SARCOPENIA - AGREEMENT AND ASSOCIATION WITH FALLS

SARCOPENIA IN THE CANADIAN LONGITUDINAL STUDY ON AGING: THE IMPACT OF DIAGNOSTIC CRITERIA ON THE AGREEMENT BETWEEN DEFINITIONS AND THE ASSOCIATION OF SARCOPENIA WITH FALLS

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Lay Abstract

Definitions for sarcopenia differ in terms of which muscle variables are included, how muscle mass is adjusted, and which cut offs to use for each variables. This thesis assessed the impact of different methods of operationalizing sarcopenia on the proportion of sarcopenic participants, agreement between definitions, and the strength of the association between sarcopenia and falls. The variables used to operationalize sarcopenia as well as different techniques for adjusting muscle mass resulted in poor agreement between definitions. In males, these factors impacted which definitions were significantly associated with falls, and in females, sarcopenia was not associated with falls for any definition. For all definitions, sarcopenia status poorly discriminated between those that would or would not fall. Together, these results show that different sarcopenia definitions are not equivalent and that a standard definition is required. However, this thesis also shows that more work is required to determine the clinical utility of sarcopenia.

Abstract

Objectives: Sarcopenia is defined using a variety of different muscle variables, muscle mass adjustment techniques and cut offs for each variable. The objectives of this thesis were to assess how operational differences in sarcopenia definitions impact the agreement between definitions and the association between sarcopenia and health outcomes such as falls.

Methods: A list of sarcopenia definitions was developed which captured the combinations of muscle variables, muscle mass adjustment techniques, and cut offs used in the literature based on a systematic review conducted for this thesis. These definitions were applied to participants taking part in the Canadian Longitudinal Study on Aging, a national study of participants aged 45 to 85 years at baseline. The agreement between the definitions and the association of each definition with falls was assessed.

Findings: Both the combination of muscle variables as well as the different muscle mass adjustment techniques generally had limited agreement. Sarcopenia definitions including muscle mass and muscle strength were associated with falls in males, but none of the sarcopenia definitions were associated with falls in females. Area under the curve analyses revealed that even sarcopenia definitions associated with more than two times the odds of falling in males, had a small impact on identifying fallers with values ≤ 0.56.

Conclusions: The results of this thesis show that the existing range of definitions used to define sarcopenia are not equivalent based on the limited agreement and inconsistent association of sarcopenia with falls. The results also show that sarcopenia may have limitations as clinically useful diagnosis for identifying fallers with area under the curve values for all definitions showing that the identification of fallers based on sarcopenic status was at best, modestly better than chance alone.

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List of Abbreviations

Abbreviation	Definition
ALM	Appendicular lean mass
AWGS	Asian Working Group on Sarcopenia
AUC	Area under the curve
BIA	Bioelectric impedance analysis
BMI	Body mass index
CI	Confidence interval
CLSA	Canadian Longitudinal Study on Aging
CT	Computed tomography
DXA	Dual x-ray absorptiometry
EWGSOP	European Working Group on Sarcopenia
FNIH	Foundation for the National Institutes of Health
IL6	Interleukin 6
IGF1	Insulin-like growth factor 1
IWGS	International Working Group on Sarcopenia
kg	Kilogram
m	Meter
m/s	Meters per second
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MRI	Magnetic resonance imaging
SPPB	Short Physical Performance Battery
ROB	Risk of bias

Declaration of Academic Achievement

This thesis has been conducted as a *sandwich thesis* and consists of four individual manuscripts. At the time of writing (October 2019), one of the four individual manuscripts (**Chapter 2**) has been accepted for publication and the remaining three individual manuscripts (**Chapters 3 through 5**) have been submitted for publication in peer-reviewed journals. The journal to which each paper has been submitted has been specified in the beginning of each chapter. The studies reported in these manuscripts were performed during the author's PhD program.

Alexandra Mayhew was the principal contributor to the conception of the research question and the design of the studies included in this thesis. The first manuscript included in this thesis (**Chapter 2**), a systematic review and meta-analyses of sarcopenia definition involved the following work: developing the research question, writing of the systematic review protocol, designing the systematic review search strategy, study eligibility criteria and data extraction forms, reviewing the studies for inclusion in the systematic review, data extraction, risk of bias assessment, qualitative and quantitative pooling of individual study data, and preparation and revisions of the manuscript. The work is primarily the undertaking of Alexandra Mayhew with guidance from Dr. Parminder Raina throughout the project. Donna Fitzpatrick Lewis provided support for the design of the systematic review search strategy, study eligibility criteria and data extraction forms. Krystal Amog completed study screening, data extraction, and risk of bias assessment in duplicate with

Alexandra Mayhew. Thesis committee members, Drs. Russell de Souza, Paul McNicholas, Gianni Parise, and Lehana Thabane, as well as Dr. Stuart Phillips provided feedback throughout the project.

