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Original article

Prevalence of sarcopenic obesity and sarcopenic overweight in the general population: The lifelines cohort study

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SUMMARY

Background & aims: Sarcopenic obesity (SO) is defined by a relatively low muscle mass in combination with obesity. Sarcopenic obesity was first noted as a health risk in geriatric populations but has recently been recognized as a scientific and clinical priority that may extend beyond geriatric settings. Obesity is generally preceded by overweight, so the prevalence and health risks of sarcopenia in those with overweight (SOW) is of interest for preventive purposes. The aim of this study, therefore, was to assess the prevalence and determinants of SO and SOW in a general population.

Methods: Participants (n = 119,494), aged 18–90 years were included from the Dutch Lifelines cohort study. Muscle mass was assessed by 24-h urine creatinine excretion and stratified for gender for analysis, and obesity was defined as a Body Mass Index (BMI) $\geq$30 kg/m^2 and overweight $\geq$25 kg/m^2. Multivariate logistic regression models were applied to assess the relevant determinants of SO and SOW.

Results: Respectively for men and women the prevalence of SO was 0.9% and 1.4%, and prevalence of SOW 6.5% and 6.0%. In subjects with sarcopenia, BMI was $\geq$25 kg/m^2 in 45.5% and $\geq$30 kg/m^2 in 6.1%. Overall females had a higher prevalence of SOW and SO in all age groups except for SOW in males between ages 40–59. Also, age was a significant determinant of SO and SOW, with a rise in prevalence as of age 50. Of all subjects with SO and SOW, respectively 82.5% and 80.4% were below the age of 70. Compared to those with no morbidities, the odds ratio of SO and SOW among participants with >3 comorbidities was 2.71 (95% CI: 1.62–4.54) and 1.33 (95% CI: 1.07–1.65) among males and 1.14 (95% CI: 0.79–1.65) and 1.28 (95% CI: 1.06–1.54) among females, independent of other determinants. Overall, an inverse association was found between SOW and SO and physical activity and macronutrient intake.

Conclusion: The results support the need for more awareness of SO beyond the field of geriatrics, in particular in subjects with comorbidities. SOW is more prevalent than SO and may provide opportunities for preventive strategies for the general population.

1. Introduction

The coexistence of obesity and decreased muscle quality (strength and performance) and quantity (muscle mass), i.e. sarcopenia, hence sarcopenic obesity (SO), has been recognized as a scientific and clinical priority [1]. The health risks of sarcopenia and obesity as separate entities, are well-established, but they may also act synergistically thus maximizing their health threatening effects [2–5]. Specifically, SO, in contrast to sarcopenia and obesity alone, has been associated with an increased risk of disability in daily living, mortality, metabolic diseases (i.e. metabolic syndrome and cardiovascular disease), and other comorbidities such as osteoarthritis, osteoporosis and depression in older populations [6].

The concept of sarcopenia has been primarily defined and studied in geriatric populations [1,7], but emerging evidence suggests that younger individuals are also at risk [8,9]. Additionally, the unprecedented rate in which the proportion of obesity in the general population is rising warrants more awareness for SO. To date there is some evidence that SO is also associated with comorbidities, such as metabolic syndrome, in the general population [10]. Yet, as the data on SO beyond the geriatric setting is scarce, evidence-based prevention, clinical care, satisfactory patient identification, and clinical stratification and treatment are limited for the general population.

The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity

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(EASO) have recently called for action [1]. Several limitations in current knowledge and/or consensus for focused, coordinated action in obese individuals with sarcopenia have been proposed. Amongst them, there is the lack of widespread consensus on diagnostic tools and established cut-offs to define SO in the general population [11–14]. To fill this gap, substantial work is needed to understand the magnitude and modifiable risk factors of SO across a wide age range.

Additionally, for preventive purposes it is relevant that obesity is often preceded by overweight. Hence, identification of sarcopenia in overweight subjects (SOW) is warranted. Moreover, data on SOW will also reflect a more conservative cut-off for those of older age, as BMI does not reflect the changes in body composition that occur with ageing [15].

In the search for diagnostic tools to estimate muscle mass, the use of 24 h urinary creatinine excretion been proposed as a promising proxy measure for estimating whole-body muscle mass [16]. Creatinine phosphate in muscles breakdown to creatinine, resulting in serum creatinine levels that are proportional to muscle mass and have been shown to be a reliable biomarker of muscle mass, provided that renal function is taken into account. As creatinine is eliminated in urine, 24-h urine creatinine excretion can also serve as a biomarker of muscle mass in those with stable renal function [17].

In this study we assessed the prevalence of SO and SOW among 102,106 men and women ages 18–90 from the Lifelines cohort study, a population-based study in the Netherlands. Additionally, we aimed to evaluate the independent association of SO and SOW with demographic characteristics, lifestyle factors, multimorbidity, and, as a preliminary analysis, mortality.

2. Materials and methods

2.1. Cohort design and study population

The Lifelines cohort study is a multi-disciplinary population-based cohort study examining in the health and health-related behaviors of 167,729 people living in the North of the Netherlands. Lifelines employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. The overall design and rationale of the study have been described in detail elsewhere [18].

