Shifting the curve – body mass index and all-cause mortality in a population-based cohort in rural South Africa

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Complete List of Authors:	Manne-Goehler, Jennifer; Massachusetts General Hospital, Division of Infectious Diseases Baisley, Kathy Vandormael, Alain Bärnighausen, Till; UniversitatsKlinikum Heidelberg, Institute for Global Health; Harvard T.H. Chan School of Public Health, Department of Global Health and Population; Africa Health Research Institute Tanser, Frank Herbst, Korbus Pillay, Deenan Siedner, Mark
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Jennifer Manne-Goehler[1,9,10], Kathy Baisley[2,3], Alain Vandormael[5,7], Till W. Bärnighausen[3,5,6], Frank Tanser[3,4,8], Korbus Herbst[3], Deenan Pillay[3], Mark J. Siedner[1,3, 9,10]

[1]Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA; [2]Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]Africa Health Research Institute, KwaZulu-Natal, South Africa; [4]School of Nursing and Public Health, University of KwaZulu-Natal, South Africa; [5]Heidelberg Institute of Global Health (HIGH), University of Heidelberg, Heidelberg, Germany; [6]Department of Global Health and Population and Harvard Center Population and Development, Harvard School of Public Health, Boston, USA; [7]KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP), UKZN, South Africa;[8]College of Social Science, University of Lincoln, Lincoln, UK; [9]Harvard Medical School, Boston, MA; [10]Massachusetts General Hospital Medical Practice Evaluation Center, Boston, MA

Address for Correspondence:
Jennifer Manne-Goehler, MD, DSc, MSc
Massachusetts General Hospital
Harvard Medical School,
55 Fruit Street, Boston, MA 02215, U.S.A;
Tel: 754-224-6060; Fax 617-432-6733,
Email: jmanne@post.harvard.edu

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STUDY IMPORTANCE

What is already known about this subject?

1. Previous research regarding the relationship between body mass index and mortality has been conducted in high-income settings but there are few studies of this relationship in sub-Saharan Africa.

2. The implications of clinically-defined body mass index thresholds for overweight and obesity are poorly characterized in low-income settings such as South Africa.

What are the new findings in your manuscript?

1. This study identifies a rightward "shift" in the J-shaped curve that describes the relationship between BMI and all-cause mortality in a large cohort of adults in rural South Africa.

2. In this setting, the curve shifts by approximately 5-10 kg/m^2, particularly for women, such that the lowest risk of short-term mortality might be afforded by a higher BMI, which has been clinically defined as overweight or obesity in higher income settings

How might your results change the direction of research or the focus of clinical practice?

1. In light of the widespread increases in the prevalence of higher BMI in sub-Saharan Africa, these findings provide important insight about risk associated with high BMI in this region and specifically suggest that clinically-defined overweight may not confer an increased risk of mortality in this context.

2. Future research should focus on corroborating these findings, while extrapolating the mechanisms by which body weight impacts morbidity and mortality in sub-Saharan Africa.

ABSTRACT

OBJECTIVE: In this study, we sought to evaluate the association between BMI, all-cause and cause-specific mortality in South Africa.

METHODS: This study analysed prospective, population-based observational cohort data from rural South Africa. BMI was measured in 2010. Demographic characteristics were recorded and deaths were verified with verbal autopsy interview. The InterVA-5 tool was used to assign causes of death. HIV testing was conducted annually. Cox proportional hazards models were fit to estimate the effect of BMI on all-cause and cause-specific mortality, accounting for the competing risk of death from other causes. Models were adjusted for sociodemographic characteristics and HIV status and we used inverse probability weighting for survey non-participation.

RESULTS: Our cohort consisted of 9,728 individuals. In adjusted models, those with a BMI of 25.0 – 29.9 kg/m^2 or 30.0 – 34.9 kg/m^2 had a lower hazard of death (aHR: 0.80; 95% CI: 0.69 - 0.92 and aHR: 0.75; 95% CI: 0.60 - 0.93, respectively), compared to those with a BMI of 18.5 – 24.9 kg/m^2.

CONCLUSIONS: Individuals in South Africa who meet clinically-defined criteria for overweight or obesity had a lower risk of all-cause mortality than those of normal BMI. These findings were stronger for women and communicable conditions.

INTRODUCTION

Overweight and obesity are rapidly increasing in low- and middle-income countries (LMICs).[1, 2] Though the prevalence of clinically-defined obesity has reached epidemic levels in some LMICs, the mortality risk associated with increased body weight remains unknown in these settings. Evidence from high-income countries (HICs) has been conflicting about whether a body mass index (BMI) between 25.0 – 29.9 kg/m^2 is associated with an increased risk of mortality compared to those with a BMI 18.0 – 24.9kg/m^2, though most prior research suggests that mortality risk is increased among those with a BMI 30.0 – 34.9 kg/m^2 and a BMI ≥35 kg/m^2, respectively.[3-6]

However, the relationship between BMI and mortality for people living in other regions of the world remains unclear, due to scarce data on body anthropometry measurements and long-term survival. There is good reason to suspect that relationships between body habitus and mortality might differ in these settings. For example, relationships between BMI and mortality appear to be different among people living with HIV or cancer, and the prevalence of HIV exceeds 20% in some Southern African countries.[3, 7] Nonetheless, in cross-sectional studies, higher BMI is associated with increased cardiovascular risk, as well as higher rates of hypertension and diabetes.[8, 9] While several studies from sub-Saharan Africa suggest an extremely high prevalence (>67%) of traditionally-defined overweight and obesity, [10, 11] particularly in women, there has not yet been a study from this region quantifying the risk posed by overweight or obesity for all-cause or cardiovascular disease-related mortality.

Given the dramatic increases in the prevalence of clinically-defined overweight and obesity in SSA in recent decades [1, 12, 13], and the lack of evidence about its relationship with mortality in the region,

we sought to measure associations between BMI and both all-cause and cause-specific mortality in a population-based cohort in South Africa. To do so, we examined data from a well-characterized, population-based cohort from a demographic health and surveillance site that included BMI measurement in 2010, followed by routine prospective data collection on mortality through verbal autopsy procedures. Given the extreme differences in the distribution of BMI and epidemiology of morbidity in our study setting, we hypothesized that higher BMI thresholds would be protective for mortality in rural South Africa as compared to settings in the global north.

METHODS

Study Population and Socio-demographic Data

The African Health Research Institution (AHRI) (formerly the Africa Centre for Health and Population Studies) is a Wellcome Trust-funded research institute in South Africa. Since 2000, AHRI has maintained one of the largest population-based cohorts in the region via periodic household-based surveys. These surveys have been used to collect demographic data from a population of approximately 100,000 individuals living in a rural area of 438 km^2 in rural uMkhanyakude District, northern KwaZulu-Natal.[14] Households are surveyed 2–3 times per year, to collect information on birth, deaths and migration patterns for all household members, including non-residents. The participation rate for household surveillance is >99%.[14] In addition, resident household members who are aged ≥15 years are invited to participate in an annual home-based individual survey, which includes an interview on general health and collection of a dried blood spot (DBS) for anonymised HIV testing. Approximately 70% of eligible residents participate in the survey at least once after five rounds, and as of 2017, 80% of individuals had participated in HIV testing at least once.[15, 16]

Body Anthropomorphic Data

In one round of the 2010 survey, all individuals who participated in the home-based individual survey were offered a physical examination in order to determine weight, height and blood pressure, using the World Health Organization STEP-wise approach to surveillance (STEPS) protocol.[17, 18] In brief, body weight was measured on a calibrated scale. Each person was weighed twice with outer clothing removed, and the second measurement was recorded if it fell within 200g of the first. If there was a difference of more than 200g between the first and second measurement, a third measurement was taken and the measurement that was obtained twice within a 200g range was recorded. To measure height, the

participant was asked to stand with both feet stepping on flat foot metal and straight knees and a measuring tape was used to assess height in centimetres. BMI was then calculated as weight in kilograms/(height in meters)^2.

HIV Infection and Clinical Care Data

In addition to offering annual HIV testing, AHRI has a memorandum of agreement with the South Africa Department of Health to access clinical care data from the local area primary health clinics (PHCs). We link surveillance site data with clinical data from the primary care and HIV care health systems using their surveillance identification numbers which are recorded by data capturers at each clinic and hospital in the DHS catchment area.

Mortality and Cause of Death Data

During each demographic visit, all deaths since the prior survey are recorded, including those of non-resident household members. All deaths are verified by a home-based follow-up verbal autopsy (VA) interview. This interview is conducted by a trained nurse with the closest available relative or caretaker of the deceased. The VA interview includes a qualitative narrative of the circumstances leading up to the death, a checklist of signs and symptoms, and a structured questionnaire, adapted from the World Health Organization (WHO) Verbal Autopsy Questionnaire.[19] The cause of death is then assigned using the InterVA-5 tool, which has been validated in this population previously.[20] Previous research has described the sensitivity and specificity of this tool for cause of death assignment.[20] These causes of death were then categorized into infectious and non-communicable causes using the WHO classification system.