For the remainder of the manuscripts included in this thesis (**Chapters 3 through 5**), the following work was involved: Developing the research question and study protocols, applying for data, analyzing data, writing and revising the drafts of the manuscripts. The work is primarily the undertaking of Alexandra Mayhew with guidance from Drs. Parminder Raina and Stuart Phillips throughout the project. Dr. Nazmul Sohel assisted with coding for the data analyses. Thesis committee members, Drs. Russell de Souza, Paul McNicholas, Gianni Parise, and Lehana Thabane provided feedback throughout the project. **Chapters 1 and 6** are unpublished works for which Alexandra Mayhew is the sole author.

Given the common focus on sarcopenia definitions throughout this thesis, the reader will encounter some overlap between chapters. Specifically, the rationale for conducting each study was similar as all chapters seek to explore the similarities and differences in sarcopenia definitions. The methods regarding the development of the sarcopenia definitions overlap, as the technique for operationalizing sarcopenia was specifically developed for this thesis and was applied in **Chapters 3 through 5**. Data from the Canadian Longitudinal Study on Aging was used for analyses in **Chapters 3 through 5**, therefore there is overlap in the description of the study sample.

Following the introduction, each paper is included in a separate chapter focusing on a specific study. A concluding chapter summarizes the key findings of the study, the overall

implications for sarcopenia research, strengths and limitations of the work included in this thesis, and suggestions for directions for future research.

Chapter 1 - Introduction

Sarcopenia is the progressive decline in muscle mass, muscle strength, and muscle function that occurs with age. [1] Beginning in approximately the fifth decade of life, muscle mass declines 0.8% annually and strength between 1% and 3% annually. [2–4] The decrease in muscle mass, strength, and function characterized by sarcopenia is associated with significantly greater risk for poor health outcomes such as disability and functional impairments [5], falls [6–8], longer hospital stays [9], and mortality. [10, 11]

Since the term "sarcopenia" was first used in 1989, sarcopenia has transformed from an almost unheard of condition to being considered a significant health concern in older adults. [1, 12] Over the past three decades, one of the goals of sarcopenia researchers has been to have the condition recognized as a diagnosis distinct from other age related diseases. [13] In 2016, sarcopenia was introduced into the International Statistical Classification of Diseases and Related Health Problems, a critical step towards the ultimate goal of having physicians routinely diagnose and treat sarcopenia. [13, 14] Although sarcopenia is now recognized as a unique disease, there is a lack of consensus on how it should be defined, which impedes consistent clinical assessment, and complicates cross-study comparisons of published studies of incidence and prevalence.

Sarcopenia was originally defined as muscle mass only. [5, 15] Dual energy x-ray absorptiometry (DXA) is considered by many to be the reference standard for muscle mass measurement in sarcopenia studies. [16] Though the measures from DXA are referred to as muscle mass by the majority of the sarcopenia literature, DXA does not actually estimate

muscle mass. Instead DXA measures lean mass which includes not only muscle mass, but also water, organs, and all other non-bone and non-fat soft tissues and therefore is only a surrogate of muscle mass. [17] Using DXA, or alternatively bioelectrical impedance analysis (BIA), the value of interest is appendicular lean mass (ALM) which refers to the lean mass present in the arms and legs. [5, 15] Based on evidence that muscle strength and physical function are more strongly associated with disability and mortality than muscle mass measured using ALM [5, 15], more recent expert group consensus definitions of sarcopenia have included measures of strength and/or function. [18–22] In addition to recommending the inclusion of different variables, the definitions also recommend different methods of adjusting muscle mass including dividing ALM by height, weight, and body mass index (BMI), as well as using the residual values after regressing ALM on height and fat mass. The cut offs recommended for identifying people with low muscle mass, strength, and physical function also differ by definition. [18–22] The sarcopenia definitions can therefore be categorized based on three components 1) which muscle variables are included; 2) the technique used to adjust muscle mass; and 3) the cut offs used for muscle mass.

Several studies have found that the prevalence of sarcopenia within the same sample differs based on which sarcopenia definition is used and that there tends to be low to modest agreement between definitions. [23–30] It also appears that the strength of the association between sarcopenia and health outcomes such as falls, is dependent on which definition of sarcopenia is used. [31–35] The majority of the sarcopenia definitions differ by more than one of the three components which makes it impossible for these studies to determine to

what extent each component of the definitions are influencing prevalence, agreement, and the strength of the association between sarcopenia and health. An additional challenge of comparing sarcopenia definitions is that not all methods of operationalizing sarcopenia are commonly used. Specifically, few studies have adjusted muscle mass for fat mass and height using regression, likely because interpreting the residuals is not as intuitive as the other muscle mass adjustment techniques. It is therefore not well understood how the regression adjustment technique compares to the other methods. [36] Furthermore, there is a paucity of guidance on how to use the regression technique when there are planned subgroup analyses. Greater understanding of this technique and how to apply it is necessary.

