blood pressure agents and statins would need greater prioritisation than blood glucose medications; survey data, however, suggested that aggressive glucose control was more prevalent than guideline-based statin treatment, despite costs being lower for statins than for many common glucose agents.

Implications of all the available evidence
Assertive treatment of prevalent hypertension and dyslipidaemia might help to mitigate a high burden of disease in South Africa, including among historically disadvantaged populations. Implementation of available guidelines for cardiovascular risk factor control such as the WHO package of essential non-communicable disease interventions or the South African Primary Care 101 guidelines would be anticipated to enable achievement of Sustainable Development Goal target 3.4: reduction in premature mortality of 30%.

Questions about management of non-communicable diseases are of particular interest to policy makers in South Africa, a country with severe levels of poverty and inequality as a result of its apartheid history.[6] South Africa notably continues to experience a high burden of HIV and tuberculosis, such that dual epidemics of infectious diseases and cardiovascular diseases co-occur in the population,[7] with dire implications on limited health-care resources. Population-level chronic disease surveys done in South Africa since 2012 provide a uniquely comprehensive understanding of the variations in cardiovascular disease risk and availability and coverage of important cardiovascular disease risk factor management interventions.[8] South Africa is also representative of many middle-income countries experiencing very large socioeconomic inequalities, a rapidly increasing burden of cardiovascular diseases and risk factors, and with a goal of providing more comprehensive health-care services by governments faced with a finite health-care budget.

Here, we address how cardiovascular risk factors are distributed across lower-income versus higher-income populations in South Africa, and which cardiovascular treatments should be prioritised. We capture both inequalities in risk factors and treatment access, including for hypertension, dyslipidaemia, and type 2 diabetes. We examine variations in cardiovascular disease risk factors by urban or rural residence, race and ethnicity, and socioeconomic status. We specifically integrate and use microsimulation to estimate the health

and economic implications of scaling up treatment to meet recommendations in two alternative guidelines: WHO's package of essential non-communicable disease interventions (PEN)[9] and South Africa's Primary Care 101 (SA PC 101) guidelines.[10] We additionally investigate whether implementation of either guideline would lead to a reduction in premature mortality (ie, <70 years of age) due to cardiovascular disease risk factors of 30% by 2030, which is a key aim of the Sustainable Development Goals (target 3.4).[3,4]

Methods
Model overview
Modelling proceeded in three main steps (figure 1). First, a demographically representative simulated population for South Africa was constructed using the most recent census data (ie, from 2011) and population projections from Statistics South Africa, incorporating estimated population sizes by age, sex, race and ethnicity, and socioeconomic status (as measured by the multidimensional poverty index).[11,12]

Second, we simulated the cardiovascular risk factors for each person in our population by repeated sampling from data from the 2012 South African National Health and Nutrition Examination Survey (SANHANES).[8] SANHANES was a stratified community-based survey, physical examination, and laboratory study of South Africans across urban and rural areas of all provinces, and had the most comprehensive data available to us
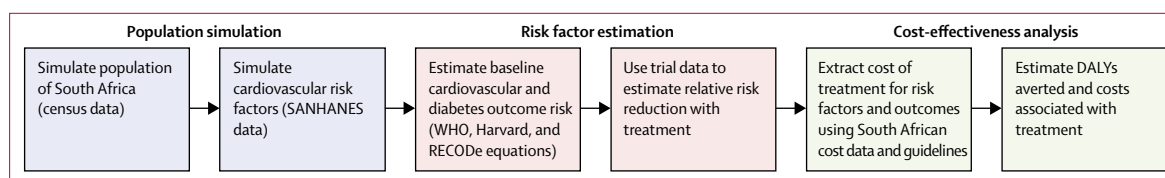
Figure 1: Modelling approach
DALYs=disability-adjusted life-years. RECODe=risk equations for complications of type 2 diabetes. SANHANES=South African National Health and Nutrition Examination Survey.

on measured cardiovascular disease risk factors. We sampled from the 17743 individuals aged 15 years and older with data available on cardiovascular risk factors. Each person in the simulated population was assigned systolic and diastolic blood pressure; total and high-density lipoproterol cholesterol; glycated haemoglobin (HbA_{1c}); and history of cardiovascular disease (myocardial infarction, stroke, or congestive heart failure), type 2 diabetes, and treatment (with blood pressure medications, statins, or diabetes medications). We defined hypertension as blood pressure of at least 140/90 mm Hg (per South African definitions) or being on blood pressure treatment;[13] dyslipidaemia as total cholesterol of at least 6·21 mmol/L, low-density lipoprotein cholesterol of at least 4·14 mmol/L, high-density lipoprotein cholesterol less than 1·03 mmol/L, triglycerides of at least 2·25 mmol/L, or being on lipid-lowering treatment;[14] and diabetes as HbA_{1c} of at least 6·5% (48 mmol/mol) or being on glucose-lowering treatment.[15] We did Monte Carlo sampling to capture the covariations between biomarkers and disease history in the survey, following multiple imputation of missing data with chained equations and adjustment with survey sample weights to construct population-representative estimates.[16] The Monte Carlo sample was equal to the South African population and used the complete census survey data, incorporating the SANHANES survey sample weights and doing repeated sampling (10 000 times) to generate the uncertainty in projecting from the stratified survey sample population to the full national population. We did prespecified subgroup analyses of the SANHANES data to identify variations in risk factors and treatment relations among key societal divisions in the population. Subgroup analyses were done by sex, black African or not black African (which includes the four census categories white, coloured, Indian or Asian, and other), and poor or not poor (as defined by South Africa's multidimensional poverty index with a composite score cutoff of >0·33 to be considered poor[11,12]).

