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Probable sarcopenia, obesity, and risk of all-cause mortality – a pooled analysis of 4,612 participants

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Abstract

Introduction: Conflicting evidence exists concerning whether having sarcopenic obesity has additive mortality risk over having only sarcopenia or obesity. We examined the independent and combined associations of obesity and probable sarcopenia with all-cause mortality.

Methods: The pooled analysis included three large, harmonized datasets (Health 2000 Survey; Health, Aging and Body Composition Study; Longitudinal Aging Study Amsterdam) with mortality follow-up data on individuals aged 70 years and over at baseline (n=4,612). Obesity indicators included body mass index (BMI) and waist circumference (WC), and probable sarcopenia was defined based on grip strength. Mixed Effects Cox Model was used for statistical analyses, adjusting for age, sex, marital status, education, race, physical activity, alcohol consumption, smoking, and baseline diseases.

Results: Risk of death increased for those having probable sarcopenia only (hazard ratio (HR) 1.61, 95% confidence interval (CI) 1.39−1.85) or probable sarcopenia with obesity (HR 1.36, 95% CI 1.13−1.64), but not for the obese only group (HR 0.92, 95% CI 0.85−1.01), when compared to non-obese non-sarcopenic individuals. The results were similar regardless of adjustments for covariates, or different obesity criteria applied.

Conclusion: Probable sarcopenia, whether combined with obesity or not, is associated with increased mortality. Obesity did not increase mortality among older adults. Maintaining muscle strength and identifying older adults at risk of sarcopenia is important for the prevention of premature mortality.

Introduction

Sarcopenic obesity (SO, the co-existence of obesity and sarcopenia) has been characterized as a confluence of the aging population and the obesity epidemic [1,2]. Both obesity and sarcopenia independently are strong risk factors for poor health, reduced functional capacity and quality of life in older persons, potentially leading to illnesses, institutionalization and mortality [1,3-5]. A recent review (including participants aged ≥60 years) estimated that SO affects more than every tenth older adult globally [6] but there is considerable variation in the prevalence estimates, e.g., due to different definitions, study settings and age groups across studies.

Obesity and sarcopenia may act synergistically on the risk of developing several adverse health outcomes [7,8]. However, findings regarding mortality remain controversial. Some cohort studies, with non-obese non-sarcopenic individuals as the reference group, suggest that SO does not confer any greater risk than sarcopenia alone [9-11]. However, some studies have found sarcopenic-obese to have the highest risk of all-cause mortality [12,13]. Although most previous studies have found SO to be a significant predictor of all-cause mortality [14], it remains uncertain whether having sarcopenic obesity has additive mortality risk over having sarcopenia only or over obesity only. Evaluating the interaction of sarcopenia and obesity and whether there is an additive risk for having both conditions is an important aspect as well. This would help in evaluating whether preventive actions should be primarily targeted against sarcopenia, obesity, or their combination.

There is yet no consensus on the definition of SO, and accordingly, the contradictory results from the previous studies may be related to the differences in definitions of SO. One of the first definitions for SO included low skeletal muscle mass index combined with a high percentage of body fat [15]. However, other operational definitions have also been proposed based on different obesity markers, including body mass index (BMI), waist circumference (WC) or visceral fat mass [16]. Even a wider selection of indicators has been used to define the sarcopenia component of SO, e.g., based on various skeletal muscle or lean mass measures, midarm muscle circumference, or muscle strength [14]. However, muscle strength and function have been found to be more strongly associated with adverse health outcomes than muscle mass [17-19], and low strength is currently considered to be the primary indicator of probable sarcopenia in the recently revised European consensus definition of sarcopenia [19].

The studies that found the highest risk of mortality for sarcopenic obese individuals defined SO according to muscle strength (knee extensor strength) and WC tertiles [12], or midarm muscle circumference (MAMC) and WC [13]. Furthermore, the study by Atkins and colleagues (2014) [13]

comparing different SO definitions, found that combining anthropometric measures of MAMC and WC was more effective in predicting all-cause mortality than indices of fat mass (for indicating obesity) and fat-free mass (for indicating sarcopenia) based on bioelectrical impedance analysis. Still, despite the efforts made to reach a consensus definition on SO, there is considerable heterogeneity in the definition, diagnostic criteria, and methodological issues in studies on sarcopenic obesity [16]. While trying to reach a consensus, attention must be paid to the applicability of the SO definition in clinical practice and the ability to identify persons at high risk of adverse health outcomes.

The aim of the present study was to examine the independent and combined associations of obesity and probable sarcopenia with all-cause mortality in three large, population-based datasets of individuals aged 70 years and over at baseline. We selected such measurements for obesity (BMI and/or WC) and probable sarcopenia (grip strength), which could easily be used in clinical practice to identify SO patients.

Materials and Methods

Study population

The present examination included three studies: the Health 2000 Survey (H2000) from Finland; the Health, Aging and Body Composition Study (HABC) from the United States of America; and the Longitudinal Aging Study Amsterdam (LASA) from the Netherlands. The participants and the methods used in these studies have been described in detail elsewhere [20-22]. These three datasets were chosen for this study because the information on core indicators and variables were very much identically collected.

Briefly, the H2000 was a population-based health examination survey carried out in 80 areas throughout Finland in 2000−2001, which aimed to examine chronic diseases, health, functioning, welfare and related factors among the adult population [20]. The H2000 included interviews, self-administered questionnaires and a comprehensive health examination. The sample included 1,617 individuals aged 70 or over, and 80.9% of them participated in the health examination.

The HABC was a prospective cohort study that focused on risk factors for the decline of function in healthier older persons, particularly change in body composition with age [21]. The study sample recruited during 1997 and 1998 from the metropolitan areas surrounding Pittsburgh, Pennsylvania

and Memphis, Tennessee included 3,075 black and white men and women, aged 70–79 years at baseline. The cohort members were selected at baseline to be free of difficulty walking a quarter of a mile or difficulty climbing up 10 steps. The present study utilizes the data collected from the baseline clinic visit and an interview.

