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# 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

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Keywords: Abdominal obesity. A body shape index. All-cause mortality. Body mass index. Cardiovascular mortality. Metabolically healthy obesity. Metabolic syndrome. Obesity. Waist circumference.

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**Abstract**

**Background:** The mortality of metabolic—obesity phenotypes has been thoroughly studied, but it is not known if or how the association between mortality and body mass index (BMI), waist circumference or a body shape index (ABSI) 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 ≥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 ≥30 kg/m$^2$ and waist circumference ≥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) BMI, waist circumference and ABSI fitted with restricted cubic splines. We adjusted for age and lifestyle, 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 groups had higher mortality than the MHNO group. Sex and phenotypes interacted with respect to CVD mortality: 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. ABSI was linearly and positively associated with all-cause and CVD mortality in men.

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

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

# 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 type 2 diabetes mellitus (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 CVD (6–8), type 2 diabetes mellitus (9,10), and mortality (11,12).

A body mass index (BMI) ≥30 kg/m$^2$ 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). 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). However, BMI and waist circumference are usually highly correlated. Krakauer et al. developed a body shape index (ABSI), which is a measure of central obesity that has a low correlation with BMI (17).

To the best of our knowledge, no studies have examined the relationships between continuous measures of BMI, waist circumference or ABSI 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 (18,19).

## 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 18th and 19th 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 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 (20).

### 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/previously, but not now/never); use of cholesterol-lowering drug (currently/previously, but not now/never); use of insulin (currently/previously, but not now/never); use of glucose-lowering drug in tablet format (currently/previously, but not now/never); smoking (currently/previously/never); 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). Alcohol consumption was categorised into "weekly alcohol consumption", "less than weekly alcohol consumption" and "never/not last year". Leisure-time physical activity was measured by a self-reported modified Saltin-Grimby 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) (21). The Saltin-Grimby Physical Activity Level scale has been used in many Nordic populations and has shown acceptable validity regarding objectively measured physical activity (21). Leisure-time physical activity was categorised into "sedentary" (the first

option), "light" (the second option) and "moderate-hard" (the last two options merged). 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 (22).

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 (23). At least three of the following five components had to be present:

hypertension, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or current use of antihypertensive drug;

elevated random glucose, defined as random serum glucose ≥7.8 mmol/L or self-reported diabetes;

increased waist circumference, defined as waist circumference ≥80 cm in women and ≥94 cm in men;

hypertriglyceridemia, defined as random serum triglycerides ≥1.7 mmol/L; and

lowered HDL cholesterol, defined as random serum 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. (24):

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 ≥30 kg/m$^2$ and waist circumference ≥88 cm in women and ≥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 (MUNAO); metabolically healthy abdominal obesity (MHAO); and metabolically unhealthy abdominal obesity (MUAO).

In addition to using BMI and waist circumference to define general and abdominal obesity, respectively, we also used them as continuous variables (BMI in kg/m$^2$ and waist circumference in cm). Due to the high correlation between BMI and waist circumference (0.88 in women and 0.86 in men in this cohort), we also applied ABSI as developed by Krakauer et al. based on a U.S. population-based cohort (NHANES) (17):

$$ABSI = \frac{waist\ circumference}{BMI^{2/3}\ height^{1/2}}$$

The ABSI was transformed to a Z-score for interpretability by subtracting the sex-specific mean and dividing by the sex-specific standard deviation. ABSI was not used as a determinant of categorical obesity because of the lack of validated cut-offs.

194 **2.5 Outcome variables**

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

201 **2.6 Missing data and exclusions**

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

210

211 **2.7 Statistical analysis**

212 Sample characteristics were described in strata of sex and metabolic–obesity phenotype and
213 reported as mean (SD) and frequency (percentage) as appropriate. One-way analysis of variance
214 and Pearson's $\chi^2$ test were used to compare characteristics across the phenotypes. We calculated
215 age-standardised mortality rates using the direct method and the 2013 European standard
216 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 (25), 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). 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, and was therefore not included in the models. 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 BMI, waist circumference and ABSI as continuous variables 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 (26). 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/ABSI 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, waist circumference and ABSI, respectively, with separate curves for metabolically healthy and unhealthy, using the sex-specific sample median of BMI, waist circumference or ABSI as reference values. In models with a significant interaction, metabolically healthy with the sex-specific sample median of BMI, waist circumference or ABSI were used as reference.

We used *R* version 3.6.2 for Windows for statistical computing (27). Code and output is found in the supplementary material.