Analysis of the representativeness of the adult study population at baseline, which compared the Lifelines population to the Dutch population register, indicate the Lifelines cohort is broadly representative for the people living in this region [19]. Yet, there are some relevant differences between the Lifelines population and the Dutch population, with an overrepresentation of middle-aged individuals (ages 25–49; 62.4% vs. 45.5), women (58.5% vs. 50.7%), and overweight or obese (40.7% and 15.7% vs. 35.8% and 12.2%) compared to the Dutch population register [19]. In short, participants were included in the study between 2006 and 2013, and written informed consent was obtained from all participants. Mortality data was obtained from the municipal register and was used in this study in a preliminary analysis. The Lifelines study is conducted according to the principles of the Declaration of Helsinki and approved by the Medical Ethics Committee of the University Medical Center Groningen, The Netherlands.

For this study participants were excluded if they were under the age of 18 years (n = 15,067) as well as any participants with missing and unreliable 24-h urine creatinine excretion (n = 33,117 and n = 11 resp.), missing BMI data (n = 40), leaving n = 119,494 participants in this study.

2.2. Sarcopenia, obesity and overweight

Total daily urinary excretion of creatinine has been a promising tool to assess muscle mass [20] and was therefore used in the present analysis to define sarcopenia. The analysis was stratified by sex as women generally have a lower muscle mass and higher fat percentage compared to men. Sex-specific quartiles of the standard deviation (SD) of the mean 24-h urine creatinine excretion ($\leq$1.0 SD, −1.0-0.0 SD, 0.0−1.0 SD, >1.0 SD) were calculated. We defined sarcopenia as a relative muscle mass of $\leq$1.0 SD from the sex-specific mean 24-h urine creatinine excretion. As this study is the first to use 24-h urine creatinine excretion to define sarcopenia, this cut-off point was based on the study by Oterdoom et al. which grouped individuals by standard deviations of the mean 24-h urine creatine excretion to analyze muscle mass [21]. The <1SD cut off point (lowest 15.8% of population) is a compromise between cut-off points used in other studies which defined sarcopenia via other methods, such as using the lowest two quintiles of muscle mass or <2SD of the mean muscle mass (lowest 2.2%) in the study population [3,4]. However, in order to establish if this is a feasible definition to define SO, various cut-offs were applied and, accordingly, the accompanied prevalence rates of SO were also calculated. The additional cut-offs for sarcopenia included 1) $\leq$1SD of the age adjusted sex-specific mean 24-h urine creatinine excretion, 2) applying the sex-specific mean 24-h urine creatinine excretion adjusted for height and 3) age, and 4) $\leq$1SD using the mean 24-h urine creatinine excretion of those 18–40 years as a reference for a healthy muscle mass.

Based on the WHO BMI cut-offs, BMI $\geq$30 kg/m^2 was used to define obesity in this study and BMI $\geq$25 kg/m^2 to define overweight. As a result, SO was defined as a relative muscle mass of $\leq$1.0 SD from the sex-specific mean 24-h urine creatinine excretion in combination with a BMI $\geq$30 kg/m^2. SOW was defined as a relative muscle mass of $\leq$1.0 SD from the sex-specific mean 24-h urine creatinine excretion in combination with a BMI $\geq$25 kg/m^2.

2.3. Independent variables

Height and weight were measured during the assessment by the researchers. Body surface area (BSA) was calculated with the Du Bois formula [22]. BSA has been included as it is an additional indicator of body dimension and can help differentiate between muscle and fat in body composition [23]. Health-enhancing physical activity, hereafter referred to as physical activity, was assessed by the validated SQUASH questionnaire ("Short questionnaire to assess health-enhancing physical activity") from which the duration of moderate and vigorous physical activity (MVPA) in minutes per week was calculated, and categorized into tertials [24]. Educational level was classified as low (primary, vocational, and lower general secondary education), moderate (higher secondary education and intermediate vocational training), and high (higher vocational education and university education). Smoking status was categorized into non-smoker, ex-smoker, and ever smoker. Energy and macronutrient intake were estimated from the Lifelines Food Frequency Questionnaire [25] using the 2011 Dutch food composition database [26]. The reliability of nutrition data was established based on the Goldberg cut-off method, which uses the Schofield equation to calculate the ratio of reported energy intake and metabolic rate [27]. In this study daily consumption of macronutrients (in grams/day) was adjusted for energy intake (per 1000 kcal).

Single morbidities were clustered into eleven disease domains: genitourinary, renal, hematologic, dermatologic, musculoskeletal, ophthalmic and ear-nose-throat (ENT), endocrine, cardiovascular, respiratory, central nervous system (CNS), and gastrointestinal

Table 1
Descriptive statistics of the whole population split by standard deviation of 24-h creatinine excretion from the mean, stratified by gender.