Smoking Status

Smoking data were not collected as part of the 2010 survey. However, there was a recently completed community-based assessment of smoking behaviour in 14,509 individuals in the same population, among which 3,030 had participated in the 2010 survey.[21] In this more recent study, 91% of individuals reported never smoking (98% of women and 76% of men). Moreover, 22% of men and only 1% of women reported that they were current smokers in this same cohort.

Statistical analysis

Individual participants were eligible for inclusion in this analysis if they had their BMI measured in the home-based 2010 survey. We assessed mortality rates over the period from 2010 to 2017. Person-time was defined from the date of the 2010 survey, until the earliest date of death or the date that the individual was last recorded as a member of a household in the surveillance area. Periods of non-residence were included in the analysis if the individual remained a household member because date and cause of death data were available for these individuals.

We first compared sociodemographic characteristics by BMI group and separately, for those who did and did not complete the BMI survey using standard statistical methods. Next, we estimated crude all-cause mortality by sex and BMI category. We then used Kaplan-Meier methods to depict all-cause mortality stratified by BMI group, and Cox proportional hazards regression models to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (CIs) for the effect of BMI on mortality, in the total population and stratified by sex. BMI was modelled as a continuous covariate by restricted cubic splines with 4 knots and aHRs were presented at selected values of BMI, comparing the median value in each BMI group to a BMI of 22.0 as the reference value. BMI groups were defined using standard cut-offs as

follows: underweight (<18.5 kg/m^2), normal weight (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), class I obesity (30.0 – 34.9 kg/m^2) and class II obesity or great (≥35.0 kg/m^2). Models were adjusted for age (as the time scale of the analysis), sex, socioeconomic status (SES) and a composite variable for HIV serostatus, categorized as HIV negative, HIV positive or HIV unknown status. Socioeconomic status and HIV status were treated as time-updated exposures. SES was measured via an asset index, which was constructed using principal component analysis of ownership of common household items, based on information gathered in the household survey.[22] HIV status was assessed using data from the HIV serosurvey and TIER.net. Seroconversion dates were imputed using a random time point along the interval between the last negative test date and the first positive test date (or date of first record in TIER.net).[23, 24] An additional category of HIV unknown was used for individuals for the period before their first HIV test date, and 2 years after their last negative test if they had no record of a positive test, given the high incidence of HIV in this region.[23]

We also estimated the cumulative incidence of cause-specific mortality (infectious disease causes and non-communicable disease causes) stratified by BMI, while accounting for the competing risk of deaths from other causes. We used competing risks proportional hazards regression to estimate the sub-distribution hazard ratio (SHR) for the effect of BMI on cause-specific mortality, adjusted for age, sex, SES and HIV status as described above. These SHRs can be interpreted as an approximation of HRs estimated in standard Cox models, but accounting for the hazard of competing events.[25]

All regression models were weighted to account for non-response in the 2010 survey (when BMI was measured), to augment population representativeness. Response weights were calculated as the inverse probability of participation in the 2010 survey, in strata defined by age group, sex, and place of

residence (urban/peri-urban/rural).[26] We assessed assumptions about proportional hazards using scaled Schoenfeld residuals.[27] We conducted the following additional sensitivity analyses: 1) we began observation time two years after the BMI measurement, effectively excluding deaths in the first two years of follow-up;[28] 2) we examined the relationship between BMI and mortality by HIV status (HIV-negative, HIV-positive; 3) we examined the effect of BMI on mortality, unweighted for non-response; and 3) we further stratified the aHR for the normal BMI group into three subgroups (BMI 18.5 – <20.0, 20.0 – <22.5, 22.5 – <25.0), as has been done previously in this literature.[4, 29]

Ethics

Ethical approval for the demographic surveillance surveys, linkage to the government ART records (TIER.net), and analyses of these data were granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa (reference BE290/16). Separate written informed consent was obtained for the main household survey, the individual general health questionnaires and the HIV serosurvey.

RESULTS

Our cohort consisted of 9,728 individuals who had a BMI measured in the 2010 individual survey. This represents 37.1% of the 26,194 individuals who were eligible for the survey in that round. The median age of participants was 31 years (IQR 20-51); most (64%) were female, married (57%), lived in a rural area (63%) and had less than a secondary school education (54%). These sociodemographic characteristics are provided in Table 1 overall and by BMI group. Additionally, 16,431 (62.7%) of individuals were not available for the survey or declined participation, and another 35 (0.1%) individuals consented but their BMI measurements were not available. The differences in demographic characteristics among those who had their BMI measured and those who did not are provided in the Supplementary Appendix Table 1. In brief, the group that did not participate in BMI measurement included more men, more peri-urban dwellers and more people who were employed than those who did participate.

In adjusted and weighted Cox proportional hazards models, those with a BMI of 25.0 – 29.9 kg/m^2 and those with a BMI of 30.0 – 34.9 kg/m^2 had a lower hazard of death (aHR 0.80; 95% CI: 0.69 - 0.92 and aHR 0.75; 95% CI: 0.60 - 0.93, respectively), compared to those with a BMI of 18.5 – 24.9 kg/m^2 (Figure 1 and Table 2). Individuals with a BMI ≥35.0 kg/m^2 also had a lower hazard ratio of death than those who had a BMI of 18.5 – 24.9 kg/m^2 (0.80, 95% CI: 0.64 -1.02). The full unadjusted and adjusted model results including AHRs for all covariates are provided in Supplementary Appendix Table 2. In sex-stratified models, these findings were consistent in women, with an aHR of 0.79 (95% CI: 0.66 – 0.94) for those with a BMI of 25.0 – 29.9 kg/m^2, 0.76 (95% CI: 0.58 – 0.94) for those with a BMI of 30.0 – 34.9 kg/m^2 and 0.84 (95% CI: 0.64 – 1.10) for those with a BMI ≥35.0 kg/m^2, as compared to those with a BMI of 18.5 – 24.9 kg/m^2. We found similar effect sizes in men. Those with a BMI ≤18.5

kg/m^2 had the highest mortality rate in the total population as compared to those with a BMI of 18.5 – 24.9 kg/m^2 overall and when stratified by sex (aHR Overall: 1.37, 95% CI: 1.12 - 1.69; aHR Women: 1.64, 95% CI: 1.25 - 2.13; aHR Men: 1.27, 95% CI: 0.95 - 1.69). The relationship between continuous BMI and the aHRs and 95% confidence intervals for mortality in this cohort are depicted in Figure 2.

In sensitivity analyses, we found that excluding deaths within the first two years of follow-up resulted in similar effect sizes for the mortality risk associated with each BMI category (aHR: 1.34; 95% CI: 1.04 – 1.71, Table 2). Second, when examining these relationships by HIV status, we found that those with a BMI 25.0 – 29.9 kg/m^2 had a lower risk of death than those with a BMI of 18.5 – 24.9 kg/m^2 in both the HIV-positive (aHR 0.73, 95% CI: 0.57 – 0.94) and HIV-negative groups (aHR 0.76, 95% CI: 0.52 – 0.94) but this relationship was not the case for the HIV unknown group. Those with a BMI of 30.0 – 34.9 kg/m^2 (aHR 0.67, 95% CI: 0.48 – 0.91) and ≥35.0 kg/m^2 (aHR 0.65, 95% CI: 0.46 – 0.92) also had a lower mortality risk in the HIV-negative group only. The confidence intervals of the HR for these relationships overlapped with 1.0 in the HIV-positive and HIV unknown groups. In a sensitivity analysis that was performed without weights for non-response, we found no differences in the mortality risk by BMI group. Finally, when we stratified the mortality risk for the normal BMI group into three subgroups, and used 20.0 – <22.5 kg/m^2 as a referent group, we found that individuals with a BMI of 18.5 – <20.0 kg/m^2 had increased mortality (aHR 1.20; 95% CI: 1.08 – 1.33), and that those with a BMI of 22.5 – <25.0 kg/m^2 had decreased mortality (aHR 0.91; 95% CI: 0.88 – 0.95). The point estimate and confidence intervals of the lower mortality risk associated with a BMI of 25.0 – 29.9 kg/m^2 compared to 20.0 – <22.5 kg/m^2 as a referent group were similar to our primary model in this sensitivity analysis. (Table 2)

The sub-distributional hazard ratios describing the relationship between BMI and death from both infectious diseases and non-communicable causes are shown in the Supplementary Appendix Figure 1. In brief, individuals who had a BMI >25 kg/m^2 had a lower hazard of infectious causes of mortality across all higher BMI strata. In contrast, relationships between BMI and non-communicable diseases were muted, such that there was no difference in the hazard of mortality between those with BMI 30.0 – 34.9 kg/m^2, or ≥35.0 kg/m^2 and those with a BMI 18.0 – 24.9 kg/m^2. Supplementary Appendix Table 3 provides a detailed list of causes of death by BMI category.