The lack of agreement between sarcopenia definitions is problematic from a research perspective because it is unclear how to interpret and synthesize results from studies using different definitions. It also makes translating research to clinical care difficult as it is unknown if a treatment shown to be effective based on one sarcopenia definition will have the same beneficial effect if a patient is diagnosed using a different definition. Working towards a unified definition for sarcopenia is a top priority in the sarcopenia research community. [22] To better understand how to interpret and synthesize results from studies using different definitions and work towards a unified definition of sarcopenia, it is necessary to understand the biological meaning of the individual components making up sarcopenia definitions.

The overall objectives of this thesis are to provide a greater understanding of how the operationalization of sarcopenia, specifically muscle measures and methods of adjusting

muscle mass, impact prevalence, agreement between definitions, and the strength of the association of sarcopenia with relevant health outcomes. **Figure 1** provides an overview of how each chapter of this thesis addresses the research objectives. The information in this thesis will provide a framework for the sarcopenia community as we move towards a unified definition of sarcopenia.

To accomplish these objective, a systematic review and meta-analyses was conducted to identify sarcopenia definitions currently used to characterise sarcopenia in community-dwelling older adults and to document the similarities and differences between prevalence estimates derived using different definitions. Using the combinations of muscle variables and methods of adjusting muscle mass captured by the systematic review, we developed a list of sarcopenia definitions that captured the range of ways sarcopenia has been operationalized in the literature. Sarcopenia was operationalized as low muscle mass alone, low muscle mass and low grip strength, and low muscle mass and low gait speed. For each combination, muscle mass was adjusted for height squared, weight, body mass index, and regressed on height and fat mass. Sex-specific cut offs corresponding to the 10^{th}, 20^{th}, and 40^{th} percentiles of muscle mass in adults identifying as European and aged 65 years and older were included to capture the range of cut offs commonly used in the literature. Grip strength cut offs of <30kg, <27kg, and <26kg for males and <20kg and <16kg for females, and gait speed cut offs of <0.8 meters per second and <1.0 meters per second were selected based on the expert group consensus definition recommendations.

Data from the Canadian Longitudinal Study on Aging (CLSA) were used to assess the impact of different methods of operationalizing sarcopenia on the prevalence of sarcopenia,

the agreement between sarcopenia definitions, and the association of sarcopenia with falls. CLSA data were also used to explore different techniques of age stratification when using regression analyses to adjust muscle mass by height and weight. The CLSA is a national, longitudinal research platform that includes 51,338 participants aged 45 to 85 years at baseline from the ten Canadian provinces. Details on the study design have been described elsewhere. [37] Participants had to be physically and cognitively able to participate on their own and not living in institutions such as long term care. Of these participants, there are 21,241 participants in the Tracking cohort who were randomly selected from all ten provinces and were interviewed by phone. The remaining 30,097 participants are a part of the Comprehensive cohort and were randomly selected from participants living within 25 to 50 km of one of 11 Data Collection Sites located in seven provinces. The Comprehensive cohort participants are interviewed in-person and complete in-depth physical assessments at the Data Collection Sites as well as provide blood and urine samples. Data from the 30,907 participants in the Comprehensive cohort at baseline who provided physical assessment data were included in the analyses. The specific objectives of this thesis are:

1. To assess the impact of different combinations of muscle mass, muscle strength, and muscle function, as well as different muscle mass adjustment techniques on the prevalence of sarcopenia
2. To determine the agreement between sarcopenia definitions operationalized using different combinations of muscle mass, muscle strength, and muscle function as well as the agreement using different muscle mass adjustment techniques

3. To assess the impact of different methods of operationalizing sarcopenia on the strength of the association between sarcopenia and falls
4. To provide guidance about how to stratify a sample by age when using the regression technique to adjust muscle mass for height and weight

Literature Review

Sarcopenia definitions

Muscle mass only definitions - Sarcopenia was first defined by Baumgartner in 1998 using appendicular lean mass (ALM) (kg/m^2). ALM values of less than two standard deviations below a young, healthy population of approximately 30 years of age was considered sarcopenic. [15] In 2002, Janssen proposed that individuals be considered sarcopenic if ALM divided by weight (kg) values were one standard deviation below the sex-specific mean for young adults. [5] Based on the evolving evidence that muscle strength and function are more strongly associated with health outcomes [38], subsequent definitions of sarcopenia have included measures of strength and function.