**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 (≥88/102 cm in women/men), random triglycerides (≥2.1 mmol/L), and random glucose (≥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 (28). 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* (29). Because metabolic health is a known mediator of the relationship between obesity and mortality, we also ran the analyses of continuous BMI/waist circumference/ABSI 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 women and men, respectively. Figure 3 and 4 (panels E) show curvilinear and linear relationships between all-cause mortality and ABSI in women and men, respectively. Figure 3 and 4 (panels B, D and F) show marked sex-differences in the relationships with CVD mortality for BMI (panel B), waist circumference (panel D) and ABSI (panel F). Interactions were present between metabolic health status and obesity measures in CVD models (except in panel 3B and 4F). In men, all obesity measures had positive, strong associations with CVD mortality. We found stronger associations (steeper slopes) in metabolically healthy than unhealthy groups in models with BMI and waist circumference, but not in models with ABSI. In women, BMI had negative associations with CVD mortality. The association between waist circumference or ABSI 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.

316 Contrary, in participants without pre-existing disease or prescribed drugs, most estimates were
317 strongly attenuated and not statistically significant (except men with MHO and MHAO)
318 compared to those observed in the whole cohort. Using more conservative cut-offs for MetS
319 resulted in increased estimates, and the apparent protective effect of MHO and MHAO in
320 women was attenuated towards the null and was no longer statistically significant. In sex-adjusted
321 analyses, HR (95%) for all-cause mortality compared to the reference groups were 0.92 (0.71–
322 1.20) for MHO and 0.92 (0.72–1.17) for MHAO, respectively. Analysis of multiply imputed data
323 gave similar results compared to the complete case analysis. Supplementary Figure 1 and 2 of
324 "unadjusted" obesity vs mortality models show overall patterns similar with the primary analyses.
325 An exception was seen for models with CVD mortality in women, which showed no association
326 with BMI or waist circumference, but a curvilinear association with ABSI indicating significantly
327 higher mortality at higher ends of the scale.

328 ## 4 Discussion

329 We followed almost 13,000 adults for 15 years and found that metabolically unhealthy status was
330 associated with a higher CVD mortality than metabolically healthy status irrespective of obesity
331 status. We found curvilinear associations between BMI (women and men), waist circumference
332 (women and men) or ABSI (women) and all-cause mortality regardless of metabolic health status.
333 However, in men, the relationship between ABSI and all-cause mortality was linear.
334 Corresponding relationships between these three continuous obesity measures and CVD
335 mortality differed by both sex and metabolic health status. Ethnicity had no impact on the
336 results.

337 To our knowledge, this study is the first to examine the relationship between continuous
338 measures of BMI, waist circumference or ABSI and mortality according to metabolic health
339 status. A recent study of a Japanese population by Izumida et al. examined the relationships
340 between four categories of BMI and 18-year mortality according to MetS status (30). 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) (31). 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 (32). However, among women and men who transitioned from MHO to MUO, only men had an increased HR compared to the non-obese comparison group (32). 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 (33). 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 (34). 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 (33).

A high ABSI seems to be a more consistent predictor of mortality in both women and men compared to a high BMI or waist circumference irrespective of metabolic health status; however, we have not formally compared the models. Studies in a US and four European (Sweden, Finland, Turkey and UK) cohorts have shown that where BMI or waist circumference tend to show curvilinear relationships with mortality, a progressively increasing ABSI corresponds to an increasing mortality (17,35). As opposed to BMI and waist circumference, ABSI was linearly and positively associated with both all-cause and CVD mortality in men. This pattern for ABSI was not found in women, perhaps owing to the weak, but existing correlation with BMI (0.17 in women vs 0.08 in men). Ideally, the correlation between ABSI and BMI should be null (17), but due to differences in distributions of height, weight and waist circumference between the participants in the NHANES and the SAMINOR Study, the formula is not a perfect fit in the latter. Recently, ABSI was derived specifically for the UK Biobank population (36), and in the future deriving population-specific formulae may avoid bias from correlations with BMI.