The LASA is a longitudinal study aiming to examine the determinants, trajectories and consequences of physical, cognitive, emotional and social functioning in relation to ageing based on a nationally representative sample of older adults [22]. Data collection began in 1992 and 1993 among a cohort of respondents aged 55−84 years (cohort 1, n=3,107, wave B). The present study utilizes the data collected three years later in wave C as a baseline for cohort 1 (n=2,545), as measurement on grip strength was not included in wave B. An additional cohort of respondents aged 55−64 years was included from the same sampling frame and was examined from 2002 to 2003 (cohort 2, n=1,002, wave 2B). These two cohorts (waves C and 2B) form the baseline data for LASA in the present study.

The studies were reviewed and approved by their respective institutional review boards (H2000: Ethical Committee for Epidemiology and Public Health in the Hospital District of Helsinki and Uusimaa in Finland; HABC: Institutional Review Boards at the University of Tennessee and the University of Pittsburgh; LASA: Medical Ethics Committee of the VU University Medical Centre Amsterdam). In all three studies, participants provided written informed consent before participating.

The analytical sample for the present study was restricted to subjects aged 70 and older because of the age-related nature of sarcopenia (n=5,595 for the pooled data). In addition, persons with BMI <22 kg/m^2 at baseline were excluded (n=594) from the analyses to reduce the effects of frailty and undernutrition on mortality risk as suggested based on earlier studies [23,24]. Furthermore, the analytical sample of this study included only individuals with no missing values on any of the following variables: age, sex, grip strength, BMI and WC. Thus, the final sample size for the study was 1,085 for H2000, 2,593 for HABC, and 934 for LASA, resulting in a total of 4,612 individuals for the pooled data analyses (2,130 men and 2,482 women).

Measurement of obesity and probable sarcopenia

In all three studies, body height, body weight and WC were measured using standard protocols, and body mass index (BMI) was calculated as kg/m^2. The protocols between the studies were rather similar, but there was a slight difference for measuring WC; in H2000 and LASA, it was measured

at the midway point between the lower rib margin and the iliac crest but in HABC at the level of largest circumference. We defined obesity based on both BMI and WC. The WHO criteria were applied to classify participants as obese with BMI value ≥30.0 kg/m^2 [25]. WC was used to indicate abdominal obesity, defined as ≥ 88 cm for women or ≥102 cm for men [25]. However, we also used an adapted definition for abdominal obesity, using cut-off points of ≥98 cm (women) and ≥109 cm (men) based on the study of Heim et al. (2011) [26] where higher cut-off points for WC were suggested to better indicate the optimal values associated with the health risks of abdominal obesity among participants aged ≥70 years (Heim et al. 2011).

In each study, grip strength was measured with a hand-held dynamometer, adjusted for hand size for each participant (H2000, dominant hand: Good Strength, IGS01, Metitur Oy, Jyväskylä, Finland; HABC, each hand: Jamar, TEC, Clifton, NJ, USA; LASA, each hand: Takei TKK 5001, Takei Scientific Instruments Co. Ltd, Tokyo, Japan). The subjects were instructed to grip the handle with maximal effort. The maximum value obtained, regardless of dominant hand or number of tests, was taken to indicate grip strength. For H2000, Newton's were transformed to kilograms by dividing the test result by 9.81. In this study, we use the term probable sarcopenia to refer to our indicator on grip strength below the cut-off points of <27 kg in men and <16 kg in women. These cut-off points were obtained from the revised European consensus definition on sarcopenia (EWGSOP2 working group) indicating probable sarcopenia.

Based on information on obesity and probable sarcopenia, we classified participants in four S/O groups: 1) No obesity, no sarcopenia; 2) Obesity only; 3) Probable sarcopenia only; and 4) Probable sarcopenia with obesity. As we used two different obesity indicators, and different WC cut-off values for older adults, we examined four different S/O criteria as described in Table 1. In addition, we also examined associations of continuous BMI, WC and grip strength, separately as exposure variables, with all-cause mortality, and the possible interaction between obesity markers and grip strength in relation to mortality.

Mortality follow-up

Mortality among the participants of the three studies was followed until the date of death or end of follow-up, i.e. 31th December in 2015 for H2000, 1st June in 2015 for HABC, and 1st August in 2018 for LASA. During follow-up, there were 815 deaths in H2000 (with total of 9,972 person-years of follow-up), 1,674 in HABC (with a total of 32,276 person-years of follow-up), and 892 in LASA (with a total of 9,719 person-years of follow-up). All-cause mortality was used as the outcome, because there was not adequate statistical power for cause-specific analyses.

The H2000 has been linked to Statistics Finland's Causes of Death Register (including date and cause of death) using the personal identity codes assigned to each Finnish resident. For LASA, mortality data are obtained through linkage with registers of the municipalities in which the respondents are living. For HABC, date and cause of death were obtained from the death certificates, hospital records, National Death Index search and interview with next of kin, and were adjudicated according to the study protocol (Health ABC Death Adjudication Protocol, 2009).

Potential confounders

Data on covariates were from health interviews or a self-administered questionnaire at baseline of each study. All three datasets were harmonized for the purposes of individual-level pooled analysis. Variables were selected carefully to obtain the most comparable information possible between datasets. Furthermore, similar categorization was applied across the datasets for the chosen variables: marital status (married; other), education (lowest; middle; highest), race (black; white), physical activity (low; middle; high), smoking (never; current; former), alcohol consumption (no consumption in the last year; less than once a week; once a week or more often), baseline chronic diseases (yes; no) such as myocardial infarction, angina pectoris, hypertension, stroke, diabetes, cancer, osteoporosis, and arthritis. Variables pertaining to race was not available in H2000 and LASA data due to the high homogeneity of the populations. Thus, for the pooled analysis where harmonized values were needed, the variable was set as "white" for all individuals from H2000 and LASA. Furthermore, in LASA and HABC the questionnaire assessed physical activity of the last seven days and the intensity level at which each activity was performed. Based on the metabolic equivalent of each activity and body weight, an overall activity score in kilocalorie per week was created. In H2000, a combination of questions on leisure-time and commuting activity assessing the habitual activity level was used.

Statistical analysis

Analyses were carried out in the individual level pooled dataset, but also in each dataset separately as presented in the supplementary online-only material. Baseline characteristics were presented as means (± standard deviation) or as percentages. Additionally, the age- and sex-adjusted means in BMI, WC and grip strength were obtained as predictive margins from linear regression model and differences between datasets were tested using the Wald test. Similarly, the age and sex-adjusted means and prevalence of baseline characteristics were obtained as predictive margins from linear and logistic regression models, and differences between the four S/O groups (using criterion 4)

were tested using the Wald test. The same method was used for age and sex-adjusted prevalence, and differences between datasets were tested.

