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Diallo, Alpha Oumar ; Ali, Mohammed K. ; Geldsetzer, Pascal; Gower, Emily W. ; Mukama, Trasiyas ; Wagner, Ryan G. ; Davies, Justine; Bijlsma, Maarten J. ; Sudharsanan, Nikkil

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Systolic blood pressure and 6-year mortality in South Africa: a country-wide, population-based cohort study



Alpha Oumar Diallo, Mohammed K Ali, Pascal Geldsetzer, Emily W Gower, Trasiyas Mukama, Ryan G Wagner, Justine Davies, Maarten J Bijlsma, Nikkil Sudharsanan



Summary

Background Improving hypertension control is an important global health priority, yet, to our knowledge, there is no direct evidence on the relationship between blood pressure and mortality in sub-Saharan Africa. We aimed to investigate the relationship between systolic blood pressure and mortality in South Africa and to assess the comparative effectiveness of different systolic blood pressure targets for clinical care and population-wide hypertension management efforts.

Methods In this country-wide, population-based cohort study, we used longitudinal data on adults aged 30 years and older from five waves (2008, 2010–11, 2012, 2014–15, and 2017) of the South African National Income Dynamics Study. We estimated the relationship between systolic blood pressure and 6-year all-cause mortality and compared the mortality reductions associated with lowering systolic blood pressure to different targets (120 mm Hg, 130 mm Hg, 140 mm Hg, 150 mm Hg). We also estimated the mean blood pressure reduction required to achieve each target, the share of the population in need of management, and the number needed to treat (NNT) to avert one death under different hypothetical population-wide scale-up scenarios.

Findings Of the 8338 age-eligible respondents in the 2010–11 survey, 4993 had all required data and were included in our study. We found a weak, non-linear relationship between systolic blood pressure and 6-year mortality, with larger incremental mortality benefits at higher systolic blood pressure values: reducing systolic blood pressure from 160 mm Hg to 150 mm Hg was associated with a relative risk of mortality of 0.95 (95% CI 0.90 to 0.99; $p=0.033$), reducing systolic blood pressure from 150 mm Hg to 140 mm Hg had a relative risk of 0.96 (0.91 to 1.01; $p=0.12$), with no evidence of incremental benefits of reducing systolic blood pressure below 140 mm Hg. At the population level, reducing systolic blood pressure to 150 mm Hg among all those with a starting systolic blood pressure of more than 150 mm Hg was associated with the lowest NNT ($n=50$), 3.3 deaths averted (95% CI -0.6 to 0.3) per 1000 population, blood pressure management for 16% (95% CI 15.2 to 17.3) of individuals, and a -2.7 mm Hg mean change in systolic blood pressure required to achieve the 150 mm Hg scale-up target (-3.0 to -2.5 ; $p<0.0001$).

Interpretation The relationship between systolic blood pressure and mortality is weaker in South Africa than in high-income and many low-income and middle-income countries. As such, we do not find compelling evidence in support of targets below 140 mm Hg and find that scaling up management based on a 150 mm Hg target is more efficient in terms of the NNT compared with strategies to reduce systolic blood pressure to lower values.

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Introduction

Hypertension is the leading modifiable risk factor for mortality worldwide.¹ Reducing blood pressure substantially lowers the risk of hypertension-related mortality; however, the vast majority of individuals with hypertension in low-income and middle-income countries (LMICs) do not have controlled blood pressure under commonly recommended thresholds.² In South Africa, 35% of the population aged 15 years and older have hypertension, yet just 9% of these individuals have their blood pressure under control.^{3,4} For this reason, and because reducing blood pressure is a highly effective way of achieving population-wide mortality reductions, substantially scaling up hypertension control is a major health priority in South Africa and other LMICs.^{5–7}

Achieving population-wide blood pressure reductions requires determining the target that blood pressure should be reduced to. Because there are no clinical comparative effectiveness trials of different blood pressure targets for any population in LMICs, these countries, such as South Africa, have to decide on treatment targets by extrapolating effects from clinical trial populations in high-income countries.⁸ This extrapolation might lead to suboptimal hypertension management decisions if the relationship between blood pressure and mortality in South Africa is different than the relationship in high-income countries, potentially due to the strong competing risk of tuberculosis and HIV mortality and poorer access to and quality of health care in South Africa.⁹