In models not controlling for metabolic health, we found linear (men) and U-shaped (women) associations between ABSI and both all-cause and CVD mortality (Supplementary Figure 1 and 2). In women, ABSI scores above the mean were strongly associated with mortality. At the lower end of ABSI, CIs were wide. In a recent study using a large European cohort, the ABSI - mortality relationship also differed by sex (37). In women, the relationship was J-shaped, with positive associations only in the higher quintiles, whereas ABSI was positively associated with mortality in all quintiles in men. Our results show some similarity to these findings. The aforementioned study showed that people with a high ABSI had approximately 30% higher mortality compared to people with low ABSI, irrespective of BMI category (37). This suggests

392 that ABSI reflects an altered, detrimental body shape that is not reflected in BMI. A small study
393 found that ABSI and BMI were negatively and positively, respectively, associated with fat free
394 mass, or lean mass, indicating that a high ABSI is a good marker of sarcopenic obesity (38). In
395 future studies, it may be interesting to replace BMI with ABSI in defining categorical obesity
396 phenotypes, i.e., to define a MHO phenotype from body shape.

397 Collider bias has been suggested to explain the "obesity paradox": obesity increases mortality and
398 causes cardiometabolic disease, but within strata of cardiometabolic disease, obesity is not
399 associated with mortality or even appears protective in some studies (39,40), as is seen in models
400 with BMI and waist circumference for women in this study. The collider bias is a type of
401 selection bias, that can be introduced through restriction, regression adjustment or stratification
402 on a variable (in this case cardiometabolic status) that is both affected by the exposure (obesity)
403 and share common causes (e.g. genes) with the outcome (death). However, the magnitude and
404 direction of the bias may be difficult to predict, and some suggest it only a partial explanation of
405 the obesity paradox (41).

406 Izumida et al. defined metabolically healthy as having no MetS components, compared to our
407 definition of two or fewer components. Hence, metabolically healthy people in our study may
408 have been in a transition phase towards full MetS and converted to metabolically unhealthy
409 during the study period. Approximately 50% of people with MHO transition to MUO (4). A
410 study with six repeated measures during 30 years of follow-up showed that duration with MHO
411 was longer in women than in men. Women transitioned back and forth between a healthy and an
412 unhealthy metabolic status while maintaining their obesity status, whereas men with MHO
413 tended to just transition once from a healthy to an unhealthy metabolic status (42). Nevertheless,
414 in a large U.S. cohort of women (N≈90,000), both those with MHO at baseline and those with
415 persistent MHO status over a period of 24 years were at increased risk of CVD compared with
416 the MHNO (43). 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 (44). 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 some of the relationships between obesity and mortality that 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. However, we did not have information on occupational physical activity, which may comprise a large part of the total physical activity level throughout the day. Therefore, some residual confounding from physical activity may be present. Further 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 (45). 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 or ABSI 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.

## 6 Abbreviations

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, MetS = metabolic syndrome, CVD = cardiovascular disease, BMI = body mass index, ABSI = a body shape index, HR = hazard ratio, CI = confidence interval, SD = standard deviation, HDL = high density lipoprotein.

## 7 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.

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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.

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## 9 Figure legends

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 (BMI, waist circumference and ABSI) 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 kg/m$^2$, a waist circumference of 79 cm or an ABSI Z-score of -0.32 (median values for metabolically healthy women). 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. ABSI = a body shape index, BMI = body mass index, WC = waist circumference.

Figure 4. The functional relationships between mortality (all-cause and CVD) and continuous obesity measures (BMI, waist circumference and ABSI) 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 kg/m$^2$, a waist circumference of 90 cm or an ABSI Z-score of -0.28 (median values for metabolically healthy men). 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. ABSI = a body shape index, BMI = body mass index, WC = waist circumference.

