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Chapter 4

Defining sarcopenia: the impact of different diagnostic criteria on the prevalence of sarcopenia in a large middle aged cohort

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Abstract

Sarcopenia, low muscle mass, is an increasing problem in our aging society. The prevalence of sarcopenia varies extremely between elderly cohorts ranging from 7 to over 50%. Without consensus on the definition of sarcopenia, a variety of diagnostic criteria are being used. We assessed the degree of agreement between seven different diagnostic criteria for sarcopenia based on muscle mass and handgrip strength, described in literature. In this cross-sectional study, we included men (n=325) and women (n=329) with complete measurements of handgrip strength and body composition values as measured by bioimpedance analysis within the Leiden Longevity Study. Prevalence of sarcopenia was stratified by gender and age. In men (mean age 64.5 years) the prevalence of sarcopenia with the different diagnostic criteria ranged from 0% to 20.8% in the lowest age category (below 60 years), from 0% to 31.2% in the middle (60 to 69 years) and from 0% to 45.2% in the highest age category (above 70 years). In women (mean age 61.8 years) the prevalence of sarcopenia ranged from 0% to 15.6%, 0% to 21.8% and 0% to 25.8% in the lowest, middle and highest age category respectively. Only one participant (0.2%) was identified having sarcopenia according to all diagnostic criteria that marked prevalence above 0%. We conclude that the prevalence of sarcopenia is highly dependent on the applied diagnostic criteria. It is necessary to reach a consensus on the definition of sarcopenia in order to make studies comparable and for implementation in clinical care.

Introduction

Sarcopenia, low muscle mass at older age, is an increasing problem in our aging society. Annual loss of muscle mass has been reported as 1 to 2 percent at the age of 50 years onwards (1;2), and it exceeds over 50% among those aged 80 years and older when compared to younger adults (3). The change of muscle mass is closely related to changes in muscle strength. Reduced muscle strength has been found to be associated with dependency in activities of daily living (4;5), cognitive decline (6-8), and mortality (9;10). Next to the generation of muscle strength, muscle tissue is an important reserve of body proteins and energy that can be used in extreme conditions of stress or malnutrition. Low muscle mass is associated with higher drug toxicity (11;12) and reduced insulin sensitivity (13).

Since the coining of the term 'sarcopenia' in 1989 by Rosenberg (14), many suggestions have been made to try to establish a clinically applicable definition. In general, three possible approaches in defining sarcopenia have been suggested. According to the first, the amount of muscle mass, measured with dual-energy x-ray absorptiometry (DXA) or bioimpedance analysis (BIA), compared to a younger reference population determines whether a person has sarcopenia. Correction factors applied using this approach are height (3;15), body mass (16), or both body height and body fat (17). In the second approach, muscle function is used as diagnostic criterion to define sarcopenia as compared to a younger reference population (18). The third approach combines both muscle mass and muscle function in the definition (19;20).

Little is known about the degree of agreement between the diagnostic criteria and their effects on estimates of the prevalence of sarcopenia, which appears to vary extremely between different cohorts ranging from 7 to over 50% in the elderly (3;16-18;21). The use of different diagnostic criteria may lead to different conclusions and may have different implications for treatment. To the best of our knowledge the differences in prevalence of sarcopenia in middle aged people comparing different diagnostic criteria has not been previously reported. In the present paper we explore the prevalence of sarcopenia using seven different diagnostic criteria in a large cohort of Dutch middle aged people. Furthermore, we assess the degree of concordance within individuals using the different criteria. Therewith, we aim to show the importance of reaching a consensus on the definition of sarcopenia, for clinical research and patient care.

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Methods

Study cohort

The Leiden Longevity Study (LLS) consists of long-living Caucasian siblings of 420 families together with their middle aged offspring, and the partners of the offspring as controls (22). The study included 674 participants of the middle aged to older offspring and their partners, who were assessed in the period from 2006 to 2008. The sample of partners in the study was representative of the Dutch population (22). Participants (n=20) with missing data for body composition measured with Direct Segmental Multi-frequency Bioelectrical Impedance Analysis (DSM-BIA) were excluded from the present analysis. There were no selection criteria on health or demographic characteristics (23). The Medical Ethics Committee of the Leiden University Medical Centre approved the study, and written informed consent was obtained from all participants.

Participant characteristics

At baseline, information on common chronic diseases and medication use was obtained from the participants' general practitioner, pharmacist's records, and from blood sample analyses. The chronic diseases recorded were diabetes mellitus, chronic obstructive pulmonary disease, malignancy, myocardial infarction, stroke, and hypertension. Health behaviour variables included current smoking status and excessive alcohol use (male > 210 g/week and female > 140 g/week).