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Department of Epidemiology, Gillings School of Global Public Health (A O Diallo MPH, E W Gower PhD) and Department of Ophthalmology, School of Medicine (E W Gower), University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; Hubert Department of Global Health, Rollins School of Public Health, and Department of Family and Preventive Medicine, School of Medicine, Emory University, Atlanta, GA, USA (M K Ali MD); Division of Primary Care and Population Health, Department of Medicine, Stanford University, Stanford, CA, USA (P Geldsetzer ScD); Heidelberg Institute of Global Health, Heidelberg University, Heidelberg, Germany (P Geldsetzer, T Mukama MPH, N Sudharsanan PhD); Department of Disease Control and Environmental Health, Makerere University School of Public Health, Kampala, Uganda (T Mukama); Division of Preventive Oncology, German Cancer Research Center, Heidelberg, Germany (T Mukama); MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa (R G Wagner PhD, Prof J Davies MD); Institute of Applied Health Research, University of Birmingham, Birmingham, UK (Prof J Davies); Centre for Global Surgery, Department of Global Health, Stellenbosch University, Cape Town, South Africa (Prof J Davies); Max Planck Institute for Demographic Research, Rostock, Germany (M J Bijlsma PhD)

Correspondence to:
Dr Nikkil Sudharsanan,
Heidelberg Institute of Global
Health, Heidelberg University
69115 Heidelberg, Germany
nikkil.sudharsanan@uni-
heidelberg.de

Research in context

Evidence before this study

We did a search in PubMed in July, 2020, using keywords related to blood pressure, hypertension, mortality, and survival with no date restrictions. We selected studies that were set in sub-Saharan Africa, had mortality as a primary outcome, and blood pressure or hypertension as a primary exposure. The majority of studies sought to estimate the total mortality burden attributable to hypertension—using a conventional definition of hypertension (blood pressure $\geq 140/90$ mm Hg)—through modelling studies that drew estimates of the relative risk of hypertension-related mortality from the Global Burden of Disease project or from clinical trials of hypertension treatment in high-income countries. These studies generally found a large and increasing burden of hypertension in sub-Saharan Africa. A small number of studies were done among small hospital samples, similarly finding that hypertension is an important predictor of mortality. None of the studies were based on population-based longitudinal data from a sub-Saharan African country and none examined the shape of the relationship between blood pressure and mortality and implications of this shape for hypertension management targets.

Added value of this study

To our knowledge, we provide the first direct, population-based estimates of the relationship between systolic blood pressure

and mortality and the comparative effectiveness of reducing systolic blood pressure to different management targets in South Africa. To our knowledge, our estimates are based on the only source of country-wide longitudinal data with measured blood pressure and mortality follow-up set in a sub-Saharan African country.

Implications of all the available evidence

The association between systolic blood pressure and 6-year mortality is weaker in South Africa compared with high-income countries and many low-income and middle-income countries, possibly due to high competing risks from other causes of mortality in South Africa. As such, among South African adults, reducing systolic blood pressure to 150 mm Hg is associated with the largest incremental mortality benefits, with little evidence in support of systolic blood-pressure targets of less than 140 mm Hg. Similarly, scaling up blood pressure management across the population based on a target of 150 mm Hg is far more efficient in terms of the number needed to treat to avert one death compared with strategies to reduce the population mean to lower systolic blood pressure values. These results can inform hypertension guideline recommendations about the target value to which systolic blood pressure should be reduced.

The choice of blood pressure management targets also has consequences for the proportion of the population who would need blood pressure management. For example, moving from the common target of less than 140/90 mm Hg to the new American College of Cardiology and American Heart Association target of less than 130/80 mm Hg would increase the number of South Africans in need of blood pressure management to nearly half of the adult population.¹⁰ Such increases place a substantial burden on health systems and individuals, and thus need to be justified with respect to the value gained (eg, fewer cardiovascular events and lower mortality) relative to the number treated.

We aimed to estimate the relationship between systolic blood pressure and 6-year all-cause mortality using country-wide, population-based longitudinal cohort data in South Africa. We aimed to estimate and compare the mortality risk reductions associated with reducing systolic blood pressure to specific targets, focusing on the incremental benefits of lower treatment targets. We also aimed to investigate the total number of deaths averted, the share of the adult population that would require treatment, and the number needed to treat (NNT) to avert one death under hypothetical population-wide scale-ups of blood pressure management using different targets. To the best of our knowledge, this is the first study to address these aims in a sub-Saharan African country.

Methods

Study design and participants

In this country-wide, population-based cohort study, we analysed longitudinal data on adults aged 30 years and older from the 2008, 2010–11, 2012, 2014–15, and 2017 waves of the South African National Income Dynamics Study (NIDS).¹¹ NIDS is a nationally representative panel study that contains detailed household demographic, social, and economic information. Importantly, trained NIDS enumerators also collected health information for individuals of all ages, including measured height, bodyweight, and blood pressure for individuals aged 18 years and older.

