

# Obesity measures, metabolic health and their association with 15-year all-cause and cardiovascular mortality in the SAMINOR 1 Survey: a population-based cohort study

Vilde Lehne Michalsen (✉ [vilde.l.michalsen@uit.no](mailto:vilde.l.michalsen@uit.no))

Center for Sami Health Research <https://orcid.org/0000-0003-0768-1032>

**Sarah H. Wild**

The University of Edinburgh Usher Institute of Population Health Sciences and Informatics

**Kirsti Kvaløy**

Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim

**Johan Svartberg**

Division of Internal Medicine, University Hospital of North Norway, Tromsø

**Marita Melhus**

Centre for Sami Health Research, Department of Community Medicine, UiT The Arctic University of Norway, Tromsø

**Ann Ragnhild Broderstad**

Centre for Sami Health Research, Department of Community Medicine, UiT The Arctic University of Norway, Tromsø

---

## Research article

**Keywords:** Abdominal obesity, All-cause mortality, Body mass index, Cardiovascular mortality, Metabolically healthy obesity, Metabolic syndrome, Obesity, Waist circumference

**Posted Date:** February 22nd, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-137391/v2>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

---

# Abstract

**Background:** The mortality of metabolic—obesity phenotypes has been thoroughly studied, but it is not known how the association between continuous measures of body mass index (BMI) or waist circumference differ in strata of cardiometabolic health status.

**Methods:** We linked data on 12,815 men and women aged 36—79 years from the SAMINOR 1 Survey with mortality data from the Norwegian Cause of Death Registry. We defined metabolically healthy and unhealthy as having zero and  $\geq 1$ , respectively, of the following: MetS, pre-existing diabetes or cardiovascular disease (CVD), or prescribed drugs for high blood pressure, hyperglycaemia or dyslipidaemia. We defined general and abdominal obesity as BMI  $\geq 30$  kg/m<sup>2</sup> and waist circumference  $\geq 88$  cm (women) or 102 cm (men), respectively, and cross-classified these categories with metabolic status to create metabolically healthy non-obese and obese (MHNO and MHO) and metabolically unhealthy non-obese and obese (MUNO and MUO) phenotypes. We used Cox regression to estimate the hazard ratio (HR) for all-cause and CVD mortality for 1) the four phenotypes and 2) continuous measures of BMI and waist circumference fitted with restricted cubic splines. We adjusted for age, leisure-time physical activity, education, smoking and alcohol consumption, and tested for interactions with sex and metabolic status (only continuous measures).

**Results:** The MHO phenotype was present in 7.8% of women and 5.8% of men. During a median follow-up of 15.3/15.2 years, 596/938 women/men had died, respectively. The MUNO and MUO group had higher mortality than the MHNO group. Sex and phenotypes interacted with respect to CVD mortality ( $p=0.05$  for general and  $p=0.02$  for abdominal obesity): relative to the MHNO group, the MHO group had an adjusted HR (95% confidence interval) for CVD mortality of 1.05 (0.38–2.88) in women and 2.92 (1.71–5.01) in men. We found curvilinear associations between BMI/waist circumference and all-cause mortality irrespective of metabolic status. Corresponding relationships with CVD mortality were linear and the slope differed by sex and metabolic status.

**Conclusion:** The relationships between continuous measures of BMI/waist circumference and mortality differed by sex, metabolic status and cause of death. Poor metabolic health substantially increases mortality regardless of obesity status.

## 1. Background

The prevalence of obesity doubled between 1980 and 2015 in more than 70 countries (1). Obesity is a strong driver of a cluster of risk factors known as metabolic syndrome (MetS). MetS is etiologically linked to insulin resistance and visceral adipose tissue that promotes a proinflammatory and prothrombotic state, making it an antecedent of both cardiovascular disease (CVD) and diabetes (2). At least half of the cardiovascular risk linked to obesity is mediated through metabolic risk factors (3,4). In Europe, approximately 7–19% of people with obesity do not have MetS, so-called metabolically healthy obesity (MHO) (5). Accumulating evidence strongly suggests that, compared to the metabolically healthy normal-weight group, people with MHO are at increased risk of cardiovascular disease (6–8), diabetes (9,10), and mortality (11,12).

A body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> is commonly used to define obesity in populations of European ancestry, but BMI is a crude marker of body fat distribution. Waist circumference is a better measure of the visceral

adipose tissue that is particularly strongly associated with cardiometabolic disease (13). Continuous measures of BMI and waist circumference usually show J- or U-shaped associations with mortality (14,15). This may indicate a functional relationship not reflected well by crude dichotomies, as dichotomisation of continuous predictors cause loss of information and statistical power to demonstrate associations (16).

To the best of our knowledge, no studies have examined the relationships between continuous measures of BMI or waist circumference and mortality by metabolic health status. We aimed to examine these relationships using a population-based multi-ethnic sample of adult women and men from rural Northern Norway, which has high prevalence of both general and abdominal obesity and MetS (17,18).

## **2. Methods**

### **2.1 Data**

We used the national 11-digit personal identity number linking individual data from the three following sources: baseline information on participants in the SAMINOR 1 Survey (the first survey of the Population-based Study on Health and Living Conditions in Regions with Sami and Norwegian Populations—the SAMINOR Study), mortality data from the Norwegian Cause of Death Registry, and information on emigration from Statistics Norway.

The population of Northern Norway includes people of Norwegian, Sami and Kven (descendants of Finnish immigrants in the 18<sup>th</sup> and 19<sup>th</sup> Century) ethnicity. The Sami is an ethnic minority and acknowledged as an indigenous people. Traditionally, the Sami inhabited Northern parts of Norway, Sweden, Finland and the Kola Peninsula in the Russian Federation.

The SAMINOR Study is a population-based study that was originally designed to investigate the health and living conditions in regions of Norway with an assumed proportion of at least 5—10% Sami inhabitants. The Centre for Sami Health Research at UiT The Arctic University of Norway and the Norwegian Institute of Public Health conducted the SAMINOR 1 Survey in 2003—2004 in 24 rural municipalities mainly in northern parts of Norway. Clinical measurements, blood samples and self-administered questionnaire data were collected on men and women aged 36—79 years. Of 27,151 invited individuals, 16,455 (60.6%) participated and consented to have their data linked to medical and national registries. Survey details have been reported previously (19).

### **2.2 Clinical measurements**

The following measurements of each participant were made by trained personnel: waist circumference, recorded to the nearest centimetre at the umbilicus, the participant standing and breathing normally; height and weight, measured to the nearest 0.1 cm and 100 g, respectively, using an electronic scale with participants wearing light clothing and no shoes; and blood pressure, measured with a Dinamap-R automatic device (Critikon, Tampa, Florida, USA). Blood pressure was measured after a 2-minute seated rest, and three measurements with 1-minute intervals were recorded. The first measurement was discarded and the average of the second and third was used. Trained personnel performed venepuncture with the participant in a seated position and non-fasting blood samples were centrifuged within 1.5 hours. Serum was sent by overnight post

to the laboratory at Ullevål University Hospital, Oslo. Lipids and glucose were measured by an enzymatic method (Hitachi 917 autoanalyzer, Roche Diagnostic, Switzerland)

### 2.3 Lifestyle and disease variables

Participants were asked to fill in a questionnaire from which we obtained the following information (answer options in parenthesis): education (total number of school years); diabetes (yes/no); angina pectoris (yes/no); previous stroke (yes/no); previous heart attack (yes/no); use of blood pressure-lowering drug (currently/previous, but not now/never); use of cholesterol-lowering drug (currently/previous, but not now/never); use of insulin (currently/previous, but not now/never); use of glucose-lowering drug in tablet format (currently/previous, but not now/never); smoking (currently/previous/never); leisure-time physical activity by a modified Saltin-Grimsby Physical Activity Level scale (reading, watching television, or engaging in sedentary activities/at least 4 hours a week of walking, bicycling, or other types of physical activity/at least 4 hours a week of participating in recreational athletics or heavy gardening/regular, vigorous training or participating in competitive sports several times a week) (20); alcohol consumption (never/not this year/a few times during this year/1 time per month/2-3 times per month/1 time per week/2-3 times per week/4-7 times per week). Leisure-time physical activity was categorised into “sedentary” (the first option), “light” (the second option) and “moderate-hard” (the last two options merged). Alcohol consumption was categorised into “weekly alcohol consumption”, “less than weekly alcohol consumption” and “never/not last year”. Participants were also asked to list any medication they had used within the last four weeks and the information was combined with information from drug-specific questions, details are found elsewhere (21).

The questionnaire also included questions (11 in total) on use of language at home by grandparents, parents and participants, ethnic background for parents and participants, and the participants’ self-perceived ethnicity (one or more of these alternatives were allowed: Norwegian, Sami, Kven, and other). Participants were categorised as Sami if they answered Sami as 1) their self-perceived ethnicity or 2) their own ethnic background. All others were categorised as non-Sami.

### 2.4 Independent variables

We defined MetS according to the ‘harmonised’ Adult Treatment Panel-III definition, with some adaptations (22). At least three of the following five components had to be present:

- hypertension, defined as systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 85$  mmHg or current use of antihypertensive drug;
- elevated random glucose, defined as random plasma glucose  $\geq 7.8$  mmol/L or self-reported diabetes;
- increased waist circumference, defined as waist circumference  $\geq 80$  cm in women and  $\geq 94$  cm in men;
- hypertriglyceridemia, defined as random plasma triglycerides  $\geq 1.7$  mmol/L; and
- lowered HDL cholesterol, defined as random plasma HDL cholesterol  $< 1.3$  mmol/L in women and  $< 1.0$  mmol/L in men.

