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Research Article

Associations of Sarcopenia Definitions, and Their Components, With the Incidence of Recurrent Falling and Fractures: The Longitudinal Aging Study Amsterdam

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Abstract

Background: The aim was to investigate the associations of sarcopenia as defined by European Working Group on Sarcopenia in Older People (EWGSOP) and Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, and their underlying components, with the incidence of recurrent falling and fractures.

Methods: In 498 older men and women (mean age = 75.2 [*SD* = 6.4]) from the Longitudinal Aging Study Amsterdam (LASA), the sarcopenia components lean mass (DXA), handgrip strength (handheld dynamometer), and gait speed were measured. Data on falls (3-year follow-up) and fractures (10-year follow-up) were collected. Cox regression analyses were performed, adjusting for age, sex, and total body fat.

Results: Recurrent falling occurred in 130 persons and 60 persons experienced a fracture during follow-up. Participants who were identified as sarcopenic based on the FNIH definitions had a more than 2-fold increased risk to become a recurrent faller. There was no association between sarcopenia based on the EWGSOP definition and incidence of recurrent falling. When the sarcopenia components were examined individually, only a low grip strength was associated with incidence of recurrent falling, independent of a low lean mass or a slow gait speed. Sarcopenia according to both definitions was not associated with incident fractures, which may be caused by low statistical power.

Conclusion: Sarcopenia according to the FNIH definitions, but not according to the EWGSOP definition was associated with recurrent falling. When examining the individual components, only a low grip strength was independently associated with recurrent falling. No associations between sarcopenia with incidence of fractures were found.

Keywords: Muscle, Gait, Outcomes, Sarcopenia.

The concept of sarcopenia was originally defined as the age-related loss of muscle mass by Rosenberg (1). Although the concept is widely used in the scientific literature and has been introduced to clinical settings, no consensus on the clinical definition of sarcopenia has been established yet (2).

Several scientific groups developed operational definitions and diagnostic criteria to be used in both scientific research and clinical practice. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed consensus-based diagnostic

criteria for age-related sarcopenia using the presence of both low muscle mass with either low muscle strength or low gait speed (3). In 2014, new criteria for sarcopenia and cut-off scores for low muscle mass and low grip strength were developed within the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, based on empirical data from a large pooled dataset of older persons (4–6).

The prevalence of sarcopenia based on the EWGSOP and FNIH definitions was 5.3% and 0.5% in older men, and 13.3% and

1.8% in older women based on data from 10,063 older persons (7). These observed sarcopenia prevalence rates were very different, and the agreement between the two definitions was very low (7). Furthermore, several cut-off scores for low muscle mass (8–12) and muscle strength (13,14) have been used in the EWGSOP definition, which adds to the variation in published sarcopenia prevalence rates based on this definition (15).

To establish a useful definition of sarcopenia, it is important to identify which sarcopenia definitions, and which of their underlying components, are associated with important health outcomes. However, only few studies have examined the association between different definitions of sarcopenia and clinically relevant outcomes such as falls (16–18) and fractures (18–20). Therefore, the aim of this study is to investigate: (a) the associations between sarcopenia as defined by EWGSOP and FNIH definitions and the incidence of recurrent falling and fractures, and (b) the association between the underlying components of these sarcopenia definitions (low lean mass, low muscle strength, and slow gait speed) and the incidence of recurrent falling and fractures.

Methods

Study Sample

Data for this study were collected in the context of the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study on predictors and consequences of changes in autonomy and well-being in the aging population in The Netherlands (21,22). The sampling and data collection procedures have been described in detail elsewhere (23). In brief, a sample of older men and women (aged 55–85 years), stratified by age and sex, was drawn from the population registries of 11 municipalities in three areas of The Netherlands. In total, 3,107 subjects were enrolled in the baseline examination (1992/1993). Follow-up measurements were done every 3 years, consisting of a face-to-face main interview, which was carried out at the participant's home by specially trained interviewers. Two to six weeks later, the main interview was followed by a medical interview and a separate visit to the hospital or health care center. During this visit lean mass was assessed with dual-X ray absorptiometry (DXA) (only respondents from Amsterdam and surrounding communities).