NIDS used a two-stage cluster stratified sampling design. NIDS first randomly selected 400 Statistics South Africa primary sampling units, which are South Africa's census enumeration areas. Within selected primary sampling units, NIDS randomly selected 24 dwellings. When there was more than one household in a dwelling, each household was assigned a unique number. If the household agreed to be interviewed, all household members were interviewed. Of the 10 642 identified households, 7305 (69%) agreed to participate in the 2008 wave, resulting in a baseline sample size of approximately 28 000 individuals. Non-respondents were more likely to be White and reside in urban areas.¹¹ The NIDS survey design weights correct for this differential pattern of non-response under the assumption that White and

urban households that did respond are similar to those that did not.¹²

We restricted our study sample to adults aged 30 years and older because hypertension among adults younger than 30 years is often due to other causes (eg, thyroid disease or adrenal tumours), which, when treated, generally decreases blood pressure.^{13,14} Additionally, there is little evidence on the benefits of blood pressure reductions among individuals younger than 30 years because they are vastly under-represented in clinical trials compared with older adults, for whom strong evidence does exist.^{15,16}

This study was exempt from institutional review board approval because the data are publicly available and de-identified.

Procedures

The primary exposure was systolic blood pressure based on measurements taken by trained NIDS survey enumerators using an Omron M7 BP Monitor with standard validated multi-size cuffs.⁴ Enumerators took measurements on the left arm of each individual while they were lying down, ensuring that individuals had been resting for at least 5 min before the initial measurement. Importantly, blood pressure measurements for the same individual can vary substantially due to both natural blood pressure variation and measurement error from either incorrect measurement technique or from the blood pressure measurement device.¹⁷ For this reason, in clinical practice, decisions around blood pressure are based on multiple measurements taken over a period of days or weeks.^{18,19} Because blood pressure for survey respondents was only measured on the day of the survey, it might not be an accurate estimate of an individual's true blood pressure. Such measurement error can bias estimates of the relationship between blood pressure and mortality towards the null (known as dilution bias).²⁰ To reduce dilution bias we used the average of the 2008 and 2010–11 blood pressure measurements as our primary exposure, which can be interpreted as a 2-year average blood pressure. For all analyses, we used individuals' measured systolic blood pressure. However, taking medicines to lower blood pressure might confound the relationship between blood pressure and mortality because individuals taking medicine might have higher mortality risk than individuals at the same untreated blood pressure if medicines are given to individuals with comorbidities or high cardiovascular disease risk, or if those who take medicine also have greater access to health care and treatment. Therefore, we additionally assessed the relationship between systolic blood pressure and mortality adjusting for whether an individual self-reported taking medicines for lowering blood pressure (measured as a binary yes or no).

Our primary outcome was 6-year all-cause mortality, measured as mortality between the 2010–11 and 2017 waves of the NIDS survey. The NIDS enumerators

determined which individuals died based on household-member reports of deaths. We classified those not interviewed and not confirmed to have died by 2017 as lost to follow-up.

We adjusted for potential confounders (all measured in 2010–11) in the relationship between systolic blood pressure and mortality, including age, sex, race (African, Coloured, Asian or Indian, White), completed schooling (none, primary, secondary, tertiary), marital status (married or living with a partner, widowed, divorced or separated, never married), residence type (urban, rural, traditional), province, self-reported health status (excellent, very good, good, fair, poor), current smoking status, weekly frequency of alcohol use (<1, 1–2, ≥3 days per week), reported frequency of exercise (<1, 1–2, ≥3 times per week), and body-mass index. We adjusted for social and geographical variables (race, schooling, residence type, and province) because they affect a wide range of potential confounders, including the availability and quality of health services and the physical environment. The term “Coloured” is used by Statistics South Africa, and is a South African ethnic label that includes children or descendants from Black-White, Black-Asian, Black-Coloured, and White-Asian unions.²¹

Statistical analysis

Our analysis had three main steps. First, we estimated the association between systolic blood pressure and mortality, adjusting for the potential confounders already described, using a logistic regression model with 6-year mortality as the primary outcome. To capture potential non-linearities in the relationship between blood pressure and mortality, we modelled mortality as a cubic function of systolic blood pressure and present the results as the confounder-adjusted probability of mortality for systolic blood pressure values between 120 mm Hg and 180 mm Hg (systolic blood pressure modelled as a quadratic function and as a natural cubic spline is shown in the appendix p 7).

Second, we estimated and compared the mortality reductions associated with lowering systolic blood pressure to targets of 120 mm Hg, 130 mm Hg, 140 mm Hg, and 150 mm Hg. Because the size of the mortality reduction associated with reducing systolic blood pressure to each target is dependent on the starting systolic blood pressure for each individual, we considered reductions to each target starting from values of 130 mm Hg, 140 mm Hg, 150 mm Hg, and 160 mm Hg. Fixing the starting values facilitates clear effectiveness comparisons of the different targets. For these analyses, we used the estimated regression model to predict the mean 6-year mortality at each starting and ending systolic blood pressure value. We then estimated the relative risk reduction as the ratio of the mean mortality at the ending systolic blood pressure value divided by the mean mortality at the starting value. This ratio is known as an average marginal effect.