Standard Deviation from the Mean of 24-Hour Creatinine Excretion		Male				Female			
		Sarcopenia	Normal muscle mass			Sarcopenia	Normal muscle mass		
		<-1.0 SD	−1.0-0.0 SD	0.0−1.0 SD	>1.0 SD	<-1.0 SD	−1.0-0.0 SD	0.0−1.0 SD	>1.0 SD
Population, N (%)		7164 (14.2)	19,532 (38.8)	16,465 (32.7)	7224 (14.3)	10,401 (15.0)	26,433 (38.2)	22,318 (32.3)	9957 (14.4)
Age at Baseline (years)		52 ± 16	47 ± 14	44 ± 12	41 ± 10	52 ± 15	47 ± 13	41 ± 12	39 ± 11
BMI (kg/m^2)		24.6 [22.6 −26.7]	25.3 [23.4 −27.4]	26.6 [24.5 −28.8]	28.4 [25.9 −31.1]	23.9 [21.7 −26.8]	24.4 [22.1 −27.2]	25.2 [22.9 −28.5]	27.5 [24.2 −31.8]
BMI ≥25 kg/m^2 (%)		45.5	54.6	70.3	84.2	40.1	44.0	52.8	69.7
BMI ≥30 kg/m^2 (%)		6.1	8.5	16.5	34.6	9.5	11.3	17.7	34.5
Waist Circumference (cm)		95.4 ± 7.1	97.2 ± 6.8	99.0 ± 7.0	103.6 ± 8.2	97.0 ± 9.8	98.2 ± 9.6	100.7 ± 10.6	105.7 ± 12.4
Body Surface Area (m^2)		2.0 ± 0.2	2.1 ± 0.1	2.1 ± 0.1	2.2 ± 0.2	1.7 ± 0.1	1.8 ± 0.1	1.9 ± 0.2	2.0 ± 0.2
24-Hour Creatinine Excretion (mmol/24hr)		11.5 ± 1.6	15.2 ± 1.0	18.4 ± 1.0	23.0 ± 2.9	7.6 ± 1.0	10.0 ± 0.7	12.2 ± 0.7	15.2 ± 2.0
Disease (%)	Cardiovascular	28.5	20.6	16.9	16.0	23.1	16.4	12.7	12.5
	Renal	1.9	1.0	1.0	1.1	0.9	0.7	0.7	0.8
	Endocrine	8.1	6.2	5.4	5.6	11.5	8.9	7.5	7.8
	Pulmonary	30.6	25.7	23.9	26.0	24.8	21.5	20.8	22.5
	Central Nervous System	16.3	16.9	16.8	17.6	28.3	28.1	27.4	27.8
	Gastrointestinal	11.5	12.0	15.9	20.9	12.5	11.6	12.6	17.7
	Dermatological	1.9	1.8	1.9	1.5	1.8	1.9	2.1	2.4
	Urologic	4.0	2.4	1.3	0.7	0.3	0.2	0.2	0.2
	Throat, nose, ear	5.7	2.9	1.7	1.3	6.5	3.6	2.3	2.0
	Hematologic	0.8	0.6	0.4	0.3	1.7	1.6	1.6	1.4
	Musculoskeletal	3.7	2.9	3.1	3.8	5.2	4.2	3.6	3.8
Number of Comorbidities (%)	0	33.7	40.8	42.4	39.2	32.3	38.4	41.3	37.8
	1	34.6	35.1	35.6	36.1	34.4	35.5	35.1	36.5
	2	19.7	16.0	15.1	16.8	20.8	17.2	16.2	17.1
	3	8.1	5.7	5.0	6.2	8.7	6.4	5.5	6.1
	>3	3.8	2.3	1.9	1.7	3.8	2.5	2.0	2.5
MVPA		1440 [0−3595]	1590 [300 −3720]	1650 [360 −3690]	1620 [240 −4080]	1260 [240 −2925]	1440 [480 −3105]	1440 [480 −3150]	1440 [420 −3354]
MVPA (%)	Low	36.9	32.9	32.0	33.8	36.4	31.6	30.7	32.4
	Moderate	28.5	31.1	30.5	28.0	34.6	37.6	37.9	35.5
	High	34.6	36.0	37.5	38.2	29.0	30.8	31.4	32.1
Education Level (%)	Low	36.1	30.0	27.5	30.4	44.1	33.0	24.4	23.1
	Moderate	32.4	36.6	40.3	41.8	32.7	38.1	43.9	45.8
	High	31.5	33.4	32.2	27.8	23.2	28.9	31.7	31.0
Monthly Income (%)	<2000 €	34.3	27.7	25.6	27.6	41.2	34.8	33.6	37.0
	2000-3000 €	34.6	34.8	33.8	33.6	31.5	32.0	31.7	31.4
	>3000 €	31.1	37.4	40.6	38.8	27.3	33.2	34.6	31.6
Smoking Habit (%)	Current Smoker	23.7	20.2	22.0	25.2	19.0	17.9	19.0	20.2
	Ex-Smoker	39.8	36.6	32.3	28.9	35.8	34.4	29.5	27.9
	Never Smoker	37.1	43.9	46.3	46.8	45.4	48.3	52.1	52.7
Alcohol Intake (g/day/kcal*1000)[a]		3.25 [1.0−6.75]	3.17 [1.11 −6.29]	3.21 [1.17 −6.13]	3.08 [1.16 −6.07]	1.46 [0.01 −4.63]	1.47 [0.24 −4.23]	1.34 [0.26 −3.68]	1.15 [0.17 −3.29]
Calories (kcal/day)[a]		2220.5 [1900.0 −2625.2]	2346.2 [2012.0 −2751.6]	2459.6 [2103.4 −2883.6]	2576.2 [2182.0 −3004.4]	1744.3 [1511.3 −2037.4]	1828.3 [1578.4 −2118.7]	1896.3 [1641.9 −2205.9]	1952.2 [1690.3 −2263.4]
Protein Intake (g/day/kcal*1000)[a]		35.12 [31.99 −38.32]	35.39 [32.43 −38.43]	35.59 [32.64 −38.63]	35.77 [32.70 −39.07]	37.17 [33.58 −41.04]	37.28 [33.93 −40.73]	37.12 [33.87 −43.47]	37.08 [33.92 −40.41]
Fat Intake (g/day/kcal*1000)[a]		39.01 [35.34 −42.66]	39.53 [35.95 −42.97]	39.99 [36.48 −43.40]	40.27 [36.69 −43.86]	38.50 [34.84 −42.20]	39.30 [35.79 −42.68]	39.76 [36.30 −43.05]	40.08 [36.62 −43.36]
Carbohydrate Intake (g/day/kcal*1000)[a]		112.86 [103.59 −122.09]	112.31 [103.67 −120.83]	111.34 [102.88 −119.74]	110.56 [101.71 −119.09]	113.88 [104.77 −123.10]	112.91 [104.53 −121.47]	112.87 [104.51 −121.12]	112.86 [104.65 −121.05]