We used Mixed Effects Cox Models [27] to assess mortality risk associated with the categorical variable on S/O groups (with the "no obesity, no sarcopenia" group used as the reference category) using follow-up time in years as the time scale. As there was no evidence of sex interaction in any of the preliminary analyses, data for men and women were analyzed together and sex-adjusted. Thus, an adjusted hazard ratio for all-cause mortality was calculated in three different models including the following covariates: Model 1= age and sex; Model 2= in addition to Model 1, marital status, education, race, physical activity, alcohol consumption and smoking. As chronic diseases may play a mediating role in the association between S/O groups and mortality, potentially leading to overadjustment, baseline chronic diseases were adjusted for in a separate model (Model 3): in addition to Model 2, myocardial infarction, angina pectoris, hypertension, stroke, diabetes, cancer, osteoporosis and arthritis. The pooled analysis, based on individual participant data, included the dataset (categorized as H2000, HABC, LASA) as well as region or study site as random effects to account for the hierarchical structure of the pooled data. For the supplementary material, analysis in separate datasets included only region or study site as a random effect. The proportional hazards assumption was tested using Schoenfeld residuals, and the assumption was found plausible [28]. The plotted survival curves were produced as predicted survival analysis based on the Cox model with Model 3 adjustments using fixed covariate values to allow better comparison between the S/O groups. This method was chosen instead of Kaplan-Meier estimator as the baseline hazard estimates (which are essential components in the survival function estimates) used the full data and thus were more accurate than the corresponding Kaplan-Meier estimates based on subgroup analyses. Also, the random effects to account for the clustering of the data were easier to incorporate in the Cox model.

Similar analysis protocol on Mixed Effects Cox Models (including dataset and region/study site as random effects) and the same three models adjusting for covariates were used for examining BMI, WC or grip strength as continuous variables, analyzed separately as independent variables. To express the HR's per SD increase, the continuous variables underwent Z-score normalization. Furthermore, interaction between grip strength and BMI, as well as between grip strength and WC, was tested to evaluate whether their effect on mortality depended on each other. The linearity of the association between independent variables and mortality was examined by adding a quadratic term in the model and comparing the Akaike information criterion (AIC) values from the models with and without quadratic term, lower AIC indicating a better fit.

As a sensitivity analysis, all analyses were repeated with exclusion of the first two and the first seven years of the follow-up to evaluate potential reverse causality.

Data management and descriptive analyses were carried out using Stata version 16. The survival analyses with Mixed Effects Cox Models were carried out using R for Windows (version 3.6.0) and RStudio (version 1.2.1335) with the packages survival and coxme [29].

Results

Abdominal obesity was more common in the HABC than in the H2000 and LASA, whereas probable sarcopenia and probable sarcopenia with obesity were more common in the H2000 than in the other cohorts (Table 1). The baseline characteristics of the H2000, LASA and HABC study populations as well as for the pooled data are shown in Table 2. The participants in the H2000 and LASA data were about five years older than those in the HABC data. The mean age at baseline for pooled data was 75.8 years. After age- and sex-adjustment, WC and grip strength were highest in the HABC compared to the other cohorts ($p < 0.001$ for both), but BMI was similar across the cohorts ($p=0.06$).

Supplementary table 1 shows baseline characteristics across the S/O groups in the pooled data. There were significant differences between the four categories of the variable on S/O groups (using criterion 4) in almost all the age and sex-adjusted baseline characteristics, e.g., low education and low level of physical activity were more prevalent among those having probable sarcopenia with obesity than among the other groups.

Supplementary figure 1 shows predicted survival curves adjusted for covariates (Model 3) contrasting the S/O groups. The two groups including those having probable sarcopenia and those having probable sarcopenia with obesity showed the lowest survival rate compared to the other two groups. As shown in Table 3 in a Cox regression analysis considering these groups, with non-obese non-sarcopenic as the reference category, the risk of death was increased for those having probable sarcopenia and those having probable sarcopenia with obesity. The results were rather similar for all four of the SO criteria, but the criterion 2 with stricter definition on abdominal obesity showed the highest hazard ratios. The results slightly attenuated with adjustments for demographic and lifestyle variables (Model 2) as well as with further adjustments for chronic diseases (Model 3), but in all models, the increased risk of mortality remained statistically significant for those having probable sarcopenia and those having probable sarcopenia with obesity. However, there were no substantial

differences in hazard ratios between probable sarcopenia only and probable sarcopenia with obesity groups. To further evaluate the potential excess risk of SO in comparison to the probable sarcopenia only group, we repeated the analyses with the probable sarcopenia only group as the reference: the risk of death for the probable sarcopenia with obesity group did not statistically significantly differ from that of probable sarcopenia only group (HR 0.84, 95% CI 0.69−1.05), but for the non-obese non-sarcopenic (HR 0.62, 95% CI 0.54−0.72) and obese only (HR 0.58, 95% CI 0.50−0.67) groups, the risk was decreased (results from Model 3 using criterion 4; for other models and criteria data are not shown as the results were substantially similar).

In Supplementary table 2, the results from Model 3 are shown in each dataset separately. The results were rather similar as in the pooled data, except for LASA data, where hazard ratios were a bit lower and the association was not statistically significant.

Results from analyses with BMI, WC and grip strength as continuous variables are presented in Table 4. In all three models, the risk of death was lower with higher grip strength. However, comparison of AIC values from the models with and without quadratic term suggested that a linear term for grip strength alone may not be adequate as the quadratic form yielded a better model fit (p for difference between the models <0.001). Furthermore, BMI was not associated with mortality in models adjusting for age and sex (Model 1) and covariates related to demographics and lifestyle habits (Model 2), but in Model 3, with further adjustments for chronic diseases, higher BMI associated with lower mortality (p for trend 0.005). Here too, comparison of AIC values suggested a non-linear association (p for difference between the models with and without quadratic term 0.004). Visual inspection of the HR values implied non-linearity after BMI values of 33 (data not shown). Furthermore, WC was not associated with mortality. In addition, there was no interaction between grip strength and BMI or WC (p for interaction >0.5 for BMI, and for WC, in all three models). Supplementary table 3 presents the results for BMI, WC and grip strength as continuous variables in each separate dataset (with Model 3 adjustments). Regarding grip strength, the result remained similar for all three datasets, but for BMI, the inverse association between BMI and mortality was only seen in H2000 data (Supplementary table 3).