See Online for appendix

Third, we examined the population-level consequences of using different systolic blood pressure targets to scale up hypertension care using the parametric g-formula

Cohort (n=4993)	
Age, years	50.5 (14.0)
Women	3432 (68.7%)
Race	
African	4226 (84.6%)
Coloured*	628 (12.6%)
Asian or Indian	52 (1.0%)
White	87 (1.7%)
Marital status	
Married or living with partner	2530 (50.7%)
Widow, divorced, or separated	980 (19.6%)
Never married	1483 (29.7%)
Completed schooling	
No schooling	1162 (23.3%)
Primary and secondary	3399 (68.1%)
Tertiary	432 (8.7%)
Residence type	
Urban	2191 (43.9%)
Traditional	2394 (47.9%)
Rural	408 (8.2%)
Province	
Western Cape	395 (7.9%)
Eastern Cape	686 (13.7%)
Northern Cape	396 (7.9%)
Free State	294 (5.9%)
KwaZulu-Natal	1492 (29.9%)
North West	351 (7.0%)
Gauteng	497 (10.0%)
Mpumalanga	396 (7.9%)
Limpopo	486 (9.7%)
Self-reported health status	
Excellent	1351 (27.1%)
Very good	1390 (27.8%)
Good	1261 (25.3%)
Fair	679 (13.6%)
Poor	312 (6.2%)
Current smoker	807 (16.2%)
Number of days of alcohol use per week	
<1	4664 (93.4%)
1–2	204 (4.1%)
≥3	125 (2.5%)
Reported frequency of exercising per week	
<1	4446 (89.0%)
1–2	332 (6.6%)
≥3	215 (4.3%)
Body-mass index (kg/m ²)	28.4 (7.6)

Data are mean (SD) or n (%). *The term "Coloured" is used by Statistics South Africa, and is a South African ethnic label that includes children or descendants from Black-White, Black-Asian, Black-Coloured, and White-Asian unions.²¹

Table 1: Descriptive characteristics of the sample in the baseline 2010–11 wave, South African National Income Dynamics Study

modelling technique. The g-formula is a form of direct standardisation used for estimating the effect of hypothetical policies and interventions using observational data.^{22,23} For this analysis, we considered all individuals with a systolic blood pressure greater than the selected target as being in need of blood pressure management.

We examined four population-level outcomes for each target (120 mm Hg, 130 mm Hg, 140 mm Hg, and 150 mm Hg) of systolic blood pressure reduction: (1) the number of deaths that would be averted in the overall population if all individuals with a systolic blood pressure greater than the target had their systolic blood pressure reduced to the target value; (2) the proportion of the population with systolic blood pressure greater than the target value and therefore in need of blood pressure management; (3) the NNT; and (4) the population-level mean systolic blood pressure reduction required to achieve each target. Because this population-level analysis is focused on the overall adult population, the resulting estimates of mortality reductions are distinct from previous analyses because this analysis is a product of mortality reductions associated with reducing blood pressure down to a specific target starting from each individual's initial systolic blood pressure (rather than from a fixed starting systolic blood pressure), the proportion of the population who have a systolic blood pressure greater than each specific target, and how much greater individuals' systolic blood pressure values are than the target values.

To estimate these hypothetical population-wide scale-up scenarios using the g-formula, we used the regression coefficients, together with observed confounder values, to estimate the risk of mortality for all included participants (the natural course estimates). Next, for each systolic blood pressure management target of interest, we decreased systolic blood pressure to the target value among those individuals with values greater than the target and re-estimated the mortality risk (the counterfactual estimates) using the original regression coefficients, the reduced systolic blood pressure values, and the unchanged values of the other covariates. We then estimated mortality averted by comparing mortality risk in the natural course and counterfactual populations. Similarly, we estimated the mean shift in systolic blood pressure required to achieve the targets for scale-up of blood pressure management as the difference in mean systolic blood pressure between the natural course and counterfactual estimates.

We weighted all analyses by the NIDS design sampling weights to adjust for the survey sampling procedures and household non-responses in the baseline survey wave.¹² We did all analyses in R version 3.6.3.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and the final responsibility for the decision to submit for publication.