Participants were categorised as metabolically unhealthy if they had any of the following, as recommended by Smith et al. (23):

- MetS (for abdominal obesity phenotypes, the MetS definition was modified to the presence of any given two or more components excluding increased waist circumference),
- self-reported diabetes, stroke, angina pectoris, or myocardial infarction,
- self-reported current treatment for high blood pressure, hyperglycaemia or dyslipidaemia.

General and abdominal obesity were defined as BMI  $\geq 30$  kg/m<sup>2</sup> and waist circumference  $\geq 88$  cm in women and  $\geq 102$  cm in men, respectively. The following general obesity phenotypes were created: metabolically healthy non-obesity (MHNO); metabolically unhealthy non-obesity (MUNO); metabolically healthy obesity (MHO); and metabolically unhealthy obesity (MUO). The following abdominal obesity phenotypes were created: metabolically healthy non-abdominal-obesity (MHNAO); metabolically unhealthy non-abdominal-obesity (MUNA0); metabolically healthy abdominal obesity (MHAO); and metabolically unhealthy abdominal obesity (MUAO).

## 2.5 Outcome variables

Mortality data comprised date of death and underlying cause of death, coded using the International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> revision. The study period started at the date of study entry (between 14th January 2003 and 5th March 2004) and ended at date of death (the event), date of emigration (censored) or the end of follow-up 31st December 2018 (censored), whichever occurred first. The outcome variables of interest were all-cause mortality and CVD mortality (death from causes I00-I99).

## 2.6 Missing data and exclusions

Figure 1 shows a flow chart describing the cohort selection. We excluded 497 participants who died within the first 5 years of follow-up and 90 participants with a BMI  $\leq 18.5$  kg/m<sup>2</sup> to avoid the potential for reverse causality (14). Because information on pre-existing disease or prescribed drugs was not necessary for the categorisation, we did not exclude participants with missing data for these variables. However, most participants with missing data for these variables were categorised into a metabolically unhealthy group by other determinants (Table 1). After exclusions, the complete case analytical sample comprised 12,815 participants, 47.2% of the invited sample.

## 2.7 Statistical analysis

Sample characteristics were described in strata of sex and metabolic-obesity phenotype and reported as mean (SD) and frequency (percentage) as appropriate. One-way analysis of variance and Pearson's  $\chi^2$  test were used to compare characteristics across the phenotypes. We calculated age-standardised mortality rates using the direct method and the 2013 European standard population.

In separate models for each pair of outcome and exposure, we modelled the relationships between all-cause mortality and CVD mortality (outcomes) and MetS, general obesity phenotypes and abdominal obesity phenotypes (exposures) using Cox proportional hazard regression. We tested interactions between exposures

and sex, and between exposures and ethnicity, and compared models with and without interaction terms using the likelihood ratio test. Interaction was considered present if  $p < 0.05$ . There were no significant interactions with ethnicity, but we found evidence of interactions between sex and general ( $p = 0.02$ ) and abdominal ( $p = 0.05$ ) obesity phenotypes for CVD mortality. Therefore, all models were stratified by sex. Attained age was set as the time-scale as recommended in observational studies (24), hence, all models were inherently and non-parametrically controlled for age (model 1). Further adjustments were made for smoking (model 2), plus leisure-time physical activity, education and alcohol consumption (model 3). The proportional hazard assumption was evaluated using Schoenfeld residuals. In models with all-cause mortality, non-proportional hazards for smoking status were handled by allowing separate baseline hazards for subgroups of the data, i.e. stratified Cox models. We reported adjusted hazard ratios (HR) with 95% confidence intervals (CI) for each pair of outcome and exposure.

Next, in separate models, we fitted continuous BMI and waist circumference using restricted cubic splines against all-cause and CVD mortality, respectively, while adjusting for the same covariates as in model 3 above, in addition to metabolic health. Fitting three knots provided the lowest Akaike information criterion and were thus sufficient, as recommended by Harrell (25). We assessed non-linearity by testing models with the linear term against models with both linear and a cubic spline term using likelihood ratio test. Non-linearity was considered present if  $p < 0.05$ . We also assessed interaction between metabolic health status and BMI/waist circumference using likelihood ratio tests. If there was a significant interaction, we kept the interaction term in the model; if there was no interaction, metabolic health status was kept in the model as a covariate. Adjusted HR (95% CI) of all-cause and CVD mortality, respectively, were plotted against BMI and waist circumference, respectively, with separate curves for metabolically healthy and unhealthy, using the sex-specific sample median of BMI or waist circumference as reference values. In models with a significant interaction, metabolically healthy with the sex-specific sample median of BMI or waist circumference were used as reference.

We used *R* software for statistical computing (26).

## 2.8 Sensitivity analysis

We excluded 1) ever-smokers and 2) participants with pre-existing diseases (or prescribed drugs for cardiometabolic disease) in sensitivity analyses. Furthermore, we analysed data with more conservative cut-offs for MetS-components: waist circumference ( $\geq 88/102$  cm in women/men), random triglycerides ( $\geq 2.1$  mmol/L), and random glucose ( $\geq 11.1$  mmol/L). We also repeated the analyses in the full sample, adjusting for sex. Finally, we used multiple imputation to address missing data on at least one variable for 2030 participants (13.7%). The variables with the largest proportion of missing data were found for leisure-time physical activity ( $n = 1322$ , 8.9%) and education ( $n = 881$ , 5.9%). Characteristics differed between participants with complete and missing data (Supplementary Table 1). The mechanism for missing information was assumed to be missing-at-random (27). We used a rich set of relevant variables, performed 20 imputations, and pooled the data according to Rubin's rules using the 'mice' package in *R* (28). Because metabolic health is a known mediator of the relationship between obesity and mortality, we also ran the analyses of continuous BMI/waist circumference vs mortality without adjusting for metabolic health.

### 3. Results

After median follow-up of 15.3 years in 6517 women and 15.2 years in 6298 men (12,815 in total), 596 (9.1%) and 938 (14.9%) had died, respectively. In both women and men, the prevalence of MetS was 29.7%.

Proportions categorised as metabolically unhealthy (defined as either having MetS, pre-existing disease or prescribed drugs) were 44.7% in women and 47.0% in men. Proportions having general obesity were 27.0% in women and 23.5% in men, and proportions having abdominal obesity were 39.0% in women and 21.1% in men.

Table 1 and 2 describe the prevalence of the four general obesity phenotypes and the distributions of characteristics across the phenotypes in women and men, respectively. Compared to the other groups, men and women with MHO were relatively young, with a higher proportion of people with Sami ethnicity, a lower proportion of current smokers, and a higher proportion of people who reported being sedentary in their leisure-time (but lower than in people with MUO). Supplementary Table 2 and 3 describe the distribution and characteristics of the four abdominal obesity phenotypes. Patterns of characteristics were generally similar to those reported for general obesity phenotypes.

The proportion of deaths during follow-up were comparable in people with MHO and people with MHNO, but they differed in the distribution of causes of death (Table 1 and 2). In general, the proportion of death from CVD was lowest in the MHNO group.

Figure 2 shows that the lowest mean mortality rates in men occurred in the MHNO and MHNAO groups, whereas in women, the metabolically healthy phenotypes regardless of obesity status had the lowest mortality rates.

Table 3 and Table 4 show the hazard ratios (HR) from Cox proportional hazards models for all-cause mortality and CVD mortality in women and men, respectively. Men and women with MetS had an approximately 50% higher 15-year risk of CVD mortality than those without MetS. The 15-year mortality in the subgroups with MHO and MHAO compared to the respective metabolically healthy non-obese groups differed markedly between the sexes, particularly for CVD mortality, with significant interactions with sex differences in the beta coefficient for MHO and MHAO primarily. We found that obesity, regardless of metabolic health, markedly increased CVD mortality in men, but there was no association in women. In the metabolically healthy, all-cause mortality was reduced in obese women (general and abdominal, respectively) compared to non-obese women. In both sexes, the mortality associated with metabolically unhealthy obesity phenotypes (MUNO, MUNAO, MUO, MUAO) were higher for CVD-specific death than for all-cause mortality.

Figure 3 and 4 (panels A and C) show curvilinear relationships between all-cause mortality and BMI (panel A) and waist circumference (panel C) in men and women, respectively. Figure 3 and 4 (panels B and D) show marked sex-differences in the relationships with CVD mortality for BMI (panel B) and waist circumference (panel D). Interactions were present between metabolic health status and BMI or waist circumference (except in panel 3B). In men, BMI and waist circumference had positive, strong associations with CVD mortality, with stronger associations in metabolically healthy than unhealthy groups. In women, BMI had negative associations with CVD mortality. The association between waist circumference and CVD mortality differed by metabolic health status.