Third, we did cost-effectiveness analyses comparing the WHO PEN and SA PC 101 guidelines.[9,10] Following current cost-effectiveness analysis guidelines,[17] the disability-adjusted life-years (DALYs) averted due to treatment of hypertension, dyslipidaemia, and type 2 diabetes and the associated costs of treatment were computed for each simulated individual, adopting a life-course approach to calculate the DALYs averted and costs accumulated over the remainder of the anticipated lifetime of each person alive or entering the population aged 16 years or older during a simulated 10-year policy planning horizon. Following current modelling guidelines,[18] the policy planning horizon is the period over which the population of interest is determined, such that a 10-year horizon means that all people aged 16 years or older or newly entering that age group over the next 10 years are simulated; the cohort is then followed over their full life-course, meaning that the actual simulation period is typically longer than 10 years, subject to the individual's simulated life-course over each stochastic iteration subject to the age-specific and sex-specific mortality rate.

Simulations were repeated 10 000 times while sampling with replacement from the distribution of all input parameter values (see appendix) to compute 95% CIs around the primary and secondary outcome metrics and around the incremental cost-effectiveness ratio (ICER) calculations.

Analyses were done in R (version 3.4.3). All parameters and equations are detailed in the appendix, with a link to the program code for replication.

The study was deemed exempt from human subjects review by the Stanford University Institutional Review Board (e-Protocol #39274).

Treatment simulations
We simulated three treatment scenarios. First, in the base case simulation, existing levels of treatment were continued on the basis of the rate of self-reported treatment for elevated blood pressure, dyslipidaemia, and type 2 diabetes, given measured levels of blood pressure, lipids, and HbA_{1c} in SANHANES. Second, in the WHO PEN simulation, treatments were added to achieve the blood pressure, lipid, and diabetes glucose control guidelines depicted in figure 2A. Alternatively, in the third and final simulation (SA PC 101), treatments were added to achieve the alternative blood pressure, lipid, and diabetes glucose control guidelines depicted in figure 2B.

In all three simulations, we compared outcomes at the aspirational level of achieving access to treatment among 70% of the population (allowing variation from 60% to 80% in sensitivity analyses), with 70% of the population with access to treatment subsequently adhering to the therapy and receiving DALY benefits and the remaining

See **Online** for appendix
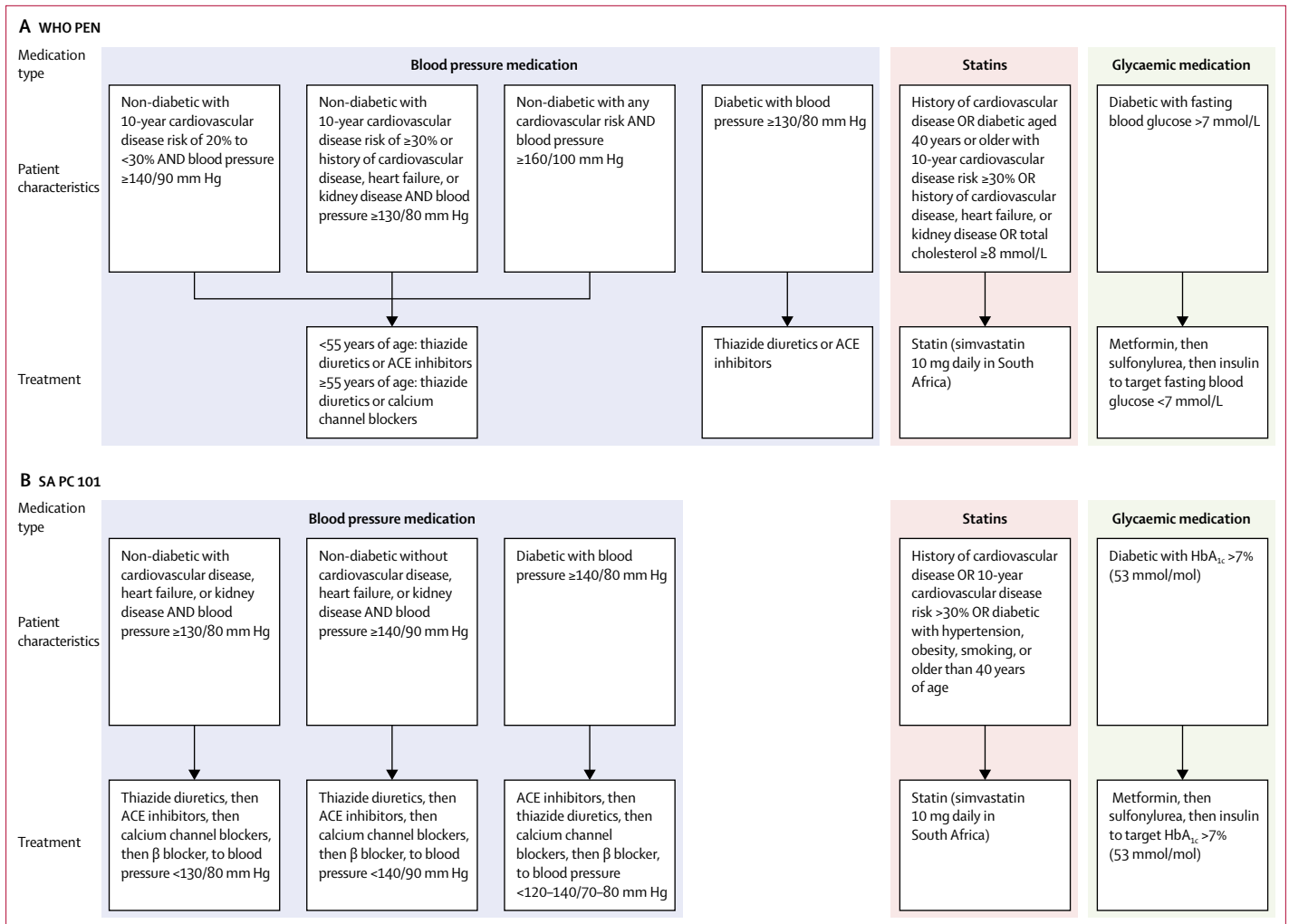
Figure 2: Alternative guidelines for management of elevated blood pressure, dyslipidaemia, and type 2 diabetes for South African providers
The management flow is shown according to the WHO PEN (A) and SA PC 101 (B) guidelines. ACE=angiotensin-converting enzyme. SA PC 101=South Africa's Primary Care 101. PEN=package of essential non-communicable disease interventions.