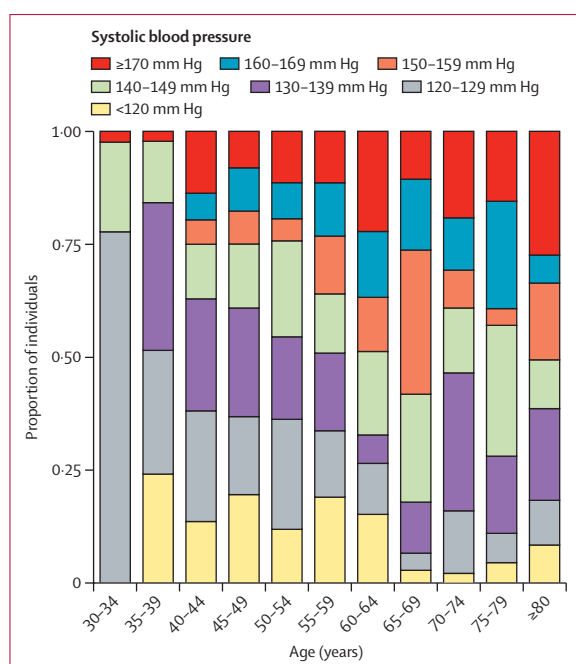


Figure 1: Age-specific proportions of individuals in different systolic blood pressure categories (2020–11 wave of the NIDS survey)

The proportions were weighted by the NIDS design weights to adjust for the survey sampling procedures and household non-responses in the baseline survey wave. NIDS=National Income Dynamics Study.

Results

Of the 8338 respondents aged 30 years or older in the 2010–11 wave of the survey, 927 (11.1%) were missing vital status information in 2017 and were therefore excluded. 2236 (30.2%) of the remaining 7411 respondents were missing blood pressure measurements in 2008 or 2010–11; 1355 (18.3%) were missing 2010–11 information on confounders. Overall, a total of 2418 (32.6%) of 7411 age-eligible respondents were missing blood pressure measurements or a confounder value. We excluded these individuals, resulting in a final sample of 4993 participants, representing 67.4% of the age-eligible sample with vital status information in 2017 (appendix p 4). Compared with participants who were included in our study (appendix p 1), those who were excluded were less likely to be women (54.6% of those excluded for missing data and 53.2% of those excluded for loss to follow-up vs 69.7% of those included), African (70.3% of those excluded for missing data and 58.7% of those excluded for loss to follow-up vs 84.6% of those included), have tertiary schooling (12.2% of those excluded for missing data and 27.4% of those excluded for loss to follow-up vs 8.7% of those included), and live in urban areas (53.6% of those excluded for missing data and 66.0% of those excluded for loss to follow-up vs 43.9% of those included).

Baseline characteristics recorded in the 2010–11 wave of the NIDS survey for the included participants are shown in table 1; characteristics of the individuals who

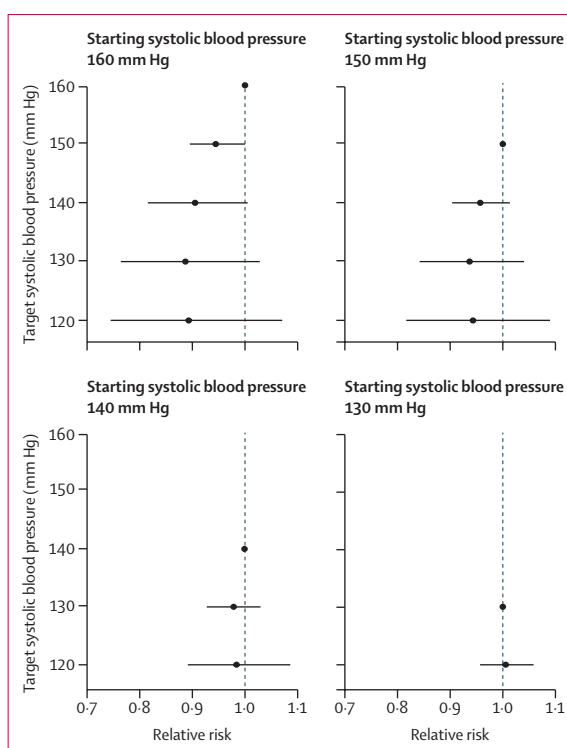


Figure 2: Mean 6-year mortality risk reductions associated with reducing systolic blood pressure from specific starting to target values

Error bars are 95% CIs. The results are adjusted for age, sex, race, marital status, formal school, residence type, province, self-reported health status, current smoking, exercise, alcohol use and bodyweight (body-mass index), and are weighted by the National Income Dynamics Study design weights to adjust for the survey sampling procedures and household non-responses in the baseline survey wave.

were lost to follow-up or who were excluded due to missing data are shown in the appendix (p 1).