Body composition

Body mass and body height were measured. DSM-BIA was performed using the In-Body (720) body composition analyser (Biospace Co., Ltd, Seoul, Korea). We have previously shown this technique to be a valid tool for the assessment of whole body composition and segmental lean mass measurements in our sample of a middle aged people (24). Excellent agreements were observed between the DSM-BIA technique and DXA in whole body lean mass (intraclass correlation coefficient (ICC) female=0.95, $p<0.001$, ICC male=0.96, $p<0.001$) and fat mass (ICC female 0.97 $p<0.001$, ICC male 0.93 $p<0.001$) (24). The DSM-BIA technique is based on the assumption that the human body is composed of 5 interconnecting cylinders and takes direct impedance measurements from the various body compartments. A tetrapolar eight point tactile electrode system is used, which separately measures impedance of the participant's trunk, arms, and legs at six different frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, and 1000 kHz) for each of the body segments. The

spectrum of electrical frequencies is used to predict the intracellular water (ICW) and extracellular water (ECW) compartments of the total body water (TBW) in the various body segments. Lean body mass is estimated as TBW (ICW + ECW)/0.73. Body fat mass is calculated as the difference between total body mass and lean mass. The machine gives immediate detailed results including quantitative values of total body and segmental lean mass, fat mass, and percentage fat mass. Appendicular lean mass (ALM) calculation was based on the sum of lean mass in all four limbs. Relative ALM was calculated as ALM divided by body height in meters squared (3). Participants wore normal indoor clothing and were asked to stand barefoot on the machine platform with their arms abducted and hands gripping on to the handle of the machine.

Handgrip strength

Handgrip strength was measured to the nearest kilogram using a Jamar hand dynamometer (Sammons Preston, Inc., Bolingbrook, IL, USA). All participants were instructed to maintain an upright standing position, arms down by the side, and holding the dynamometer in the dominant hand without squeezing the arm against the body. The width of the dynamometer's handle was adjusted to the hand size of the participants such that the middle phalanx rested on the inner handle. Participants were allowed to perform one test trial, followed by three trials, and the best measurement was taken for analysis.

Diagnostic criteria of sarcopenia

An overview of different diagnostic criteria of sarcopenia (coded A to G) as described in the literature, which included muscle mass and handgrip strength is given in table 1 (3;15;16;18;25). Only diagnostic criteria based on measurements of muscle mass by BIA (definition E and F) or DXA (definition A, B, C, and D) scanning were used in this comparison. For each of these formulas, a different reference population had been used to derive a cut-off point for sarcopenia. For the formula ALM divided by height squared (definition A, B, and C), we found three different cut-off points for men and women, established in different reference populations (3;25;26). Reference populations were different in age and ethnicity, consisting of younger participants of the Rosetta study (definition A)(3), the NHANES survey (definition C)(26), and the NHANES III study (definition E)(16); elderly participants were included as reference population in the Health ABC study (definition B)(25), and the NHANES III study (definition F)(15); the whole adult age range was included in the reference population in the InCHIANTI study (definition G)(18). The formula described in

definition D, was applied to our cohort, using the 20th percentile as cut-off point for sarcopenia (25). Consequently, we used a total of seven different diagnostic criteria of sarcopenia in our analysis.

Statistical analysis

Data were analysed for men and women separately. Because there was no significant difference in fat percentage, relative ALM, and handgrip strength between offspring and partners of the LLS, data for both groups were combined (27). The prevalence of sarcopenia in this population was assessed for all seven diagnostic criteria as described in table 1. For definition D, the residuals of linear regression of ALM with height and fat mass were calculated.

After assigning the status of sarcopenia being present or not present in the participants according to each of the seven diagnostic criteria, participants were stratified by gender and age. The lowest age category included participants aged below 60 years, the middle age category included participants aged 60 to 69 years and the highest included participants aged 70 years and above. Differences between age groups in characteristics were assessed with linear regression or binary logistic regression. The degree of concordance within individuals using the different diagnostic criteria of sarcopenia was assessed in all participants.

All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago), version 17. P values <0.05 were considered statistically significant.

Results

Baseline characteristics of the study participants stratified by gender and age are presented in Table 2. Overall, the prevalence of comorbidity was slightly higher in older participants (statistically not significant). Skeletal lean mass as a percentage of body mass and grip strength were significantly lower in the older age groups. ALM divided by height squared was significantly different between the age groups in men, but not in women.

The prevalence of sarcopenia using the seven different diagnostic criteria is shown in Table 3. In men, the prevalence ranged from 0% to 20.8% in the lowest age category, from 0% to 31.2% in the middle age category and from 0% to 45.2% in the highest age category. In women, percentages ranged from 0% to 15.6%, 0% to 21.8% and 0% to 25.8% in the lowest, middle and highest age category respectively.