30% who have access producing costs from receiving therapy but not DALY benefits; these estimates are based on the best-case scenarios observed in European countries[19–22] and were applied equally between the two guideline simulations for fair comparison.

Outcomes

The primary outcome was total DALYs averted through treatment of all cardiovascular disease or microvascular type 2 diabetes complications per 1000 population. Secondary component outcomes included in the total were DALYs averted from each of atherosclerotic cardiovascular disease (non-fatal myocardial infarctions or coronary heart disease deaths, or fatal or non-fatal stroke); congestive heart failure exacerbations; renal failure or end-stage renal disease due to hypertensive or diabetic nephropathy; severe vision loss attributable to diabetic retinopathy; and pressure sensation loss or

further severe diabetic neuropathy. DALY disutility weights for all outcomes were taken from previously published primary surveys[23] and incorporated into a total DALY calculation for each simulated individual by calculating their individualised baseline annual risk of each outcome, subject to competing risks from cardiovascular and non-cardiovascular all-cause mortality for their age and sex, and adjusted for the disability weight for each condition.[24–26] As per each guidelines' recommendation, the baseline risk of myocardial infarction and stroke was estimated using the WHO and International Society of Hypertension equations calibrated to the South African population for the WHO PEN guidelines by calibrating the baseline hazard rate in the equations to the myocardial infarction and stroke rate in the population,[27] and using the Harvard and National Health and Nutrition Examination Survey equations for the SA PC 101 guidelines,[28] with twice the

baseline risk of recurrence estimated for those with a prior history of myocardial infarction or stroke.[29] The baseline risk of all other outcomes was based on the risk equations for complications of type 2 diabetes[30,31] calibrated to the South African population, for the portion of the population without previous self-reported history of the pertinent outcome; the baseline hazard rate was calibrated for each outcome to match the Global Burden of Disease incidence estimates.[32] No cardiovascular risk equations have been developed using longitudinal data from South Africa, so we deferred to the risk equations specified in each guideline to estimate that guideline's impact, for unbiased comparison.

Relative risk reductions through treatment

To estimate the DALYs averted by treatment, the baseline DALYs associated with each individual for each condition were adjusted by the relative risk reduction attributable to each treatment (see detailed tables and equations in the appendix). For blood pressure treatment, the relative risk reductions for myocardial infarctions and strokes were estimated using the Smith-Spangler equation calculating relative risk as a function of age and change in systolic blood pressure;[33] the equations had been previously validated against data from a meta-analysis[29] of 61 randomised trials. Anticipated change in systolic blood pressure was estimated from the mean reduction in systolic blood pressure estimated for each medication in a prospective meta-analysis[34] of 354 randomised trials, given the typical drug choice and dosing recommended by each guideline (figure 2). The relative risk reduction from blood pressure therapy (specifically angiotensin-converting enzyme inhibitors) for congestive heart failure exacerbations was estimated from the SOLVD trial[35] whereas for renal failure, we used a prior systematic review[36] estimating relative risk reduction by systolic blood pressure reduction. For dyslipidaemia treatment, the relative risk reduction for myocardial infarction and stroke from statin treatment (given the South African guideline's recommendation of simvastatin 10 mg daily) was obtained from a meta-analysis[37] of 27 randomised trials. Finally, for glycaemic treatment of type 2 diabetes, the relative risk reductions for each of the nephropathy, neuropathy, and retinopathy outcomes from glucose control were taken from a prior systematic review and meta-analysis[36] of randomised trials estimating relative risk reduction by HbA_{1c} achieved, where the estimated HbA_{1c} reduction typically produced by each therapy in the guidelines was taken from an evidence-based review[38] incorporating the dosing guidelines detailed in the appendix.

Cost-effectiveness analysis

Concordant with recent updates to cost-effectiveness analysis guidelines,[18] we analysed cost-effectiveness over the life-courses of individuals in the simulated population. DALYs and costs were calculated from a health-care sector perspective in the absence of reliable and consistent data on time costs, unpaid caregiver costs, transportation costs, labour market earnings lost, and social service costs for a societal perspective. An impact inventory specifying each set of costs and their sources is specified in the appendix, along with the CHEERS guideline checklist for cost-effectiveness analysis reporting.[39] In short, to calculate costs, we extracted information on the costs of care for each risk factor and outcome from the 2012 South Africa Department of Health Uniform Patient Fee Schedule for externally funded patients because these most closely align with the costs to the health-care services of providing care. For the costs of blood tests, 2012 data were not available, so we used fees from the South Africa National Health Laboratory Services for 2013. Where there were two or more cost options for the treatment components of a given risk factor or outcome, we chose the most conservative one. All costs were updated for inflation to 2018 US$ for global comparison, and both costs and DALYs were discounted at a standard 3% annual rate. Two ICERs were computed: the ICER of expanding from existing levels of treatment reflected in SANHANES to the WHO PEN guidelines and the ICER of expanding from existing levels of treatment reflected in SANHANES to the SA PC 101 guidelines.