The share of the population with a systolic blood pressure of 140 mm Hg or more increased from 7% at age 30 years to 57% by age 80 years (figure 1). Among adults aged 30–49 years ($n=2607$), 12.4% (95% CI 10.6–14.3) had a systolic blood pressure of 140 mm Hg or more, 6.6% (5.2–7.9) had a systolic blood pressure of 150 mm Hg or more, and 3.5% (2.4–4.6) had a systolic blood pressure of 160 mm Hg or more. Among adults aged 50 years or older ($n=2386$), 44.0% (95% CI 41.0–46.9) had a systolic blood pressure of 140 mm Hg or more, 28.0% (25.4–30.7) had a systolic blood pressure of 150 mm Hg or more, and 18.2% (15.9–20.5) had a systolic blood pressure of 160 mm Hg or more.

There was a non-linear relationship between systolic blood pressure and 6-year all-cause mortality (appendix p 5), with the lowest absolute mortality risk (8.1%) at 128 mm Hg. This non-linear association resulted in larger incremental mortality reductions at greater systolic blood pressure values, with a substantial flattening of benefits for targets below 140 mm Hg. Reducing systolic blood pressure from 160 mm Hg to 150 mm Hg was associated with a relative risk [RR] of mortality of 0.95

	120 mm Hg		130 mm Hg		140 mm Hg		150 mm Hg	
	Deaths averted per 1000 (95% CI)	p value	Deaths averted per 1000 (95% CI)	p value	Deaths averted per 1000 (95% CI)	p value	Deaths averted per 1000 (95% CI)	p value
Overall	-5.6 (-14.8 to 3.6)	0.24	-6.2 (-12.6 to 0.2)	0.059	-4.9 (-9.3 to -0.5)	0.028	-3.3 (-6.5 to -0.1)	0.044
Sex								
Male	-5.6 (-15.9 to 4.6)	0.28	-6.4 (-13.2 to 0.5)	0.067	-5.0 (-9.6 to -0.5)	0.031	-3.4 (-6.6 to -0.1)	0.043
Female	-5.5 (-14.3 to 3.2)	0.22	-6.1 (-12.3 to 0.2)	0.057	-4.9 (-9.2 to -0.5)	0.028	-3.2 (-6.4 to 0.0)	0.047
Race								
African	-5.4 (-14.5 to 3.6)	0.24	-6.0 (-12.3 to 0.2)	0.060	-4.8 (-9.1 to -0.5)	0.029	-3.2 (-6.4 to -0.1)	0.046
Coloured*	-8.1 (-20.8 to 4.5)	0.21	-8.9 (-18.1 to 0.3)	0.057	-7.2 (-13.7 to -0.7)	0.030	-4.9 (-9.7 to -0.1)	0.046
Asian or Indian	-3.6 (-13.3 to 6.0)	0.46	-4.2 (-11.1 to 2.7)	0.24	-3.0 (-7.4 to 1.4)	0.18	-1.4 (-3.3 to 0.6)	0.17
White	-4.2 (-12.3 to 3.9)	0.31	-4.7 (-10.4 to 0.9)	0.098	-3.7 (-7.4 to 0.1)	0.054	-2.3 (-4.8 to 0.2)	0.073
Residence type								
Urban	-5.2 (-13.3 to 2.9)	0.21	-5.7 (-11.5 to 0.0)	0.049	-4.7 (-8.8 to -0.5)	0.028	-3.2 (-6.5 to 0.0)	0.052
Traditional	-6.1 (-16.9 to 4.7)	0.27	-6.8 (-14.3 to 0.7)	0.075	-5.3 (-10.2 to -0.5)	0.032	-3.4 (-6.7 to -0.2)	0.040
Rural	-5.2 (-14.7 to 4.3)	0.29	-5.8 (-12.5 to 0.8)	0.085	-4.6 (-9.2 to 0.0)	0.051	-2.9 (-6.2 to 0.4)	0.084

Results are adjusted for age, sex, race, marital status, formal schooling, residence type, province, self-reported health status, current smoking, exercise, alcohol use, and bodyweight (body-mass index). *The term "Coloured" is used by Statistics South Africa, and is a South African ethnic label that includes children or descendants from Black-White, Black-Asian, Black-Coloured, and White-Asian unions.²¹

Table 2: Estimated deaths averted per 1000 population for different systolic blood pressure reduction scenarios by sex, race, and residence type

(95% CI 0.90–0.99; $p=0.033$), incrementally reducing systolic blood pressure from 150 mm Hg to 140 mm Hg resulted in RR 0.96 (0.91–1.01; $p=0.12$), with no evidence of further incremental benefits from reducing systolic blood pressure from 140 mm Hg to 130 mm Hg (RR 0.98 [0.93–1.03], $p=0.40$) or from 130 mm Hg to 120 mm Hg (RR 1.01 [0.96–1.06], $p=0.81$; figure 2). The analysis of the relationship between systolic blood pressure and mortality adjusted for self-reported medicines that lower blood pressure are shown in the appendix (p 6).