DISCUSSION

In one of the largest population-based cohorts in sub-Saharan Africa, with near complete mortality estimation, we found that all-cause mortality over seven years of observation was lower in those who had a BMI of 25.0 – 29.9 kg/m^2 or 30.0 – 34.9 kg/m^2, compared to those who had a BMI 18.0 – 24.9 kg/m^2, according to standard, clinically-defined BMI definitions. This is consistent with a modest rightward "shift" in the traditional J-shaped curve that links BMI and mortality. This pattern was consistent in a sub-analysis of women, though our ability to describe these relationships in men was limited by smaller sample size. The protective effect of overweight and mild obesity was also best demonstrated for infectious causes of death; whereas we found neither a strong protective or harmful effect of higher BMI when restricted to non-communicable causes of death.

The current understanding of relationships between BMI and mortality is primarily based on evidence from HICs. These data have been conflicted about the mortality risk associated with being overweight. For instance, in one large collaborative study, the overweight range conferred a slightly increased risk of mortality while another meta-analysis did not show any increased mortality risk with that BMI category.[3, 6] However, this literature has had important clinical implications in terms of recommendations about ideal weight and healthy lifestyle, which have largely been incorporated into global primary and clinical care guidelines around weight loss and obesity prevention. Our study demonstrates that in this South African setting, the relationship between BMI and mortality also conforms to a J-shaped curve, however with a rightward "shift" in the curve by approximately 5 kg/m^2 compared to many such studies in HICs. This was particularly the case for women, such that the lowest risk of short-term mortality might be afforded by a higher BMI, which is clinically defined as overweight or obesity in current guidelines. This was also true in those who were confirmed to be HIV-

uninfected in this analysis. The reasons for this shift in the curve are unclear and will require further study. One potential hypothesis to be tested is that the determinants of higher BMI might be associated with improved access to healthcare, which in turn may be protective against many causes of premature mortality. Alternatively, this finding could be driven by differences in diet quality, or differences in the risk of cardiovascular disease associated with different BMI thresholds, among other factors.

Finally, we observed a lower risk of mortality due to infectious disease causes for those who were overweight versus those of normal weight. This finding was expected given that these deaths are likely driven in part by HIV and tuberculosis, both of which are highly prevalent and associated with wasting in their more advanced stages. In contrast, we were unable to draw definitive conclusions about the relationship between BMI and mortality due to non-communicable diseases, but our preliminary data do not show a strong protective or harmful effect of relatively higher weight in this population.

While data from LMICs are scarce, our findings are consistent with another recent population-based study of the relationship between BMI and cardiovascular outcomes from Chennai, India.[29] In that study, investigators enrolled over 400,000 participants between the ages of 35 and 69 years between 2002 and 2005 and then visited them biennially through 2015. While they uncovered a strong relationship between BMI and systolic blood pressure, they also found a weak relationship between BMI and cardiovascular mortality.[29] After adjusting for systolic blood pressure, BMI was inversely related to cardiac and stroke mortality, with underweight participants having a greater relative risk of cardiac and stroke, when compared with overweight participants.[29] Furthermore, among all participants in that study, as well as in a subset of lifelong non-smoking individuals, those who were overweight had a

similarly low risk of mortality to those who were normal weight. This risk of mortality did not increase substantially until a threshold of BMI ≥30.0 kg/m^2 was reached.

Efforts to confidently identify the causal framework and quantify the direction of the association between overweight or obesity and mortality have been subject to several major methodological concerns, all of which were carefully considered in the design and execution of this study. First, the causal direction of the relationship between BMI and mortality has long been subject to concerns about reverse causation bias, due to the fact that weight loss accompanies many life-limiting illnesses and if present, this bias may attenuate the apparent effect of overweight or obesity on mortality risk.[3, 30] The potential methodological challenge in such analyses is confounding by risk factors such as smoking, which is associated with lower body mass and thus may also lead to underestimates of the mortality risk associated with overweight or obesity. Third, valid assessment of BMI-associated mortality requires anthropomorphic measurement in population cohorts with long-term follow-up and near complete death reporting. Finally, while each of these methodological considerations has been raised previously, there is little empirical data to verify the magnitude of these adjustments on estimates of the relationship between BMI and mortality.

We attempted to assess each of these challenges through close attention to methodological details and various sensitivity analyses. First, in a sensitivity analysis, we excluded deaths within the first two years of observation to reduce reverse causation bias. We found the magnitude and direction of relationships were stable, but the confidence intervals around our HR estimates for those with a BMI 18.0 – 24.9 kg/m^2, 25.0 – 29.9 kg/m^2 or 30.0 – 34.9 kg/m^2 all increased, due to reduced power with a smaller number of outcomes in this sub-analyses. Further, we performed a sensitivity analysis in which we

stratified the normal BMI group into a low-normal and high-normal BMI and found that those with a low-normal BMI (18.5 – <20.0 kg/m^2) had a greater aHR of death, while those who had a high-normal BMI (22.5 – <25.0 kg/m^2) had a lower aHR of death, both as compared to those with a BMI of 20 – <22.5 kg/m^2. This reinforced our findings from the primary analysis. Finally, while there were no data collected on the smoking status of the participants in this survey, we believe that its influence on these results is likely modest at best, particularly among women, because recent studies have shown extremely low smoking rates. In a survey of smoking that was conducted in this population in 2012, only 4.1% (95% CI: 2.3 – 7.4%) of women in KwaZulu-Natal reported that they smoked and in a recent population-based survey in this area, only 1% of women self-reported that they were current smokers.[31]

There were several additional limitations to this study. First, while the sample size is large at over 9,000 individuals and the data comes from one of the largest population-based cohorts in southern Africa, the rate of participation in the one-time collection of BMI in 2010 was only 37%. Furthermore, participation was greater in women, who represented 62.0% of individuals who were eligible to participate in the study but 69.5% of those who consented to have their BMI measured. The cohort that took part in the data collection was also slightly more likely to be rural (61.6% overall v. 63.8% in participants) and somewhat less likely to be employed (22.7% overall v. 15.3% in participants), than the total eligible sample population. Otherwise, we did not observe major differences between those who did and did not participate in the survey, which somewhat mitigates the risk of selection bias. Moreover, we attempted to address any such differences by weighting all regression models for non-response in the 2010 survey, with weights calculated as the inverse probability of participation in the 2010 survey, in strata defined by age group, sex, and place of residence. We had a single BMI measurement followed by a relatively

short follow-up time in this study of 7 years and it is possible that non-communicable causes of death associated with higher BMI would require a longer period of follow-up to observe, or that these relationships may differ when considering the maximum lifetime or change in BMI.[32] Third, verbal autopsy is imperfect as an assessment of cause of death and thus our death assignment may be subject to misclassification, but this would not affect estimates of all-cause mortality in our primary analyses. Finally, we did not have data on waist-to-hip ratio and thus were unable to explore this alternative measure of body composition in these analyses.

In summary, we found that those with a BMI 25 – 29.9 kg/m^2 or a BMI 30.0 – 34.9 kg/m^2 had a lower overall risk of all-cause 7-year mortality in this large prospective cohort in rural South Africa. These findings were strongest for women, and for infectious causes of death, but were consistent in the overall cohort and robust to key sensitivity analyses.[5] In light of the widespread increases in the prevalence of higher BMI in these settings [2], future research should seek to corroborate our findings, while extrapolating the mechanisms by which body weight impacts morbidity and mortality.

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Reviewer: 1

Comments to the Author

COMMENT: This study represents findings in a cohort in rural South Africa. The data appear to be of good quality and the study appears to have been carefully done.

The authors found lower mortality in the overweight category (BMI 25-29.9) and Grade 1 obesity category (BMI 30-34.9) than in the normal weight category (BMI 18.5-24.9). Although the authors seem to regard these findings as different from those usually observed in 'high income' countries, this is not correct. The meta-analysis they cite as Reference 3 (Flegal et al) found exactly the same results both for overweight and for Grade 1 obesity as the present study in a sample of almost 3 million people, mostly from high income countries. Indeed, the analysis that they cite in Reference 6 from the Global BMI Mortality Collaboration actually also found almost exactly the same results in their initial results (see eTable 4 in the supplemental tables) with a hazard ratio significantly below 1 for overweight. Even after performing extremely large deletions, they still found a hazard ratio of 1.00 for overweight in their North American sample with measured height and weight (see eTable 22). In fact the US guidelines from Jensen et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults:. Circulation. 2014;129(25 Suppl 2):S102–S138 also state that overweight is not associated with increased mortality. Similar results were reported from a very large Korean study of 12 million people (see Flegal KM, Graubard BI, Yi SW. Comparative effects of the restriction method in two large observational studies of body mass index and mortality among adults. Eur J Clin Invest. 2017;47(6):415–421. doi:10.1111/eci.12756). The Berrington de Gonzalez article has a smaller sample size than Reference 3, Reference 6 or the Korean study and depends entirely on self-reported weight and height values, which have been demonstrated to produce higher results than the use of measured weight and height. The Berrington article should not be depended on. The authors need to remove the statements suggesting that their findings are different from those in high income countries and put in the information that their findings are similar to many of those from high income countries. The sentence beginning on line 10 on page 4 should be deleted.