643 # 10 Tables

644 **Table 1. Sample characteristics in mean (standard deviation) or frequency (percent) according to general obesity phenotypes in**
645 **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 |
|---|---|---|---|---|---|---|
| **Age (years)** | 49.4 (9.4) | 57.4 (10.7) | 52.1 (10.2) | 57.4 (11.0) | 53.2 (10.8) | <0.001[1] |
| **Ethnicity** | | | | | | <0.001[2] |
| 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%) | |
| **Smoking** | | | | | | <0.001[2] |
| 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%) | |
| **Died during follow-up** | 154 (5.0%) | 230 (13.8%) | 25 (4.9%) | 187 (15.0%) | 596 (9.1%) | <0.001[2] |
| **Cause of death** | | | | | | <0.001[2] |
| 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%) | |
| **Alcohol consumption** | | | | | | <0.001[2] |
| 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%) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Leisure-time physical activity** | | | | | | <0.001[2] |
| 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%) | |
| **Education (years)** | 12.6 (3.9) | 10.6 (3.7) | 11.6 (4.1) | 10.5 (3.9) | 11.6 (4.0) | <0.001[1] |
| **General obesity** | 0 (0.0%) | 0 (0.0%) | 510 (100.0%) | 1250 (100.0%) | 1760 (27.0%) | |
| **Metabolic syndrome** | 0 (0.0%) | 948 (57.0%) | 0 (0.0%) | 990 (79.2%) | 1938 (29.7%) | <0.001[2] |
| **Hypertension** | 802 (25.9%) | 1173 (70.6%) | 176 (34.5%) | 1023 (81.8%) | 3174 (48.7%) | <0.001[2] |
| **Increased waist circumference** | 1274 (41.2%) | 1267 (76.2%) | 503 (98.6%) | 1244 (99.5%) | 4288 (65.8%) | <0.001[2] |
| **Low HDL cholesterol** | 542 (17.5%) | 768 (46.2%) | 102 (20.0%) | 768 (61.4%) | 2180 (33.5%) | <0.001[2] |
| **Elevated triglycerides** | 308 (10.0%) | 810 (48.7%) | 59 (11.6%) | 792 (63.4%) | 1969 (30.2%) | <0.001[2] |
| **Hyperglycemia** | 30 (1.0%) | 157 (9.4%) | 2 (0.4%) | 194 (15.5%) | 383 (5.9%) | <0.001[2] |
| **Stroke** | 0 (0.0%) | 68 (4.5%) | 0 (0.0%) | 37 (3.2%) | 105 (1.7%) | <0.001[2] |
| Missing data | 3 | 166 | 2 | 83 | 254 | |
| **Angina pectoris** | 0 (0.0%) | 146 (9.8%) | 0 (0.0%) | 134 (11.4%) | 280 (4.5%) | <0.001[2] |
| Missing data | 3 | 167 | 2 | 73 | 245 | |
| **Myocardial infarction** | 0 (0.0%) | 58 (3.9%) | 0 (0.0%) | 36 (3.1%) | 94 (1.5%) | <0.001[2] |
| Missing data | 3 | 165 | 2 | 80 | 250 | |
| **Diabetes** | 0 (0.0%) | 101 (6.7%) | 0 (0.0%) | 133 (11.3%) | 234 (3.7%) | <0.001[2] |
| Missing data | 3 | 163 | 2 | 74 | 242 | |
| **Blood pressure-lowering drug** | 0 (0.0%) | 713 (43.8%) | 0 (0.0%) | 629 (50.9%) | 1342 (20.8%) | <0.001[2] |
| Missing data | 3 | 36 | 2 | 14 | 55 | |
| **Cholesterol-lowering drug** | 0 (0.0%) | 460 (29.0%) | 0 (0.0%) | 303 (25.5%) | 763 (12.0%) | <0.001[2] |
| Missing data | 3 | 75 | 2 | 60 | 140 | |
| **Glucose-lowering drug** | 0 (0.0%) | 96 (6.3%) | 0 (0.0%) | 108 (9.3%) | 204 (3.2%) | <0.001[2] |

| | | | | | |
|---|---|---|---|---|---|
| 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.