Although adjustments in Model 3 accounted for baseline chronic diseases, we performed further sensitivity analyses to take into account the potential confounding by pre-existing diseases. Thus, all analyses were re-run with exclusion of the first two years, and in addition seven years, of the follow-up, but the results were similar to those described above (data not shown).

Discussion

Based on three cohort studies from Finland, the Netherlands and the United States, we found that the risk of death was increased for those older adults having probable sarcopenia or probable sarcopenia with obesity when compared with non-obese non-sarcopenic individuals. Risk of death was not increased for the obese only group. There were no substantial differences in hazard ratios between probable sarcopenia only and probable sarcopenia with obesity groups. Thus, the main finding of this study was that probable sarcopenia regardless of obesity status was associated with increased mortality, and this applied to all the SO definitions with varying obesity definitions that we examined. When examined separately, higher grip strength was consistently associated with lower mortality, whereas higher BMI was associated with lower mortality only after adjustments for potential confounders, including baseline diseases. Although these associations were not linear, these findings further suggest that it is the probable sarcopenia component that accounts for the association between probable sarcopenia with obesity and increased mortality, not obesity, among participants of this study aged 70 years or older. We did not find an interaction between probable sarcopenia and obesity, implying that having probable sarcopenia and being obese at the same time does not increase the mortality risk over only having probable sarcopenia.

A recent meta-analysis found that sarcopenic obesity was significantly increasing all-cause mortality when compared to non-sarcopenic non-obese subjects [14]. However, that analysis did not evaluate the importance of the two underlying components of SO (sarcopenia versus obesity). Our results are in line with previous findings from a large cohort study, using SO criteria based on grip strength and BMI, concluding that sarcopenic obesity did not confer any greater mortality risk than sarcopenia alone [9]. Furthermore, our results are in line with a study using SO criteria based on muscle mass and body fat percentage where older women (aged 60+ years) with sarcopenia had an increased mortality risk independent of obesity [10]. However, in contrast to that study, we did not find evidence for a sex interaction. Furthermore, our results resemble results from a study on participants aged 70+ years, using measures of BMI and grip strength, which found that normal weight participants with low grip strength had highest mortality risk whereas overweight and obese participants with high grip strength had significantly lower mortality than normal weight participants with high grip strength [30]. The inverse association between grip strength and mortality, independent of BMI, was also observed in a cohort study among men aged 45−68 years [31]. However, not all studies have found an association between SO and mortality. A cohort study using body composition phenotypes to define SO did not find an association of SO with mortality in an age-adjusted model among participants aged 70 years and older [32]. Similarly, no association

was found in a cohort study using criteria combining low muscle mass and body fat percentage for SO among men aged ≥ 70 years [33]. Perhaps, muscle strength based definitions may predict mortality better than the muscle mass and body composition based definitions of SO in this age group.

Although previous findings have been inconsistent regarding the obesity component of SO definition, Rossi et al. (2016), studying participants aged 66−78 years, found that abdominal obesity increased the risk of mortality, and abdominal obese subjects with muscle strength indicated sarcopenia were at higher risk of mortality than subjects with sarcopenia or central fat distribution only [12]. Similar results were obtained from a study on participants aged 60−79 year where sarcopenia and abdominal obesity were associated with all-cause mortality, with the highest risk among sarcopenic obese [13]. In our study, obesity, regardless of its definition, was not a risk factor for mortality among participants aged 70 years or older. The lack of association between mortality and abdominal obesity could be due to the more advanced age of the subjects in our study. This is in line with previous studies suggesting that obesity is a risk factor for mortality in mid-life, but overweight could be beneficial for older individuals [34]. Even so, obesity has other negative health outcomes such as poor physical functioning, arthritis, pain, wrist and ankle fractures etc. among older adults [35]. Furthermore, we did not observe differences between different obesity definitions in relation to mortality, but when examined as continuous variables, the associations of BMI and WC differed. The inverse association between BMI and mortality is in line with the obesity paradox, whereas the absence of inverse association between WC and mortality could be interpreted so that measuring WC better captures the potential risks associated with obesity even among individuals aged ≥70 years. The BMI measurement also captures muscle mass, while WC mainly reflects fat mass.

The different obesity criteria applied in this study produced slightly different prevalence rates for obesity and SO. However, as there were no substantial differences in the mortality risk, it could be argued that the adapted definition for abdominal obesity for older adults, using cut-off points of ≥109 cm (men) and ≥98 cm (women) [26], suites also for studying the mortality risk associated with SO. The benefits of the adapted cut-off values include, e.g., optimally differentiating low-risk groups from high-risk groups, and better allocation of resources [26], especially because of the high prevalence of large WC among older adults, which was also noted in our study. However, more research on these proposed cut-off values is needed before application in clinical practice.

The strengths of this study include large sample size, comparable measures on obesity and probable sarcopenia from three different studies across three countries, and possibility to control for several confounding factors. The challenges in harmonizing the variables between datasets could be seen as a limitation, despite of the careful work conducted to harmonize the datasets. For example, distributions of education were quite different, probably not only due to the differences in age structure but also the different educational systems. Furthermore, the information regarding baseline diseases was challenging to harmonize, and thus the prevalence of certain diseases may not be comparable. For example, arthritis probably includes both age-related osteoarthritis and inflammatory rheumatoid arthritis in LASA and HABC, but in H2000 data, it mostly refers to inflammatory joint diseases. However, the core indicators on probable sarcopenia and obesity (i.e., grip strength, BMI and WC) were based on very similar methods and standard study protocols. Furthermore, regarding covariates in fully adjusted model, it should be noted that baseline chronic diseases could also be mediators of the association examined here, potentially causing overadjustment. This could be a reason for why the inverse association between BMI and mortality appeared when the baseline diseases were adjusted for.