## 3.2 Sensitivity analysis

Supplementary Table 4, 5 and 6 show the results of the sensitivity analyses. In never-smokers, most associations between general and abdominal obesity phenotypes and mortality were stronger than those observed in the whole cohort, but several estimates included 1.0 in the CI. Contrary, in participants without pre-existing disease or prescribed drugs, most estimates were strongly attenuated and not statistically significant (except men with MHO and MHAO) compared to those observed in the whole cohort. Using more conservative cut-offs for MetS resulted in increased estimates, and the apparent protective effect of MHO and MHAO in women was attenuated towards the null and was no longer statistically significant. In sex-adjusted analyses, HR (95%) for all-cause mortality compared to the reference groups were 0.92 (0.71–1.20) for MHO and 0.92 (0.72–1.17) for MHAO, respectively. Analysis of multiply imputed data gave similar results compared to the complete case analysis. Supplementary Figure 1 and 2 show overall patterns similar with the primary analyses, except for models with CVD mortality in women, which showed no association with neither BMI nor waist circumference.

## 4. Discussion

We followed almost 13,000 adults for 15 years and found that metabolically unhealthy status was associated with a higher CVD mortality than metabolically healthy status irrespective of obesity status. We found curvilinear associations between BMI or waist circumference and all-cause mortality regardless of metabolic health status and sex. In contrast, corresponding relationships between continuous obesity measures and CVD mortality differed by both sex and metabolic health status.

Higher proportions of women than men had MHO, consistent with findings in an analysis of ten European cohorts (5). The highest proportion of Sami ethnicity was found in the MHO group. Sami have higher BMI than non-Sami, particularly in women (18), and healthier values of metabolic parameters than non-Sami with the same values of BMI; however, these were attenuated by height-adjustment (21). The formula for BMI is deceptively simple (weight in kg/height in m<sup>2</sup>); however, weight scales to a different power of height than 2 in most populations, particularly in women (29). Consequently, the uneven sex- and ethnicity distribution of phenotypes may be a result of misclassification, which is supported in preliminary analysis of the data from the cohort in this study. Sami ethnicity is primarily regarded a sociocultural category in this cohort, and neither interacted with nor affected the beta coefficient for the exposures in the models.

The association between MetS and mortality was weaker than in a previous meta-analysis of 87 studies on MetS and mortality (30). MetS is still a controversial concept (31), and the Endocrine Society recently replaced the term 'metabolic syndrome' with 'elevated metabolic risk' to avoid the implication that the cluster represents a diagnostic entity (32). Regardless of terminology, long-term risk of CVD and mortality is increased with MetS, and should motivate clinicians to perform CVD risk assessments and recommend lifestyle changes and pharmaceutical treatment where appropriate (32).

To our knowledge, this study is the first to examine the relationship between continuous measures of BMI or waist circumference and mortality according to metabolic health status. A recent study of a Japanese population by Izumida et al. examined the relationships between four categories of BMI and 18-year mortality

according to MetS status (33). The relationship between BMI categories and all-cause and CVD mortality were J-shaped in metabolically unhealthy people, whereas no associations were found in metabolically healthy people. In contrast, we show that the relationships between BMI and CVD mortality in a Norwegian population differ by sex: with no or negative association in women and positive association in men. A meta-analysis of 21 prospective studies showed that compared to the MHNO group, the HR for CVD in women with MHO were lower than those in men with MHO (HR 1.71 vs 2.15, respectively) (34). However, the meta-analysis included few sex-stratified studies. In a recent Iranian study, neither women nor men with persistent MHO status had increased HR for CVD incidence compared to the non-obese comparison group (35). However, among women and men who transitioned from MHO to MUO, only men had an increased HR compared to the non-obese comparison group (35). In the study by Izumida et al., the authors adjusted for sex, whereas we found an interaction, but only regarding CVD mortality. The association between BMI/waist circumference and all-cause mortality was U-shaped in both sexes. Although the HR of MHO for all-cause mortality differed by sex (HR of 0.63 in women and 1.25 in men), there was no evidence of statistically significant effect modification. In sensitivity analyses, the (sex-adjusted) HR (95% CI) of MHO was 0.92 (0.71–1.21).

The amount of visceral adipose tissue may differ between people with the same value of BMI or even waist circumference, and men typically have more visceral adipose tissue than women (13). This may have contributed to the sex-differences in associations between obesity measures and CVD mortality in women and men. A recent UK Biobank study including nearly 300,000 men and women without CVD at baseline showed that BMI had J-shaped associations with CVD events and mortality in both sexes (36). In men, the association with CVD events was linear when restricted to non-smokers. Residual confounding when adjusting for crude smoking categories has been pointed out as a potential cause of obesity paradoxes (37). We also show that when the analyses were restricted to non-smokers, most estimates increased, and women with MHO had a HR of approximately 1.50 for CVD mortality, albeit non-statistically significant due to low power. Importantly, in the UK Biobank study, all measures of central obesity, including waist circumference, and fat mass were positively associated with CVD mortality in both sexes (36).

Collider bias has been suggested to explain the “obesity paradox”: obesity increases mortality and causes cardiometabolic disease, but within strata of cardiometabolic disease, obesity is not associated with mortality or even appears protective in some studies (38,39), as is seen in women in this study. The collider bias is a type of selection bias, that can be introduced through restriction, regression adjustment or stratification on a variable (in this case cardiometabolic status) that is both affected by the exposure (obesity) and share common causes (e.g. genes) with the outcome (death). However, the magnitude and direction of the bias may be difficult to predict, and some suggest it only a partial explanation of the obesity paradox (40).

Izumida et al. defined metabolic health as no MetS components, compared to our definition of two or fewer components. Hence, metabolically healthy people in our study may have been in a transition phase towards full MetS and converted to metabolically unhealthy during the study period. Approximately 50% of people with MHO transition to MUO (4). A study with six repeated measures during 30 years of follow-up showed that duration with MHO was longer in women than in men. Women transitioned back and forth between a healthy and an unhealthy metabolic status while maintaining their obesity status, whereas men with MHO tended to just transition once from a healthy to an unhealthy metabolic status (41). Nevertheless, in a large U.S. cohort of women (N≈90,000), both those with MHO at baseline and those with persistent MHO status over a period

of 24 years were at increased risk of CVD compared with the MHNO (42). Hence, even if women spend a longer time in the MHO state before transitioning to MUO than men, MHO may not be a benign state in a perspective of several decades.

Furthermore, in a study with repeated measures, people with MHO had higher all-cause mortality only when compared to people with stable MHNO status identified during several assessments, and not in comparison to the larger group that were MHNO at baseline (43). This serves as a reminder that exposure status in the reference group can change over time and a single measurement at baseline may give biased results. The implications for this study is that the strength of associations may have been under-estimated.

In summary, collider bias, residual confounding by smoking and misclassification may have distorted the relationship between obesity and mortality we observed. The pathways linking obesity, metabolic health and mortality is complex and dynamic, making it a challenge to study using only data measured at a single point in time. Although obesity is heterogeneous in presentation, it is unlikely a healthy state over time, as is evident particularly for the men in our study.

### **Strengths and limitations**

Strengths of the study include the population-based nature of the study, the long follow-up time and standardised measurements of clinical and biochemical variables by trained personnel. Linkage to the high quality Norwegian Cause of Death Registry enabled virtually complete follow-up of total and CVD deaths. We included important confounders, such as physical activity, smoking, alcohol and education. The Saltin-Grimsby Physical Activity Level Scale has acceptable validity in Nordic countries (20). Limitations include non-fasting blood samples, and a modest participation rate that may have resulted in 'healthy participation' bias. There are no valid cut-offs for random glucose regarding prediabetes or impaired glucose tolerance. Non-fasting triglycerides reflect increases over fasting values by a maximum of 0.3 mmol/L (44). Inclusion of inflammation markers (e.g. C-reactive protein) and information on non-alcoholic fatty liver disease may have enabled us to categorise more precisely into metabolically healthy vs unhealthy.

## **5. Conclusion**

Metabolically unhealthy people have increased risks of 15-year all-cause and CVD mortality irrespective of obesity status compared to people who were metabolically healthy at baseline. Associations between BMI/waist circumference and CVD mortality differed between the sexes, with strong, positive associations in both metabolically healthy and unhealthy men. The relationship between metabolic risk factors and adipose tissue is dynamic and continuous; therefore, efforts should continue to be made to reduce obesity and metabolic abnormalities across the population.

## **Declarations**

Ethics approval and consent to participate: This study has been approved by the SAMINOR Project Board and The Regional Committee for Medical and Health Research Ethics (reference: 2017/1974/REK North). Written informed consent was obtained from all participants.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available due to privacy regulations. Data from the SAMINOR Study may be made available upon reasonable request to the SAMINOR Project Board and with permission of the Regional Committee for Medical and Health Research Ethics.

Competing interests: None.

Funding: The Norwegian Ministry of Health and Care Services and the Northern Norway Regional Health Authority.

Authors' contributions: ARB and VLM conceived the idea behind the study. VLM performed all the data analysis and wrote the first draft of the manuscript. SHW aided with the planning of the analysis. SHW, KK, JS, MM and ARB contributed with interpretation of the results and critically revised the manuscript.

Acknowledgements: Many thanks to the participants in the SAMINOR Study, and to MSc Kelly Fleetwood for statistical advice. The publication charges for this article have been funded by a grant from the publication fund of UiT The Arctic University of Norway.