For the present study, the baseline study sample included participants aged 65 years and older as of January 1, 1996, who participated in the main interview and the medical interview of the second follow-up of LASA (1995/1996) and who had complete data on sarcopenia parameters (lean mass, grip strength, and gait speed, $n = 498$). Of these included respondents, 9 participants had missing data on the falls follow-up, resulting in 489 participants included in the analyses with incident falling. Fracture follow-up was complete for all 498 included respondents.

Muscle Mass

Muscle mass (kilograms) was assessed using DXA (Hologic QDR 2000 scanner, Hologic, Inc., Waltham, MA) in the enhanced array mode and software version V5.70A. We used the sum of fat-free, bone-free mass of the arms and legs as lean mass. Low lean mass (kg) was determined using sex-specific cut-off scores of <19.75 kg for men and <15.02 kg for women, based on the FNIH approach (6). Muscle mass index (kg/m^2) was calculated by lean mass divided by body height squared. Low muscle mass index was determined using sex-specific cut-off scores of <7.26 kg/m^2 for men and <5.45 kg/m^2 for

women, which represents 2 *SD* below the mean observed in young adults (8). These cut-off scores were used in the EWGSOP definition.

Grip Strength

Handgrip strength (kilograms) was measured using a strain-gauged dynamometer (Takei TKK 5001, Takei Scientific Instruments Co. Ltd., Tokyo, Japan) at the participants' homes. Participants were asked to perform two maximum force trials with each hand. For the final scores, the maximum values of the right and the left hand were summed. We used sex-specific cut-off scores of <30 kg for men and <20 kg for women to define low handgrip strength according to the EWGSOP definition (13). We used cut-off scores of <26 kg for men and <16 kg for women to define low handgrip strength according to the FNIH definition (5).

Gait Speed

Gait speed was assessed by recording the total time it took to walk 3 m, make a turn of 180 degrees and walk the 3 m back as quickly as possible. We used a cut-off score of ≤ 0.8 m/s for slow gait speed according to the definitions of EWGSOP and FNIH (13).

Sarcopenia Definitions

According to the algorithm developed by the EWGSOP, sarcopenia is defined as having both low lean mass and either low muscle strength or low gait speed (3). Several definitions were developed by the FNIH, including combinations of a low lean mass (absolute or divided by body mass index [BMI]), a low grip strength and a slow gait speed (4). In the current study, two sarcopenia definitions according FNIH will be used. Definition 1: having a low lean mass and a low grip strength. Definition 2: having a low lean mass, low muscle strength and a slow gait speed.

Recurrent Falling

For a period of 3 years, participants were asked to report their falls on a fall calendar every week and to mail the calendar to the research center every 3 months. A fall was defined as "an unintentional change in position resulting in coming to rest at a lower level or on the ground." A "recurrent faller" was defined as a subject who fell at least two times in 6 months during the 3-year fall follow-up.

Fractures

Fractures were assessed using two different methods. In the first 3-year period (1995/1996–1998/1999), a fracture calendar was used. Participants were instructed to complete a set of questions regarding fractures every 3 months, and to send them to our institute. In the second 7-year period (1998/1999–2005/2006), fractures were assessed during the regular LASA medical interviews. The exact date of the fracture was verified with the general practitioner or hospital. Eighty-three percent of the fractures included in the analyses could be verified.

Confounders

Age and sex were considered confounders in the association between sarcopenia parameters and falling and fractures. Furthermore, analyses were adjusted for total body fat mass measured by DXA (Hologic QDR 2000 scanner, Hologic Inc.), to take the influence of body fat into account.

Statistical Analysis

Data were analyzed with SPSS 23.0 (IBM SPSS Statistics). Descriptive statistics (mean \pm *SD*, proportions) were calculated for all variables

of interest. Cox Proportional-Hazards regression analyses were used to assess the time to a second fall of a pair of falls that occurred less than 6 months apart, during 3 years of follow-up. These analyses were also conducted to assess the time to a fracture during 10 years of follow-up. Follow-up time was calculated as the number of days from the baseline interview until date of death or the last date of contact with the participant until 3 or 10 years of follow-up, respectively. Analyses were done according to the two sarcopenia definitions under study. First, the associations of each sarcopenia definition with incidence of recurrent falling and fractures were examined. For all models, the event rate (proportion of participants who became a recurrent faller or experienced a fracture according to sarcopenia status) was calculated. Next, the associations of individual sarcopenia components (low lean mass, low grip strength, and slow gait speed) with recurrent falling and fractures were examined using separate models for each parameter. Cut-off scores of the muscle parameters differed, depending on the definition used. Third, to show the associations of individual sarcopenia components with incidence of recurrent falling and fractures, independent of other sarcopenia parameters, a single model was created that included all parameters of interest simultaneously. All regression analyses were adjusted for age, sex, and total body fat mass.