Definitions A, B, and C are based on the same formula taking height into account, but each comprised different reference populations and strategies to define cut-

Tabel 1 Seven different diagnostic criteria to define sarcopenia

Code	Formula	Cut-off point Sarcopenia present	Men	Women	Cohort used as reference population	Reference[a]
A	ALM/height²	>2 SD below reference population	7.26 kg/m²	5.45 kg/m²	Rosetta Study (1986-1992)m 229 non-Hispanic white men and women aged 18-40 years	Baumgartner et al., 1998
B	ALM/height²	Under 20th percentile	7.25 kg/m²	5.67 kg/m²	Health ABC Study (1997/1998), 2976 men and women 70-79 years old black and white, Pittsburgh, Pennsylvania and Memphis, Tenessee	Delmonico et al., 2007
C	ALM/height²	>2 SD below reference population	6.19 kg/m²	4.73 kg/m²	NHANES survey (1999 - 2004) white men and women aged 20 years	Kelly et al., 2009
D	Residuals of linear regression of ALM with height and fat mass	Under 20th percentile	NA	NA	NA	Delmonico et al., 2007[b]
E (1)(2)	Skeletal lean mass/body mass * 100%	1-2 SD below reference population is class I sarcopenia >2 SD below reference population is class II sarcopenia	37% 31%	28% 22%	NHANES III (1988-1994), 6414 men and women aged 18-39 years non-Hispanic white, non-Hispanic black and	Janssen et al., 2002
F (1)(2)	Skeletal lean mass/height²	ROC analysis was used to develop cutpoints associated with moderate (1) and high (2) physical disability	10.75 8.50 kg/m²	6.75 5.75 kg/m²	NHANES III (1988-1994), 4502 subjects aged 60 years plus, non-Hispanic white, non-Hispanic black and Mexican-American	Janssen et al., 2004
G	Optimal cutpoint for grip strength, identified in the ROC curve, predicting walking slower than 0.8 m/s	Below optimal cutpoint	30.3 kg	19.3 kg	InCHIANTI (1998-2000), 1030 subjects aged 20 - 102 years, Tuscany, Italy	Lauretani et al., 2003

[a]Reference describes the formula and cut-off points, unless indicated otherwise. [b]Reference describes the formula which was applied to the Leiden Longevity Study population. ALM=appendicular lean mass, sum measurement of lean mass in all 4 limbs; ROC=receiver operating characteristics; NA=not applicable.

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off points. In men prevalence varied from 0% to 3.9% (lowest age category), 0% to 4.3% (middle age category) and 0% to 6.5% (highest age category). In women this variation for definitions A, B, and C was 0% to 3.1% (lowest age category), 0% to 3.5% (middle age category) and 0% (highest age category). When applying cut-off points for definition E class II, two men (0.6%) and 1 woman (0.3%) were classified as sarcopenic. The prevalence of sarcopenia was higher when applying cut-off points for definition E class I. Only one of the men (0.3%) was sarcopenic according to definition F class II criteria, based on muscle mass and height. The prevalence was higher using definition F class I criteria. The use of definition G which included handgrip strength gave a prevalence of less than 4% in this middle aged cohort.

Figure 1 shows the distribution of participants identified as sarcopenic according to the different diagnostic criteria. Definition C, which gave zero prevalence of sarcopenia is omitted. For definition E and F, class I and class II sarcopenia are combined. Out of the 654 participants, 436 did not have sarcopenia according to any definition. For 218 participants, the diagnosis of sarcopenia depended on the diagnostic criteria applied. Only one of the participants (0.2%) was sarcopenic according to all six definitions.

Discussion

In this large middle aged Dutch cohort, the prevalence of sarcopenia varied widely depending on which diagnostic criteria were used. Criteria based on low grip strength and skeletal lean mass failed to match with criteria based on appendicular lean mass. There was substantial overlap between diagnostic criteria A and B which are both based on the amount of appendicular lean mass, yet another cut-off point for the amount of appendicular lean mass resulted in the absence of sarcopenia (diagnostic criterium C). These findings clearly demonstrate the highly different selection of participants with the diagnosis sarcopenia using various criteria. Consequently, there are concerns about the validity of comparisons between studies using different criteria to diagnose sarcopenia.

The question arises which properties of skeletal muscle are represented by the term sarcopenia. Besides the production of force, muscle tissue is also an important regulator of biological processes. For instance, as a protein store it provides a homeostatic reserve to recover from disease (28). Furthermore, skeletal muscle has been identified as the major tissue involved in glucose metabolism (29;30). Current evidence suggests that lean body mass may be a better measure for normalising dosages of drugs that are distributed and metabolised in lean tissue, compared

Table 2: Baseline characteristics of study participants, stratified for gender and age.