[a] Participants with unreliable or missing nutritional data were excluded.

disease. A detailed list of the single morbidities within each disease domain can be found in the study of Meems et al. [28]. We calculated a simple morbidity score as a composite end-point, in which a disease domain is considered as 'affected' when at least one single disease is present within this disease domain shortly before and during the first visit at Lifelines outpatient clinic (a minimum score of zero and a maximum score of eleven). This score was then categorized in five groups, i.e. 0 to ≥4 morbidities respectively.

2.4. Statistical analysis

Descriptive statistics of the total population were expressed as means (SD) for normally distributed variables, medians (interquartile range, IQR) for skewed distributed variables, and percentages for categorical variables. Subsequently, logistic regression analyses were applied to test the (independent) associations of sarcopenia in combination with obesity and overweight with age, number of comorbidities, MVPA, education level, current smoking status, alcohol consumption and macronutrient intake. A preliminary analysis has been done on the association between mortality and sarcopenia, SO, SOW per gender and per age groups using logistic regression. A one-sided probability value of <0.05 was considered significant. Data were analyzed with IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp. Released 2013).

3. Results

3.1. Population characteristics

In the total population, 14.2% of the male and 15.0% of the female participants had a relative low muscle mass, based on ≤1.0 SD from the sex-specific mean 24-h urine creatinine, i.e. our primary definition of sarcopenia. Muscle mass was found to be inversely associated with age and multimorbidity, and positively associated with BMI (Table 1). Overall those with sarcopenia had a lower intake of protein and fat, and a greater consumption of alcohol and carbohydrates compared to those with higher muscle mass. In general, women had a lower muscle mass, were less physical active, and consumed fewer macronutrients than men. Among those with sarcopenia, 45.5% of men and 40.1% of females were found to have a BMI ≥25 kg/m^2 and 6.1% of men and 9.5% of females have a BMI ≥30 kg/m^2. Population descriptives stratified by age groups are shown in Supplementary Tables 1a and 1b

3.2. Prevalence of sarcopenic obesity and overweight

Among men and women, the prevalence of SO and SOW were found to be 0.9% and 1.4%, and 6.5% and 6.0%, respectively. The prevalence of SO and SOW was found to increase with age. Specifically, in those aged 20–29.9 years the prevalence of SO was 0.4%, while the prevalence increased to 2.6% in those aged 60–69.9 years; 4.2% in those aged 70–79.9 years; and 12.2% in those aged 80–89.9 years (Fig. 1). For those with SOW a similar trend was seen where in those aged 20–29.9 years the prevalence of SOW was 2.1%, while the prevalence increased to 6.9% in those aged 50–59.9 years; 26.6% in those aged 70–79.9 years; and 51.1% in those aged 80–89.9 years.

Additionally, unstable kidney function could be a potential confounder of muscle mass assessment from 24-h urine creatinine excretion. As a result, a sensitivity analysis was performed in which the prevalence of SO and SOW was determined while excluding

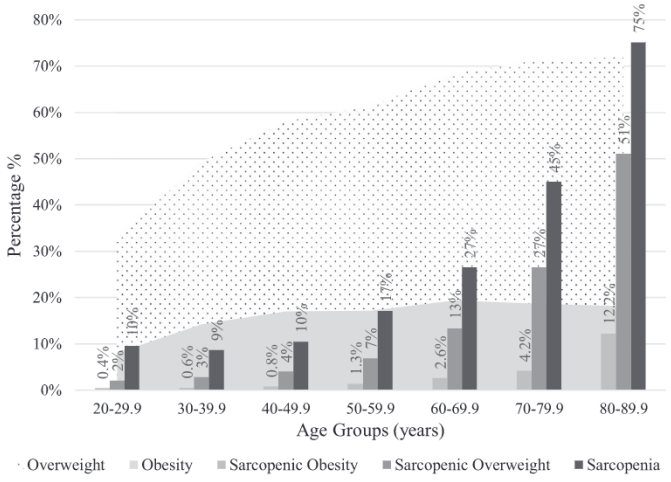

Fig. 1. Percentage of individuals with sarcopenia, sarcopenic obesity (SO), and sarcopenic overweight (SOW) per age group based on < -1.0SD 24-h urine creatinine excretion. The top shaded area indicates the percentage of overweight individuals in the general population, whereas the bottom shaded area shows the percentage of those obesity. The bars show the sarcopenic obesity, sarcopenic overweight, and sarcopenia prevalence. Data labels show %.