At the population level, the number of deaths averted per 1000 population was similar across different hypothetical population-wide scale-up scenarios. For example, reducing systolic blood pressure to 120 mm Hg among all those with a starting systolic blood pressure of more than 120 mm Hg (120 mm Hg scenario) was associated with 5.6 deaths averted per 1000 population (95% CI -14.8 to 3.6; $p=0.24$), compared with 3.3 deaths averted per 1000 population (-6.5 to -0.1; $p=0.044$) associated with reducing systolic blood pressure to 150 mm Hg among all those with a starting systolic blood pressure of more than 150 mm Hg (150 mm Hg scenario; table 2 and figure 3). However, there were large differences between scenarios in the proportion of the population that would require treatment, ranging from 65% (95% CI 64.0 to 66.7; $p<0.0001$) in the 120 mm Hg scenario to 16% (15.2 to 17.3; $p<0.0001$) in the 150 mm Hg scenario (figure 3; appendix p 8). Similarly, to achieve the target, the 120 mm Hg scenario required a mean shift of -13.8 mm Hg in systolic blood pressure (95% CI -14.4 to -13.3; $p<0.0001$) compared with a -2.7 mm Hg mean change (-3.0 to -2.5; $p<0.0001$) for the 150 mm Hg scenario (figure 3; appendix p 8). Based

on the ratio of number of deaths averted to the proportion requiring treatment, the 150 mm Hg scenario had the smallest NNT ($n=50$), followed by the 140 mm Hg scenario ($n=54$), the 130 mm Hg scenario ($n=70$), and the 120 mm Hg scenario ($n=117$).

The number of deaths averted per 1000 population was similar between men and women and for different residence types across all scenarios (table 2). However, there were important differences between racial groups. For all scenarios, individuals in the Coloured group had the highest number of deaths averted per 1000 population, followed by the African, White, and Asian or Indian groups. The number needed to treat in the analytic sample and among adults aged 50 years and older is shown in the appendix (p 9).

Appendix pp 10–11 shows the main results when imputing the missing data using multiple imputation by chained equations. These results should be cautiously interpreted because they assume that data are missing at random, conditional on the observed covariates.

Discussion

In this population-based cohort study, we found a weak and non-linear relationship between systolic blood pressure and mortality in South Africa that resulted in larger incremental mortality benefits at greater systolic blood pressure values. We found the greatest benefits associated with reducing systolic blood pressure down to 140–150 mm Hg, with small incremental benefits of reductions to less than 140 mm Hg, and no evidence of an incremental benefit from further reductions to 120 mm Hg. At the population level, scaling up blood pressure management to achieve a 150 mm Hg target was far more efficient in terms of the NNT compared with

strategies to achieve lower population systolic blood pressure targets. This was because strategies to reduce systolic blood pressure to values lower than 150 mm Hg would require providing management to a far greater share of the adult population who have starting systolic blood pressure levels for which reductions were only associated with small incremental mortality benefits. In addition to efficiency, higher targets might also be more realistic to accomplish because they would require substantially fewer health services and personnel.¹⁰ Although our findings, which suggest that there is little evidence in support of reducing systolic blood pressure below 140 mm Hg are in line with the WHO HEARTS and South African Society of Hypertension guidelines, these guideline recommendations were not based on actual longitudinal data from the country.^{18,19} To our knowledge, our findings thus provide some of the first population-based longitudinal evidence in support of these systolic blood pressure targets.

Our results contrast with the continuous linear relationship between systolic blood pressure and mortality starting from as low as 90 mm Hg observed in high-income countries and some populous LMICs, such as China, India, and Indonesia.^{6,24–26} This difference in findings might be explained by competing causes of death from tuberculosis and HIV in South Africa. Tuberculosis and HIV accounted for 12% of deaths in South Africa in 2015–17, with the greatest mortality burden among adults aged between 30 and 55 years²⁷ who constitute the majority of our study population and generally have systolic blood pressure values less than 150 mm Hg. These prominent competing causes of mortality might thus explain the weaker relationship between systolic blood pressure and mortality in our study. One important question is whether our results apply to other sub-Saharan African countries. If the weaker relationship is indeed due to competing causes of death, our results might apply to southern and eastern African countries with similar health profiles (eg, high tuberculosis and HIV mortality) as South Africa, but potentially not to western African countries where tuberculosis and HIV mortality is much lower.²⁸

This study has several key limitations. First, because we used an observational study design, our results are subject to confounding bias, although the direction of bias is unclear. Although clinical trials generally produce unbiased estimates for their target population, when these estimates are extrapolated to other contexts, as is often done in modelling studies,⁸ it is unclear whether the bias resulting from this extrapolation is greater or less than the confounding bias resulting from observational data.²⁹ Therefore, our findings are not a replacement for modelling studies but should be considered in conjunction with other approaches. Second, although in clinical practice blood pressure management decisions are based on blood pressure measured on at least two