Expert group consensus definitions

A summary of the measures recommended by each of the expert groups, the European Working Group on Sarcopenia (EWGSOP), the International Working Group on Sarcopenia (IWGS), the Foundation for the National Institutes of Health (FNIH), and the Asian Working Group on Sarcopenia (AWGS) consensus definitions are available in **Table 1**.

European Working Group on Sarcopenia - In 2010, the first of four sarcopenia consensus definitions was released by the EWGSOP. The EWGSOP definition recommends that low muscle mass as well as either low muscle strength or low physical performance be used to identify sarcopenia. The definition includes multiple different methods for measuring each muscle component. In research settings, the EWGSOP criteria recommend that **muscle mass** be measured using computed tomography (CT), magnetic resonance imaging (MRI), DXA, BIA, or total or partial body potassium per fat-free soft tissue**.** It is recommended that muscle mass be adjusted by dividing by height^2 or regressing on fat mass and height. **Muscle strength** can be measured using one of three options; hand grip strength, knee flexion/extension or peak expiratory flow, and **physical performance** can be measured using the Short Physical Performance Battery (SPPB), usual gait speed, the timed get-up-and-go test or the stair climb power test. However, in practice, the majority of studies applying the EWGSOP definition only include muscle mass measured using BIA or DXA, grip strength, and gait speed. [36] The EWGSOP definition includes references to commonly used cut offs in the literature, but also acknowledges that it may be more appropriate for studies to determine their own cut offs and references several studies which defined the lowest sex-specific quintile of the study sample as having low muscle mass. [19, 22]

In 2019, the EWGSOP guidelines were updated to better reflect the greater understanding of the role of muscle in health as well as in consideration of practical considerations for how sarcopenia can be measured in research and clinical settings. Specifically, based on substantial evidence that muscle strength is more strongly associated with function than

muscle mass, the revised EWGSOP2 definition considers people with low muscle strength as having probable sarcopenia which is then confirmed if low muscle mass is also present. [33] In contrast, the original EWGSOP definition defines pre-sarcopenia as having low muscle mass and sarcopenia when either low muscle strength or low physical performance are also present. This change has substantial benefits to clinicians as muscle strength is less expensive and easier to measure in comparison to muscle mass. Based on the new EWGSOP algorithm, only people with low muscle strength, operationalized as low grip strength or impaired performance on the five-times sit to stand chair rise test, require muscle mass measures. Like the original EWGSOP definition, there are several options for the measurement of muscle mass, muscle strength, and physical performance. Muscle strength can be measured using grip strength or the chair rise test. BIA, DXA, CT, and MRI are all accepted methods of measuring muscle mass. Though the new EWGSOP guidelines do not recommend one specific strategy, it is recognized that muscle mass should be adjusted for body size by dividing ALM by height^2, weight, or BMI. To determine the severity of sarcopenia, gait speed, the short physical performance battery, the timed up and go, or a 400 meter walk test can be used as measures of physical performance.

International Working Group on Sarcopenia - The next sarcopenia consensus definition was released in 2011 by the IWGS. The IWGS definition operationalizes sarcopenia as low muscle mass and low physical function. DXA is specifically recommended to measure muscle mass, though urinary creatinine, anthropometry, BIA, CT, MRI, ultrasound, total body potassium, and neutron activation are mentioned as measurement options. The definition recommends adjusting muscle mass for height using the cut offs of $\leq$7.23kg/m^2

for males and ≤5.67kg/m^2 for females. Other adjustment options are also discussed and there is a list of cut offs used in previous studies provided. For physical function, only the gait speed test using a four meter course is recommended with a cut off of less than 1.0 meters per second. [20]

Foundation for the National Institutes of Health - The FNIH released their consensus definition in 2014. Recognizing that there is not a strong causal pathway between muscle mass to strength to function, the FNIH definition was developed with the goal of aiding clinicians in making a differential diagnosis of people who have low physical function due to low muscle mass and strength (sarcopenia) versus those with low physical function due to other causes. Based on this goal, sarcopenia was defined as low muscle mass and low muscle strength. Unlike the EWGSOP and IWGS definitions which determine low muscle mass and strength based on the distribution of values in a young, healthy population, the FNIH conducted analyses to determine the optimal cut offs. [21] The FNIH pooled data from nine studies of community-dwelling older adults. Classification and Regression Tree analysis was used to determine the grip strength values which best classified individuals with walking speeds of less than 0.8m/s. [39] The resulting grip strength cut offs of 26kg for males and 16kg for males were then used in Classification and Regression Tree analysis to determine what low muscle mass cut offs best classified individuals with poor grip strength. [40] Both ALM and leg lean mass measured using DXA were tested without adjustment as well as adjusted for height, weight, height^2, BMI, and total body fat. Based on these analyses, two measures of muscle mass were recommended based on their ability to discriminate those with low grip strength. The first was unadjusted ALM using the cut

offs of 19.75kg for males and 15.02kg for females and the second was ALM adjusted for BMI with cut offs of 0.789 for males and 0.512 for females. Though both measures are included in the definition guidelines, ALM adjusted for BMI is the preferred method. The FNIH also recommends adjusting grip strength for BMI with cut offs of <1.0 in males and <0.56 in females, [21] though this technique is not commonly used in practice. [36]