## References

1. The GBD 2015 Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N. Engl. J. Med.* 2017;377(1):13–27.
2. Cornier M-A, Dabelea D, Hernandez TL, et al. The Metabolic Syndrome. *Endocr. Rev.* 2008;29(7):777–822.
3. The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. *The Lancet.* 2014;383(9921):970–983.
4. Mongraw-Chaffin M, Foster MC, Anderson CAM, et al. Metabolically Healthy Obesity, Transition to Metabolic Syndrome, and Cardiovascular Risk. *J. Am. Coll. Cardiol.* 2018;71(17):1857–1865.
5. van Vliet-Ostaptchouk JV, Nuotio M-L, Slagter SN, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC Endocr. Disord.* 2014;14:9.
6. Caleyachetty R, Thomas GN, Toulis KA, et al. Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women. *J. Am. Coll. Cardiol.* 2017;70(12):1429–1437.
7. Lassale C, Tzoulaki I, Moons KGM, et al. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. *Eur. Heart J.* 2018;39(5):397–406.
8. Fan J, Song Y, Chen Y, et al. Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: A meta-analysis of prospective cohort studies. *Int. J. Cardiol.* 2013;168(5):4761–4768.
9. Bell JA, Kivimaki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. *Obes. Rev.* 2014;15(6):504–515.

10. Hinnouho G-M, Czernichow S, Dugravot A, et al. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. *Eur. Heart J.* 2015;36(9):551–559.
11. Ärnlöv J, Ingelsson E, Sundström J, et al. Impact of Body Mass Index and the Metabolic Syndrome on the Risk of Cardiovascular Disease and Death in Middle-Aged Men. *Circulation.* 2010;121(2):230–236.
12. Hinnouho G-M, Czernichow S, Dugravot A, et al. Metabolically Healthy Obesity and Risk of Mortality: Does the definition of metabolic health matter? *Diabetes Care.* 2013;36(8):2294–2300.
13. Neeland IJ, Ross R, Després J, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. 2019;7(9):715–725.
14. Angelantonio ED, Bhupathiraju SN, Wormser D, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *The Lancet.* 2016;388(10046):776–786.
15. Carmienke S, Freitag MH, Pischon T, et al. General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis. *Eur. J. Clin. Nutr.* 2013;67(6):573–585.
16. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat. Med.* 2006;25(1):127–141.
17. Michalsen VL, Kvaløy K, Svartberg J, et al. Change in prevalence and severity of metabolic syndrome in the Sami and non-Sami population in rural Northern Norway using a repeated cross-sectional population-based study design: the SAMINOR Study. *BMJ Open.* 2019;9(6):e027791.
18. Nystad T, Melhus M, Brustad M, et al. Ethnic differences in the prevalence of general and central obesity among the Sami and Norwegian populations: the SAMINOR study. *Scand. J. Public Health.* 2010;38(1):17–24.
19. Lund E, Melhus M, Hansen KL, et al. Population based study of health and living conditions in areas with both Sámi and Norwegian populations—the SAMINOR study. *Int. J. Circumpolar Health.* 2007;66(2):113–128.
20. Grimby G, Börjesson M, Jonsdottir IH, et al. The “Saltin–Grimby Physical Activity Level Scale” and its application to health research. *Scand. J. Med. Sci. Sports.* 2015;25(S4):119–125.
21. Michalsen VL, Braaten T, Kvaløy K, et al. Relationships between metabolic markers and obesity measures in two populations that differ in stature—The SAMINOR Study. *Obes. Sci. Pract.* 2020;6:324–339.
22. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the Metabolic Syndrome. *Circulation.* 2009;120(16):1640–1645.
23. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. *J. Clin. Investig. Ann Arbor.* 2019;129(10):3978–3989.
24. Cologne J, Hsu W-L, Abbott RD, et al. Proportional Hazards Regression in Epidemiologic Follow-up Studies: An Intuitive Consideration of Primary Time Scale. *Epidemiology.* 2012;23(4):565–573.
25. Harrell Jr FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. 2nd ed. 2015. Cham: Springer International Publishing: Imprint: Springer; 2015 582 p.

26. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.
27. Little RJA, Rubin DB. Statistical analysis with missing data. 2nd ed. Hoboken, N.J: Wiley; 2002 381 p.
28. Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J. Stat. Softw.* 2011;45(1):1–67.
29. Diverse Populations Collaborative Group. Weight-height relationships and body mass index: Some observations from the diverse populations collaboration. *Am J Phys Anthropol.* 2005;128:220–229.
30. Mottillo S, Filion KB, Genest J, et al. The Metabolic Syndrome and Cardiovascular Risk. *J. Am. Coll. Cardiol.* 2010;56(14):1113–1132.
31. Simmons RK, Alberti KGMM, Gale EA, et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. *Diabetologia.* 2010;53(4):600–605.
32. Rosenzweig JL, Bakris GL, Berglund LF, et al. Primary Prevention of ASCVD and T2DM in Patients at Metabolic Risk: An Endocrine Society Clinical Practice Guideline. *J. Clin. Endocrinol. Metab.* 2019;104(9):3939–3985.
33. Izumida T, Nakamura Y, Ishikawa S. Impact of body mass index and metabolically unhealthy status on mortality in the Japanese general population: The JMS cohort study. *PLOS ONE.* 2019;14(11):e0224802.
34. Opio J, Croker E, Odongo GS, et al. Metabolically healthy overweight/obesity are associated with increased risk of cardiovascular disease in adults, even in the absence of metabolic risk factors: A systematic review and meta-analysis of prospective cohort studies. *Obes. Rev.* 2020;1–13.
35. Hosseini F, Tasdighi E, Barzin M, et al. The association between transition from metabolically healthy obesity to metabolic syndrome, and incidence of cardiovascular disease: Tehran lipid and glucose study. *PLOS ONE.* 2020;15(9):e0239164.
36. Iliodromiti S, Celis-Morales CA, Lyall DM, et al. The impact of confounding on the associations of different adiposity measures with the incidence of cardiovascular disease: a cohort study of 296 535 adults of white European descent. *Eur. Heart J.* 2018;39(17):1514–1520.
37. Preston S, Stokes A. Obesity Paradox: Conditioning on Disease Enhances Biases in Estimating the Mortality Risks of Obesity. *Epidemiology.* 2014;25(3):454–461.
38. Banack HR, Kaufman JS. The obesity paradox: Understanding the effect of obesity on mortality among individuals with cardiovascular disease. *Prev. Med.* 2014;62:96–102.
39. Stovitz SD, Banack HR, Kaufman JS. Selection bias can creep into unselected cohorts and produce counterintuitive findings. *Int. J. Obes.* 2020;1–2.
40. Sperrin M, Candlish J, Badrick E, et al. Collider Bias Is Only a Partial Explanation for the Obesity Paradox. *Epidemiology.* 2016;27(4):525–530.
41. Camhi SM, Must A, Gona PN, et al. Duration and stability of metabolically healthy obesity over 30 years. *Int. J. Obes.* 2019;43(9):1803–1810.
42. Eckel N, Li Y, Kuxhaus O, et al. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol.* 2018;6(9):714–724.

43. Hamer M, Johnson W, Bell JA. Improving risk estimates for metabolically healthy obesity and mortality using a refined healthy reference group. *Eur. J. Endocrinol.* 2017;177(2):169–174.
44. Langsted Anne, Freiberg Jacob J., Nordestgaard Børge G. Fasting and Nonfasting Lipid Levels. *Circulation.* 2008;118(20):2047–2056.

## Tables

**Table 1. Sample characteristics in mean (standard deviation) or frequency (percent) according to general obesity phenotypes in 6517 women in the SAMINOR 1 Survey (2003—2004)**

	Metabolically healthy non-obesity (N=3095, 47.5%)	Metabolically unhealthy non-obesity (N=1662, 25.5%)	Metabolically healthy obesity (N=510, 7.8%)	Metabolically unhealthy obesity (N=1250, 19.2%)	Total (N=6517)	p-value
<b>Age (years)</b>	49.4 (9.4)	57.4 (10.7)	52.1 (10.2)	57.4 (11.0)	53.2 (10.8)	<0.001 <sup>1</sup>
<b>Ethnicity</b>						<0.001 <sup>2</sup>
non-Sami	2462 (79.5%)	1319 (79.4%)	349 (68.4%)	920 (73.6%)	5050 (77.5%)	
Sami	633 (20.5%)	343 (20.6%)	161 (31.6%)	330 (26.4%)	1467 (22.5%)	
<b>Smoking</b>						<0.001 <sup>2</sup>
Yes, currently	1063 (34.3%)	588 (35.4%)	120 (23.5%)	277 (22.2%)	2048 (31.4%)	
Yes, previously	948 (30.6%)	481 (28.9%)	192 (37.6%)	441 (35.3%)	2062 (31.6%)	
Never	1084 (35.0%)	593 (35.7%)	198 (38.8%)	532 (42.6%)	2407 (36.9%)	
<b>Died during follow-up</b>	154 (5.0%)	230 (13.8%)	25 (4.9%)	187 (15.0%)	596 (9.1%)	<0.001 <sup>2</sup>
<b>Cause of death</b>						<0.001 <sup>2</sup>
Malignant tumor	83 (53.9%)	63 (27.4%)	12 (48.0%)	60 (32.1%)	218 (36.6%)	
CVD	16 (10.4%)	73 (31.7%)	5 (20.0%)	58 (31.0%)	152 (25.5%)	
Respiratory	19 (12.3%)	25 (10.9%)	3 (12.0%)	15 (8.0%)	62 (10.4%)	
Other	33 (21.4%)	67 (29.1%)	4 (16.0%)	51 (27.3%)	155 (26.0%)	
Unknown	3 (1.9%)	2 (0.9%)	1 (4.0%)	3 (1.6%)	9 (1.5%)	
<b>Alcohol consumption</b>						<0.001 <sup>2</sup>
Weekly	822 (26.6%)	296 (17.8%)	89 (17.5%)	132 (10.6%)	1339 (20.5%)	
Less than weekly	1881 (60.8%)	958 (57.6%)	312 (61.2%)	741 (59.3%)	3892 (59.7%)	
Never/not last year	392 (12.7%)	408 (24.5%)	109 (21.4%)	377 (30.2%)	1286 (19.7%)	