Results

Table 1 shows the characteristics of the 496 respondents included in the statistical analyses. Of the sample, 50.4% was female, and the mean age was 75.2 (SD = 6.4) years. Mean lean mass was 18.0 (SD = 4.2) kg, mean muscle mass index was 6.3 (SD = 1.0) kg/m², mean grip strength was 28.0 (SD = 9.2) kg and mean gait speed was 0.79 (SD = 0.25) m/s.

The cut-off scores of low lean mass, low muscle strength and slow gait speed according to the EWGSOP and FNIH definitions are shown in Table 2.

Table 1. Characteristics of the Longitudinal Aging Study Amsterdam Sample (N = 496)

Age, years	75.2 (6.4)
Sex, % women	50.4
Total body fat, kg	26.8 (9.9)
Muscle mass, kg	18.0 (4.2)
Muscle mass index, kg/m ²	6.3 (1.0)
Grip strength, kg	28.0 (9.2)
Gait speed, m/s	0.79 (0.25)
Incidence of recurrent falls, N (%)	130 (26.6)
Incidence of fractures, N (%)	60 (12.1)

Note: Results in mean (SD) unless stated otherwise.

Table 2. Cut-Off Scores of Low Muscle Mass, Low Muscle Strength, and Slow Gait Speed According to the EWGSOP and FNIH Definitions

Muscle Parameter	EWGSOP Definition		FNIH Definitions	
	Men	Women	Men	Women
Low muscle mass	ALM/height ² ≤ 7.26 kg/m ²	ALM/height ² ≤ 5.45 kg/m ²	ALM < 19.75 kg	ALM < 15.09 kg
Low grip strength	<30 kg	<20 kg	<26 kg	<16 kg
Slow gait speed	≤0.8 m/s	≤0.8 m/s	≤0.8 m/s	≤0.8 m/s

Note: EWGSOP = European Working Group on Sarcopenia in Older People; FNIH = Foundation of the National Institutes of Health sarcopenia project; ALM = appendicular lean mass.

Table 3 shows the prevalence rates of low lean mass (or low muscle mass index, in case of the EWGSOP definition), low grip strength, and slow gait speed, according to the sarcopenia definitions of the EWGSOP and FNIH. Low muscle mass index was present in 52.4% of the study sample, according to the cut-off scores of EWGSOP. According to the FNIH definition, low lean mass was present in 45.6% of the study sample. A low grip strength was present in 28.0% of the study sample according to the EWGSOP and in 10.7% according to the FNIH definition. A slow gait speed was present in 54.2% of the study sample according to both definitions. When we used the complete sarcopenia definitions and algorithms, prevalence rates of sarcopenia were 31.9% for the EWGSOP definition and 7.9% and 6.3% for FNIH definitions 1 and 2.

Table 4 shows the associations between the sarcopenia definitions and incident recurrent falling and fractures. Sarcopenia according to the EWGSOP definition was not associated with incidence of recurrent falls or with fractures. Both FNIH sarcopenia definitions were associated with an increased risk of becoming a recurrent faller (definition 1: hazard ratio (HR) = 2.04 [1.22–3.41]; definition 2: HR = 2.38 [1.37–4.14]). Event rates were 48.7% vs 24.7% and 54.8% vs 24.7%, respectively. Both FNIH sarcopenia definitions were not associated with incidence of fractures.

Figure 1 shows the HRs of the individual sarcopenia components with incidence of recurrent falling according to the cut-off scores used for the EWGSOP and FNIH definitions, adjusted for age, sex, and total body fat. Low grip strength showed the strongest association with incidence of recurrent falling (HR = 1.60 [1.09–2.37] based on the EWGSOP cut-off score and HR 2.05 [1.28–3.28]) based on the FNIH cut-off score). Slow gait speed was borderline significantly associated with incidence of recurrent falling (HR of 1.47 [1.00–2.17]). Figure 2 shows the associations between individual sarcopenia parameters with incidence of fractures. None of the parameters was significantly associated with incidence of fractures.