RESPONSE: We appreciate the reviewer's concerns and agree that the data about this relationship are also fraught in high-income settings. We have removed the references to Berrington de Gonzalez and rewritten the relevant sections of the introduction and discussion to reflect the reviewer's concerns.

Revised section of the introduction:

"Overweight and obesity are rapidly increasing in low- and middle-income countries (LMICs).[1, 2] Though the prevalence of clinically-defined obesity has reached epidemic levels in some LMICs, the mortality risk associated with increased body weight remains unknown in these settings. Evidence from high-income countries (HICs) has been conflicted about whether a body mass index (BMI) between 25.0 – 29.9 kg/m^2 is associated with an increased risk of mortality compared to those with a BMI 18.0 – 24.9kg/m^2, though most prior research suggests that mortality risk is increased among those with a BMI 30.0 – 34.9 kg/m^2 and a BMI ≥35 kg/m^2, respectively.[3-6]

However, the relationship between BMI and mortality for people living in other regions of the world remains unclear, due to scarce data on body anthropometry measurements and long-term survival. There is good reason to suspect that relationships between body habitus and mortality might differ in these settings."

Revised section of the discussion:

"The current understanding of relationships between BMI and mortality is primarily based on evidence from HICs. These data have been conflicted about the mortality risk associated with being overweight. For instance, in one large collaborative study, the overweight range conferred a slightly increased risk of mortality while another meta-analysis did not show any increased mortality risk with that category.[3, 6] However, this literature has had important clinical implications in terms of recommendations about ideal weight and healthy lifestyle, which have largely been incorporated into global primary and clinical care guidelines around weight loss and obesity prevention. Our study suggests that in this South African setting, the relationship between BMI and morality also conforms to a J-shaped curve, however with a modest rightward "shift" in the curve by approximately 5 kg/m^2 compared to many such studies in HICs, particularly for women, such that the lowest risk of short-term mortality might be afforded by a higher BMI, which is clinically defined as overweight or obesity in current guidelines."

COMMENT: In terms of "Study Importance" the second bullet under 'what is already known' should be removed. It is not really the case that prior research defined the BMI cutoffs, which are quite arbitrary. Also it is inappropriate to describe these cut-offs as 'traditional." Tradition has no place in science, and these cut-offs have not been around so long as to be viewed as 'traditional' anyway. They could be described as conventional arbitrary cut-offs. Under "new findings" the authors should remove the clause reading "which has traditionally been defined as overweight or obesity in higher income settings."

RESPONSE: We appreciate this comment and have now revised the second bullet point to reflect the concerns of the reviewer. The new passage reads as follows:

"The clinical implications of conventional body mass index cut-offs for defining overweight and obesity are poorly characterized in low-income settings such as South Africa."

COMMENT: On page 14, the authors should eliminate most of the discussion of the Berrington article. That article deleted a large proportion of their sample (probably more than half) and was not really based on analysis of 1.46 million people. In addition, it used only self-reported weight and height, which has been shown to bias results upwards. Recommendations for healthy weight are not based on the Berrington article.

RESPONSE: We appreciate this comment and have now revised this passage to reflect the reviewer's suggestion as follows:

"The current understanding of relationships between BMI and mortality is primarily based on evidence from HICs. These data have been conflicted about the mortality risk associated with being overweight. For instance, in one large collaborative study, the overweight range conferred a slightly increased risk of mortality while another meta-analysis did not show any increased mortality risk with that category.[3, 6] However, this literature has had important clinical implications in terms of recommendations about ideal weight and healthy lifestyle, which have largely been incorporated into global primary and clinical care guidelines around weight loss and obesity prevention. Our study suggests that in this South African setting, the relationship between BMI and morality also conforms to a J-shaped curve, however with a modest rightward "shift" in the curve by approximately 5 kg/m^2 compared to many such studies in HICs, particularly for women, such that the lowest risk of short-term mortality might be afforded by a higher BMI, which is clinically defined as overweight or obesity in current guidelines."

COMMENT: Page 16. Here the authors discuss the concept of 'reverse causation' but fail to mention that most studies that delete pre-existing illness actually do not show any important impact of such deletions. Almost no evidence actually supports the idea that this is an important issue. This is also true of smoking as a strong confounder. No data supports this. If the authors look at the Berrington article supplement, they will see that in fact the distribution of BMI in the sample (shown in the supplement) is almost identical before and after these deletions, again suggesting these are not actually important confounders at all. The cited article by Tobias (Ref 22) just making these assertions but without evidence and should not be cited.

RESPONSE: We appreciate this comment by reviewer and have revised this passage on page 16, including adding a sentence to specifically highlight the reviewer's concern that these confounders have not been demonstrated with empirical data. We have also removed the references to the Tobias article in this passage. The revised section reads as follows:

"Efforts to confidently identify the causal framework and quantify the direction of the association between overweight or obesity and mortality have been subject to several major methodological concerns, all of which were carefully considered in the design and execution of this study. First, the causal direction of the relationship between BMI and mortality has long been subject to concerns about reverse causation bias, due to the fact that weight loss accompanies many life-limiting illnesses and if present, this bias may attenuate the apparent effect of overweight or obesity on mortality risk.[3, 24] A second potential methodological challenge in such analyses is confounding by risk factors such as smoking, which is associated with lower body mass and thus may also lead to underestimates of the mortality risk associated with overweight or obesity. Third, valid assessment of BMI-associated mortality requires anthropomorphic measurement in population cohorts with long-term follow-up and near complete death reporting. Finally, while each of these methodological considerations has been raised previously, there is little empirical data to verify the magnitude of these adjustments on estimates of the relationship between BMI and mortality."

COMMENT: Page 18: the sentence on line 22 about 'novel evidence' and 'mostly shaped' should be removed.

RESPONSE: We appreciate this comment and have now removed this sentence.

Reviewer: 2

Comments to the Author
In this manuscript the investigators assessed the relationship of BMI with mortality (cause-specific and all-cause) among adults in rural South Africa. Their results indicate that the risk of short-term mortality, particularly for women, is lowest among those considered overweight or obese in higher income settings.

COMMENT: This is a well-written manuscript on an important topic. The authors have conducted appropriate analysis. However, I have some comments that I have listed below by sections in the manuscript.

Their results bring up the question of whether one should use the same categories of BMI in all regions. I think BMI cut-offs into 'Normal', 'Overweight', 'Obese' and 'Very Obese' cannot be standardized across regions and should be based on the distribution in each country/region. I am not even sure if all developing countries have a similar distribution of BMI. Similar to BMI, the distribution of risk of diseases and mortality also varies across regions and might not be related only to weight gain. Using BMI as a major risk factor and the advice to lose weight might not be appropriate to reduce conditions/mortality in all populations. Also, Waist-to-Hip ratio or another measure of (un-)health might be more appropriate than BMI to assess mortality risk.

RESPONSE: The reviewer's comment about the use of the same BMI categories across regions is thought provoking. It will be interesting to see if the field gravitates away from using these categories across contexts. We agree with the reviewer and have added the lack of data on waist-to-hip ratio to the limitations section, as follows:

"Finally, we did not have data on waist-to-hip ratio and thus were unable to explore this alternative measure of body composition in these analyses."

Methods:
COMMENT: 1. Were the individuals included in the study healthy with no comorbidities in 2010? If not, was this information collected?

RESPONSE: This was a population-based study which did not exclude individuals based on co-morbidities or other health conditions. The prevalence of hypertension in this cohort was 26.2% around the time of this BMI data measurement. While blood pressure was measured in this survey and several other comorbidities are self-reported, we felt it could be methodologically unacceptable to adjust for hypertension, diabetes or other conditions that we believe lie on the causal pathway between body mass index and mortality, and thus did not adjust for these conditions.

COMMENT: 2. What was the methodology used to compute the asset index? Why was the wealth index developed by WHO not used?

RESPONSE: We appreciate the reviewer raising this point of clarification. As described in the paper, the wealth measure was an asset index. This index was constructed using principal component analysis of ownership of common household items, based on information gathered in the household survey, and based on the established methods described by Filmer and Pritchett. Furthermore, this wealth index is what is typically used by investigators from the Africa Health Research Institute to ensure consistency across studies. We have added a citation to support the use of these methods to the manuscript.

COMMENT: 3. Why was seroconversion date imputed?

RESPONSE: The exact date of seroconversion is unobserved and known only to occur between the latest-negative and earliest-positive tests dates, which can be up to a year or more apart. As such, we randomly selected a date between the last negative and first positive HIV test, to minimize bias of HIV estimation. We have added a relevant citation to support use of this approach.