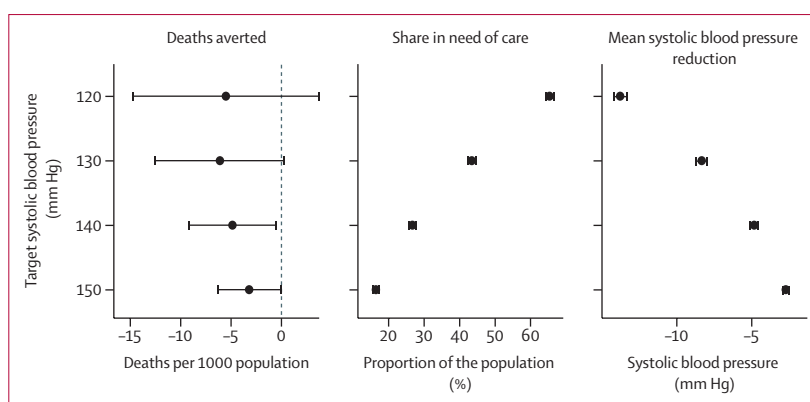


Figure 3: Estimated mortality averted per 1000 population, the proportion of the population in need of care, and mean systolic blood pressure reduction for different reduction scenarios

Error bars represent 95% CIs. The results are adjusted for age, sex, race, marital status, completed schooling, residence type, province, self-reported health status, current smoking, exercise, alcohol use, and bodyweight (body-mass index), and are weighted by the National Income Dynamics Study design weights to adjust for the survey sampling procedures and household non-responses in the baseline survey wave.

consecutive health-care visits approximately 2 weeks apart, our results are based on averaging two systolic blood pressure measurements taken approximately 2 years apart. Third, although the survey aimed to collect nationally representative data, we excluded age-eligible adults who were missing blood pressure or confounder values (32.6%) or who were missing vital status information in the 2017 wave of the NIDS survey (11.1% lost to follow-up), which might result in selection bias. Compared with participants included in our study (appendix p 1), those lost to follow-up were more likely to be White, reside in urban areas, and report excellent health. Therefore, our results might not represent the overall South African population. However, it is unclear how non-response might affect the results. White individuals, those living in urban areas, and those who report better health might have a stronger relationship between systolic blood pressure and mortality due to fewer competing causes of mortality; on the other hand, the relationship between systolic blood pressure and mortality might be weaker because these individuals have greater access to health services in the event of blood pressure-related conditions. Fourth, blood pressure measurement error might have contributed to the attenuated relationship between systolic blood pressure and mortality in our study.²⁰ Although we used a 2-year average of systolic blood pressure measurements to reduce dilution bias, our approach might not have fully accounted for this source of error. A recently developed approach using random effects to represent the variation in blood pressure measurements is promising for reducing dilution bias.³⁰ However, we did not implement this method here because it is not yet clear how to combine it with the parametric g-formula. Fifth, our approach assumes that adjusted comparisons of individuals at different starting systolic blood pressure values are representative of the effect of lowering systolic blood

pressure between two different levels through lifestyle changes or medicines. However, large meta-analyses have found a strong concordance between clinical-trial effects of blood pressure reductions and the difference in mortality between individuals at different starting systolic blood pressure levels in prospective studies.³¹ Last, our approach estimated the mean 6-year mortality reduction associated with systolic blood pressure changes and did not assess mortality beyond 6 years. We also did not explore potential heterogeneities in the relationship between systolic blood pressure and mortality, such as interactions with body-mass index or cardiovascular disease risk, because our data were not sufficiently powered to detect such differences. Identifying such treatment heterogeneities is an important future area of work for further improving the effectiveness of blood pressure reduction efforts.

Despite these limitations, our study has important strengths. We use the only source of country-wide, population-based longitudinal data from South Africa to directly estimate the relationship between systolic blood pressure and mortality. As a result, our estimates might more closely represent the effects of a real population scale-up of blood pressure management compared with estimates from studies based on small samples or clinics, or estimates extrapolated from other contexts to LMICs. Ultimately, our results add to a growing body of evidence that shows that applying estimates from one context to another context—such as applying estimates from high-income countries to South Africa—can lead to misleading results.²⁹ This is an especially important consideration for other sub-Saharan African countries seeking to formulate and introduce policies to lower blood pressure.

Contributors

NS conceived of the manuscript idea. All authors were involved in the design of the study. AOD, MJB, and NS did the data analysis. AOD wrote the initial manuscript. All authors contributed to writing and editing the main manuscript. AOD, MJB, and NS accessed and verified the data.

Declaration of interests

MKA reports a grant from Merck to his institution, outside the submitted work. All other authors declare no competing interests.

Data sharing

All study data and related documents are publicly available from the National Income Dynamics Study.

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