<b>Leisure-time physical activity</b>						<0.001 <sup>2</sup>
Sedentary	594 (19.2%)	394 (23.7%)	140 (27.5%)	397 (31.8%)	1525 (23.4%)	
Light	2082 (67.3%)	1100 (66.2%)	324 (63.5%)	751 (60.1%)	4257 (65.3%)	
Moderate-hard	419 (13.5%)	168 (10.1%)	46 (9.0%)	102 (8.2%)	735 (11.3%)	
<b>Education (years)</b>	12.6 (3.9)	10.6 (3.7)	11.6 (4.1)	10.5 (3.9)	11.6 (4.0)	<0.001 <sup>1</sup>
<b>General obesity</b>	0 (0.0%)	0 (0.0%)	510 (100.0%)	1250 (100.0%)	1760 (27.0%)	
<b>Metabolic syndrome</b>	0 (0.0%)	948 (57.0%)	0 (0.0%)	990 (79.2%)	1938 (29.7%)	<0.001 <sup>2</sup>
<b>Hypertension</b>	802 (25.9%)	1173 (70.6%)	176 (34.5%)	1023 (81.8%)	3174 (48.7%)	<0.001 <sup>2</sup>
<b>Increased waist circumference</b>	1274 (41.2%)	1267 (76.2%)	503 (98.6%)	1244 (99.5%)	4288 (65.8%)	<0.001 <sup>2</sup>
<b>Low HDL cholesterol</b>	542 (17.5%)	768 (46.2%)	102 (20.0%)	768 (61.4%)	2180 (33.5%)	<0.001 <sup>2</sup>
<b>Elevated triglycerides</b>	308 (10.0%)	810 (48.7%)	59 (11.6%)	792 (63.4%)	1969 (30.2%)	<0.001 <sup>2</sup>
<b>Hyperglycemia</b>	30 (1.0%)	157 (9.4%)	2 (0.4%)	194 (15.5%)	383 (5.9%)	<0.001 <sup>2</sup>
<b>Stroke</b>	0 (0.0%)	68 (4.5%)	0 (0.0%)	37 (3.2%)	105 (1.7%)	<0.001 <sup>2</sup>
Missing data	3	166	2	83	254	
<b>Angina pectoris</b>	0 (0.0%)	146 (9.8%)	0 (0.0%)	134 (11.4%)	280 (4.5%)	<0.001 <sup>2</sup>
Missing data	3	167	2	73	245	
<b>Myocardial infarction</b>	0 (0.0%)	58 (3.9%)	0 (0.0%)	36 (3.1%)	94 (1.5%)	<0.001 <sup>2</sup>
Missing data	3	165	2	80	250	
<b>Diabetes</b>	0 (0.0%)	101 (6.7%)	0 (0.0%)	133 (11.3%)	234 (3.7%)	<0.001 <sup>2</sup>
Missing data	3	163	2	74	242	
<b>Blood pressure-lowering drug</b>	0 (0.0%)	713 (43.8%)	0 (0.0%)	629 (50.9%)	1342 (20.8%)	<0.001 <sup>2</sup>

Missing data	3	36	2	14	55	
<b>Cholesterol-lowering drug</b>	0 (0.0%)	460 (29.0%)	0 (0.0%)	303 (25.5%)	763 (12.0%)	<0.001 <sup>2</sup>
Missing data	3	75	2	60	140	
<b>Glucose-lowering drug</b>	0 (0.0%)	96 (6.3%)	0 (0.0%)	108 (9.3%)	204 (3.2%)	<0.001 <sup>2</sup>
Missing data	3	136	2	93	234	

HDL = high-density lipoprotein, CVD = cardiovascular disease.

Continuous variables are reported as mean (standard deviation) and categorical variables are given as frequency (percent). In the final sample, missing data existed only in pre-existing disease and drug variables; in categorisation of metabolic health status, missing was assumed “no”, but frequencies of missing are shown in this table. It is evident that most people with missing nevertheless was categorised in an unhealthy group.

<sup>1</sup>One way analysis of variance

<sup>2</sup>Pearson’s  $\chi^2$  test

**Table 2. Sample characteristics in mean (standard deviation) or frequency (percent) according to general obesity phenotypes in 6298 men in the SAMINOR 1 Survey (2003—2004)**

	Metabolically healthy non-obesity (N=2972, 47.2%)	Metabolically unhealthy non-obesity (N=1843, 29.2%)	Metabolically healthy obesity (N=363, 5.8%)	Metabolically unhealthy obesity (N=1120, 17.8%)	Total (N=6298)	p-value
<b>Age (years)</b>	51.4 (9.9)	57.8 (10.8)	51.3 (10.1)	55.4 (10.3)	54.0 (10.6)	<0.001 <sup>1</sup>
<b>Ethnicity</b>						0.002 <sup>2</sup>
non-Sami	2264 (76.2%)	1452 (78.8%)	253 (69.7%)	865 (77.2%)	4834 (76.8%)	
Sami	708 (23.8%)	391 (21.2%)	110 (30.3%)	255 (22.8%)	1464 (23.2%)	
<b>Smoking</b>						<0.001 <sup>2</sup>
Yes, currently	1060 (35.7%)	549 (29.8%)	86 (23.7%)	260 (23.2%)	1955 (31.0%)	
Yes, previously	982 (33.0%)	830 (45.0%)	158 (43.5%)	571 (51.0%)	2541 (40.3%)	
Never	930 (31.3%)	464 (25.2%)	119 (32.8%)	289 (25.8%)	1802 (28.6%)	
<b>Died during follow-up</b>	297 (10.0%)	402 (21.8%)	39 (10.7%)	200 (17.9%)	938 (14.9%)	<0.001 <sup>2</sup>
<b>Cause of death</b>						<0.001 <sup>2</sup>
Malignant tumor	124 (41.8%)	123 (30.6%)	12 (30.8%)	63 (31.5%)	322 (34.3%)	
CVD	56 (18.9%)	135 (33.6%)	18 (46.2%)	75 (37.5%)	284 (30.3%)	
Respiratory	38 (12.8%)	47 (11.7%)	5 (12.8%)	14 (7.0%)	104 (11.1%)	
Other	75 (25.3%)	91 (22.6%)	3 (7.7%)	41 (20.5%)	210 (22.4%)	
Unknown	4 (1.3%)	6 (1.5%)	1 (2.6%)	7 (3.5%)	18 (1.9%)	
<b>Alcohol consumption</b>						<0.001 <sup>2</sup>
Weekly	1046 (35.2%)	545 (29.6%)	117 (32.2%)	315 (28.1%)	2023 (32.1%)	
Less than weekly	1691 (56.9%)	1057 (57.4%)	213 (58.7%)	683 (61.0%)	3644 (57.9%)	
Never/not last year	235 (7.9%)	241 (13.1%)	33 (9.1%)	122 (10.9%)	631 (10.0%)	

<b>Leisure-time physical activity</b>						<0.001 <sup>2</sup>
Sedentary	602 (20.3%)	417 (22.6%)	93 (25.6%)	339 (30.3%)	1451 (23.0%)	
Light	1571 (52.9%)	1088 (59.0%)	200 (55.1%)	616 (55.0%)	3475 (55.2%)	
Moderate-hard	799 (26.9%)	338 (18.3%)	70 (19.3%)	165 (14.7%)	1372 (21.8%)	
<b>Education (years)</b>	11.7 (3.8)	10.6 (3.7)	11.2 (3.4)	10.8 (3.7)	11.2 (3.8)	<0.001 <sup>1</sup>
<b>General obesity</b>	0 (0.0%)	0 (0.0%)	363 (100.0%)	1120 (100.0%)	1483 (23.5%)	
<b>Metabolic syndrome</b>	0 (0.0%)	970 (52.6%)	0 (0.0%)	900 (80.4%)	1870 (29.7%)	<0.001 <sup>2</sup>
<b>Hypertension</b>	1271 (42.8%)	1493 (81.0%)	164 (45.2%)	972 (86.8%)	3900 (61.9%)	<0.001 <sup>2</sup>
<b>Increased waist circumference</b>	636 (21.4%)	1031 (55.9%)	331 (91.2%)	1097 (97.9%)	3095 (49.1%)	<0.001 <sup>2</sup>
<b>Low HDL cholesterol</b>	258 (8.7%)	592 (32.1%)	22 (6.1%)	488 (43.6%)	1360 (21.6%)	<0.001 <sup>2</sup>
<b>Elevated triglycerides</b>	825 (27.8%)	1040 (56.4%)	93 (25.6%)	815 (72.8%)	2773 (44.0%)	<0.001 <sup>2</sup>
<b>Hyperglycemia</b>	44 (1.5%)	230 (12.5%)	3 (0.8%)	163 (14.6%)	440 (7.0%)	<0.001 <sup>2</sup>
<b>Stroke</b>	0 (0.0%)	100 (5.9%)	0 (0.0%)	51 (4.8%)	151 (2.5%)	<0.001 <sup>2</sup>
Missing data	6	145	0	52	203	
<b>Angina pectoris</b>	0 (0.0%)	318 (18.6%)	0 (0.0%)	138 (12.9%)	456 (7.5%)	<0.001 <sup>2</sup>
Missing data	6	137	0	48	191	
<b>Myocardial infarction</b>	0 (0.0%)	236 (13.7%)	0 (0.0%)	110 (10.2%)	346 (5.7%)	<0.001 <sup>2</sup>
Missing data	6	124	0	45	175	
<b>Diabetes</b>	0 (0.0%)	135 (7.9%)	0 (0.0%)	85 (7.9%)	220 (3.6%)	<0.001 <sup>2</sup>
Missing data	6	134	0	45	185	
<b>Blood pressure-lowering drug</b>	0 (0.0%)	837 (46.4%)	0 (0.0%)	504 (45.4%)	1341 (21.5%)	<0.001 <sup>2</sup>