COMMENT: 4. Did the regression models account for comorbidities?

RESPONSE: As described above, we remain concerned that it would be methodologically inappropriate to adjust for co-morbidities such as hypertension and diabetes that may lie on the causal pathway between BMI and mortality.

COMMENT: 5. They compared the median of each category with 22 (median of normal) to estimate the risk. Doesn't this assume that everyone in the particular category has the same risk as those who are at the median? Since they used BMI as a continuous covariate they might be able to look at the range of risk within each category at different values including the median.

RESPONSE: We appreciate this comment by the reviewer. We've shown the HRs at selected values of 5 clinically-recognized categories of BMI for ease of interpretation only. BMI is modelled as a continuous covariate using restricted cubic splines (smoothed curves) and Figure 2 (as well as Supplementary Figure 1) shows the estimated hazard ratios across the full range of continuous values of BMI. We believe that figures are the best way to interpret the results of a model using splines, and clearly show the relationship between BMI on a continuous scale and mortality. Unfortunately the full information cannot easily be presented in a table.

COMMENT: 6. In the statement 'An additional category of HIV unknown was used for individuals for the period before their first HIV test date, and 2 years after their last negative test if they had no record of a positive test.', why would they not assume that the individual is negative unless they have a positive test rather than unknown? Would that affect the results? They could try this as a sensitivity analysis.

RESPONSE: We appreciate the reviewer raising this point of clarification. This is a standard approach that is used in the HIV literature. Given that HIV incidence is as high as 8% per year in this region, the assumption of a negative test would be a strong one that

is less accepted among HIV researchers. We have now added a phrase and appropriate citation to clarify this point, as follows:

"An additional category of HIV unknown was used for individuals for the period before their first HIV test date, and 2 years after their last negative test if they had no record of a positive test. A cutoff of 2 years was used because of the high HIV incidence in this region.[21]"

COMMENT: 7. Why did the authors need to compute a non-response weight? Doesn't the survey administrator provide weights that account for the design and non-response? Was the weight for the non-response of individuals or the household?

RESPONSE: We apologize for the confusion. This was not a cluster-sample survey. The data is collected as part of a population-wide demographic health and surveillance site, so census data on the entire population is available. All people living in the pre-specified catchment area are approached to participate, and this dataset reflects those who were available and consented to participate in this round of measurements. To estimate population-level estimates, we constructed probability weights of participation, and then accounted for this by applying inverse probability weights to our regression models. We have added a citation to support this methodological approach.

COMMENT: 8. Did they have any missing values for the variables in their analyses? How did they account for it?

RESPONSE: We appreciate this comment. We have provided this information in both Table 1 and Supplementary Table 1 to clarify the number of missingness for key variables used in this analysis. As the reviewer will see, the rate of missingness among people who had their BMI measured in the survey was minimal. We performed a complete case analysis and did not impute missing data.

Results:
COMMENT: 9. Authors should focus more on the clinically meaningful differences and the point/interval estimates rather than statistical significance. They should consider replacing terms like 'statistically significant' or 'significant' with an interpretation of the point and interval estimates. There has been quite a lot of discussion with the American Statistical Association providing some guidelines for reporting results (https://doi.org/10.1080/00031305.2016.1154108; https://doi.org/10.1080/00031305.2019.1583913; https://www.amstat.org/asa/files/pdfs/P-ValueStatement.pdf)

RESPONSE: We appreciate this suggestion and have edited the text to better meet the ASA guidelines cited here. The revised passage now reads as follows:

"In adjusted and weighted Cox proportional hazards models, those with a BMI of 25.0 – 29.9 kg/m^2 and those with a BMI of 30.0 – 34.9 kg/m^2 had a lower hazard of death (AHR 0.80; 95% CI: 0.69 - 0.92 and AHR 0.75; 95% CI: 0.60 - 0.93, respectively), compared to those with a BMI of 18.5 – 24.9 kg/m^2 (Figure 1 and Table 2). Individuals with a BMI ≥35.0 kg/m^2 also had a lower hazard ratio of death than those who had a BMI of 18.5 – 24.9 kg/m^2 (0.80, 95%

CI: 0.64 -1.02). The full unadjusted and adjusted model results including AHRs for all covariates are provided in Supplementary Appendix Table 2. In sex-stratified models, these findings were consistent in women, with an AHR of 0.79 (95% CI: 0.66 – 0.94) for those with a BMI of 25.0 – 29.9 kg/m^2, 0.76 (95% CI: 0.58 – 0.94) for those with a BMI of 30.0 – 34.9 kg/m^2 and 0.84 (95% CI: 0.64 – 1.10) for those with a BMI ≥35.0 kg/m^2, as compared to those with a BMI of 18.5 – 24.9 kg/m^2. We found similar effect sizes in men. Those with a BMI ≤18.5 kg/m^2 had the highest mortality rate in the total population as compared to those with a BMI of 18.5 – 24.9 kg/m^2 overall and when stratified by sex (AHR Overall: 1.37, 95% CI: 1.12 - 1.69; AHR Women: 1.64, 95% CI: 1.25 - 2.13; AHR Men: 1.27, 95% CI: 0.95 - 1.69). The relationship between continuous BMI and the AHRs and 95% confidence intervals for mortality in this cohort are depicted in Figure 2.

In sensitivity analyses, we found that excluding deaths within the first two years of follow-up resulted in similar effect sizes for the mortality risk associated with each BMI category (AHR: 1.34; 95% CI: 1.04 – 1.71, Table 2). Second, when examining these relationships by HIV status, we found that those with a BMI 25.0 – 29.9 kg/m^2 had a substantially lower risk of death than those with a BMI of 18.5 – 24.9 kg/m^2 in both the HIV-positive (AHR 0.73, 95% CI: 0.57 – 0.94) and HIV-negative groups (AHR 0.76, 95% CI: 0.52 – 0.94) but this relationship was not the case for the HIV unknown group. Those with a BMI of 30.0 – 34.9 kg/m^2 (AHR 0.67, 95% CI: 0.48 – 0.91) and ≥35.0 kg/m^2 (AHR 0.65, 95% CI: 0.46 – 0.92) also had a substantially lower mortality risk in the HIV-negative group only but these relationships were non-significant in the HIV-positive and HIV unknown groups. In a sensitivity analysis that was performed without weights for non-response, we found no differences in the mortality risk by BMI group. Finally, when we stratified the mortality risk for the normal BMI group into three subgroups, and used 20.0 – <22.5 kg/m^2 as a referent group, we found that individuals with a BMI of 18.5 – <20.0 kg/m^2 had increased mortality (AHR 1.20; 95% CI: 1.08 – 1.33), and that those with a BMI of 22.5 – <25.0 kg/m^2 had decreased mortality (AHR 0.91; 95% CI: 0.88 – 0.95). The magnitude and significance of the lower mortality risk associated with a BMI of 25.0 – 29.9 kg/m^2 were robust to this sensitivity analysis. (Table 2)"

COMMENT: 10. Further, in describing the statistical analyses they do not set the threshold at which they consider something as statistically significant. Also, they do not provide any p-values (in the text or the main tables) with the estimates for the reader to interpret or infer the significance of the result.

RESPONSE: Per the most recent guidance from the American Statistical Association s (Wasserstein 2019, *The American Statistician*) that the reviewers also raise, we have opted to present 95% confidence intervals and do not provide a threshold for statistical significance. We feel that this is more consistent with current guidance about presentation of results and consideration of significance that the reviewer has also raised. Furthermore, and as relates to this study, we have modelled BMI using restricted cubic splines, and thus a p-value constructed for the individual categories of BMI (e.g. in Table 2) would correspond with the confidence interval of a HR for a somewhat arbitrarily assigned category (see response to Comment 5 above). If either the editors or reviewer feel that p-values should be added in the final version, we would be happy to do so to comply with journal or other policy.

COMMENT: 11. On page 13, line 22, they mention that only one BMI category had statistically significant results. They need to provide overall p-values of the association of BMI with the outcome rather than for individual categories.

RESPONSE: To remain consistent with current guidance (Wasserstein 2019, *The American Statistician*), and in keeping with the rationale discussed in Comment 10, we have removed p-values form our manuscript, along with the terminology of significance. We do provide confidence intervals for all estimates to ensure there is sufficient detail for the reader to interpret our findings. If either the editors or reviewer feel that p-values should be added in the final version, we would be happy to do so to comply with journal or other policy.

Specific Comments:
COMMENT: 1. Page 2, Line 11: Change 'defined' to 'define'.

RESPONSE: Thank you to the reviewer for highlighting this mistake. We have revised the sentence accordingly.

COMMENT: 2. Page 16, Line 24: Change 'diseases' to 'disease'.

RESPONSE: Thank you for pointing out this mistake. We have revised this sentence.