Asian Working Group for Sarcopenia - The AWGS definition released in 2014 uses the same algorithm as the EWGSOP. [18] The cut off values suggested in the EWGSOP have been shown to not be appropriate in Asian populations due to differences in ethnicity, body size, lifestyles, and cultural backgrounds. Consequently, the AWGS recommends Asian-specific cut offs for their variables. DXA and BIA are the recommended methods of measuring muscle mass. The AWGS definition recommends adjusting ALM by height^2 and using cut offs of 7.0kg/m^2 for males and 5.4kg/m^2 for females using DXA, and cut offs of 7.0kg/m^2 for males and 5.7kg/m^2 for females using BIA which are the values corresponding to two standard deviations below the mean muscle mass of a young reference group. Grip strength is recommended as the measure of muscle strength with cut offs of 26kg for males and 18kg for females. The six meter walk test is suggested as the measure of physical function with a cut offs of 0.8 meters per second.

Development of muscle cut offs

Muscle strength and muscle function - Each expert group consensus definition includes recommended cut offs for tests such as muscle mass, grip strength, and gait speed. [18–22] With the exception of the FNIH definition which used Classification and Regression Tree

analysis to determine optimal grip strength and muscle mass values [39, 40], the other studies report cut offs based on the results of previous literature. There are two common cut offs recommended for grip strength in European studies. The grip strength values of 30kg and 20kg are based on the findings of the InCHIANTI study which randomly recruited 1,453 participants aged 20 to 102 years from Tuscany, Italy. [41] Receiver operator characteristic curves were used to determine the hand grip strength cut offs which optimally identified participants with gait speed values below 0.8 meters per second and unable to walk for 1km without difficulty. The cut offs for both outcomes were approximately 30kg for males and 20kg for females. The other commonly reported cut offs are 26kg for males and 16kg for females based on the FNIH definition. [39] An infrequently used set of cut offs for grip strength stratified by BMI based on the lowest quintile of values in the Cardiovascular Health Study are also suggested in the original EWGSOP definition. [19, 42] Due to grip strength values being lower in Asian populations compared to Europeans, the AWGS recommends cut offs of 26kg for males and 18kg for females, or for studies to consider the lowest quintile of the study group as having impaired grip strength. [18]

For gait speed, there are also two commonly used cut offs. The cut point of 1.0 meters per second is recommended by the original EWGSOP definition as well as the IWGS. [19, 20] The EWGSOP cites the Health ABC study for developing the cut point, while the IWGS does not provided a citation. The Health ABC study included 2,031 participants and found that a gait speed of less than 1.0 meters per second best categorized participants based on the rate of incident persistent lower extremity limitation events over five years. [43] The InCHIANTI study is referenced as the source for the 0.8 meters per second cut point, but it

is unclear how data from this study were used to determine the cut point. [41] The AWGS also recommends the use of the 0.8 meters per second cut off. [18] The EWGSOP recommends gait speed cut offs stratified by height with cut offs corresponding to the lowest 20th percentile of the Cardiovascular Health Study, though these cut offs are rarely used in research. [19, 42]

Muscle mass **-** There are a substantially greater number of cut offs recommended for muscle mass compared to grip strength and gait speed. Nearly all the cut offs are based on values a set number of standard deviations below a healthy young reference population or the values corresponding to the lowest sex-specific quantile of a study. [15, 44, 45] One set of cut offs for ALM adjusted for height^2 were developed using receiver operator curve analysis in older adults from the National Health and Nutrition Examination Survey to determine the values which classified participants according to their risk of disability. [46] Another set of cut offs is based on the change in muscle mass annually estimated using unadjusted ALM from the Longitudinal Aging Study Amsterdam. [47] Due to lower muscle mass values observed in Asian populations compared to Europeans populations [48], the AWGS recommends different cut offs from ALM adjusted for height based on values two standard deviations below a healthy young reference population, though it is unclear what young healthy reference group is being used. [18] Reviewing the literature, numerous studies use cut offs other than those recommended by the expert group consensus definitions. [49–68]

The strategies used to develop low muscle mass cut offs in the sarcopenia literature are problematic. Thresholds which rely on the distribution of the study sample such as the

lowest quantile approach may lack generalizability to other samples because the cut point lacks any clinical meaning. This is particularly problematic for studies which use linear regression to adjust ALM for height and fat mass. This technique uses the residual values, calculated as the actual ALM value minus the estimated ALM value to determine if the participant has low muscle mass. The residual value for each person is influenced by the regression equation developed in the sample. Unless two samples have identical distributions of ALM, height, and fat mass, the residuals developed in one sample do not have the same meaning as the residuals developed in another sample. Consequently, cut offs developed in one study cannot be used in another. This also has implications for studies that are stratified by other variables such as age. If stratification occurs before the residuals are calculated, the residuals between the two samples are no longer comparable and therefore the same cut point cannot be applied. Further discussion of this issue is required to promote the use of the regression adjustment technique.