Variables[a]	Men				Women			
	<=59 y (n=77)	60-69 y (n=186)	>=70 y (n=62)	P trend	<=59 y (n=128)	60-69 y (n=170)	>=70 y (n=31)	P trend
Age (y, mean, range)	56.1 (45-59)	64.9 (60-69)	73.5 (70-82)		55.6 (38-59)	64.5 (60-69)	72.3 (70-78)	
Height (m)	1.81 (0.07)	1.78 (0.06)	1.76 (0.07)	<0.001	1.67 (0.06)	1.66 (0.1)	1.64 (0.6)	0.02
Body mass (kg)	86.7 (11.0)	85.5 (11.8)	84.1 (10.1)	0.17	71.7 (12.5)	72.6 (13.1)	76.0 (11.4)	0.15
Body Mass Index (kg/m²)	26.6 (3.3)	27.0 (3.2)	27.2 (2.9)	0.25	25.8 (4.4)	26.4 (4.7)	28.2 (4.0)	0.01
Total body fat mass (%)	23.4 (6.1)	25.8 (5.9)	28.0 (7.1)	<0.001	33.7 (7.5)	35.2 (7.1)	39.4 (6.7)	<0.001
Skeletal lean mass (kg)	37.2 (4.1)	35.3 (4.0)	33.3 (3.9)	<0.001	25.7 (3.3)	25.3 (3.3)	24.7 (3.0)	0.10
Skeletal lean mass (%)[b]	43.1 (3.5)	41.5 (3.4)	39.8 (4.0)	<0.001	36.2 (4.1)	35.3 (3.9)	32.8 (3.8)	<0.001
ALM[c] (kg)	28.0 (3.3)	26.7 (3.2)	25.5 (3.3)	<0.001	19.3 (2.7)	18.9 (2.7)	18.9 (2.5)	0.31
Relative ALM[d] (kg/m2)	8.6 (0.6)	8.4 (0.6)	8.2 (0.6)	0.002	6.9 (0.7)	6.9 (0.8)	7.0 (0.7)	0.78
Handgrip strength (kg)	51.1 (7.9)	46.8 (7.2)	41.7 (8.1)	<0.001		29.0 (5.0)	26.6 (4.8)	<0.001
Comorbidities (n %)								
Myocardial infarction	1 (1.3)	8 (4.3)	3 (4.8)	0.25	0	1 (0.6)	1 (3.2)	0.11
Stroke	1 (1.3)	5 (2.7)	5 (8.1)	0.04	2 (1.6)	3 (1.8)	0	0.70
Hypertension	10 (13.0)	50 (26.9)	20 (32.3)	0.006	25 (19.5)	47 (27.6)	13 (41.9)	0.008
Diabetes Mellitus	5 (6.5)	16 (8.6)	6 (9.7)	0.48	6 (4.7)	7 (4.1)	4 (12.9)	0.25
Neoplasm	2 (2.6)	12 (6.5)	6 (9.7)	0.08	6 (4.7)	14 (8.2)	3 (9.7)	0.18
COPD	3 (3.9)	7 (3.8)	5 (8.1)	0.26	5 (3.9)	3 (1.8)	2 (6.5)	0.99
Rheumatoid arthritis	1 (1.3)	1 (0.5)	1 (1.6)	0.90	1 (0.8)	2 (1.2)	0	0.91
Medicatione, median (IQR)[e]	0 (0-0)	0 (0-1)	0 (0-1)	<0.001	0 (0-1)	0 (0-1)	0 (0-2)	0.02
Smoking (n %)	10 (13.0)	24 (12.9)	6 (9.7)	0.61	21 (16.4)	16 (9.4)	1 (3.2)	0.02
Excessive alcohol use (n %)[f]	20 (26.0)	57 (30.6)	14 (22.6)	0.95	19 (14.8)	24 (14.1)	5 (16.1)	0.90

[a]Variables are presented in mean, SD, unless indicated otherwise. P values for trend were calculated using linear or logistic regression. [b]skeletal lean mass/total body mass•100%. [c]Appendicular lean mass, sum measurement of lean mass in all 4 limbs. [d]Appendicular lean mass adjusted for height (appendicular lean mass/height2). [e]Sum score of total number of oral medication, data available in males (n=272) and females (n=268). [f]Male≥210 g/week and female>140 g/week.