Table 1. Baseline characteristics of those with a BMI measurement in the 2010 survey, overall and by BMI group

	All survey participants (N=9728)	BMI <18.5 kg/m² (N=861)	BMI 18.5– 24.9 kg/m² (N=4412)	BMI 25.0–29.9 kg/m² (N=2167)	BMI 30.0–34.9 kg/m² (N=1284)	BMI ≥35.0 kg/m² (N=1004)
	Unweighted N (weighted population proportion)[1]					
Age group						
<30	4656 (47.3%)	609 (69.3%)	2844 (62.9%)	813 (35.9%)	271 (20.5%)	119 (11.9%)
35-44	1817 (20.0%)	97 (12.5%)	652 (16.3%)	478 (23.7%)	318 (26.3%)	272 (28.6%)
45-59	1771 (17.7%)	80 (9.5 %)	474 (10.8%)	454 (20.8%)	377 (28.7%)	386 (37.3%)
60+	1484 (15.0%)	75 (8.8 %)	442 (10.0%)	422 (19.5%)	318 (24.5%)	227 (22.1%)
Sex						
Male	2969 (35.9%)	528 (67.1%)	1964 (50.9%)	325 (18.7%)	106 (10.5%)	46 (5.7 %)
Female	6759 (64.1%)	333 (32.9%)	2448 (49.1%)	1842 (81.3%)	1178 (89.5%)	958 (94.3%)
Marital status						
Single (never married)	3044 (31.7%)	452 (53.5%)	1808 (41.2%)	462 (20.7%)	200 (15.2%)	122 (12.1%)
Married/informal union	5436 (56.7%)	357 (42.3%)	2284 (52.8%)	1349 (63.5%)	813 (64.4%)	633 (63.8%)
Widow/sep/divorced	1185 (11.5%)	38 (4.2 %)	279 (6.0 %)	351 (15.7%)	269 (20.4%)	248 (24.1%)
Missing	*63*	*14*	*41*	*5*	*2*	*1*
Education						
None	1824 (18.6%)	154 (18.2%)	663 (15.0%)	450 (20.8%)	304 (23.4%)	253 (24.7%)
Less than complete secondary	5287 (54.3%)	531 (62.3%)	2572 (58.1%)	1060 (48.3%)	617 (47.6%)	507 (50.3%)
Complete secondary/above	2589 (27.2%)	167 (19.5%)	1164 (26.9%)	653 (30.9%)	362 (28.9%)	243 (25.0%)
Missing	*28*	*9*	*13*	*4*	*1*	*1*
Employed						
No	8164 (83.9%)	737 (87.2%)	3718 (84.3%)	1803 (82.6%)	1077 (83.3%)	829 (82.2%)
Yes	1476 (16.1%)	103 (12.8%)	642 (15.7%)	353 (17.4%)	204 (16.7%)	174 (17.8%)
Missing	*88*	*21*	*52*	*11*	*3*	*1*
HIV status[2]						
Negative	6843 (70.0%)	644 (74.9%)	3053 (68.9%)	1437 (65.8%)	933 (72.2%)	776 (76.9%)
Positive not on ART	1561 (16.0%)	104 (11.7%)	713 (16.1%)	397 (18.4%)	208 (16.4%)	139 (14.0%)
Positive on ART	614 (6.5 %)	60 (7.2 %)	288 (6.7 %)	174 (8.1 %)	62 (5.0 %)	30 (3.1 %)
Unknown[3]	710 (7.5 %)	53 (6.2 %)	358 (8.4 %)	159 (7.6 %)	81 (6.4 %)	59 (6.1 %)
Residence						
Urban	537 (5.6 %)	40 (4.7 %)	249 (5.7 %)	118 (5.6 %)	75 (6.0 %)	55 (5.6 %)

Peri-urban	2980 (31.0%)	301 (35.4%)	1376 (31.6%)	622 (29.0%)	374 (29.6%)	307 (30.5%)
Rural	6195 (63.4%)	515 (59.9%)	2779 (62.7%)	1425 (65.4%)	835 (64.4%)	641 (63.9%)
Missing	*16*	*5*	*8*	*2*	*0*	*1*
SES tertile[4]						
Low	3451 (36.0%)	325 (38.3%)	1664 (38.3%)	779 (36.1%)	393 (30.8%)	290 (29.3%)
Middle	3199 (33.4%)	278 (33.2%)	1441 (33.1%)	700 (32.9%)	448 (35.3%)	332 (33.6%)
High	2934 (30.6%)	244 (28.5%)	1231 (28.6%)	662 (31.0%)	430 (34.0%)	367 (37.1%)
Missing	*144*	*14*	*76*	*26*	*13*	*15*

[1]N is the actual number of participants, without sampling weights applied. Proportions are weighted to adjust for non-response in the 2010 survey; weights calculated as the inverse probability of participation in the 2010 survey, in strata defined by age group, sex, and residence. [2]Imputed HIV status in 2010, based on complete history of testing in the DSS, including subsequent years. [3]Includes 402 individuals who never tested, 138 whose last test was negative but >2 years before the survey, and individuals whose first test was after 2010, and was positive. [4]Calculated from an asset index derived using principal component analysis, based on ownership of household items as measured in the annual household survey.

Table 2. Association of BMI with all-cause mortality

	BMI (kg/m²)[1]				
	<18.5	**18.5-24.9**	**25.0-29.9**	**30.0-34.9**	**≥35.0**
All individuals					
Deaths	84	335	184	93	83
Person-years	4931	25,796	12,831	7688	6056
Individuals	861	4412	2167	1284	1004
HR (95% CI)[2]	1.37 (1.12 -1.69)	1 (reference)	0.80 (0.69 -0.92)	0.75 (0.60 -0.93)	0.80 (0.64 -1.02)
Males					
Deaths	52	179	56	18	5
Person-years	3073	11,423	1815	608	271
Individuals	528	1963	325	106	46
HR (95% CI)[2]	1.27 (0.95 -1.69)	1 (reference)	0.85 (0.66 -1.11)	0.82 (0.57 -1.19)	0.88 (0.46 -1.69)
Females					
Deaths	32	156	128	75	78
Person-years	1857	14,373	11,015	7080	5785
Individuals	333	2449	1842	1178	958
HR (95% CI)[2]	1.64 (1.25 -2.13)	1 (reference)	0.79 (0.66 -0.94)	0.76 (0.58 -0.99)	0.84 (0.64 -1.10)
Excluding first 2 years of follow-up					
Deaths	84	335	184	93	83
Person-years	4931	25,796	12,831	7688	6056
Individuals	861	4412	2167	1284	1004
HR (95% CI)[2]	1.34 (1.04 -1.71)	1 (reference)	0.85 (0.72 -1.01)	0.84 (0.65 -1.09)	0.93 (0.70 -1.22)
HIV negative					
Deaths	33	140	82	42	38
Person-years	2671	12761	6996	4956	4248
Individuals	644	3053	1437	933	776
HR (95% CI)[2]	1.21 (0.89 -1.65)	1 (ref)	0.76 (0.62 -0.94)	0.67 (0.48 -0.91)	0.65 (0.46 -0.92)
HIV positive					
Deaths	26	131	52	25	20
Person-years	1055	6994	3850	1800	1095
Individuals	211	1394	720	341	213
HR (95% CI)[2]	1.33 (0.98 -1.81)	1 (ref)	0.73 (0.57 -0.94)	0.71 (0.49 -1.03)	0.96 (0.65 -1.41)

HIV unknown							
Deaths	25	64	50	26	25		
Person-years	1205	6042	1985	932	712		
Individuals	351	1676	547	283	206		
HR (95% CI)[2]	1.74 (1.21 -2.48)	1 (ref)	0.94 (0.70 -1.26)	0.99 (0.63 -1.55)	1.03 (0.64 -1.64)		
Unweighted for non-response							
HR (95% CI)[3]	1.39 (1.15 -1.67)	1 (reference)	0.80 (0.69 -0.91)	0.75 (0.61 -0.92)	0.81 (0.64 -1.01)		
All individuals	**<18.5**	**18.5-<20.0**	**20.0- <22.5**	**22.5- <25.0**	**25.0-29.9**	**30.0-34.9**	**≥35**
Deaths	84	62	145	128	184	93	83
Person-years	4931	5005	11398	9393	12831	7688	6056
Individuals	861	861	1938	1613	2167	1284	1004
HR (95% CI)[2]	1.37 (1.12 -1.69)	1.20 (1.08 -1.33)	1 (reference)	0.91 (0.88 -0.95)	0.80 (0.69 -0.92)	0.80 (0.60 -0.93)	0.80 (0.64 -1.02)

[1]BMI modelled as a continuous covariate by restricted cubic splines with 4 knots; deaths / person-years in each group shown for information only. HRs are presented at selected values of BMI, comparing the median value in each BMI group to BMI 22 as the reference. [2]HRs estimated from Cox regression; adjusted for current age (as timescale), sex, HIV status and socioeconomic status. Models were weighted to account for non-response in the 2010 survey.
[3]HRs estimated from Cox regression as described in footnote 2, but unweighted for non-response.