Role of the funding source

The funders had no role in the design, conduct, analysis, or writing up of the study. The corresponding author had full access to the data and took the decision to submit for publication.

Results

The SANHANES input data revealed high levels of hypertension, dyslipidaemia, and type 2 diabetes among the South African population aged 15 years or older, yet most of the population reported being untreated for these conditions (table 1). Based on the SANHANES study sample weights, 24·8% of the South African population aged 15 years and older would have hypertension, 17·5% would have dyslipidaemia, and 15·3% would have diabetes.

The SANHANES data revealed that for blood pressure treatment, treatment was particularly low among men. For lipid treatment, treatment rates were particularly low among black Africans (table 1). SANHANES self-reported treatment survey questions suggested that 1257 (71·4%) of the 1761 people with hypertension received treatment, of whom 888 (70·6%) achieved blood pressure no higher than 140/90 mm Hg (table 1). By contrast, only 106 (3·5%) of the 3042 people with dyslipidaemia received statin treatment, among whom 12 (11·3%) achieved low-density lipoprotein no higher than 2·5 mmol/L. However, 436 (58·4%) of the 747 people with diabetes received glucose-lowering treatment, among whom 39 (8·9%) achieved HbA_{1c} no higher than 7% (53 mmol/mol; table 1).

	Male				Female			
	Black African		Not black African		Black African		Not black African	
	Poor (n=3654)	Not poor (n=1276)	Poor (n=1222)	Not poor (n=1521)	Poor (n=5055)	Not poor (n=1638)	Poor (n=1505)	Not poor (n=1872)
Demographics								
Age, years (n=17 633)	35·2 (16·0–69·0)	35·9 (16·0–66·0)	39·8 (16·0–68·0)	40·0 (16·0–69·0)	38·7 (16·0–74·0)	38·9 (17·0–72·0)	40·8 (17·0–72·0)	41·4 (17·0–70·0)
Blood pressure								
Systolic, mm Hg (n=7048)	130·7 (102·0–173·0)	130·6 (103·0–172·0)	133·3 (101·0–171·0)	133·8 (105·0–175·0)	128·5 (100·0–175·0)	128·9 (99·0–174·0)	130·0 (101·0–171·5)	131·1 (101·0–176·0)
Diastolic, mm Hg (n=7039)	72·9 (53·0–98·0)	72·7 (52·0–94·0)	75·6 (54·0–99·0)	74·9 (54·0–96·0)	74·5 (55·0–98·0)	75·5 (55·0–99·0)	75·5 (57·0–97·0)	75·4 (55·0–98·0)
Hypertension (n=7099)*	236/1341 (18%)	66/357 (18%)	97/394 (25%)	100/407 (25%)	636/2551 (25%)	202/649 (31%)	198/662 (30%)	226/738 (31%)
Undergoing blood pressure treatment (n=1761)	128/236 (54%)	46/66 (70%)	58/97 (60%)	64/100 (64%)	464/636 (73%)	161/202 (78%)	151/198 (76%)	185/226 (82%)
Blood pressure ≤140/90 mm Hg with treatment (n=1257)	81/128 (63%)	36/46 (78%)	42/58 (72%)	52/64 (81%)	316/464 (68%)	111/161 (69%)	116/151 (77%)	134/185 (72%)
Lipids								
Total cholesterol, mmol/L (n=5419)	4·1 (2·7–5·8)	4·1 (2·7–5·8)	4·5 (2·9–6·4)	4·7 (3·1–6·8)	4·4 (2·8–6·4)	4·5 (3·0–6·5)	4·8 (3·1–7·0)	5·0 (3·2–7·3)
High-density lipoprotein cholesterol, mmol/L (n=5394)	1·2 (0·7–2·0)	1·2 (0·7–2·0)	1·3 (0·8–2·2)	1·2 (0·7–2·0)	1·3 (0·7–2·0)	1·3 (0·8–2·1)	1·3 (0·8–2·2)	1·3 (0·8–2·0)
Low-density lipoprotein cholesterol, mmol/L (n=3308)	2·2 (1·2–3·7)	2·3 (1·2–3·7)	2·4 (1·1–4·4)	2·7 (1·3–4·4)	2·6 (1·3–4·2)	2·7 (1·2–4·6)	2·9 (1·4–4·6)	3·0 (1·4–5·1)
Triglycerides (fasting), mmol/L (n=534)	1·4 (0·5–2·7)	1·6 (0·5–5·0)	1·1 (0·5–1·9)	2·1 (0·6–9·3)	1·2 (0·4–2·9)	1·0 (0·4–2·2)	1·1 (0·6–1·9)	1·2 (0·5–2·7)
Dyslipidaemia (n=17 743)†	514/3654 (14%)	141/1276 (11%)	243/1222 (20%)	243/1521 (16%)	911/5055 (18%)	258/1638 (16%)	379/1505 (25%)	453/1872 (24%)
Undergoing lipid-lowering treatment (n=3042)	0	3/141 (2%)	16/243 (7%)	22/243 (9%)	6/911 (1%)	6/258 (2%)	17/379 (4%)	36/453 (8%)
Achieving low-density lipoprotein ≤2·5 mmol/L with treatment (n=106)	··	0	3/16 (19%)	2/22 (9%)	0	0	5/17 (29%)	2/36 (6%)
Diabetes								
HbA1c [mmol/mol] (n=4710)	5·8% (4·9–6·5) [40 (30–48)]	5·9% (5·0–7·4) [41 (31–57)]	5·9% (5·0–6·8) [41 (31–51)]	6·1% (5·1–8·7) [43 (32–72)]	5·9% (4·9–7·1) [41 (30–54)]	5·1% (5·0–9·1) [32 (31–76)]	6·0% (5·0–8·8) [42 (31–73)]	6·1% (5·1–8·6) [42 (32–70)]
Diabetes (n=4877)‡	81/873 (9%)	36/255 (14%)	38/317 (12%)	64/312 (21%)	227/1603 (14%)	87/443 (20%)	90/511 (18%)	124/563 (22%)
Undergoing glucose-lowering treatment (n=747)	47/81 (58%)	23/36 (64%)	26/38 (68%)	40/64 (63%)	119/227 (52%)	49/87 (56%)	57/90 (63%)	75/124 (60%)
Achieving HbA1c ≤7% (53 mmol/mol) with treatment (n=436)	6/47 (13%)	1/23 (4%)	4/26 (15%)	3/40 (8%)	10/119 (8%)	5/49 (10%)	4/57 (7%)	6/75 (8%)
Prior cardiovascular history (self-reported)								
Myocardial infarction (n=15 267)	110/3079 (4%)	25/1072 (2%)	45/1008 (4%)	41/1198 (3%)	261/4522 (6%)	73/1483 (5%)	47/1298 (4%)	58/1607 (4%)
Congestive heart failure (n=15 232)	39/3067 (1%)	13/1064 (1%)	12/1010 (1%)	11/1197 (1%)	120/4512 (3%)	26/1476 (2%)	22/1299 (2%)	28/1607 (2%)
Stroke (n=15 282)	57/3088 (2%)	15/1067 (1%)	30/1007 (3%)	36/1199 (3%)	105/4533 (2%)	29/1474 (2%)	25/1305 (2%)	47/1609 (3%)