Missing data	6	38	0	10	54	
<b>Cholesterol-lowering drug</b>	0 (0.0%)	630 (35.6%)	0 (0.0%)	320 (29.5%)	950 (15.4%)	<0.001 <sup>2</sup>
Missing data	6	74	0	35	115	
<b>Glucose-lowering drug</b>	0 (0.0%)	131 (7.7%)	0 (0.0%)	66 (6.3%)	197 (3.2%)	<0.001 <sup>2</sup>
Missing data	6	141	0	68	215	

HDL = high-density lipoprotein, CVD = cardiovascular disease.

Continuous variables are reported as mean (standard deviation) and categorical variables are given as frequency (percent). In the final sample, missing data existed only in pre-existing disease and drug variables; in categorisation of metabolic health status, missing was assumed “no”, but frequencies of missing are shown in this table. It is evident that most people with missing nevertheless was categorised in an unhealthy group.

<sup>1</sup>One way analysis of variance

<sup>2</sup>Pearson’s  $\chi^2$  test

**Table 3. All-cause and CVD mortality according to MetS, general and abdominal obesity phenotypes: Hazard ratios (HR) and 95% confidence intervals (CI) from Cox proportional hazards models of 6517 women in the SAMINOR 1 Survey (2003–2004)**

				Model 1		Model 2		Model 3	
	Cases	Person-years	IR	HR	95% CI	HR	95% CI	HR	95% CI
<b>Outcome: All-cause mortality</b>									
<b>Metabolic syndrome</b>									
No	343	68588.7	5.0	Ref.		Ref.		Ref.	
Yes	253	28604.7	8.8	1.14	0.97 – 1.35	1.15	0.97 – 1.35	1.11	0.94 – 1.31
<b>General obesity phenotypes</b>									
Metabolically healthy non-obese	154	46629.4	3.3	Ref.		Ref.		Ref.	
Metabolically unhealthy non-obese	230	24487.6	9.4	1.13	0.92 – 1.40	1.14	0.92 – 1.41	1.11	0.90 – 1.38
Metabolically healthy obese	25	7753.5	3.2	0.64	0.42 – 0.97	0.68	0.44 – 1.04	0.63	0.41 – 0.97
Metabolically unhealthy obese	187	18322.8	10.2	1.17	0.94 – 1.46	1.27	1.02 – 1.59	1.17	0.93 – 1.47
<b>Abdominal obesity phenotypes</b>									
Metabolically healthy non-abdominally obese	119	39259.1	3.0	Ref.		Ref.		Ref.	
Metabolically unhealthy non-abdominally obese	170	20308.6	8.4	1.12	0.88 – 1.43	1.14	0.89 – 1.45	1.12	0.88 – 1.43
Metabolically healthy abdominally obese	42	12571.2	3.3	0.71	0.50 – 1.01	0.75	0.53 – 1.07	0.71	0.50 – 1.02
Metabolically unhealthy abdominally obese	265	25054.5	10.6	1.23	0.99 – 1.55	1.31	1.04 – 1.64	1.22	0.97 – 1.54
<b>Outcome: CVD mortality</b>									
<b>Metabolic syndrome</b>									
No	73	68588.7	1.1	Ref.		Ref.		Ref.	
Yes	79	28604.7	2.8	1.55	1.12 – 2.13	1.53	1.11 – 2.11	1.46	1.06 – 2.02
<b>General obesity phenotypes</b>									
Metabolically healthy non-obese	16	46629.4	0.3	Ref.		Ref.		Ref.	

Metabolically unhealthy non-obese	73	24487.6	3.0	2.86	1.65 – 4.95	2.88	1.66 – 4.99	2.77	1.59 – 4.80
Metabolically healthy obese	5	7753.5	0.6	1.08	0.40 – 2.96	1.12	0.41 – 3.07	1.05	0.38 – 2.88
Metabolically unhealthy obese	58	18322.8	3.2	2.81	1.60 – 4.94	2.93	1.66 – 5.15	2.65	1.49 – 4.72
<b>Abdominal obesity phenotypes</b>									
Metabolically healthy non-abdominally obese	16	39259.1	0.4	Ref.		Ref.		Ref.	
Metabolically unhealthy non-abdominally obese	48	20308.6	2.4	1.90	1.07 – 3.38	1.93	1.09 – 3.43	1.86	1.05 – 3.32
Metabolically healthy abdominally obese	5	12571.2	0.4	0.55	0.20 – 1.50	0.57	0.21 – 1.56	0.54	0.20 – 1.47
Metabolically unhealthy abdominally obese	83	25054.5	3.3	2.25	1.30 – 3.88	2.31	1.34 – 3.99	2.11	1.21 – 3.69

IR = crude incidence rate per 1000 person-years , HR = hazard ratio, CI = confidence interval.

Model 1 is the crude model (all models inherently adjusted for age by using attained age as the time-scale).

Model 2 was additionally adjusted for smoking, and model 3 was additionally adjusted for leisure-time physical activity, education and alcohol consumption (model 3). We applied stratified Cox models with separate baseline hazards for subgroups of smoking status to satisfy the proportional hazard assumption in all-cause mortality models.

**Table 4. All-cause and CVD mortality according to MetS, general and abdominal obesity phenotypes: Hazard ratios (HR) and 95% confidence intervals (CI) from Cox proportional hazards models of 6298 men in SAMINOR 1 (2003–2004)**

				Model 1		Model 2		Model 3	
	Cases	Person-years	IR	HR	95% CI	HR	95% CI	HR	95% CI
<b>Outcome: All-cause mortality</b>									
<b>Metabolic syndrome</b>									
No	627	65040.4	9.6	Ref.		Ref.		Ref.	
Yes	311	27124.8	11.5	1.06	0.93 – 1.22	1.11	0.97 – 1.28	1.10	0.96 – 1.26
<b>General obesity phenotypes</b>									
Metabolically healthy non-obese	297	44234.7	6.7	Ref.		Ref.		Ref.	
Metabolically unhealthy non-obese	402	26321.0	15.3	1.12	0.96 – 1.31	1.18	1.01 – 1.38	1.16	0.99 – 1.35
Metabolically healthy obese	39	5381.8	7.2	1.13	0.81 – 1.57	1.28	0.91 – 1.79	1.25	0.89 – 1.75
Metabolically unhealthy obese	200	16227.8	12.3	1.22	1.02 – 1.46	1.38	1.14 – 1.65	1.33	1.11 – 1.61
<b>Abdominal obesity phenotypes</b>									
Metabolically healthy non-abdominally obese	241	38178.8	6.3	Ref.		Ref.		Ref.	
Metabolically unhealthy non-abdominally obese	430	34896.0	12.3	1.13	0.97 – 1.33	1.20	1.02 – 1.41	1.18	1.00 – 1.38
Metabolically healthy abdominally obese	40	4344.3	9.2	1.12	0.80 – 1.57	1.23	0.88 – 1.73	1.20	0.86 – 1.69
Metabolically unhealthy abdominally obese	227	14746.1	15.4	1.39	1.16 – 1.67	1.53	1.27 – 1.84	1.49	1.23 – 1.79
<b>Outcome: CVD mortality</b>									
<b>Metabolic syndrome</b>									
No	170	65040.4	2.6	Ref.		Ref.		Ref.	
Yes	114	27124.8	4.2	1.43	1.13 – 1.82	1.53	1.20 – 1.94	1.51	1.18 – 1.91
<b>General obesity phenotypes</b>									
Metabolically healthy non-obese	56	44234.7	1.3	Ref.		Ref.		Ref.	