Table 5 shows the associations between individual sarcopenia components combined in one model with incidence of recurrent falling and fractures, respectively. Low grip strength according to the EWGSOP suggested cut-off score was significantly associated with incidence of recurrent falling (HR 1.51 [1.01–2.25]), independent of low muscle mass index and slow gait speed. Similar associations were observed for low muscle strength based on the FNIH definition (HR 2.05 [1.26–3.33]). Low lean mass, muscle mass index and slow gait speed were not independently associated with incidence of recurrent falling. No independent associations between any sarcopenia component and incidence of fractures were observed.

Discussion

We examined the associations of two frequently used sarcopenia definitions and their individual components with incidence of recurrent

Table 3. Prevalence Rates (*N* (%)) of Low Muscle Mass, Low Muscle Strength, and Slow Gait Speed According to the EWGSOP and FNIH Definitions

	EWGSOP Definition	FNIH Definitions
Low muscle mass/ muscle mass index	260 (52.4)	226 (45.6)
Low muscle strength	139 (28.0)	53 (10.7)
Slow gait speed	269 (54.2)	269 (54.2)

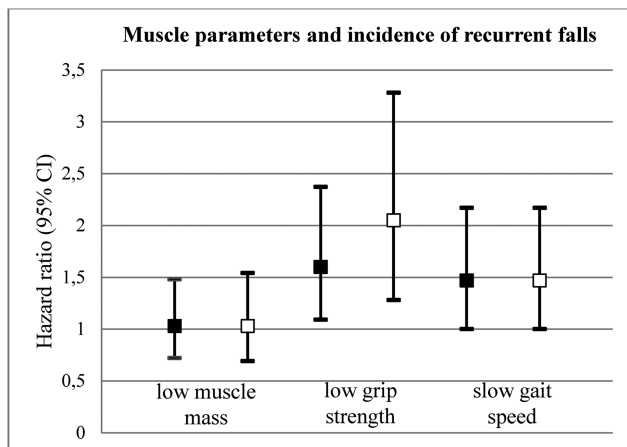


Figure 1. Adjusted hazard ratios for the association between single sarcopenia components and 3-year incidence of recurrent falls among 489 older adults. *Note:* Black squares: hazard ratios of sarcopenia components based on cut-off scores of the European Working Group on Sarcopenia in Older People; white squares: hazard ratios of sarcopenia components based on cut-off scores of the Foundation of the National Institutes of Health sarcopenia project.

falling and fractures. Participants who were identified as sarcopenic based on the FNIH definitions had a more than 2-fold increased risk to become a recurrent faller. When the sarcopenia components were examined individually, only a low grip strength was associated with incidence of recurrent falling, independent of a low muscle mass or a slow gait speed. Sarcopenia according to both definitions was not associated with incident fractures. However, it is important to keep in mind that only 60 persons experienced a fracture during follow-up, resulting in a low statistical power to detect an association. Indeed, post hoc power analyses revealed that a HR of at least 3.8 (with a power of 0.80 and alpha of 5%) might have given significant results for the FNIH definitions in association with fracture incidence, assuming that an association actually exists.

Previous studies have examined the association between sarcopenia and falls. In 2014, a study among older men and women in Tasmania (17) revealed that persons in the lowest quintile of grip strength had an increased 5-year fall risk, while a low muscle mass was associated with fall risk in men only. Our study confirms the strongest impact of grip strength on fall risk compared to the other sarcopenia components. In a recent study (16) of Bischoff-Ferrari et al., several sarcopenia definitions were compared regarding the extent to which they related to 3-year fall rate. The sarcopenia definition according to the definition of the EWGSOP and low muscle mass index as defined by Baumgartner et al. (8) predicted rate of falls best. In contrast, in our study sarcopenia according to the EWGSOP definition was not associated with 3-year fall risk. Findings from the Observational Osteoporotic Fractures in Men Cohort Study (MrOS) showed that the association between sarcopenia according to both