Data are n/N (%) or mean (95% CI). Studied population comprised 17 743 individuals aged 15 and older with data available on cardiovascular risk factors. Results incorporate survey sample weights to adjust for sample selection and provide nationally representative estimates. Poverty was defined by the South African multidimensional poverty index, which defines poor versus non-poor status based on health and nutrition assets, educational attainment, and material assets. HbA1c=glycated haemoglobin. SANHANES=South African National Health and Nutrition Examination Survey. *Hypertension was defined as blood pressure ≥140/90 mm Hg or taking blood pressure-lowering medications. †Dyslipidemia was defined as measured total cholesterol ≥6·21 mmol/L, low-density lipoprotein cholesterol ≥4·14 mmol/L, high-density lipoprotein cholesterol <1·03 mmol/L, fasting triglycerides ≥2·25 mmol/L, or taking lipid-lowering medications. ‡Diabetes was defined as measured haemoglobin A1c ≥6·5% (48 mmol/mol) or taking glucose-lowering medications.

Table 1: Characteristics of the studied SANHANES population

In the base case simulation in which the existing levels of treatment were continued, our micro-simulation—accounting for competing mortality risks over the life-course—suggested that the simulated population would experience a burden of 40·0 DALYs (95% CI 29·5–52·0) from cardiovascular disease or

	Base case (current levels of treatment)	WHO PEN guidelines implemented	SA PC 101 guidelines implemented
DALYs per 1000 population per year			
All simulated outcomes	40·0 (29·5 to 52·0)	32·9 (24·4 to 44·7)	32·5 (24·4 to 44·8)
Atherosclerotic cardiovascular disease	18·7 (15·8 to 21·8)	13·7 (11·7 to 16·3)	13·4 (11·7 to 16·2)
Congestive heart failure	10·7 (7·3 to 14·6)	9·9 (6·6 to 13·9)	9·8 (6·6 to 13·9)
Renal failure or end-stage renal disease	9·2 (5·5 to 13·5)	8·2 (5·2 to 12·8)	8·2 (5·2 to 13·0)
Diabetic retinopathy	0·8 (0·5 to 1·3)	0·6 (0·5 to 1·0)	0·6 (0·5 to 1·0)
Diabetic neuropathy	0·6 (0·4 to 0·8)	0·5 (0·4 to 0·7)	0·5 (0·4 to 0·7)
Health-care costs per 1000 population per year (2018 US$)			
All simulated risk factors and outcomes	607 820 (513 818 to 705 805)	482 950 (296 612 to 692 370)	421 055 (194 667 to 600 208)
Hypertension	26 429 (26 326 to 26 533)	27 019 (23 761 to 29 750)	39 165 (35 564 to 42 830)
Dyslipidaemia	6585 (6308 to 6860)	10 347 (9575 to 10 484)	10 506 (9743 to 11 237)
Type 2 diabetes	183 006 (170 185 to 195 023)	139 011 (84 559 to 192 761)	77 502 (52 783 to 95 728)
Atherosclerotic cardiovascular disease	248 108 (226 170 to 270 567)	189 288 (153 101 to 225 400)	187 799 (151 400 to 235 606)
Congestive heart failure	29 243 (21 778 to 37 251)	24 533 (11 958 to 40 659)	24 451 (11 958 to 40 659)
Renal failure or end-stage renal disease	138 195 (87 520 to 192 544)	117 461 (36 524 to 219 146)	118 475 (30 437 to 213 058)
Diabetic retinopathy	587 (371 to 808)	426 (91 to 820)	438 (68 to 820)
Diabetic neuropathy	2096 (1486 to 2752)	1884 (804 to 3100)	1884 (804 to 3100)
Incremental cost-effectiveness ratio*	··	–17 587 (–42 589 to –1840)	–24 902 (–62 579 to –14 666)