[1]One way analysis of variance

[2]Pearson's $\chi^2$ test

659 **Table 2. Sample characteristics in mean (standard deviation) or frequency (percent) according to general obesity phenotypes in**
660 **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 |
|---|---|---|---|---|---|---|
| **Age (years)** | 51.4 (9.9) | 57.8 (10.8) | 51.3 (10.1) | 55.4 (10.3) | 54.0 (10.6) | <0.001[1] |
| **Ethnicity** | | | | | | 0.002[2] |
| 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%) | |
| **Smoking** | | | | | | <0.001[2] |
| 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%) | |
| **Died during follow-up** | 297 (10.0%) | 402 (21.8%) | 39 (10.7%) | 200 (17.9%) | 938 (14.9%) | <0.001[2] |
| **Cause of death** | | | | | | <0.001[2] |
| 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%) | |
| **Alcohol consumption** | | | | | | <0.001[2] |
| 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%) | |
| **Leisure-time physical activity** | | | | | | <0.001[2] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 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%) | |
| **Education (years)** | 11.7 (3.8) | 10.6 (3.7) | 11.2 (3.4) | 10.8 (3.7) | 11.2 (3.8) | <0.001[1] |
| **General obesity** | 0 (0.0%) | 0 (0.0%) | 363 (100.0%) | 1120 (100.0%) | 1483 (23.5%) | |
| **Metabolic syndrome** | 0 (0.0%) | 970 (52.6%) | 0 (0.0%) | 900 (80.4%) | 1870 (29.7%) | <0.001[2] |
| **Hypertension** | 1271 (42.8%) | 1493 (81.0%) | 164 (45.2%) | 972 (86.8%) | 3900 (61.9%) | <0.001[2] |
| **Increased waist circumference** | 636 (21.4%) | 1031 (55.9%) | 331 (91.2%) | 1097 (97.9%) | 3095 (49.1%) | <0.001[2] |
| **Low HDL cholesterol** | 258 (8.7%) | 592 (32.1%) | 22 (6.1%) | 488 (43.6%) | 1360 (21.6%) | <0.001[2] |
| **Elevated triglycerides** | 825 (27.8%) | 1040 (56.4%) | 93 (25.6%) | 815 (72.8%) | 2773 (44.0%) | <0.001[2] |
| **Hyperglycemia** | 44 (1.5%) | 230 (12.5%) | 3 (0.8%) | 163 (14.6%) | 440 (7.0%) | <0.001[2] |
| **Stroke** | 0 (0.0%) | 100 (5.9%) | 0 (0.0%) | 51 (4.8%) | 151 (2.5%) | <0.001[2] |
| Missing data | 6 | 145 | 0 | 52 | 203 | |
| **Angina pectoris** | 0 (0.0%) | 318 (18.6%) | 0 (0.0%) | 138 (12.9%) | 456 (7.5%) | <0.001[2] |
| Missing data | 6 | 137 | 0 | 48 | 191 | |
| **Myocardial infarction** | 0 (0.0%) | 236 (13.7%) | 0 (0.0%) | 110 (10.2%) | 346 (5.7%) | <0.001[2] |
| Missing data | 6 | 124 | 0 | 45 | 175 | |
| **Diabetes** | 0 (0.0%) | 135 (7.9%) | 0 (0.0%) | 85 (7.9%) | 220 (3.6%) | <0.001[2] |
| Missing data | 6 | 134 | 0 | 45 | 185 | |
| **Blood pressure-lowering drug** | 0 (0.0%) | 837 (46.4%) | 0 (0.0%) | 504 (45.4%) | 1341 (21.5%) | <0.001[2] |
| Missing data | 6 | 38 | 0 | 10 | 54 | |
| **Cholesterol-lowering drug** | 0 (0.0%) | 630 (35.6%) | 0 (0.0%) | 320 (29.5%) | 950 (15.4%) | <0.001[2] |
| Missing data | 6 | 74 | 0 | 35 | 115 | |
| **Glucose-lowering drug** | 0 (0.0%) | 131 (7.7%) | 0 (0.0%) | 66 (6.3%) | 197 (3.2%) | <0.001[2] |

| | | | | | |
|---|---|---|---|---|---|
| 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.

[1]One way analysis of variance

[2]Pearson's $\chi^2$ test

677 **Table 3. All-cause and CVD mortality according to MetS, general and abdominal obesity phenotypes: Hazard ratios (HR) and 95%**
678 **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 |
| **Outcome: All-cause mortality** | | | | | | | | | |
| **Metabolic syndrome** | | | | | | | | | |
| 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 |
| **General obesity phenotypes** | | | | | | | | | |
| 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 |
| **Abdominal obesity phenotypes** | | | | | | | | | |
| 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 |
| | | | | | | | | | |
| **Outcome: CVD mortality** | | | | | | | | | |
| **Metabolic syndrome** | | | | | | | | | |
| 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 |
| **General obesity phenotypes** | | | | | | | | | |
| 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 |
| **Abdominal obesity phenotypes** | | | | | | | | | |
| 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.

699 **Table 4. All-cause and CVD mortality according to MetS, general and abdominal obesity phenotypes: Hazard ratios (HR) and 95%**
700 **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** |
| **Outcome: All-cause mortality** | | | | | | | | | |
| **Metabolic syndrome** | | | | | | | | | |
| 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 |
| **General obesity phenotypes** | | | | | | | | | |
| 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 |
| **Abdominal obesity phenotypes** | | | | | | | | | |
| 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 |
| | | | | | | | | | |
| **Outcome: CVD mortality** | | | | | | | | | |
| **Metabolic syndrome** | | | | | | | | | |
| 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 |
| **General obesity phenotypes** | | | | | | | | | |
| 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 |
| **Abdominal obesity phenotypes** | | | | | | | | | |
| 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.