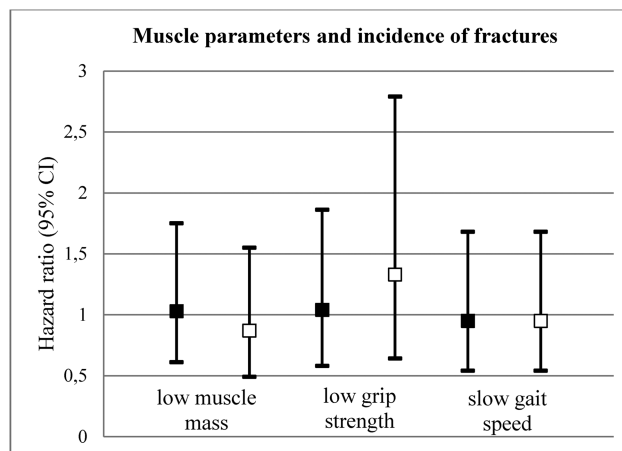


Figure 2. Adjusted hazard ratios for the association between single sarcopenia components and 10-year incidence of fractures in 496 older adults. *Note:* Black squares: hazard ratios of sarcopenia components based on cut-off scores of the European Working Group on Sarcopenia in Older People; white squares: hazard ratios of sarcopenia components based on cut-off scores of the Foundation of the National Institutes of Health sarcopenia project.

the FNIH and EWGSOP definitions and risk of recurrent falling was significant. However, further in-depth analyses examining change in area under the curve (AUC) for the definitions compared to a reference model with age alone showed that the discriminative abilities of the sarcopenia definitions were poor. Also no improvement in overall reclassification was seen when compared to the reference model. It is difficult to compare the above mentioned studies with our findings due to differences in study sample and differences in the measurement of sarcopenia components, for example, differences in DXA machines and differences in grip strength and gait speed assessment.

Recently, in a cohort of 913 older persons aged 63–67 years, it was shown that a low muscle mass index was associated with a twofold higher 3-year fracture risk, while no significant associations were found for other definitions including those from the EWGSOP and FNIH (19). In our study, low lean mass according to the FNIH cut-off score showed a HR of 1.67 in the association with incidence of fractures, but this was not statistically significant. However, the models with incident fractures as the outcome might have been underpowered to detect a significant association.

Sarcopenia definitions have also been investigated regarding their ability to predict other negative health outcomes. The FNIH definitions predicted 15-year all-cause mortality in a community-based sample of 191 older men in Belgium (24). In that study, the EWGSOP sarcopenia definition was not examined. Recently, a study among older women from the Study of Osteoporotic Fractures (SOF) (25) showed that current definitions, including the definitions of EWGSOP and FNIH are unable to identify older women with an increased risk of greater health care utilization, such as hospitalization and short-term stay in a nursing home. Only a slow gait speed was associated with a twofold increased risk of greater health care utilization. To conclude from previous studies and our current study, a sarcopenia definition might be useful to predict one adverse health outcome, but not another. Moreover, a sarcopenia definition might be useful to predict a certain outcome in one study sample, but not in the other.

Although there is general agreement that a sarcopenia definition should include a measure of muscle mass as well as measures of muscle function, a uniform operational definition is currently not

Table 4. Adjusted HRs of the Associations Between Sarcopenia Definitions and Incidence of Recurrent Falls and Fractures

	Recurrent Falls		Fractures	
	HR (95% CI)	ER (%)	HR (95% CI)	ER (%)
Sarcopenia EWGSOP definition	1.29 (0.89–1.87)	32.7	0.94 (0.54–1.64)	12.0
No sarcopenia	1.0	23.7	1.0	12.1
Sarcopenia FNIH definition 1	2.04 (1.22–3.41)	48.7	1.53 (0.70–3.31)	20.5
No sarcopenia	1.0	24.7	1.0	11.4
Sarcopenia FNIH definition 2	2.38 (1.37–4.14)	54.8	1.41 (0.58–3.43)	19.4
No sarcopenia	1.0	24.7	1.0	11.6

Note: Models adjusted for age, sex, and total body fat. See Table 2 for cut-off scores used in the sarcopenia definitions. EWGSOP = European Working Group on Sarcopenia in Older People; FNIH = Foundation of the National Institutes of Health sarcopenia project; HR = hazard ratio; CI = confidence interval; ER = event rate.