Using a healthy young reference population to develop low muscle mass cut offs may also be problematic. Several studies have noted that using this technique to determine low muscle mass cut offs had let to marked differences in prevalence between males and females. [23, 26] In the study by Lee et al., a young, healthy sample was recruited into the study for the purpose of developing low muscle mass cut offs. The cut offs corresponded to the sex-specific 20^{th} percentile values in the young adults for ALM adjusted for height^2 and ALM adjusted for weight. Only 6.7% of older females had low muscle mass based on ALM adjusted for height^2 versus 42.9% of males. Similarly, 32.9% of older females had low muscle mass based on ALM adjusted for weight versus 67.3% of males. It is assumed

that the amount of lean mass relative to height and weight would be lower in older than in younger adults. However, the older women were 8cm shorter on average than the young women. To have the same mean ALM adjusted for height^2 values as the younger women, the older women would have to have 1.65kg less ALM on average. However, the older women only had 0.5kg less ALM on average than the younger women, explaining why the prevalence of low muscle mass was only 6.7%. Ideally, cut offs developed based on their ability to predict future relevant outcomes should be used, however there are a paucity of these cut offs in the literature.

Prevalence of sarcopenia according to different definitions

Many studies have reported on the prevalence of sarcopenia. Generally sarcopenia is estimated to affect between 1% and 29% of community-dwelling older adults, though some studies have found prevalence estimates as high as 70%. [69, 70] Due to the differences in participant characteristics such as the distribution of age and health status and the wide range of methods used to operationalize sarcopenia, it is difficult to make meaningful comparisons of prevalence between studies. Consequently, the most informative studies for understanding the impact of the method of operationalizing sarcopenia on prevalence are those that use multiple definitions within the same sample. When the same sample of participants is used, any differences in sarcopenia prevalence can be attributed to the definitions rather than to differences in participant characteristics.

Sixteen studies have compared multiple sarcopenia definitions within a sample of community-dwelling older adults. [23, 24, 26–30, 32–34, 71–76] In general, these studies

have found that even within the same sample, the difference in sarcopenia prevalence between definitions was quite large. Twelve out of Fourteen studies that included composite definitions (EWGSOP, FNIH, IWGS, and AWGS) generally found that prevalence was between 0% and 19%. [23, 24, 27–30, 32, 34, 71–76] One of the studies that fell outside of this range found that prevalence was between 7.5% and 45.6% which may be attributable to the unusually high percentage of participants with impaired muscle strength. [26] Approximately 50% of participants had low muscle strength using cut offs of <30kg for males and <20kg for females. This high prevalence may be attributable to the cut offs not being appropriate for Brazilians, or could be related to the specific protocol used to measure hand grip strength. [26] The other study found that prevalence was 31.9% for the EWGSOP definitions and 6.3 and 7.9% according to different FNIH definitions. [33] In this study, the mean gait speed was 0.79 (0.25) meters per second which is lower than expected. A cut point of 0.8m/s for gait speed was used with the EWGSOP definition which means that approximately 50% of participants would have been identified as having low gait speed. In combination with the more liberal muscle mass cut offs ($\leq$7.26kg/m^2 for males and $\leq$5.45kg/m^2 for females) frequently used for the EWGSOP definition, the higher prevalence is accounted for.

Five studies operationalized sarcopenia as muscle mass only. [23, 30, 32, 34, 70] These studies found a wide range of prevalence estimates depending on how low muscle mass was operationalized. Bijlsma et al. found that between 0% and 31.4% of males and 0% and 19.8% of females were sarcopenic. [23] Of the eight definitions explored, the prevalence was lower than 5% for five of the definitions in males and six of the definitions in females,

even after limiting their sample to those aged 60 years and older. The low prevalence may be attributable to the use of BIA to measure muscle mass. Though the authors found that the intraclass correlation coefficients were >0.95 for muscle mass between DXA and BIA, this does not mean that the absolute values are comparable. Therefore applying DXA cut offs set at absolute (rather than relative measures) to BIA data may underestimate sarcopenia prevalence. Reijnierse et al. found that sarcopenia prevalence based on muscle mass only was between 0% and 14.9% for healthy older adults. [30] However, the recruitment strategy selected for healthier than average participants by excluding people with most co-morbidities. Consequently, lean mass, grip strength, and physical performance values were much higher than is typical within a population based sample of similarly aged adults. [77] The third study found that sarcopenia prevalence was between 17.6% and 61.4% for males and between 11.1% and 67.5% for females using nine different methods of operationalizing low muscle mass. [70] Unlike the other two studies, this study used a community-based sample of older adults and measured both DXA and BIA and used cut offs developed specifically for each measurement technique. The final two studies had more moderate estimates of sarcopenia prevalence of between 11.0% and 21.4. [32, 34]