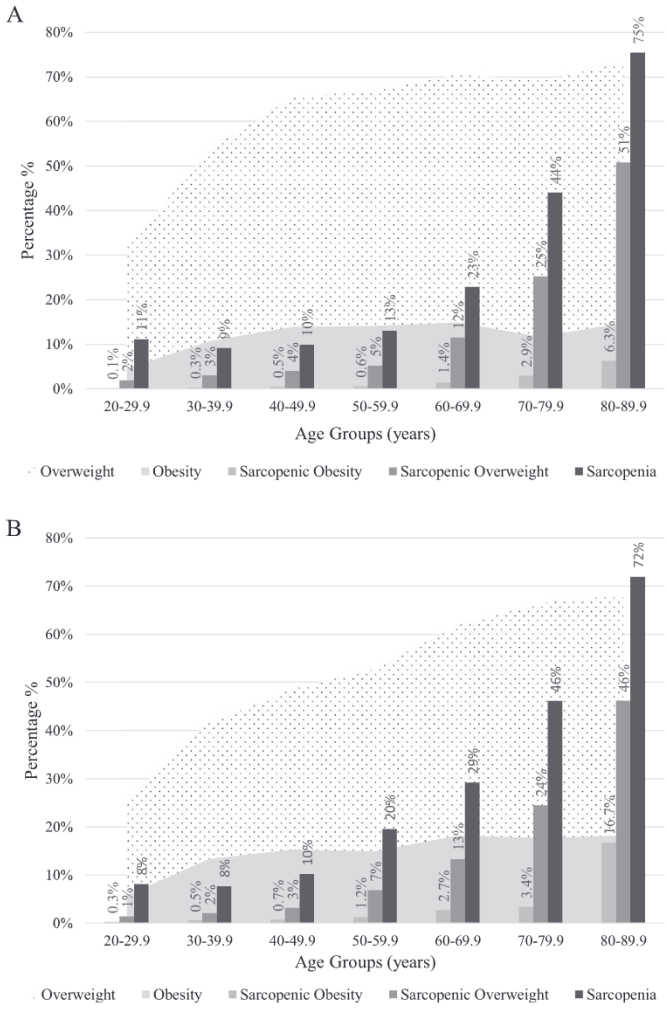

Fig. 2. a and 2b Percentage of individuals with sarcopenia, sarcopenic obesity (SO), and sarcopenic overweight (SOW) per age group based on < -1.0SD 24-h urine creatinine excretion for males (a) and females (b). The top shaded area indicates the percentage of overweight individuals in the general population, whereas the bottom shaded area shows the percentage of those obesity. The bars show the sarcopenic obesity, sarcopenic overweight, and sarcopenia prevalence. Data labels show %.

participants with kidney disease and thus those with potentially unstable kidney function. Overall the prevalences were very similar, yet slightly smaller, than the original findings: prevalence of SO was 0.59% for males and 1.0% for females; prevalence of SOW was 5.5% for males and 5.0% for females.

When stratifying per gender overall males have more overweight especially in the middle age groups compared to females: between ages 40–49 16.8% more males are overweight compared to females (65% vs. 49%) (Fig. 2a and b). Contrarily females have a higher prevalence of obesity in all age groups, although the prevalence only differs between 1 and 3%. There is a similar trend of sarcopenia prevalence for both genders. Also, although the differences are small males have a higher prevalence of SOW in younger and older age groups while the prevalence of SOW is higher for females in those between 50 and 69. Additionally in all age groups females have a higher prevalence of SO compared to males, especially in those ages 80–89 (16.7% vs 6.3%).

Of subjects with SO, 68.7% was between 40 and 70 years of age compared to 17.4% aged 70 years and over. Among those with SOW, 67.2% was between 40 and 70 years of age, compared to 19.2% aged 70 years and over (Fig. 3).

3.3. The prevalence of SO and SOW according to various criteria for sarcopenia

By definition, the prevalence of SO and SOW differed according to the underlying cut-offs for sarcopenia with prevalence's, ranging between 0.8% and 2.2% for SO and 4.4% and 9.2% for SOW (Table 2), whereby using the mean 24-h urine creatinine excretion of those 18–40 years as a reference point for healthy muscle mass had the largest impact on the prevalence. Applying age and height adjusted 24-h creatinine excretion had little effect on the prevalence of SO.