Table shows current treatment levels (base case) compared with the scale-up from currently observed levels of treatment to 70% population access per the WHO PEN or SA PC 101 guidelines. 95% CIs in brackets are calculated by re-running the model 10 000 times while repeatedly Monte Carlo sampling with replacement from the distributions of all input parameters to estimate uncertainty in the outcome metrics. Costs are given in US$. DALYs=disability-adjusted life-years. PEN=package of essential non-communicable disease interventions. SA PC 101=South Africa's Primary Care 101. *Change in cost divided by change in DALYs, compared with the base case.

Table 2: DALYs, costs, and incremental cost-effectiveness of treating elevated blood pressure, dyslipidemia, and type 2 diabetes for the South African population

type 2 diabetes microvascular complications per 1000 population per year (table 2).[40] Of these DALYs, 16·8 (42%) were from years of life lost (based on WHO life expectancy estimates[41]) and the remaining 23·2 (58%) were from years of life lived with disability. The total 40·0 DALYs per 1000 population per year were also 74% attributable to cardiovascular disease versus 23% attributable to type 2 diabetes microvascular complications. The base case simulation suggested that most estimated DALYs were attributable to atherosclerotic cardiovascular disease, followed by congestive heart failure, renal failure or end-stage renal disease, diabetic retinopathy, and diabetic neuropathy (table 2).

In the base case simulation, the overall premature mortality rate (defined as mortality for those younger than 70 years of age) due to cardiovascular disease was 39·5 deaths (95% CI 28·0–52·0) per 1000 population per year. The populations facing the highest DALY burden from cardiovascular disease and type 2 diabetes complications were men (25·7 [64%] of total DALYs *vs* 14·3 [36%] among women), black Africans (23·0 [58%] of total DALYs *vs* 17·0 [43%] among non-black Africans), and the poor (24·1 [60%] of total DALYs *vs* 15·9 [40%] among non-poor populations).

The base case cost analysis suggested an average cost of US$607 820 (95% CI 513 818–705 805) per 1000 population per year for cardiovascular and type 2 diabetes complications, most of which was attributable to medical treatment for atherosclerotic cardiovascular disease, followed by type 2 diabetes and end-stage renal disease (table 2).

WHO PEN guideline implementation would be expected to produce a 4·2 percentage point rise in the proportion of the population prescribed blood pressure medications, a 16·0 percentage point rise in the proportion prescribed statins, and a 1·2 percentage point rise in the proportion prescribed glucose-lowering medications. A small portion of people would be removed from medication because they would not be indicated to have treatment under the WHO PEN guidelines despite currently being on treatment (7% of those currently on blood pressure medications, 1% of those currently on statins, and 1% of those currently on glucose-lowering medications). Rather than simply prescribing a higher number of medications, the WHO PEN implementation also increased the targeting of medications towards those at highest risk for cardiovascular disease and type 2 diabetes complications. Specifically, the average risk over 10 years of atherosclerotic cardiovascular disease for those prescribed blood pressure or statin medications was 25·9% in the base case simulation compared with 31·1% in the WHO PEN simulation; similarly, the average risk over 10 years for any microvascular complication of diabetes for those prescribed glucose-lowering medications was 24·4% in the base case simulation compared with 26·7% in the WHO PEN simulation.
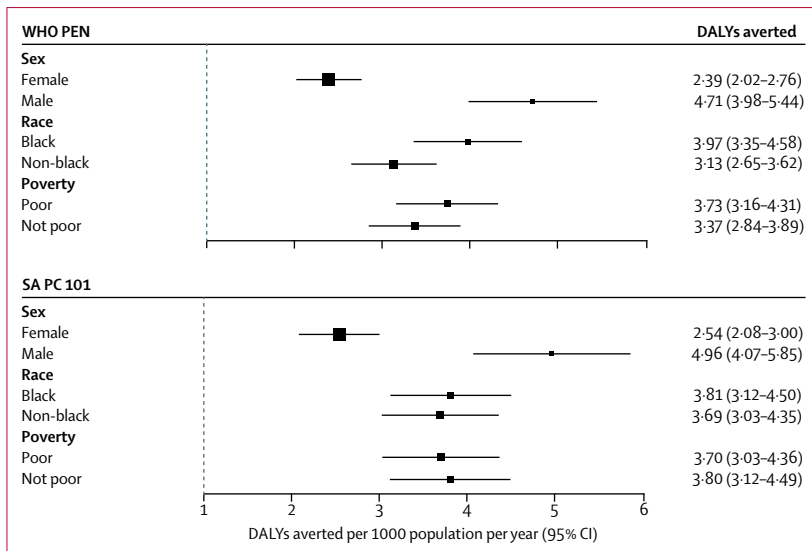
Figure 3: DALYs averted from treatment according to different guidelines of elevated blood pressure, dyslipidaemia, and type 2 diabetes for the South African population, by sex, race and ethnicity, and socioeconomic status

The figure shows DALYs averted by treatment according to the WHO PEN and SA PC 101 guidelines. DALY=disability-adjusted life-year. PEN=package of essential non-communicable disease interventions. SA PC 101=South Africa's Primary Care 101.