The single use of anthropometric obesity indicators could be seen as a limitation of this study as it does not acknowledge the differences in body composition, although WC represents visceral fat accumulation quite well [36]. Furthermore, by following the operational definition of sarcopenia with the EWGSOP2 working group [19], diagnosing sarcopenia cases would have required identification of both low muscle strength and low muscle quantity/quality. As the three datasets used in this study did not include comparable muscle quantity or quality assessments, the diagnostic criteria suggested by the EWGSOP2 working group to identify true sarcopenia could not be used. However, the EWGSOP2 working group [19] also states that low muscle strength has overtaken the role of low muscle mass as a principal determinant of sarcopenia, and that low muscle strength is enough to trigger assessment of causes and start intervention in clinical practice. Grip strength is a widely used indicator of overall strength as it correlates well with the strength of other muscle groups [37]. Moreover, grip strength as a measure is an easy and safe test often used in large surveys. The same aspect applies to the anthropometric obesity indicators. The advantage of the methods used in our current study is the reliance on relatively simple measures which may enhance the application in clinical practice [19,35], and promote research of SO in large population-based cohorts. Another justification for using muscle strength as an indicator of probable sarcopenia is that grip strength is a more important predictor of mobility disability than lean or muscle mass [38,39]. Furthermore, it could be speculated that in obesity, skeletal muscle function may be low

even if muscle mass is preserved, perhaps due to metabolic and biological effects of excess fat and intramuscular lipids [40].

In conclusion, our results showed that older adults aged 70 years or more with low grip strength, regardless of their obesity status, had increased mortality risk when compared to non-obese individuals with grip strength above cut-off points for probable sarcopenia. In clinical practice, individuals with high weight may be falsely perceived as not being weak. However, older adults complaining about functional limitations or weakness should always be screened for sarcopenia, independent of their weight, although for other outcomes than mortality obesity screening is warranted too. According to the EWGSOP2, the Strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire could be used to identify people at risk of sarcopenia [19]. Then, a grip strength measurement is advised. Both maintaining good muscle strength and identifying all older adults with low muscle strength is important through aging, and at risk population should be provided guidance and support for increasing muscle strength. Furthermore, future studies should not only investigate SO but also take into account the independent associations of sarcopenia and obesity with mortality, as well as with other health and functional outcomes.

Statements

Statement of Ethics

The studies were reviewed and approved by their respective institutional review boards (H2000: Ethical Committee for Epidemiology and Public Health in the Hospital District of Helsinki and Uusimaa in Finland, approval 407/E3/2000; HABC: University of Tennessee IRB approval 95-05531-FB, University of Pittsburgh IRB approval 960212, and University of California, San Francisco IRB approval H5254-12688-15); LASA: Medical Ethics Committee of the VU University Medical Centre Amsterdam, approval 92/138). In all three studies, participants provided written informed consent before participating.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Katri Sääksjärvi performed the analysis and wrote the first draft of the manuscript. Tommi Härkänen advised on statistical methods. Katri Sääksjärvi, Tommi Härkänen, Sari Stenholm, Laura Schaap, Annamari Lundqvist, Seppo Koskinen, Katja Borodulin, and Marjolein Visser all contributed to the design of the study and analysis, interpretation of the results, and reviewed the manuscript revising it critically for important intellectual content.

Data Availability Statement

The data used in this study are not publicly available due to containing information that could compromise the privacy of research participants. The data are available for use for specific research questions provided that an agreement is made up. Research proposals should be submitted to the corresponding organizations/institutions responsible for the data through the instructions provided on study websites (i.e. The Health 2000 Survey, https://thl.fi/en/web/thlfi-en/research-and-development/research-and-projects/health-2000-2011 ; The Health, Aging, and Body Composition Study, https://healthabc.nia.nih.gov/ ; The Longitudinal Aging Study Amsterdam, https://lasa-vu.nl/en/). Further enquiries can be directed to the corresponding author.

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562

Table 1. Criteria used in the study and prevalence (%) for probable sarcopenia and obesity.

	Criteria	Prevalence (%)				
		H2000 [a]	HABC [a]	LASA [a]	p [b]	Pooled data
Probable sarcopenia (based on grip strength)	EWGSOP2: <27 kg in men, <16 kg in women	20.4	6.8	7.6	<0.001	11.2
Obesity (based on anthropometrics)						
1)	BMI ≥30 kg/m^2	29.5	27.5	24.6	0.05	27.4
2)	WC ≥102 cm (men) / 88 cm (women)	58.2	67.0	62.7	<0.001	64.2
3)	WC ≥109 cm (men) / 98 cm (women)	29.5	41.4	30.1	<0.001	36.2
4)	BMI ≥30 kg/m^2 **or** WC according to obesity criterion 3)	35.7	45.6	35.5	<0.001	41.2
Probable sarcopenia with obesity						
	Probable sarcopenia + obesity 1)	5.8	1.4	1.3	<0.001	2.7
	Probable sarcopenia + obesity 2)	12.6	4.3	5.0	<0.001	7.2

Probable sarcopenia + obesity 3)	6.5	2.0	2.4	<0.001	3.5
Probable sarcopenia + obesity 4)	7.7	2.1	2.6	<0.001	4.0

Note. H2000, the Health 2000 Study; HABC, the Health, Aging and Body Composition Study; LASA, the Longitudinal Aging Study Amsterdam; EWGSOP2, the European Working Group on Sarcopenia in Older People 2; BMI, body mass index; WC, waist circumference.

[a] Age- and sex-adjusted

[b] for the difference between the datasets

Table 2. Baseline characteristics of the study populations.