Assessing prevalence across studies, it appears that sarcopenia prevalence is within a similar range regardless of if sarcopenia is operationalized as muscle mass only or as muscle mass with grip strength or gait speed. This is unexpected because the association between measures of grip strength and gait speed with muscle mass are relatively weak. [78, 79] Most of the composite definitions recommend the same muscle mass adjustment techniques and cut offs that are commonly utilized in muscle mass only definitions. [5, 15,

18–21] Therefore only a subset of participants with low muscle mass are also expected to have impaired strength or performance and it is expected that sarcopenia prevalence using composite definitions should be lower than muscle mass only definitions. Studies that have assessed both muscle only definitions as well as composite definitions show the expected trend and have found that sarcopenia prevalence is between 5% and 20% higher using muscle mass only definitions compared to composite definitions. [30, 32, 34, 70]

It is difficult to interpret sarcopenia prevalence estimates between studies for several reasons. Firstly, the study samples may not be comparable. Factors such as the age distribution and overall health of the study sample, as well as the ethnic groups included alter the expected values for measures of muscle mass, muscle strength, and physical function. [15, 80–82] Though we have limited our review to community-dwelling older adults, it is important to note that differences in sampling strategies such as convenience samples versus community-based samples may also influence prevalence. While both types of samples are susceptible to volunteer bias where the people who agree to participate are healthier on average than the population they are supposed to represent, the risk of underestimation of sarcopenia prevalence due to volunteer bias is higher in studies that use convenience samples. [83] For many sarcopenia studies, convenience samples are recruited by placing ads in places like community centres which may selectively recruit people with certain healthy behaviours.

Secondly, even within the same definition, there can be multiple methods of measuring the components of sarcopenia. For example, the new EWGSOP definition recommends using DXA, BIA, computerized tomography scans, or magnetic resonance imaging to measure

appendicular skeletal mass. Even if using the same method of measurement, problems may arise. Though DXA is used to estimate muscle mass by the majority of studies, estimates of body composition can differ depending on which brand of machine used. [84] Differences in body composition using the same machine brand have also been observed due to differ indicating challenges with calibration. [85] Muscle strength may be measured using grip strength or the chair rise test and gait speed and physical performance by the short physical performance battery, the timed up and go, or a 400 meter walk test. [22] Though in the literature each expert group consensus definition tends to be treated as a single method of operationalizing sarcopenia, there is poor agreement between who is considered sarcopenic using the different criteria. [24] Lastly, there are numerous cut offs suggested in the literature for identifying low muscle mass, strength, and physical function as well as many studies choosing their own. [18–22] Different cut offs have been shown to have a substantial impact on sarcopenia prevalence. [86] Multiple sources of differences in study samples and methods of operationalizing sarcopenia, are the reasons for differences in prevalence between studies.

The agreement between sarcopenia definitions

Many of the studies which have investigated the impact of different sarcopenia definitions on prevalence within the same cohort have simultaneously assessed the level of agreement between definitions. [23, 24, 26–30, 32–34, 76] The majority of the studies formally assessed agreement using Cohen's kappa. [24, 26–29, 76] For most comparisons, Cohen's kappa values were between 0.40 and 0.60 indicating moderate agreement. Two studies consistently found lower agreement between definitions. [27, 29]

Kim et al. found that the agreement between ALM adjusted for height^2 and ALM adjusted for BMI was 0.38 in males and 0.09 in females. Dam et al. found that with the exception of low ALM adjusted for BMI combined with low grip strength versus low ALM adjusted for height^2 with either low grip strength or low gait speed for which the Cohen's kappa value was 0.53, agreement between various expert group consensus definitions ranged from a Cohen's kappa of 0.04 to 0.23. [29] Two studies found that the agreement was markedly different dependent on definition. [70, 76] In the study by Pagotto et al. Cohen's kappa values were between 0.29 and 0.89 for the same techniques of measuring muscle mass with different cut offs when sarcopenia was operationalized as muscle mass only. When grip strength was included in the definition, the agreement improved marginally. Agreement was lower when comparing between different methods of measuring muscle mass. Of 21 comparisons with sarcopenia operationalized as muscle mass only, eight had negative Cohen's kappa values which can be interpreted as less agreement than would be expected by chance, 11 had values below 0.40 and only two had Cohen's kappa values between 0.4 and 0.5. Agreement modestly improved when grip strength was included. In the study by Locquet et al. agreement was between 0.14 to 0.22 for all definitions in comparison to the FNIH definition, between 0.44 to 0.48 for AWGS with EWGSOP and the Society of Sarcopenia definitions and the Society of Sarcopenia and EWGSOP definitions and between 0.56 and 0.71 for IWGS with EWGSOP, Society of Sarcopenia, and AWGS. [76] Two studies did not formally assess agreement but graphically showed the number of participants identified as having sarcopenia according

to multiple definitions. [23, 30] Both studies found that that there was poor overlap between most of the definitions.