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Table 3: Prevalence of sarcopenia (n %) in the middle aged study population stratified by gender and age.

| Code[a]	Men				Women			
	<=59 y	60-69 y	>=70 y	Total	<=59 y	60-69 y	>=70 y	Total
	(n=77)	(n=186)	(n=62)	(n=325)	(n=128)	(n=170)	(n=31)	(n=329)
A	3 (3.9)	8 (4.3)	4 (6.5)	15 (4.6)	2 (1.6)	5 (2.9)	0	7 (2.1)
B	3 (3.9)	8 (4.3)	4 (6.5)	15 (4.6)	4 (3.1)	6 (3.5)	0	10 (3.0)
C	0	0	0	0	0	0	0	0
D	12 (15.6)	35 (18.8)	18 (29.0)	65 (20.0)	20 (15.6)	37 (21.8)	8 (25.8)	65 (19.8)
E1	3 (3.9)	17 (9.1)	16 (25.8)	36 (11.1)	4 (3.1)	8 (4.7)	4 (12.9)	16 (4.9)
E2	1 (1.3)	0	1 (1.6)	2 (0.6)	0	0	1 (3.2)	1 (0.3)
F1	16 (20.8)	58 (31.2)	28 (45.2)	102 (31.4)	0	0	1 (3.2)	1 (0.3)
F2	0	0	1 (1.6)	1 (0.3)	0	0	0	0
G	1 (1.3)	2 (1.1)	5 (8.1)	8 (2.5)	3 (2.3)	6 (3.5)	0	9 (2.7)

[a]The letters represent codes for the applied definition. The code is fully described in Table 1.

with body surface area alone (11;12;31). This underlines the importance to evaluate muscle mass in aging subjects.

In the present study, there was little overlap between individuals with low grip strength and low muscle mass using the diagnostic criteria. A possible explanation is that muscle strength is not only determined by muscle mass. The amount of muscle mass represents the number of sarcomeres that are in parallel. As each sarcomere is capable of exerting an amount of force, the number of sarcomeres in parallel, together with the quality of proteins and connective tissue determines the amount of force that a muscle can potentially exert. Additionally, muscle function is dictated by energy supply and neural control. Consequently, the terms muscle mass and muscle strength cannot be used interchangeably (32). The rate of decline in muscle strength at older age appears to be higher than the decline in muscle mass in a 3-year longitudinal study, suggesting that factors other than muscle mass are influential (33). Additionally, the increase of strength after resistance training is higher than the increase in muscle mass in older adults (34-37). In a recent meta-analysis it was shown that handgrip strength decreases each year with 0.37 kg (95% CI 0.31-0.44) after 50 years of age (38). Still, the low prevalence of sarcopenia in our cohort based on cut-off points for handgrip strength can possibly be explained by the fact that our cohort was middle aged and not over 80 years of age, where lower muscle strength becomes even more apparent (39). Recently a new term, dynapenia, has been developed to describe low muscle strength at old age (32). The use of the terms dynapenia for low muscle strength, and sarcopenia for low muscle

mass, emphasises the differences between muscle strength and mass. However, this terminology might overcomplicate the situation unnecessarily, since muscle mass is also needed to generate strength. In other words, low muscle strength is one of the possible consequences of low muscle mass.

The prevalence of sarcopenia determined by diagnostic criteria using ALM corrected for height was not related to chronological age in women. However, the total lean mass as a percentage of total body mass was lower in all older subjects. This provides evidence that the interpretation of the amount of muscle mass is highly dependent on applied correction factors, such as fat mass and height. This is supported by Newman et al., who found that correction for height only could lead to an overestimation of sarcopenia in underweight individuals, compared to an underestimation of sarcopenia in obese individuals (17). Furthermore, recent
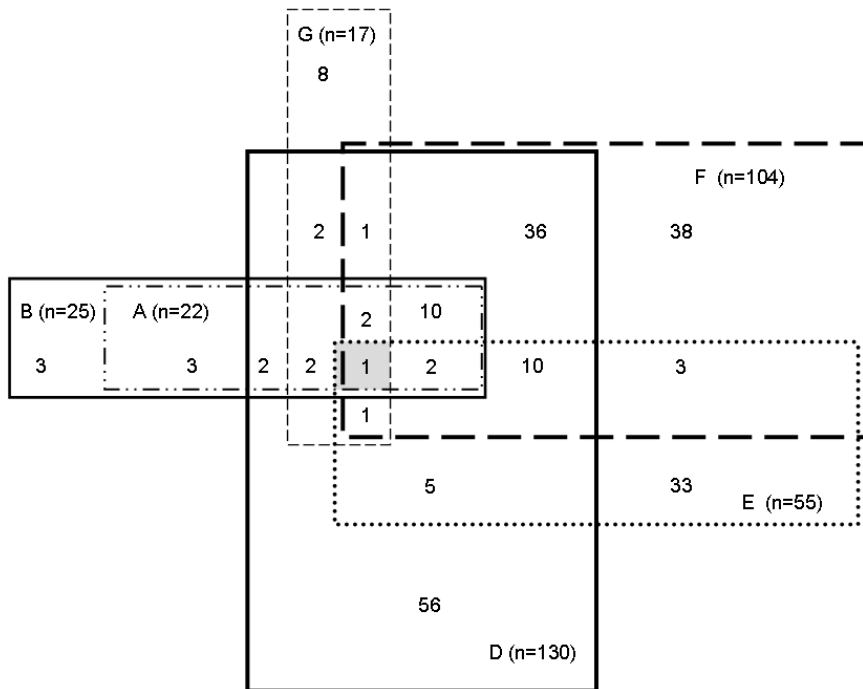
Figure 1: Number of participants identified as having sarcopenia according to various definitions, represented by letter codes. A description of the codes can be found in table 1. A total of 654 were evaluated. Definition C, in which no participants were sarcopenic, is not shown. In definition E and F, class I and II sarcopenia are combined. Two subjects, one in whom sarcopenia was diagnosed according to F, G and E, and one in whom sarcopenia was diagnosed according to B and D are not shown in the figure.