	H2000 n= 1,085	HABC n= 2,593	LASA n= 934	Pooled data n= 4,612
Age, years, mean (SD)	78.5 (5.9)	73.8 (2.8)	78.2 (5.2)	75.8 (4.8)
Age range	70-100	70-80	70-89	70-100
Men %	34.5	50.5	47.9	46.2
Hand grip strength, kg, mean (SD)	24.4 (10.3)	33.2 (10.9)	28.4 (9.9)	30.1 (11.2)
BMI, kg/m^2, mean (SD)	28.3 (4.0)	28.2 (4.3)	27.7 (3.7)	28.1 (4.1)
WC, cm, mean (SD)	97.1 (11.1)	101.4 (11.9)	98.3 (10.0)	99.8 (11.5)
Education %				
High	8.9	41.3	10.8	27.5
Intermediate	15.5	33.6	24.7	27.5
Low	75.7	25.1	64.5	45.0
Married %	41.4	55.9	50.2	51.2
White race %	NA [c]	57.6	NA [c]	76.2
Current smokers %	5.1	8.9	16.6	9.5
Frequent alcohol consumption % [a]	14.9	28.6	50.0	29.9
Low physical activity % [b]	45.8	30.2	38.1	35.3
Myocardial infarction %	13.9	11.9	12.0	12.4
Angina pectoris %	23.3	11.9	17.9	15.8
Hypertension %	47.2	52.8	25.8	46.0
Stroke %	8.9	2.4	10.1	5.5

Diabetes %	14.5	16.0	9.3	14.3
Cancer %	13.7	19.2	11.9	16.4
Osteoporosis %	7.5	7.3	0.8	6.0
Arthritis %	7.8	57.7	52.2	44.8

Note. H2000, the Health 2000 Study; HABC, the Health, Aging and Body Composition Study; LASA, the Longitudinal Aging Study Amsterdam; BMI, body mass index; WC, waist circumference.

[a] once a week or more often

[b] H2000: leisure-time and commuting physical activity combined, low=those who are inactive according to both questions; HABC: total activity < 43 kcal/kg/week; LASA: total activity <35 kcal/kg/week

[c] information on race was not available in H2000 and LASA studies. For pooled analysis, this variable in H2000 and LASA datasets was set as white.

Table 3. Hazard ratios (and 95% confidence intervals) for all-cause mortality by S/O groups. A pooled analysis of Health 2000, Health ABC and LASA studies.

		Model 1[a]		Model 2[b]		Model 3[c]
	HR	95% CI	HR	95% CI	HR	95% CI
SO criterion 1 (BMI) [d]						
No obesity, no sarcopenia	ref.	-	ref.	-	ref.	-
Obesity only	1.02	0.94, 1.11	0.96	0.88, 1.04	0.92	0.84, 1.00
Probable sarcopenia only	1.71	1.51, 1.92	1.65	1.45, 1.87	1.60	1.40, 1.83
Probable sarcopenia with obesity	1.69	1.38, 2.06	1.47	1.19, 1.82	1.30	1.04, 1.63
SO criterion 2 (WC WHO cut-off) [e]						
No obesity, no sarcopenia	ref.	-	ref.	-	ref.	-
Obesity only	1.09	1.01, 1.18	1.06	0.97, 1.15	1.02	0.93, 1.11
Probable sarcopenia only	1.87	1.58, 2.22	1.85	1.54, 2.21	1.76	1.46, 2.12
Probable sarcopenia with obesity	1.75	1.52, 2.01	1.59	1.38, 1.85	1.49	1.28, 1.74

SO criterion 3 (WC adapted cut-off) [f]						
No obesity, no sarcopenia	ref.	-	ref.	-	ref.	-
Obesity only	1.05	0.97, 1.14	0.99	0.91, 1.08	0.94	0.87, 1.03
Probable sarcopenia only	1.68	1.48, 1.90	1.65	1.44, 1.88	1.57	1.36, 1.81
Probable sarcopenia with obesity	1.83	1.53, 2.18	1.56	1.29, 1.88	1.45	1.19, 1.76
SO criterion 4 (BMI or WC adapted cut-off) [g]						
No obesity, no sarcopenia	ref.	-	ref.	-	ref.	-
Obesity only	1.03	0.95, 1.11	0.97	0.89, 1.05	0.92	0.85, 1.01
Probable sarcopenia only	1.68	1.48, 1.92	1.65	1.44, 1.90	1.61	1.39, 1.85
Probable sarcopenia with obesity	1.76	1.49, 2.08	1.51	1.26, 1.81	1.36	1.13, 1.64

Note. HR, hazard ratio; CI, confidence interval; S/O groups, sarcopenic/obesity variable with four categories; BMI, body mass index; WC, waist circumference; Model 1: adjusted for age and sex; Model 2: in addition to Model 1, adjusted for marital status, education, race, physical activity, alcohol consumption and smoking; Model 3: in addition to Model 2, adjusted for baseline chronic diseases (myocardial infarction, angina pectoris, hypertension, stroke, diabetes, cancer, osteoporosis, and arthritis).

[a] n=4,612

[b] n=4,300

[c] n=4,102

[d] criterion 1: probable sarcopenia, hand grip strength <27 kg in men, <16 kg in women and BMI ≥30 kg/m^2

[e] criterion 2: probable sarcopenia, hand grip strength <27 kg in men, <16 kg in women and waist circumference ≥102 cm (men)/ 88 cm (women)

[f] criterion 3: probable sarcopenia, hand grip strength <27 kg in men, <16 kg in women and waist circumference ≥109 cm (men)/ 98 cm (women)

[g] criterion 4: probable sarcopenia, hand grip strength <27 kg in men, <16 kg in women and waist circumference ≥109 cm (men)/ 98 cm (women) or BMI ≥30 kg/m^2

Table 4. Hazard ratios (and 95% confidence intervals) for all-cause mortality by indicators on obesity and probable sarcopenia as continuous variables (analyzed per SD increase). A pooled analysis of Health 2000, Health ABC and LASA studies.

	Model 1[a]			Model 2[b]			Model 3[c]		
	HR	95% CI	p for trend	HR	95% CI	p for trend	HR	95% CI	p for trend
Body mass index	1.00	0.97, 1.04	0.88	0.97	0.94, 1.01	0.13	0.94	0.91, 0.98	0.005
Waist circumference	1.04	1.00, 1.08	0.04	1.01	0.97, 1.05	0.54	0.99	0.95, 1.03	0.55
Hand grip strength	0.75	0.71, 0.80	< 0.001	0.75	0.71, 0.80	< 0.001	0.77	0.73, 0.83	< 0.001

Note. SD, standard deviation; HR, hazard ratio; CI, confidence interval; Model 1: age and sex adjusted; Model 2: in addition to Model 1, marital status, education, race, physical activity, alcohol consumption and smoking; Model 3: in addition to Model 2, baseline chronic diseases (myocardial infarction, angina pectoris, hypertension, stroke, diabetes, cancer, osteoporosis, and arthritis).