Table 5. HRs for the Associations Between Individual Sarcopenia Components Combined in One Model With Incidence of Recurrent Falls and Fractures

	EWGSOP Definition		FNIH Definition 1		FNIH Definition 2	
	Recurrent Falls	Fractures	Recurrent Falls	Fractures	Recurrent Falls	Fractures
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Low muscle mass	0.98 (0.68–1.42)	1.02 (0.60–1.75)	0.97 (0.65–1.43)	1.66 (0.93–2.97)	0.94 (0.63–1.39)	1.67 (0.94–2.99)
Low muscle strength	1.51 (1.01–2.25)	1.05 (0.57–1.93)	2.06 (1.27–3.35)	1.17 (0.55–2.48)	2.05 (1.26–3.33)	1.18 (0.55–2.50)
Slow gait speed	1.36 (0.91–2.04)	0.94 (0.53–1.69)	—	—	1.46 (0.99–2.16)	0.90 (0.51–1.60)

Note: Models adjusted for age, sex, total body fat, and the other sarcopenia components; see Table 2 for cut-off scores used in the sarcopenia definitions. EWGSOP = European Working Group on Sarcopenia in Older People; FNIH = Foundation of the National Institutes of Health sarcopenia project; HR = hazard ratio; CI = confidence interval.

available. Based on the results of the current study, risk assessment of future falls may be conducted by measurement of muscle strength only, as this measurement was associated with a twofold increased risk of falls, independent of muscle mass and gait speed. However, low muscle mass or slow gait speed might be more important risk factors for other important clinical health outcomes in older persons. As sarcopenia has received an ICD-10 code recently, which is an important step toward better awareness among clinicians, it is now warranted to provide clinicians with a useful and feasible operational definition of sarcopenia to identify older adults with an increased risk of adverse clinical health outcomes. Unfortunately, the evidence thus far does not allow a clear advice. Currently, a large follow-up study is being conducted by the FNIH Sarcopenia Working Group including more (diverse) cohorts to validate and refine current FNIH definitions. This will be another important step toward an evidence-based, generally accepted definition of sarcopenia.

Strengths of this study include the use of data of a well-characterized cohort of older men and women and the long follow-up time regarding two hard clinical endpoints: incidence of recurrent falling and fractures. Several limitations need to be discussed. In the current study, we decided to strictly focus on muscle components and therefore excluded FNIH definitions that incorporate BMI. Body fat mass was however taken into account in the statistical models to expose the independent role of muscle components on the risk of recurrent falls and fractures. This approach is preferred above using ratios of muscle mass divided by BMI as a sarcopenia indicator, as the denominator of this ratio may drive the association between the ratio and the outcome. Second, we only included two sarcopenia definitions in this study, while more exist (8,9,26–28). We think this selection

is justified as these two sarcopenia definitions were most recently constructed and are most often being used in research and clinical practice. Third, the LASA study uses a slightly different gait speed measure compared to others; participants are asked to walk 3 m, make a turn and walk back 3 m. Therefore, the cut-off score of 0.8 m/s might be too strict. Indeed, more than 50% of the study sample had a slow gait speed according to this cut-off score. Recently, additional data has been collected within the LASA study, including a 3 m as well as the usual 6 m walk test. Based on these data we were able to develop a formula which can be used to recode the time to walk 6 m into an estimated time to walk 3 m. When performing sensitivity analyses using this newly created variable, the prevalence rate of slow gait speed (≤ 0.8 m/s) was reduced from 54.2% to 26.5%. Similar findings were observed when we included the new variable in the models. We observed a HR of 1.31 (0.87–1.98) compared to a HR of 1.36 (0.91–2.04) in the association between slow gait speed and recurrent falls, independent of low lean mass and low muscle strength, based on the EWGSOP definition, and a HR of 1.37 (0.91–2.05) compared to 1.46 (0.99–2.16) in the association between slow gait speed and recurrent falls, independent of low lean mass and low muscle strength, based on the FNIH 2 definition.

In conclusion, this study showed an association between the FNIH sarcopenia definitions, but not the EWGSOP definition, and the risk to become a recurrent faller in older men and women during a 3-year follow-up. When examining the individual sarcopenia components, a low grip strength was associated with incidence of falling, independent of a low lean mass and a slow gait speed. No associations between the two sarcopenia definitions, or the individual sarcopenia components, were observed with incident fractures.

Other studies are needed to confirm these findings. Furthermore, large studies with a long fracture follow-up are needed to establish a possible association between sarcopenia definitions and risk of fractures.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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