3.4. Determinants of sarcopenic obesity

The independent association between SO and various modifiable risk factors, estimated by univariate and multivariate logistic regression, is shown in Table 3. In the relatively larger population of SOW, among men and women the odds of SOW were higher in those with increasing age and with increasing number of comorbidities. SOW prevalence was lower for those who were more physical active, with a higher educational level and fat intake. For women an inverse association was found with SOW and alcohol, protein, and carbohydrate intake.

As for SOW, age was the most consistent determinant of SO, as well as the number of morbidities, albeit not quit consistently so for women. Compared to those with no morbidities, and independent of other risk factors, the odds of SO among individuals with >3 comorbidities were 2.71 (95% CI: 1.62–4.54) for men and 1.14 (95% CI: 0.79–1.65) for women. Alcohol and carbohydrate intake were inversely associated with SO among women.

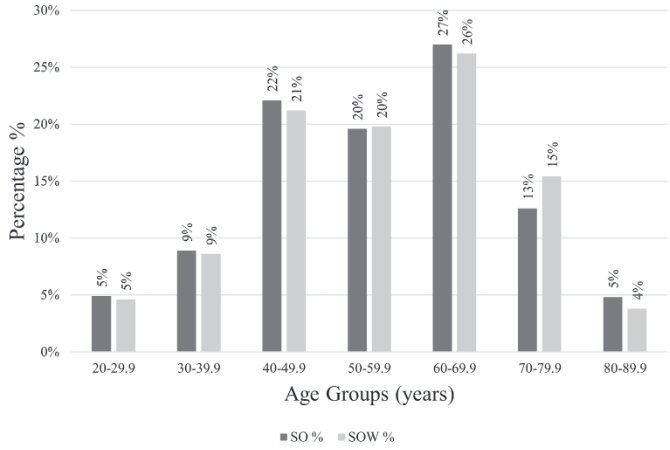

Fig. 3. Percentage the total prevalence of Sarcopenic Obesity (SO) and Sarcopenic Overweight (SOW) per age group.

3.5. Mortality

A preliminary analysis of the association between mortality and sarcopenia, SO, and SOW per gender and per age groups is shown in Supplementary Table 2. Analyses for both genders together show a significant positive association with sarcopenia (OR 1.37, 95% CI: 1.21–1.55) and SOW (OR 1.46, 95% CI: 1.33–1.72) and mortality in all age groups combined. Similar significant associations were found when stratifying per gender for sarcopenia and SOW. Additionally, a significant positive association with SOW and mortality was also found for those in age groups 30–39 years (OR 2.64, 95% CI: 1.00–6.96), 60–69 (OR 1.43, 95% CI: 1.09–1.87), and 70–79 (OR 1.646, 95% CI: 1.20–2.25]). There was no significant association found between SO and mortality. The mortality analyses require further substantiation.

4. Discussion

In this general population of adults of ≥18 years, the prevalence of SO was 0.9% and 1.4% among men and women respectively. Additionally, the prevalence of SOW was 6.5% and 6.0% for men and women. Between ages 40–59 males have a higher prevalence of SOW while overall females have more SO in all age groups, especially between ages 80–89. Similar to findings in geriatric populations, older age was a significant determinant of SO, however,

Table 2
Gender specific prevalence of sarcopenic obesity and overweight.

Obesity Cut-off	24-Hour Creatinine Excretion Cut-off	Male		Female	
		N	%	N	%
Sarcopenic Obesity (BMI ≥30 kg/m^2)	<-1SD	440	0.87%	983	1.42%
	<-1SD Adjusted for Height	376	0.75%	816	1.18%
	<-1SD Adjusted for Age	391	0.78%	735	1.06%
	<-1SD using the mean 24-h urine creatinine excretion of those 18–40 years as a reference point for healthy muscle mass	542	1.08%	1499	2.17%
Sarcopenic Overweight (BMI ≥25 kg/m^2)	<-1SD	3259	6.47%	4174	6.04%
	<-1SD Adjusted for Height	2944	5.84%	3649	5.28%
	<-1SD Adjusted for Age	2733	5.42%	3036	4.39%
	<-1SD using the mean 24-h urine creatinine excretion of those 18–40 years as a reference point for healthy muscle mass	3925	7.79%	6355	9.20%

Table 3
Univariate and multivariate analysis of determinants of sarcopenic obesity and sarcopenic overweight, stratified by gender.