[a] n=4,612

[b] n=4,300

[c] n=4,102

Online-only material

eTable 1. Age and sex-adjusted baseline characteristics by S/O groups using criterion 4 [a] on probable sarcopenia and obesity in the pooled dataset.

eTable 2. Hazard ratios (and 95% confidence intervals) for all-cause mortality by S/O groups in the three separate data sets adjusted for potential confounders (Model 3).

eTable 3. Hazard ratios (and 95% confidence intervals) for all-cause mortality by obesity and sarcopenia indicators as continuous variables (analyzed per SD increase) in the three separate datasets adjusted for potential confounders (Model 3).

eFig. 1. Predicted survival curves adjusted for covariates (Model 3) contrasting the S/O groups.

eTable 1. Age and sex-adjusted baseline characteristics by S/O groups using criterion 4 [a] on probable sarcopenia and obesity in the pooled dataset.

	No obesity, no sarcopenia	Obesity only	Probable sarcopenia only	Probable sarcopenia with obesity	p [b]
Age, years, mean (SE) [c]	75.5 (0.1)	74.9 (0.1)	80.7 (0.2)	79.8 (0.3)	<0.001
Men % [d]	58.6	30.7	49.8	24.0	<0.001
BMI, kg/m^2, mean (SE)	25.7 (0.1)	31.5 (0.1)	25.6 (0.2)	31.5 (0.2)	<0.001
WC, cm, mean (SE)	92.6 (0.2)	110.1 (0.2)	92.5 (0.4)	109.0 (0.6)	<0.001
Hand grip strength, kg, mean (SE)	31.3 (0.1)	31.9 (0.2)	18.4 (0.4)	20.1 (0.5)	<0.001
Low education %	42.6	46.3	46.5	63.1	<0.001
Married %	54.3	48.4	48.5	41.9	<0.001
Current smokers %	9.7	9.1	12.3	6.0	0.002
Frequent alcohol consumption % [e]	32.1	28.9	22.7	22.2	0.003
Low physical activity % [f]	30.4	38.1	44.3	60.7	<0.001
Myocardial infarction %	11.7	12.6	14.5	16.2	0.22
Angina pectoris %	14.7	16.1	16.2	26.3	<0.001
Hypertension %	40.4	53.0	45.5	53.7	<0.001
Stroke %	4.6	5.2	9.5	7.8	<0.001
Diabetes %	10.2	18.9	14.1	27.5	<0.001
Cancer %	16.4	16.6	17.3	14.4	0.86
Osteoporosis %	6.0	5.5	9.9	6.1	0.04
Arthritis %	41.4	51.2	40.0	35.5	<0.001

Note. S/O groups, sarcopenic/obesity variable with four categories; BMI, body mass index; WC, waist circumference.

[a] criterion 4: 1) No obesity, no sarcopenia; 2) Obesity only = waist circumference ≥109 cm (men)/ 98 cm (women) or BMI ≥30 kg/m^2; 3) Probable sarcopenia only = grip strength: <27 kg in men, <16 kg in women; 4) Probable sarcopenia with obesity = Probable sarcopenia (based on grip strength: <27 kg (men)/ <16 kg (women) and simultaneous obesity (waist circumference ≥109 cm (men)/ 98 cm (women) or BMI ≥30 kg/m^2)

[b] for the difference between the four categories of sarcopenic obesity variable, Wald test

[c] sex adjusted

[d] age adjusted

[e] once a week or more often

[f] low= H2000, leisure-time and commuting physical activity combined, those who are inactive according to both questions; HABC, total activity < 43 kcal/kg/week; LASA, total activity <35 kcal/kg/week

eTable 2. Hazard ratios (and 95% confidence intervals) for all-cause mortality by S/O groups in the three separate data sets adjusted for potential confounders (Model 3 [a]).

		H2000 [b]		HABC [c]		LASA [d]
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
SO criteria 1						
No obesity, no sarcopenia	ref.	-	ref.		ref.	
Obesity only	0.84	0.68, 1.03	0.89	0.79, 1.01	1.02	0.85, 1.22
Probable sarcopenia only	1.69	1.37, 2.07	1.81	1.38, 2.37	1.25	0.96, 1.64
Probable sarcopenia with obesity	1.27	0.95, 1.70	1.48	0.89, 2.44	1.29	0.73, 2.28
SO criteria 2						
No obesity, no sarcopenia	ref.	-	ref.	-	ref.	-
Obesity only	0.92	0.75, 1.12	1.05	0.92, 1.18	1.03	0.88, 1.22
Probable sarcopenia only	1.63	1.24, 2.15	2.00	1.38, 2.90	1.53	1.01, 2.30
Probable sarcopenia with obesity	1.50	1.17, 1.92	1.72	1.25, 2.37	1.18	0.86, 1.62
SO criteria 3						
No obesity, no sarcopenia	ref.	-	ref.	-	ref.	-
Obesity only	0.79	0.64, 0.96	0.96	0.85, 1.08	1.04	0.88, 1.23
Probable sarcopenia only	1.49	1.21, 1.83	2.02	1.51, 2.70	1.32	0.99, 1.76
Probable sarcopenia with obesity	1.52	1.15, 2.01	1.37	0.91, 2.08	1.16	0.75, 1.80
SO criteria 4						
No obesity, no sarcopenia	ref.	-	ref.	-	ref.	-
Obesity only	0.79	0.65, 0.96	0.91	0.81, 1.02	1.07	0.91, 1.26
Probable sarcopenia only	1.57	1.26, 1.95	1.94	1.45, 2.60	1.32	0.99, 1.77
Probable sarcopenia with obesity	1.35	1.03, 1.76	1.39	0.93, 2.09	1.22	0.80, 1.87

Note. S/O groups, sarcopenic/obesity variable with four categories; HR, hazard ratio; CI, confidence interval

[a] adjusted for age, sex, marital status, education, race, physical activity, alcohol consumption, smoking, baseline chronic diseases (myocardial infarction, angina pectoris, hypertension, stroke, diabetes, cancer, osteoporosis and arthritis)

[b] n=978

[c] n=2242

[d] n=882

eTable 3. Hazard ratios (and 95% confidence intervals) for all-cause mortality by indicators on obesity and probable sarcopenia as continuous variables (analyzed per SD increase) in the three separate datasets adjusted for potential confounders (Model 3 [a]).