studies suggest that high fat mass is an important and independent determinant of functional status in elderly, even after adjustment for the level of physical activity (40-43).

Next to a valid assessment of the amount of muscle mass, some variability emerges from the comparison to different reference populations and different cut-off points. Even with this variability, the degree of agreement between diagnostic criteria with the same formula but different cut-off points (definition A and B) was substantial. The prevalence of sarcopenia of zero percent using definition C can be explained by differences in reference populations. Furthermore, the prevalence of sarcopenia with definition A in this study cohort was much lower than reported in the same age categories by Baumgartner et al. (1998). In that study, using the same cut-off points in non-Hispanic whites, the prevalence of sarcopenia was found to be 13.5%-23.1% below 70 years, and 19.8%-33.3% between 70-74 years, in men and women respectively. Differences in reference groups may be caused by age, ethnicity, genetic background, and environmental factors such as the level of physical activity. Therefore, it is important to agree on reference populations that can be used in specific ethnic groups. Establishing reference databases generally requires a large sample size to achieve reliable results. Reference databases established to diagnose osteoporosis could function as a role model. Furthermore, it remains important to invest in longitudinal studies including the general population assessing the relation between muscle mass and functional outcomes to establish possible critical thresholds of muscle mass needed for muscle function.

Until now, attempts to approve on a consensus definition for sarcopenia failed. To the best of our knowledge, three international consortia have agreed on distinct definitions, which have not been generally accepted in the medical community. The first consensus definition was published by the Special Interest Groups (SIG) in 2009 (20). Here, the diagnosis sarcopenia is based on a combination of low muscle mass as defined by Janssen in 2002 (definition E)(16), together with low gait speed, which is walking speed below 0.8 m/s in the 4-m walking test, or another functional test (20). The second consensus definition was published by The European Working Group on Sarcopenia in Older People (EWGSOP) in 2010. The EWGSOP included a degree of severity of sarcopenia in the definition. 'Presarcopenia' was defined as low muscle mass, 'sarcopenia' as low muscle mass together with either low muscle strength or performance and 'severe sarcopenia' as a combination of all three. In addition, it was proposed that sarcopenia should be considered 'primary' when no other cause is evident but aging itself, and 'secondary' when one or more other causes are evident (19). This terminology is not acceptable in modern gerontology, as age in itself is no

longer considered a causal factor of disease (44). In the third consensus definition, Fielding et al. based the diagnosis of sarcopenia on low muscle mass as defined by Delmonico et al. (definition B)(25), together with low gait speed defined as less than 1 m/sec (45).

In our opinion, these consensus definitions are not clinically applicable. First of all, using the SIG definition none of the participants in the present study fulfilled the criteria for low muscle mass. Furthermore, gait speed is not a parameter of muscle function alone, but also dependent on other factors such as cognition, neural control, joint function, and cardiovascular fitness (46). The EWGSOP definition lists different ways to diagnose sarcopenia, without making a choice which measurement should be used. Consequently, the huge variability of prevalence of sarcopenia highlighted in the present study would therefore still be present. Defining sarcopenia based solely on the amount of muscle mass avoids all afore mentioned problems.