Figure 1. Kaplan-Meier estimates of survival, by BMI group

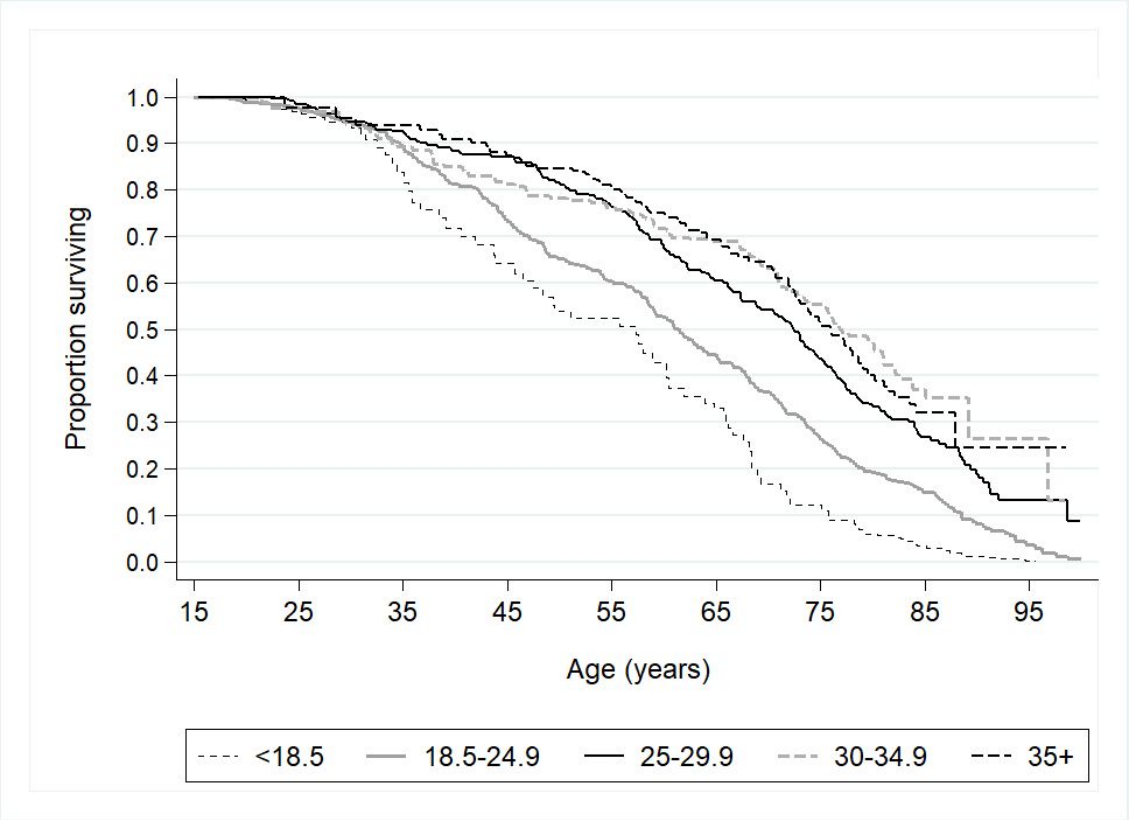
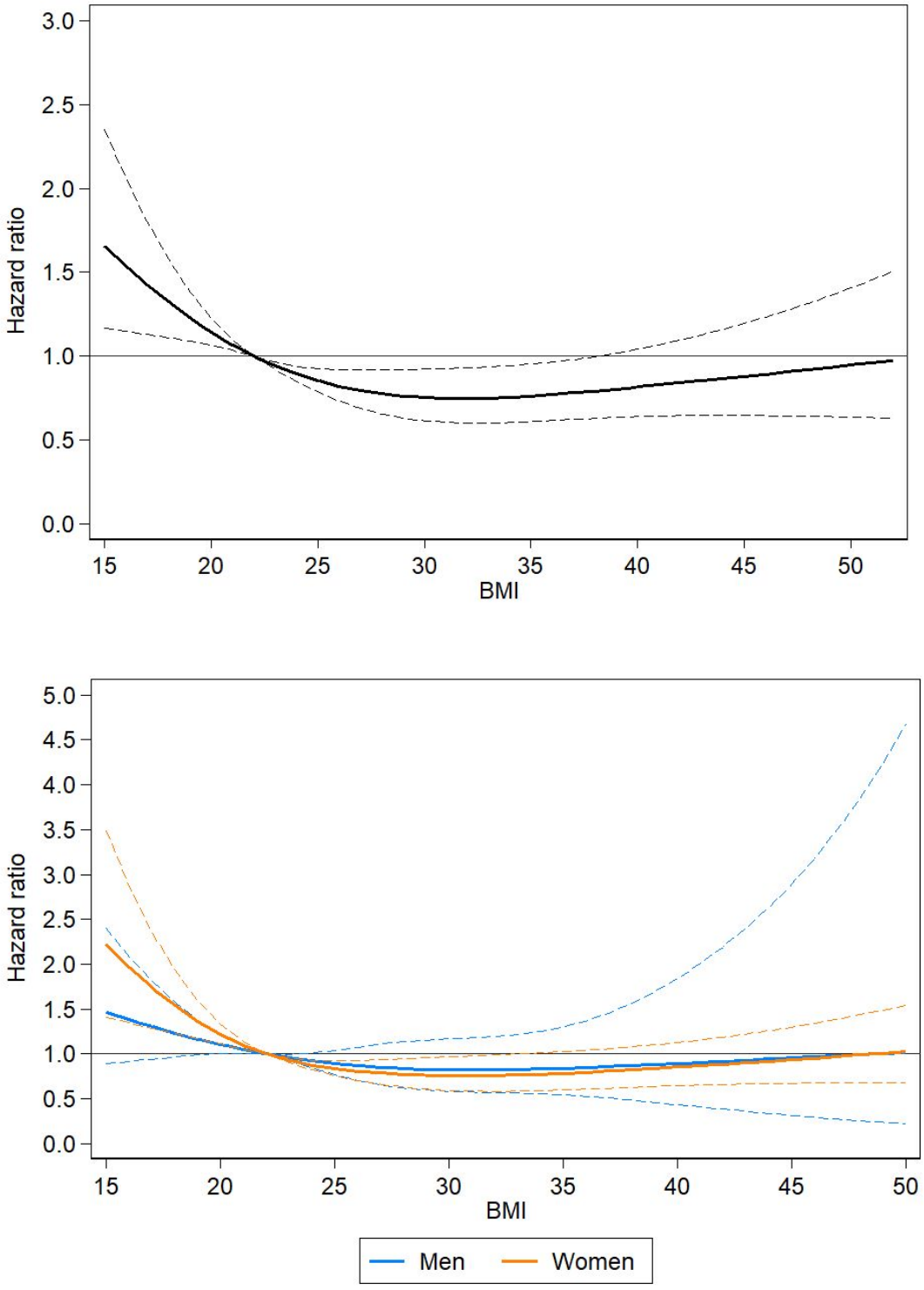
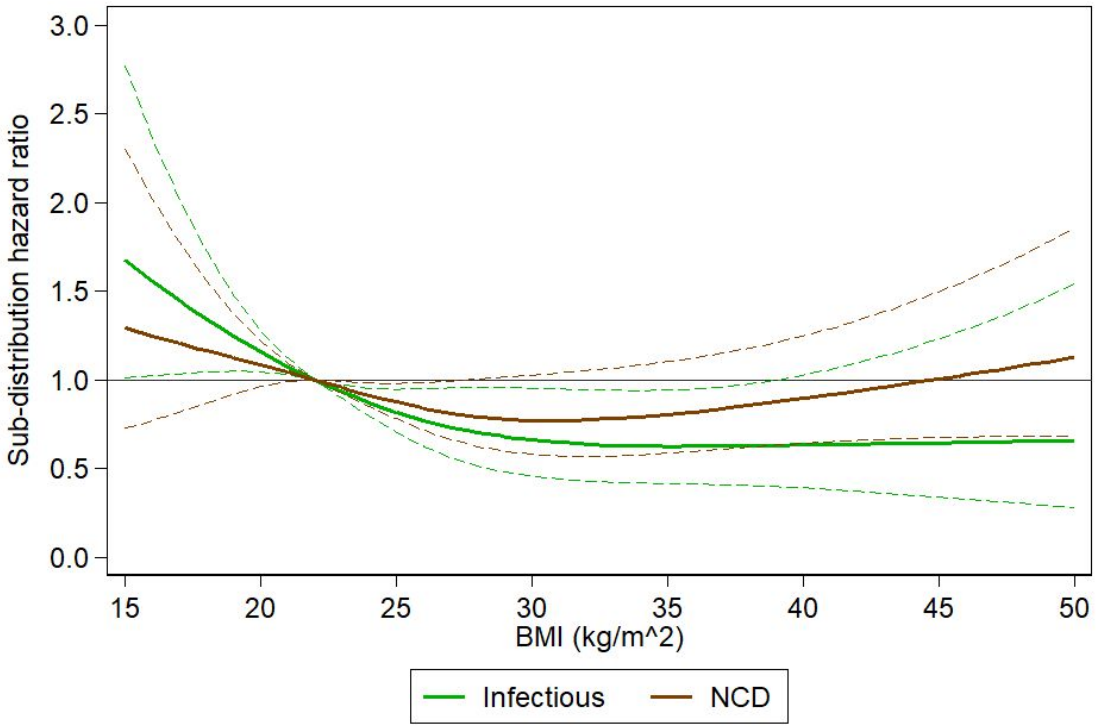


Figure 2. Association of BMI with all-cause mortality (hazard ratios and 95 % confidence intervals), modelled using restricted cubic splines with 4 knots in a Cox regression model, adjusted for age, sex, HIV status and socioeconomic status, in all individuals (top) and stratified by sex (bottom). A BMI of 22 was used as the reference to display the hazard ratios.