		Sarcopenic Overweight				Sarcopenic Obesity			
		Male N = 31,585 (N = 25,764)		Female N = 34,536 (N = 27,642)		Male N = 7317 (N = 5250)		Female N = 11,355 (N = 8219)	
		Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age at Baseline (years)		1.056 [1.053 −1.059]*	1.049 [1.045 −1.053]*	1.062 [1.059 −1.065]*	1.053 [1.049 −1.057]*	1.052 [1.044 −1.061]*	1.050 [1.037 −1.063]*	1.057 [1.052 −1.063]*	1.051 [1.042 −1.060]*
Number of Comorbidities[a]	1	1.254 [1.141 −1.379]*	1.036 [0.926 −1.160]	1.177 [1.078 −1.284]*	1.050 [0.944 −1.168]	1.252 [0.910 −1.723]	1.255 [0.817 −1.929]	1.040 [0.847 −1.276]	1.025 [0.786 −1.338]
	2	1.755 [1.583 −1.945]*	1.162 [1.024 −1.320]*	1.529 [1.451 −1.747]*	1.131 [1.007 −1.270]*	1.973 [1.436 −2.710]*	1.675 [1.085 −2.586]*	1.551 [1.266 −1.902]*	1.171 [0.891 −1.539]
	3	2.103 [1.844 −2.399]*	1.200 [1.017 −1.415]*	1.919 [1.713 −2.149]*	1.137 [0.984 −1.315]	2.792 [1.985 −3.926]*	1.931 [1.201 −3.105]*	1.918 [1.534 −2.399]*	1.316 [0.973 −1.781]
	>3	2.857 [2.407 −3.391]*	1.333 [1.074 −1.654]*	2.413 [2.086 −2.791]*	1.279 [1.063 −1.540]*	4.201 [2.897 −6.092]*	2.708 [1.615 −4.541]*	2.278 [1.754 −2.957]*	1.143 [0.792 −1.651]
Physical Activity Level[b]	Moderate	0.775 [0.709 −0.849]*	0.828 [0.745 −0.955]*	0.768 [0.712 −0.829]*	0.876 [0.795 −0.965]*	0.749 [0.593 −0.947]*	0.908 [0.673 −1.225]	0.699 [0.598 −0.816]*	0.836 [0.677 −1.031]
	High	0.795 [0.729 −0.865]*	0.934 [0.840 −1.038]	0.740 [0.682 −0.802]*	0.863 [0.782 −0.952]*	0.681 [538 −0.861]*	0.831 [0.605 −1.143]	0.734 [0.624 −0.865]*	0.940 [0.762 −1.159]
Education Level[c]	Moderate	0.617 [0.565 −0.673]*	0.859 [0.774 −0.955]*	0.451 [0.418 −0.486]*	0.837 [0.761 −0.922]*	0.643 [0.513 −0.804]*	0.811 [0.605 −1.086]	0.464 [0.0.398 −0.540]*	0.886 [0.721 −1.088]
	High	0.730 [0.667 −0.800]*	0.926 [0.833 −1.037]	0.397 [0.361 −0.437]*	0.711 [0.632 −0.799]*	0.648 [0.495 −0.847]*	0.736 [0.518 −1.046]	0.404 [0.327 −0.500]*	0.787 [0.599 −1.033]
Current Smoker		1.024 [0.937 −1.119]	–	0.974 [0.893 −1.061]	–	1.047 [0.828 −1.323]	–	0.766 [0.631 −0.929]*	0.976 [0.744 −1.258]
Alcohol Intake (g/day/kcal*1000)[d]		1.027 [1.018 −1.036]*	1.011 [1.002 −1.020]*	1.030 [1.021 −1.040]*	0.859 [0.801 −0.921]*	1.038 [1.1015 −1.060]*	1.023 [0.996 −1.051]	1.024 [1.001 −1.048]*	1.045 [1.008 −1.083]*
Protein Intake (g/day/kcal*1000)[d]		1.003 [0.994 −1.012	–	1.013 [1.006 −1.020]*	0.883 [0.846 −0.922]*	1.028 [1.005 −1.053]	1.001 [0.972 −1.030]	1.008 [0.993 −1.023]	–
Fat Intake (g/day/kcal*1000)[d]		0.973 [0.966 −0.981]*	0.979 [0.970 −0.987]*	0.959 [0.953 −0.966]*	0.798 [0.731 −0.871]*	0.988 [0.979 −0.997]	–	0.960 [0.945 −0.974]*	1.030 [0.991 −1.070]
Carbohydrate Intake (g/day/kcal*1000)[d]		1.002 [0.999 −1.005]	–	1.006 [1.003 −1.009]*	0.910 [0.874 −0.948]*	0.988 [0.979 −0.997]*	0.998 [0.987 −1.009]	1.009 [1.003 −1.015]*	1.026 [1.009 −1.042]*

Results shown as odds ratio [C1 95%], * = P < 0.05.
[a] No comorbidities = reference.
[b] very low physical activity = reference.
[c] Low education = reference. Gender-specific potential determinants significantly associated with SO in univariate analysis were included in the multivariate logistic regression.
[d] Participants with unreliable or missing nutritional data were excluded (n = 17,338).

based on the absolute numbers, SO and SOW was more prevalent in those under 70 years.

Although the prevalence of SO and SOW increases with age, SO and SOW are also prevalent in younger age groups, with higher absolute numbers in middle aged individuals. While the described prevalences are low, especially in the younger age groups, in a preliminary analysis there was a significant association with SOW and mortality, even in those between ages 30–39. This shows the risk assessment of SO and SOW should go beyond the geriatric setting, and SO and SOW are both indicators of population health, not just for older people. Additionally, the substantial prevalence of SOW in the general population shows a potential area for primary prevention of SO and its potential health risks. On the other hand, no significant association between SO and mortality was found possibly due to a lack of power. Overall additional mortality analyses are required for substantiation.