The strength of the present study is that the currently used diagnostic criteria of sarcopenia were applied to one study population. Previously, we have shown an excellent correlation between BIA and DXA measurements (24); therefore we were able to apply diagnostic criteria based on both DXA and BIA measurements. A possible limitation of this study is selection bias of the participants, since only the partners of the offspring of nonagenarian siblings are considered to be representatives of the general population. However, the offspring of long-lived families did not differ significantly from their partners in fat percentage, muscle mass, and handgrip strength (27). Therefore, this would not influence conclusions made in the present study. Moreover, participants were middle aged; the degree of agreement between the different diagnostic criteria for sarcopenia might be different in an oldest old population. Another limitation is that we had no functional outcome measures available for participants in this study. We were not able to apply diagnostic criteria for sarcopenia based on gait speed.

In conclusion, the prevalence of sarcopenia varies widely depending on the applied diagnostic criteria. A consensus definition is necessary in order to make studies comparable and for implementation in clinical care. We suggest defining sarcopenia as 'low muscle mass', to do justice to the multifunctionality of muscle tissue. 'Low muscle mass' can be diagnosed with DXA and BIA, while 'loss of muscle mass with aging' cannot be measured in an individual at one time point. Further research should focus on establishing an appropriate formula to correct the amount of muscle mass for factors such as height and fat mass, and take into account differences in ethnicity when subjects are compared to reference populations.

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Acknowledgements

Reference List

(1) Buford TW, Anton SD, Judge AR, Marzetti E, Wohlgemuth SE, Carter CS, et al. Models of accelerated sarcopenia: critical pieces for solving the puzzle of age-related muscle atrophy. Ageing Res Rev 2010 Oct;9(4):369-83.

(2) Marcell TJ. Sarcopenia: causes, consequences, and preventions. J Gerontol A Biol Sci Med Sci 2003 Oct;58(10):M911-M916.

(3) Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998 Apr 15;147(8):755-63.

(4) Rantanen T, Avlund K, Suominen H, Schroll M, Frandin K, Pertti E. Muscle strength as a predictor of onset of ADL dependence in people aged 75 years. Aging Clin Exp Res 2002 Jun;14(3 Suppl):10-5.

(5) Taekema DG, Gussekloo J, Maier AB, Westendorp RG, de Craen AJ. Handgrip strength as a predictor of functional, psychological and social health. A prospective population-based study among the oldest old. Age Ageing 2010 May;39(3):331-7.

(6) Alfaro-Acha A, Al SS, Raji MA, Kuo YF, Markides KS, Ottenbacher KJ. Handgrip strength and cognitive decline in older Mexican Americans. J Gerontol A Biol Sci Med Sci 2006 Aug;61(8):859-65.

(7) Burns JM, Johnson DK, Watts A, Swerdlow RH, Brooks WM. Reduced lean mass in early Alzheimer disease and its association with brain atrophy. Arch Neurol 2010 Apr;67(4):428-33.

(8) Taekema DG, Ling HY, Kurrle S, Cameron ID, Meskers CG, Blauw GJ, et al. Temporal relationship between handgrip strength and cognitive performance in oldest old people. Age Ageing 2012 Jul;41(4):506-12.

(9) Ling CH, Taekema D, de Craen AJ, Gussekloo J, Westendorp RG, Maier AB. Handgrip strength and mortality in the oldest old population: the Leiden 85-plus study. CMAJ 2010 Mar 23;182(5):429-35.

(10) Cooper R, Kuh D, Hardy R. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. BMJ 2010;341:c4467.

(11) Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage. Implications for drug therapy. Clin Pharmacokinet 1994 Apr;26(4):292-307.

(12) Nawaratne S, Brien JE, Seeman E, Fabiny R, Zalcberg J, Cosolo W, et al. Relationships among liver and kidney volumes, lean body mass and drug clearance. Br J Clin Pharmacol 1998 Nov;46(5):447-52.

(13) Kalyani RR, Metter EJ, Ramachandran R, Chia CW, Saudek CD, Ferrucci L.

4

Glucose and Insulin Measurements From the Oral Glucose Tolerance Test and Relationship to Muscle Mass. J Gerontol A Biol Sci Med Sci 2011 Feb 24.

(14) Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr 1997 May;127(5 Suppl):990S-1S.

(15) Janssen I, Baumgartner RN, Ross R, Rosenberg IH, Roubenoff R. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. Am J Epidemiol 2004 Feb 15;159(4):413-21.

(16) Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002 May;50(5):889-96.

(17) Newman AB, Kupelian V, Visser M, Simonsick E, Goodpaster B, Nevitt M, et al. Sarcopenia: alternative definitions and associations with lower extremity function. J Am Geriatr Soc 2003 Nov;51(11):1602-9.

(18) Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di IA, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol 2003 Nov;95(5):1851-60.

(19) Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010 Apr 13.

(20) Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 2010 Apr;29(2):154-9.