Supplementary Figure 1. Association of BMI with cause-specific mortality (sub-distribution hazard ratios and 95 % confidence intervals), modelled using restricted cubic splines with 4 knots in a competing risks regression model, adjusted for age, sex, HIV status and socioeconomic status. A BMI of 22 was used as the reference to display the hazard ratios.



Supplementary Table 1. Baseline characteristics of those who had BMI measured in the 2010 survey, and those who were eligible for survey but did not have BMI measured

	Eligible for survey[1]	BMI measured	BMI not measured[2]
	N=26,194	N=9,728	N=16,466
Median (IQR) age (years)	32 (20–50)	31 (20–51)	32 (21–49)
Age group			**P<0.001[3]**
<30	12175 (46.5%)	4656 (47.9%)	7519 (45.7%)
35-44	5516 (21.1%)	1817 (18.7%)	3699 (22.5%)
45-59	4602 (17.6%)	1771 (18.2%)	2831 (17.2%)
60+	3901 (14.9%)	1484 (15.3%)	2417 (14.7%)
Sex			**P<0.001**
Male	9966 (38.0%)	2969 (30.5%)	6997 (42.5%)
Female	16228 (62.0%)	6759 (69.5%)	9469 (57.5%)
Marital status			**P<0.001**
Single (never married)	8114 (31.2%)	3044 (31.5%)	5070 (31.1%)
Married/informal union	14958 (57.6%)	5436 (56.2%)	9522 (58.4%)
Widow/sep/divorced	2910 (11.2%)	1185 (12.3%)	1725 (10.6%)
Missing	*212*	*63*	*149*
Education			**P<0.001**
None	4558 (17.5%)	1824 (18.8%)	2734 (16.7%)
Less than complete secondary	13466 (51.6%)	5287 (54.5%)	8179 (49.9%)
Complete secondary/above	8051 (30.9%)	2589 (26.7%)	5462 (33.4%)
Missing	*119*	*28*	*91*
Employed			**P<0.001**
No	19998 (77.3%)	8164 (84.7%)	11834 (73.0%)
Yes	5859 (22.7%)	1476 (15.3%)	4383 (27.0%)
Missing	*337*	*88*	*249*
Residence			**P<0.001**
Urban	1953 (7.5 %)	537 (5.5 %)	1416 (8.6 %)
Peri-urban	8084 (30.9%)	2980 (30.7%)	5104 (31.1%)
Rural	16092 (61.6%)	6195 (63.8%)	9897 (60.3%)
Missing	*65*	*16*	*49*
SES tertile[4]			**P<0.001**
Low	8566 (33.6%)	3451 (36.0%)	5115 (32.2%)
Middle	8330 (32.7%)	3199 (33.4%)	5131 (32.3%)
High	8569 (33.7%)	2934 (30.6%)	5635 (35.5%)
Missing	*729*	*144*	*585*

[1]Individuals who were on the eligibility list for the 2010 survey (aged ≥15 years as of Dec 2009 and resident in the DSS), were successfully contacted (92% of all on the list) and still eligible at the time of contact (75% of those contacted). [2]Includes 16,431 individuals who refused consent, and 35 individuals who consented but for whom BMI measurements were not available. [3]P-value from Chi-squared test comparing those with BMI measurements and those without (excludes missing values). [4]Calculated from an asset index derived using principal component analysis, based on ownership of household items as measured in the annual household survey.

Supplementary Table 2. Association of BMI and other covariates with all-cause mortality

	Crude HR[1] (95% CI)	Adjusted HR[1] (95% CI)
BMI (kg/m²) [2]	P<0.001	P<0.001
<18.5	1.54 (1.28 -1.86)	1.37 (1.12 -1.69)
18.5-24.9	1	1
25.0-29.9	0.64 (0.56 -0.73)	0.80 (0.69 -0.92)
30.0-34.9	0.53 (0.43 -0.65)	0.75 (0.60 -0.93)
≥35	0.54 (0.44 -0.67)	0.80 (0.64 -1.02)
Sex	P<0.001	P<0.001
Male	1	1
Female	0.43 (0.37 -0.50)	0.52 (0.44 -0.62)
HIV status[3]	P<0.001	P<0.001
Negative	1	1
Positive not on ART	3.68 (2.91 -4.67)	3.73 (2.93 -4.75)
Positive on ART	3.27 (2.59 -4.12)	3.11 (2.44 -3.95)
Unknown[4]	3.44 (2.83 -4.19)	3.11 (2.54 -3.81)
SES tertile[5]	P=0.49	P=0.68
Low	1	1
Middle	0.96 (0.81 -1.14)	0.96 (0.81 -1.15)
High	0.90 (0.76 -1.07)	0.93 (0.78 -1.10)

[1]HRs estimated from Cox regression; adjusted for current age (as timescale). Models were weighted to account for non-response in the 2010 survey. [2]BMI modelled as a continuous covariate by restricted cubic splines with 4 knots; deaths / person-years in each group shown for information only. HRs are presented at selected values of BMI, comparing the median value in each BMI group to BMI 22 as the reference. [3]Imputed HIV status in 2010, based on complete history of testing in the DSS, including subsequent years. [4]Includes 402 individuals who never tested, 138 whose last test was negative but >2 years before the survey, and individuals whose first test was after 2010, and was positive. [5]Calculated from an asset index derived using principal component analysis, based on ownership of household items as measured in the annual household survey.

Supplementary Table 3. Causes of death, by BMI category

	All deaths	BMI (kg/m²)[1]				
		<18.5	**18.5– 24.9**	**25.0–29.9**	**30.0–34.9**	**≥35.0**
Infectious/parasitic	261 (33.5%)	31 (36.9%)	131 (39.1%)	52 (28.3%)	29 (31.2%)	18 (21.7%)
Neoplasms	97 (12.5%)	18 (21.4%)	39 (11.6%)	15 (8.2 %)	9 (9.7 %)	16 (19.3%)
Endocrine/metabolic	26 (3.3 %)	0 (0.0 %)	10 (3.0 %)	9 (4.9 %)	4 (4.3 %)	3 (3.6 %)
Cardiovascular	169 (21.7%)	14 (16.7%)	55 (16.4%)	49 (26.6%)	25 (26.9%)	26 (31.3%)
COPD/asthma	8 (1.0 %)	1 (1.2 %)	3 (0.9 %)	1 (0.5 %)	0 (0.0 %)	3 (3.6 %)
Acute abdomen/liver failure	27 (3.5 %)	3 (3.6 %)	7 (2.1 %)	10 (5.4 %)	2 (2.2 %)	5 (6.0 %)
Renal failure	32 (4.1 %)	1 (1.2 %)	7 (2.1 %)	17 (9.2 %)	5 (5.4 %)	2 (2.4 %)
Epilepsy	3 (0.4 %)	1 (1.2 %)	0 (0.0 %)	2 (1.1 %)	0 (0.0 %)	0 (0.0 %)
Pregnancy/childbirth	5 (0.6 %)	0 (0.0 %)	1 (0.3 %)	1 (0.5 %)	1 (1.1 %)	2 (2.4 %)
Injury/accident/poisoning	83 (10.7%)	8 (9.5 %)	52 (15.5%)	18 (9.8 %)	3 (3.2 %)	2 (2.4 %)
Unknown	68 (8.7 %)	7 (8.3 %)	30 (9.0 %)	10 (5.4 %)	15 (16.1%)	6 (7.2 %)
Total	**779**	**84**	**335**	**184**	**93**	**83**

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	a. 6-7 b. N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	16-17
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	a. 8-10 b. 8-10 c. 8-10 d. 8-10 e. 16-17
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	a-b. 11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11 + Supp Appendix 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13 (a-c)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.