When WHO PEN guidelines were implemented, South Africans in our simulated population experienced a burden of 32·9 DALYs (95% CI 24·4–44·7) per 1000 population per year from cardiovascular disease or type 2 diabetes complications, a decrease of 7·1 DALYs from the base case simulation of current treatment levels (table 2). The largest improvements in DALYs due to cardiovascular disease and type 2 diabetes complications gained from implementing WHO PEN were from atherosclerotic cardiovascular disease (5·0 DALYs averted per 1000 population per year), followed by renal failure or end-stage renal disease (1·0 DALYs averted), then congestive heart failure (0·8 DALYs averted), diabetic retinopathy (0·2 DALYs averted), and finally diabetic neuropathy (0·1 DALYs averted; table 2). Our results suggested that male, black African, and poor populations benefited most, although all population estimates had wide CIs (figure 3). The overall premature mortality rate due to cardiovascular disease was 23·4 deaths (95% CI 14·0–34·0) per 1000 population per year, a 40·8% reduction from the base case.

Implementation of the WHO PEN guidelines increased costs from treatment of hypertension and dyslipidaemia, while saving costs through averted atherosclerotic cardiovascular disease events, congestive heart failure exacerbations, and microvascular complications of diabetes (table 2). The net cost estimates for the WHO PEN simulation were negative due to averted cardiovascular and microvascular events, saving on average $124 870 (95% CI 13 435–217 206) per 1000 population per year compared with the base case. The incremental cost-effectiveness of implementing WHO PEN rather

than the current treatment would be a saving of $17 587 (1840–42 589) per DALY averted. The total absolute cost, however, would be $482 950 (296 612–692 370) per 1000 population per year, as compared with the current South African health-care budget for primary health-care services of $374 per 1000 population per year (excluding services for tuberculosis and HIV).[42]

SA PC 101 guideline implementation produced a 12·6 percentage point rise in the proportion of the population prescribed blood pressure medications, a 14·9 percentage point rise in the proportion prescribed statins, and a 0·6 percentage point rise in the proportion prescribed glucose-lowering medications. 7% of those currently on blood pressure medications, 1% of those currently on statins, and 1% of those currently on glucose-lowering medications would be removed from medication because they would not be indicated to have treatment under the SA PC 101 guidelines, nearly fully overlapping with those removed by WHO PEN.

When SA PC 101 guidelines were implemented, South Africans in our simulated population experienced a burden of 32·5 DALYs (95% CI 24·4–44·8) from cardiovascular disease or type 2 diabetes complications per 1000 population per year, fewer than both in the base case and WHO PEN simulations (table 2). The slightly higher number of DALYs averted under SA PC 101 than under the WHO PEN guidelines was due to a greater proportion of the population being prescribed blood pressure medication and the associated reductions in atherosclerotic cardiovascular disease; a larger number of people with slightly lower average risk were treated under SA PC 101 compared with the smaller number of people with higher average risk treated under WHO PEN. In the SA PC 101 simulation, the average risk over 10 years of atherosclerotic cardiovascular disease for those prescribed blood pressure or statin medications was 23·1% and the average risk for any microvascular complication of diabetes for those prescribed glucose-lowering medications was 27·8%. Compared with the base case simulation, the greatest reductions in DALYs were from atherosclerotic cardiovascular disease (5·3 DALYs averted per 1000 population per year), followed by renal failure or end-stage renal disease (1·0 DALYs averted), then congestive heart failure (0·9 DALYs averted), diabetic retinopathy (0·2 DALYs averted), and finally diabetic neuropathy (0·1 DALYs averted; table 2). The male population benefited more than the female population but no disproportionate benefits were observed between black Africans and non-black Africans or between poor and non-poor populations (figure 3). The overall premature mortality rate due to cardiovascular disease was 22·1 deaths (95% CI 13·0–32·0) per 1000 population per year, a 44·1% reduction from the base case and a 5·6% reduction from the WHO PEN simulation.

Compared with the WHO PEN guidelines, implementation of the SA PC 101 guidelines would be expected to

increase costs for treatment of blood pressure. They would require similar costs for dyslipidaemia—the costs would be slightly higher than under the WHO PEN guidelines due to a younger group being treated and thus a longer time of paying for statins over the life-course—and would reduce costs for glycaemic treatment for type 2 diabetes (table 2). Most medical costs from complications through the SA PC 101 implementation were averted from atherosclerotic cardiovascular disease events but compared with the WHO PEN implementation, fewer costs were averted from microvascular complications of diabetes (table 2). Overall, the SA PC 101 implementation was more cost saving than the WHO PEN guideline, saving on average $186 765 (95% CI 105 597–319 151) per 1000 population per year compared with the base case. The total absolute cost, however, of SA PC 101 would be only marginally lower than under WHO PEN at $421 055 (194 667–600 208) per 1000 population per year. The incremental cost-effectiveness of implementing SA PC 101 over the current treatment would be a saving of $24 902 (14 666–62 579) per DALY averted.[42]

In sensitivity analyses, ICERs were not substantially changed under either guideline if access to treatment changed from the base case of 70% of the population to 60% or 80% (appendix). The incremental cost-effectiveness of blood pressure and lipid therapies became more pronounced at lower levels of baseline treatment because the incremental impact of treatment was more potent with lower baseline coverage levels. We found that at least 46·7% of the population with hypertension and hyperlipidaemia would need to be diagnosed and treated for these conditions to achieve the 30% premature mortality reduction Sustainable Development Goal, which would not require new blood pressure or lipid screening but would require more treatment initiation and adherence.