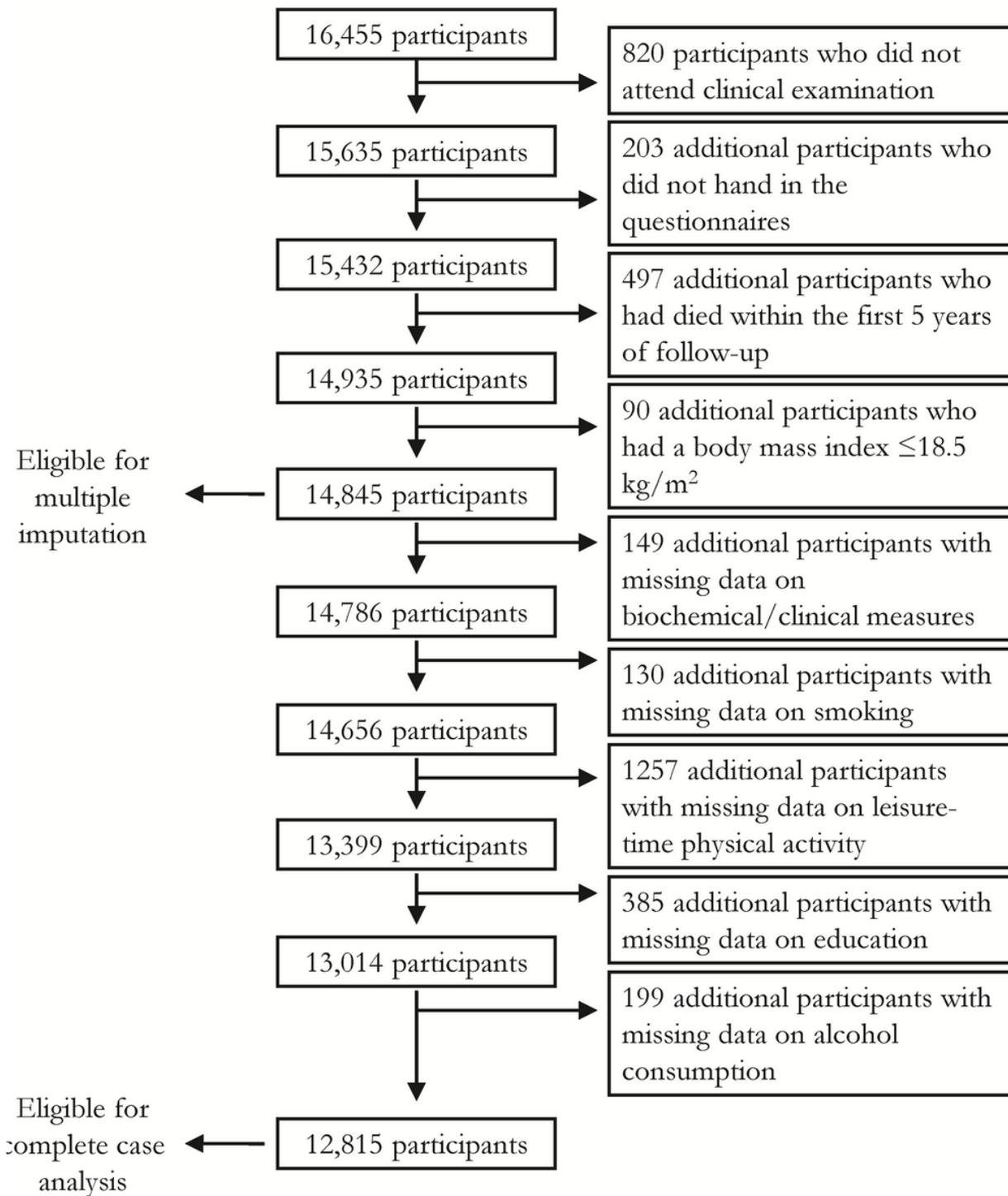
Metabolically unhealthy non-obese	135	26321.0	5.1	1.95	1.42 – 2.68	2.11	1.54 – 2.90	2.08	1.51 – 2.86
Metabolically healthy obese	18	5381.8	3.3	2.68	1.57 – 4.56	3.03	1.77 – 5.19	2.92	1.71 – 5.01
Metabolically unhealthy obese	75	16227.8	4.6	2.40	1.69 – 3.40	2.83	1.98 – 4.03	2.72	1.90 – 3.89
<b>Abdominal obesity phenotypes</b>									
Metabolically healthy non-abdominally obese	47	38178.8	1.2	Ref.		Ref.		Ref.	
Metabolically unhealthy non-abdominally obese	137	34896.0	3.9	1.81	1.30 – 2.54	1.98	1.41 – 2.76	1.94	1.38 – 2.72
Metabolically healthy abdominally obese	15	4344.3	3.5	2.07	1.15 – 3.70	2.28	1.27 – 4.09	2.18	1.21 – 3.92
Metabolically unhealthy abdominally obese	85	14746.1	5.8	2.61	1.82 – 3.74	3.00	2.08 – 4.32	2.89	2.00 – 4.17

IR = crude incidence rate per 1000 person-years, HR = hazard ratio, CI = confidence interval.

Model 1 is the crude model (all models inherently adjusted for age by using attained age as the time-scale).

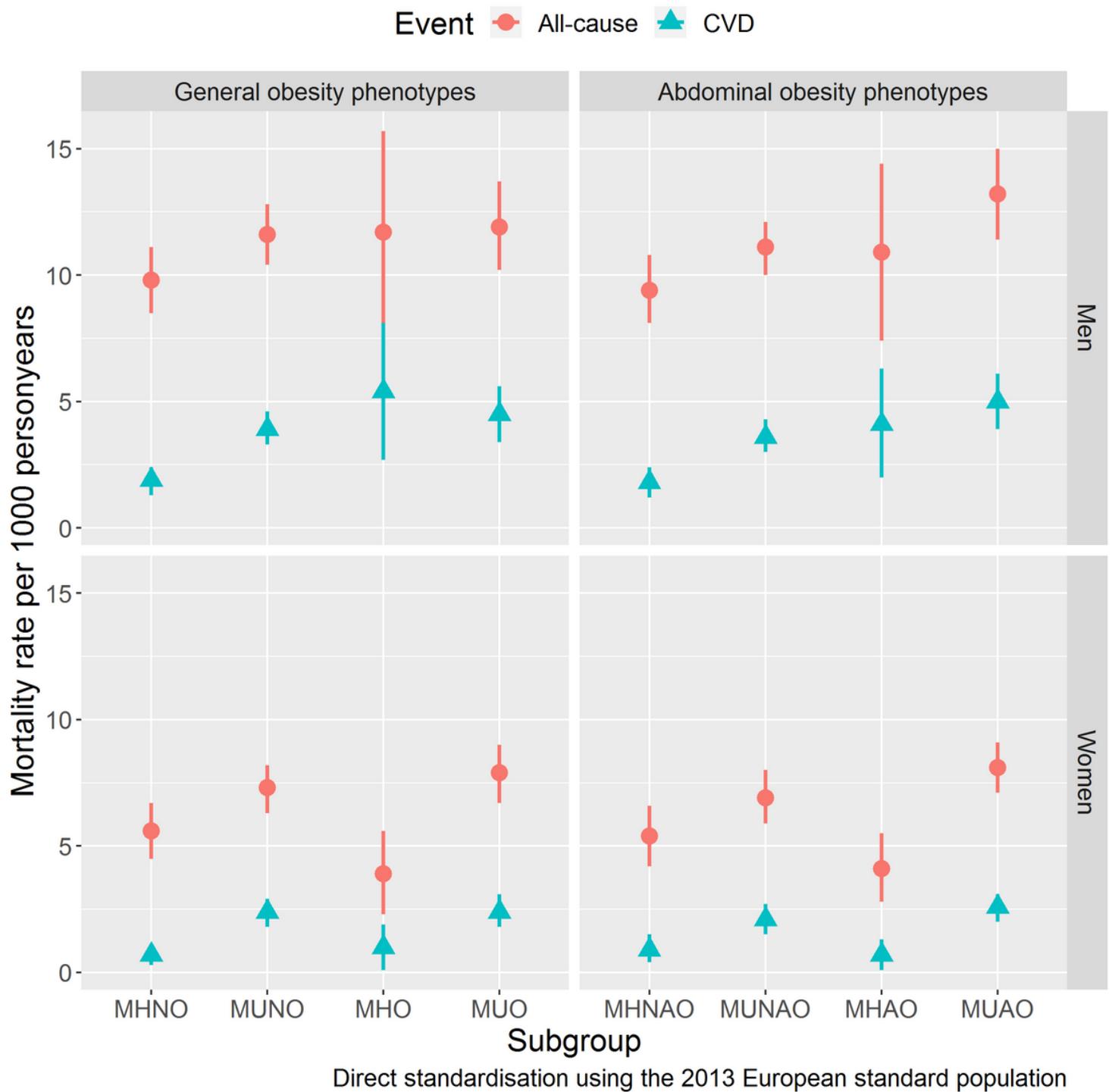
Model 2 was additionally adjusted for smoking, and model 3 was additionally adjusted for leisure-time physical activity, education and alcohol consumption (model 3). We applied stratified Cox models with separate baseline hazards for subgroups of smoking status to satisfy the proportional hazard assumption in all-cause mortality models.