		H2000 [b]			HABC [c]			LASA [d]	
	HR	95% CI	p for trend	HR	95% CI	p for trend	HR	95% CI	p for trend
Body mass index	0.97	0.950, 0.990	0.004	0.99	0.98, 1.00	0.11	0.99	0.97, 1.01	0.42
Waist circumference	0.99	0.986, 1.00	0.07	1.00	1.00, 1.01	0.99	1.00	1.00, 1.01	0.46
Hand grip strength	0.97	0.958, 0.98	< 0.001	0.99	0.98, 0.99	< 0.001	0.97	0.96, 0.98	< 0.001

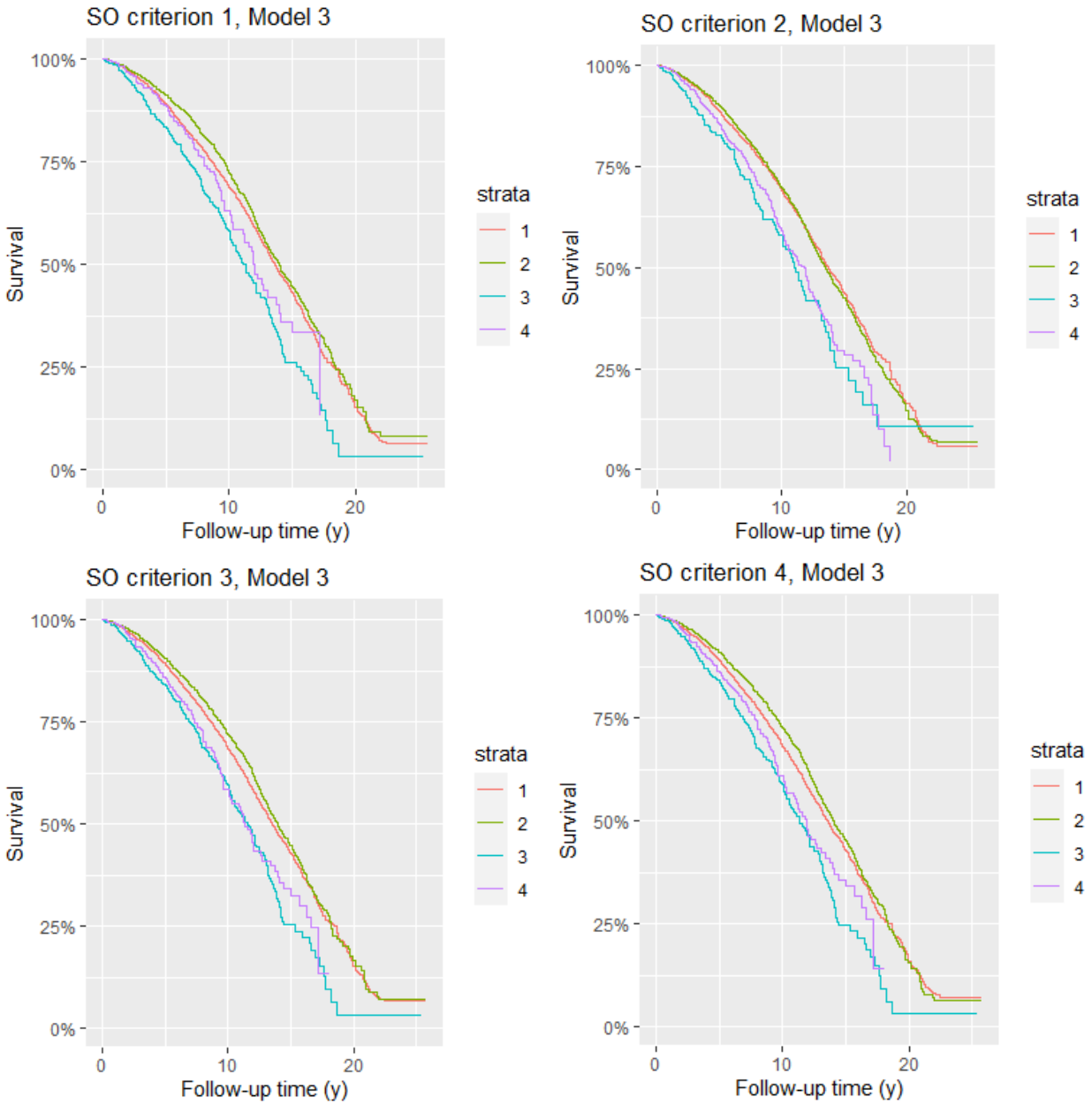
Note. HR, hazard ratio; CI, confidence interval; H2000, the Health 2000 Study; HABC, the Health, Aging and Body Composition Study; LASA, the Longitudinal Aging Study Amsterdam;

[a] adjusted for age, sex, marital status, education, race, physical activity, alcohol consumption, smoking, baseline chronic diseases (myocardial infarction, angina pectoris, hypertension, stroke, diabetes, cancer, osteoporosis and arthritis)

[b] n=978

[c] n=2242

[d] n=882



eFig. 1. Predicted survival curves adjusted for covariates (Model 3) contrasting the S/O groups.

Note. S/O groups, sarcopenic/obesity variable with four categories, strata: 1=No obesity, no sarcopenia, 2=Obesity only, 3=Probable sarcopenia only, 4= Probable sarcopenia with obesity. Criterion 1: probable sarcopenia, hand grip strength <27 kg in men, <16 kg in women and BMI ≥30 kg/m^2; criterion 2: probable sarcopenia, hand grip strength <27 kg (men)/ <16 kg (women) and waist circumference ≥102 cm (men)/ 88 cm (women); criterion 3: probable sarcopenia, hand grip strength <27 kg (men)/ <16 kg (women) and waist circumference ≥109 cm (men)/ 98 cm (women); criterion 4: probable sarcopenia, hand grip strength <27 kg (men)/ <16 kg (women) and waist circumference ≥109 cm (men)/ 98 cm (women) or BMI ≥30 kg/m^2. Model 3=adjusted for age, sex, marital status, education, race, physical activity, alcohol consumption, smoking, and baseline chronic diseases (myocardial infarction, angina pectoris, hypertension, stroke, diabetes, cancer, osteoporosis, and arthritis).