In this study sarcopenia was defined with muscle mass using 24-h urine creatinine excretion, which is a promising method for estimation of total-body skeletal muscle mass [20]. The low prevalence of sarcopenia in co-existence with a BMI $\geq$30 kg/m^2 questions, however, the applicability of BMI to define fat mass in the context of sarcopenia. Important changes in body composition occur with age, including a relative increase in fat tissue and a gradual decline in muscle mass, meaning overall body weight and BMI may remain relatively unchanged. It is therefore argued that BMI might not an appropriate measure of adiposity among older people [15]. Alternatively, and in the quest of other surrogate markers with routine applicability, waist circumference could be used as a measure of excess adiposity. However, there is an ongoing debate whether the waist circumference cut-off points should be shifted upwards in older adults [29]. Additionally, a single cut-off point for international use is not possible due to its wide variation across populations.

Reduced muscle mass is a phenotypic criterion with strong evidence to support its inclusion in the The Global Leadership Initiative on Malnutrition (GLIM) consensus criteria [30]. However, there are currently various accepted methods and cut-off points used to define reduced muscle mass and sarcopenia, particularly in clinical settings. This current lack of a uniform measurement seriously hampers comparison between studies [2,31–36]. Further consensus on diagnostic tools and criteria may help the emerging (research) field of sarcopenia forward. There is likely no ideal methodology to simultaneously achieve maximal precision, safety and routine applicability to measure SO; since the latter is ultimately sought, surrogate markers may have to be accepted as a compromise. So far, in the sarcopenia field, 24-h urine creatinine has received little emphasis, but is a cheap and noninvasive measurement of muscle mass and its use has been proposed as a promising proxy measure for estimating whole-body muscle mass [16,37]. An important point to consider is what threshold of muscle mass loss is clinically relevant in the context of obesity.

In the present study, SO was strongly associated with accumulation of chronic diseases. The concept of SO is complex with various underlying elements such as endocrine, inflammatory, and lifestyle factors [38,39]. The presence of obesity with low muscle mass or strength is highly related with metabolism-related diseases, such as metabolic syndrome and functional disabilities [32,40]. Previously, it has been found that sarcopenia and obesity are independently associated with increased risk of multimorbidity, but when coexistent, as with SO, the risk of multimorbidity is greater [31].

The determinants and causes of SO must be identified to develop prevention and treatment strategies for this disease, particularly concerning lifestyle habits, which are more controllable in comparison to age-related systemic changes and genetic factors. Inadequate nutrition is one of the major mechanisms underlying sarcopenia [41]. This study provided supporting evidence about the association of nutrient intake and SO, but evidence to recommend specific interventions has yet to be established. Recent studies have demonstrated the intake of nutrients, such as protein and a greater poly-unsaturated fat to saturated fat ratio, has an influence on skeletal muscle metabolism [37,42], suggesting a potential role of nutritional interventions.

This study is not without limitations. The cross-sectional design limits the potential for etiological conclusions. Future longitudinal research is warranted to determine causal determinants and risk factors of SO and SOW. Additionally, the prevalence of SO and SOW was determined separately for males and females as there is a large sex-difference in muscle mass. Although women have a lower muscle mass, studies show older men have a greater loss of absolute muscle mass compared to women even when accounting for their larger initial muscle mass [43]. Consequently, when stratifying SO for gender the age at which males and females reach a critically low muscle mass cannot be adequately compared. In light of the absolute numbers on SO and SOW in different age categories, it should be noted that, although the cohort is broadly representative for the North of the Netherlands, middle aged individuals are overrepresented in the Lifelines Cohort Study [19].

Using 24-h urinary creatinine excretion to measure muscle mass also has potential limitations. Deviation from steady state of muscle mass turnover and kidney function stability can be sources of error (44). Although presence of these steady states were not formally tested, it is reasonable to assume stable conditions were present, as data was obtained from ambulant subjects in the general population able to come to the study site and undergo extensive measurements. Also, the main cause of deviation from steady state is acute (intercurrent) illness, which, according to the Lifelines protocol, is reason to postpone measurements until after full recovery. Additionally, the prevalence of SO and SOW were very similar when participants with kidney disease, and thus potentially unstable kidney function, were excluded compared to our original findings. Therefore, we consider it unlikely deviation from steady state muscle turnover and kidney function stability are relevant confounders in our data set.

5. Conclusion

To conclude, in this general population of adults, we observed a prevalence of SO of 0.9% among males and 1.4% among females, and a prevalence of SOW of 6.5% for males and 6.0% for females. The results support the need for more awareness of SO beyond the field of geriatrics; SO is more prevalent in middle age groups, in particular in subjects with comorbidities. Additionally, SOW is more prevalent than SO and may therefore provide opportunities for preventive strategies for the general population. In order to better identify those with, or at risk for, SO it is essential to focus on generating a consensus of diagnostic tools and criteria for the general population. 24-hour urine creatinine excretion may serve as a reasonable surrogate markers of muscle mass but should further be examined in the context of obesity.

Statement of authorship

Carlijn A. Wagenaar: Formal Analysis, Writing - Original Draft, Visualization. **Louise H. Dekker**: Methodology, Conceptualization, Writing - Review & Editing. **Gerjan J. Navis**: Resources, Conceptualization, Writing - Review & Editing, Supervision.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.01.005.

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