## Figures



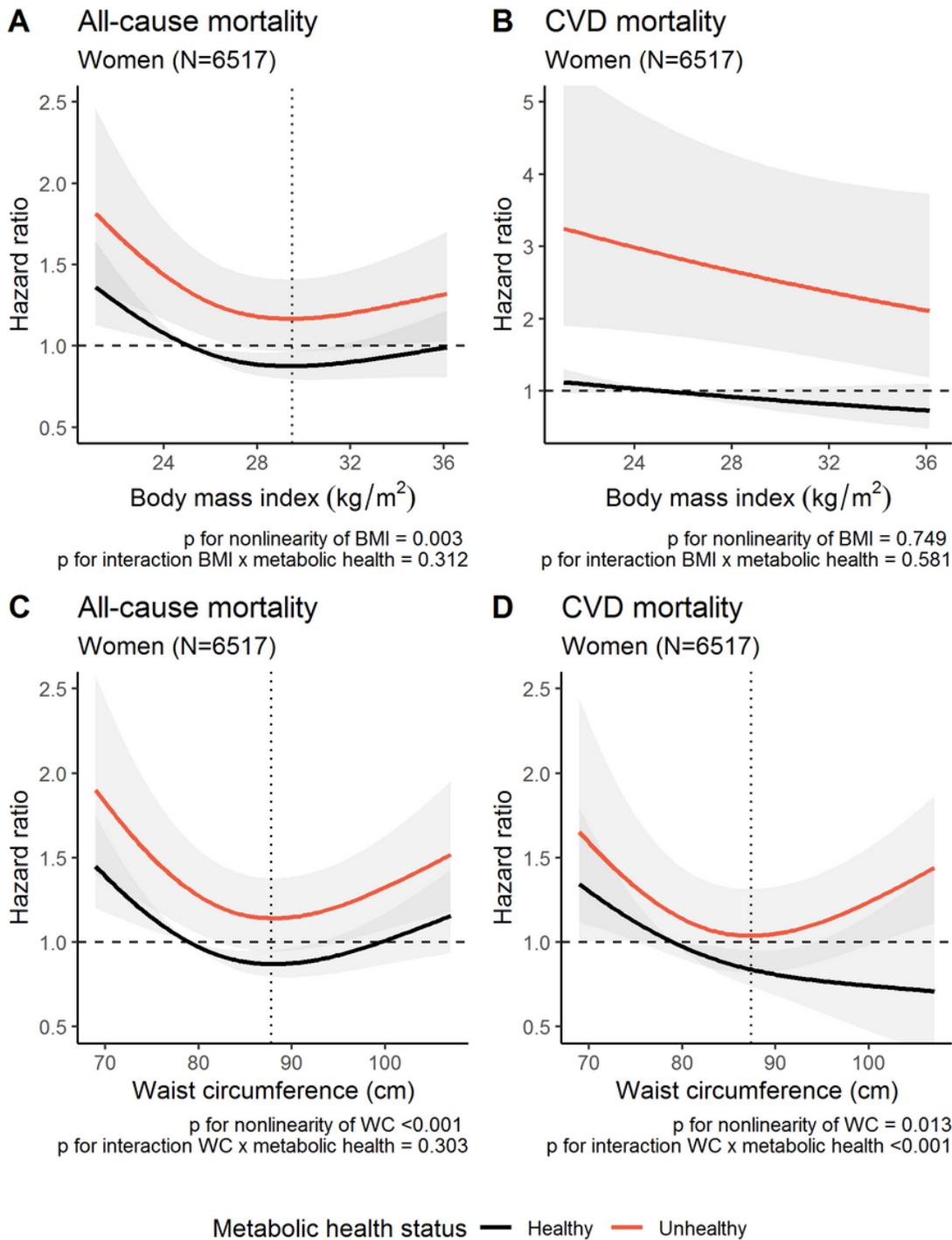
**Figure 1**

Flow-chart describing cohort selection from SAMINOR 1 participants and patterns of missing data.



**Figure 2**

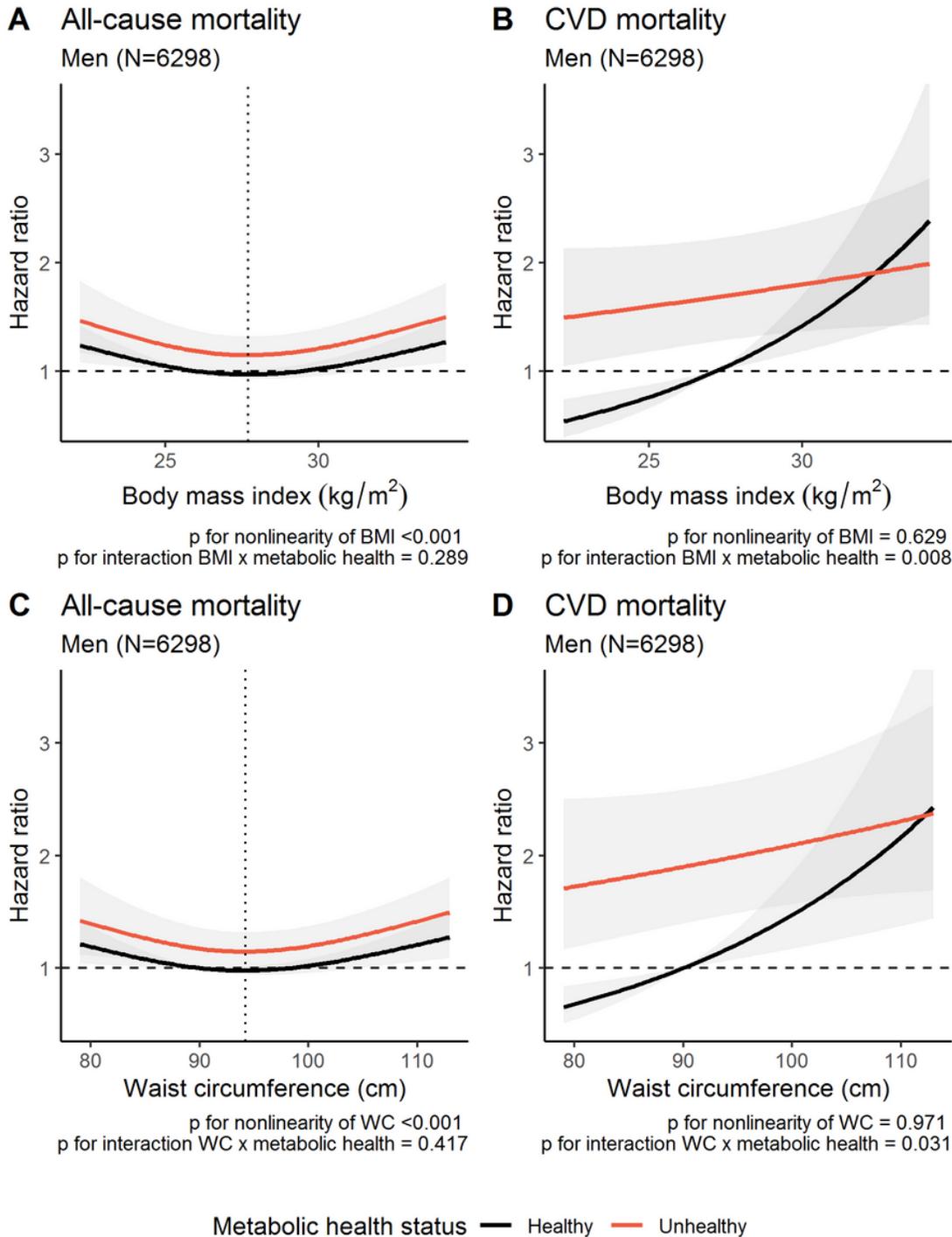
Age-standardised mortality rates per 1000 person-years with 95% CI for all-cause and CVD mortality given by general and abdominal obesity phenotypes. MHNO = metabolically healthy non-obesity, MUNO = metabolically unhealthy non-obesity, MHO = metabolically healthy obesity, MUO = metabolically unhealthy obesity, MHNAO = metabolically healthy non-abdominal obesity, MUNAO = metabolically unhealthy non-abdominal obesity, MHAO = metabolically healthy abdominal obesity, MUAO = metabolically unhealthy abdominal obesity.



**Figure 3**

The functional relationships between mortality (all-cause and CVD) and continuous obesity measures (body mass index and waist circumference) with corresponding hazard ratios with 95% confidence bands in women. The reference of all curves were metabolically healthy women with a BMI of 26.7 and waist circumference of 79 cm (median values). P-values originates from likelihood ratio tests comparing models with/without linear terms/interaction terms. The beta coefficient for metabolic health status was statistically significant in all models. Estimates are predicted for median values of confounders (smoking, leisure-time physical activity, education, alcohol consumption). All models were inherently adjusted for age by using attained age as the

time-scale. The vertical, dotted lines represent the nadir of risk. In panel D, the nadir of risk of metabolically healthy and unhealthy differ due to a significant interaction (nadir lower in unhealthy than healthy). Note that panel B has different dimensions on the y-axis than the other panels. BMI = body mass index, WC = waist circumference.



**Figure 4**

The functional relationships between mortality (all-cause and CVD) and continuous obesity measures (body mass index and waist circumference) with corresponding hazard ratios with 95% confidence bands in men. The reference of all curves were metabolically healthy men with a BMI of 27.2 and waist circumference of 90

cm (median values). P-values originates from likelihood ratio tests comparing models with/without linear terms/interaction terms. The beta coefficient for metabolic health status was statistically significant in all models. Estimates are predicted for median values of confounders (smoking, leisure-time physical activity, education, alcohol consumption). All models were inherently adjusted for age by using attained age as the time-scale. The vertical, dotted lines represent the nadir of risk. BMI = body mass index, WC = waist circumference.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementary.pdf](#)