(21) Abellan van KG. Epidemiology and consequences of sarcopenia. J Nutr Health Aging 2009 Oct;13(8):708-12.

(22) Schoenmaker M, de Craen AJ, de Meijer PH, Beekman M, Blauw GJ, Slagboom PE, et al. Evidence of genetic enrichment for exceptional survival using a family approach: the Leiden Longevity Study. Eur J Hum Genet 2006 Jan;14(1):79-84.

(23) Westendorp RG, van Heemst D., Rozing MP, Frolich M, Mooijaart SP, Blauw GJ, et al. Nonagenarian siblings and their offspring display lower risk of mortality and morbidity than sporadic nonagenarians: The Leiden Longevity Study. J Am Geriatr Soc 2009 Sep;57(9):1634-7.

(24) Ling CH, de Craen AJ, Slagboom PE, Gunn DA, Stokkel MP, Westendorp RG, et al. Accuracy of direct segmental multi-frequency bioimpedance

analysis in the assessment of total body and segmental body composition in middle-aged adult population. Clin Nutr 2011 May 7.

(25) Delmonico MJ, Harris TB, Lee JS, Visser M, Nevitt M, Kritchevsky SB, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. J Am Geriatr Soc 2007 May;55(5):769-74.

(26) Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-Ray absorptiometry body composition reference values from NHANES. PLoS One 2009;4(9):e7038.

(27) Ling CH, de Craen AJ, Slagboom PE, Westendorp RG, Maier AB. Handgrip strength at midlife and familial longevity: the Leiden Longevity Study. Accepted in AGE 2011.

(28) Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg 2010 Aug;211(2):271-8.

(29) Corcoran MP, Lamon-Fava S, Fielding RA. Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. Am J Clin Nutr 2007 Mar;85(3):662-77.

(30) Shulman GI, Rothman DL, Jue T, Stein P, DeFronzo RA, Shulman RG. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy. N Engl J Med 1990 Jan 25;322(4):223-8.

(31) Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009 Apr 15;15(8):2920-6.

(32) Clark BC, Manini TM. Sarcopenia =/= dynapenia. J Gerontol A Biol Sci Med Sci 2008 Aug;63(8):829-34.

(33) Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci 2006 Oct;61(10):1059-64.

(34) Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med 1994 Jun 23;330(25):1769-75.

(35) Kemmler W, von SS, Engelke K, Haberle L, Mayhew JL, Kalender WA. Exercise, body composition, and functional ability: a randomized controlled trial. Am J Prev Med 2010 Mar;38(3):279-87.

4

(36) Orsatti FL, Nahas EA, Maesta N, Nahas-Neto J, Burini RC. Plasma hormones, muscle mass and strength in resistance-trained postmenopausal women. Maturitas 2008 Apr 20;59(4):394-404.

(37) Sillanpaa E, Laaksonen DE, Hakkinen A, Karavirta L, Jensen B, Kraemer WJ, et al. Body composition, fitness, and metabolic health during strength and endurance training and their combination in middle-aged and older women. Eur J Appl Physiol 2009 May;106(2):285-96.

(38) Beenakker KG, Ling CH, Meskers CG, de Craen AJ, Stijnen T, Westendorp RG, et al. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. Ageing Res Rev 2010 Oct;9(4):431-6.

(39) McNeil CJ, Doherty TJ, Stashuk DW, Rice CL. Motor unit number estimates in the tibialis anterior muscle of young, old, and very old men. Muscle Nerve 2005 Apr;31(4):461-7.

(40) Lebrun CE, van der Schouw YT, de Jong FH, Grobbee DE, Lamberts SW. Fat mass rather than muscle strength is the major determinant of physical function and disability in postmenopausal women younger than 75 years of age. Menopause 2006 May;13(3):474-81.

(41) Rolland Y, Lauwers-Cances V, Cristini C, Abellan van KG, Janssen I, Morley JE, et al. Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: the EPIDOS (EPIDemiologie de l'OSteoporose) Study. Am J Clin Nutr 2009 Jun;89(6):1895-900.

(42) Visser M, Langlois J, Guralnik JM, Cauley JA, Kronmal RA, Robbins J, et al. High body fatness, but not low fat-free mass, predicts disability in older men and women: the Cardiovascular Health Study. Am J Clin Nutr 1998 Sep;68(3):584-90.

(43) Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 2005 Mar;60(3):324-33.

(44) Holliday R. Ageing in the 21st century. Lancet 1999 Dec;354 Suppl:SIV4.

(45) Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 2011 May;12(4):249-56.

(46) Hajjar I, Quach L, Yang F, Chaves PH, Newman AB, Mukamal K, et al.

Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: the Cardiovascular Health Study. Circulation 2011 Mar 1;123(8):858-65.

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