Discussion

We found high rates of cardiovascular and microvascular risk factors across demographic groups, with low treatment levels (particularly for lipid treatment) among male, black African, and poor populations in South Africa. Although treatment subsidisation is high among the poor in South Africa, various barriers to access to care—including cultural, trust, and financial barriers to getting to care—conspire with a higher level of risk factors in poor people to result in a disproportionate burden. Given the distribution of risk factors and treatments at present, our microsimulation suggested a high burden of DALYs from atherosclerotic cardiovascular disease, followed by congestive heart failure and diabetes microvascular complications. With implementation of the WHO PEN guidelines, we would anticipate a considerably higher proportion of the population treated with statins, followed by increased treatment for hypertension and then glycaemic control for diabetes. But we additionally found that implementation of the

SA PC 101 guidelines averted slightly more overall DALYs and had better cost-effectiveness than did implementation of the WHO PEN guidelines. The key benefits of the SA PC 101 guidelines in terms of DALYs was a result of more assertive blood pressure treatment, particularly for high-risk patients, whereas the benefits, in terms of costs, were primarily from less assertive blood glucose control than under the WHO PEN guidelines. We found that if either guidelines were implemented with coverage rates similar to a well performing European health system, the Sustainable Development Goals target 3.4 (reduction in premature mortality from non-communicable diseases of one third) would be readily achieved.

Our findings address considerable debate in the literature regarding whether or not cardiovascular diseases and their risk factors affect a sufficient proportion of the population, particularly lower-income groups, to justify widespread treatment.[43,44] Our microsimulation modelling approach has a key advantage over traditional Markov models of simulating entire distributions of risk, rather than just an average risk level, thus capturing heterogeneities in risk and benefit of treatment. Our results are notable for uniquely assessing inequalities in the disease burden and benefit from using nationally representative data, which suggest that particularly disadvantaged populations might disproportionately benefit from assertive treatment. Additionally, we address questions about risk factor prioritisation. Our results suggest that treatment with blood pressure agents and statins might need greater prioritisation at the population level for people at high cardiovascular risk than blood glucose medications, while recognising the importance of the latter at the individual level. This contrasts with observed treatment levels despite a lower monthly cost of blood pressure or statin treatment than of sulfonylurea or insulin treatment in South Africa, as is the case in many other middle-income countries.[45] Our findings on prioritisation are relevant to many countries implementing WHO PEN or SA PC 101 guidelines; notably, the South African PC 101 guidelines are now being implemented in Botswana, Nigeria, and Brazil.[46] The SA PC 101 guidelines have an explicit focus on population equity.

There are important limitations to our analysis. Simulation studies cannot predict the future and can only anticipate potential outcomes under the premise that the effectiveness observed in randomised trials and meta-analyses will be realised in practice. Achieving European levels of treatment access will undoubtedly require access and adherence initiatives that would increase costs and make the cost-effectiveness of this approach less attractive. Improving access to care goes beyond improving availability of treatment and requires overcoming barriers including culture, trust, and the financial implications of getting to care. These issues are particularly relevant in South Africa given its apartheid past. Lack of reliable data on costs of successful access and adherence initiatives in South Africa mean that we

have not included these in our analysis. However, the costs that we have used do include the costs of infrastructure and personnel to deliver treatment and are not limited to the costs of medications or equipment. Additionally, improving availability of treatment and hence results of accessing health care can engender trust in and usage of those services.[47] An additional consideration is that randomised trials and meta-analyses that focus on estimating results among mostly North American and European populations might not accurately reflect the effectiveness of therapy among diverse South African populations. We have also calculated cost-effectiveness using broad international guidelines that focus on value per dollar spent; however, ministries of finance have numerous competing priorities when allocating resources, even among highly cost-effective interventions, that must be considered on the basis of often fluctuating budgets, as well as the training needs and physical infrastructure of health-care providers and delivery organisations. The SANHANES data on which our simulations rely have important gaps, particularly the absence of detail concerning access to and pricing of tobacco cessation treatments, and incomplete coverage of all risk factors across the entire sample. However, the data do provide important estimates of how the distributions of other major cardiovascular disease risk factors are prevalent among minority and poor populations, contrary to claims that cardiovascular risk would be isolated to higher-income groups. The data are nevertheless self-reported for key treatment questions, which might lead to overestimation of treatment levels due to social acceptability bias (eg, not admitting non-adherence) or underestimation of treatment if individuals are confused about what medications they are taking and what those medications are for.

Future research efforts should address the question of what key implementation barriers have prevented more assertive statin treatment in the South African population. Additionally, research efforts should identify how to better reach male, black, and poor populations who appear to be disproportionately undertreated for their chronic disease risk—including analysis of the barriers to treatment, such as cultural, social, and economic contexts faced by those underserved populations.

As such research is initiated, our results suggest that the departments of health of South Africa and similar nations prepare assertively for increased burdens of non-communicable diseases. Our results suggest that the SA PC 101 guidelines might be more effective in terms of DALYs averted and net overall costs saved than the current WHO guidelines for management of blood pressure, lipids, and diabetes. Particularly assertive treatment across people with hypertension and hyperlipidaemia with blood pressure and statin medications might help to mitigate a high burden of disease, including among historically disadvantaged populations.

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