Based on the literature there is generally poor agreement between sarcopenia definitions with only a few exceptions. It is difficult to disentangle what drives the differences in the level of agreement between definitions. Of the studies assessing agreement, none of them assessed the same two definitions operationalized using the same technique. Some were close, for example Lee et al. and Locquet et al examined the agreement between the EWGSOP and IWGS definitions. [28, 76] However, Lee et al. operationalized the muscle strength component of the EWGSOP definition using grip strength, knee extensor strength, peak expiratory flow and the physical performance component with the SPPB, gait speed, timed up and go, and a stair climb tests. [28] In contrast, Locquet only used measures of grip strength and gait speed which means that the definitions, though labeled using the same terminology, are not comparable. [76]

Association between sarcopenia and falls

Approximately one third of adults aged 65 years and older fall each year. [87] Falls and injuries related to falls are one of the largest contributors to a loss of independence in older adults and are also associated with fractures, hospitalization and mortality. [31, 88–91]. The risk factors for falls are numerous and range from polypharmacy, history of previous falls, age, visual impairments, cognitive decline and environmental factors. [92] There is also a strong biological link between muscle strength and function with falls which has made them one of the outcomes of greatest interest for sarcopenia. [91]

The evidence to date about the association between sarcopenia and falls has been inconsistent. A recent systematic review and meta-analyses pooled the available evidence on the association of sarcopenia with falls. [31]. The systematic review searched the MEDLINE, EMBASE, Cochrane, and CINAHL databases from inception to May 2018. Inclusion criteria were studies in English, participants aged 65 years and older, sarcopenia diagnosed by any definition, and having falls as an outcome. The systematic review found 22 studies assessing the association of sarcopenia with falls. Overall, the meta-analyses of 20 studies with data suitable for pooling found that sarcopenia was associated with a 1.60 (95% CI 1.37 to 1.86, $p<0.001$) greater odds of falling in cross-sectional studies and a 1.89 (95% CI 1.33 to 2.68, $p <0.001$) greater odds of falling in prospective studies. When stratified by definition, sarcopenia defined by muscle mass only (ALM/height and ALM/weight) as well as three of four consensus definitions (AWGS, EWGSOP, IWGS), but not the FNIH definition, were associated with a significantly higher risk of falls when pooled across studies. [31]

In contrast to the meta-analyses, studies that compared definitions within the same population have found that definitions including muscle strength and/or muscle function, but generally not muscle mass only definitions, were significantly associated with falls. [32–34] The study by Schaap et al. was of particular interest as they compared the strength of the association between each component of the sarcopenia definitions with three year incidence of recurrent falls, adjusting for the other components. [33] In this study, there were 498 males and females aged 55 to 85 years from the Longitudinal Aging Study Amsterdam. Low muscle mass operationalized as ALM adjusted for height^2 or as

unadjusted ALM, was not significantly associated with recurrent falls. In contrast, low muscle strength and slow gait speed were significantly associated with recurrent falls with hazard ratios between 1.36 and 2.06 depending on the sarcopenia definition. The results of the Osteoporotic Fractures in Men cohort study which includes 5,934 community dwelling males aged 65 years and older similarly found that muscle mass only definitions based on ALM adjusted for height^2 and the residuals of ALM regressed on height and fat mass were not associated with recurrent falls, but the IWGS, EWGSOP, and FNIH definitions were with odds ratios of between 2.23 and 2.38. [32] Bischoff-Ferrari et al. investigated seven sarcopenia definitions in 445 community-dwelling adults aged 65 years and older from the Boston STOP-IT cohort. [34] While their results generally showed that the odds of falling were greater for the definitions including strength or function in contrast to muscle mass only definitions, the confidence intervals were very wide, likely attributable to the low prevalence (<7.5%) for four of the five composite definitions.

Two other studies have investigated the association between sarcopenia defined using more than one definition and falls. [6, 93] However, unlike the other studies which used the outcomes of recurrent falls after one or three years, or the rate of falls over three years of follow up [32–34], these studies assessed falls risk after five years, [6] and falls-related hospitalizations after five years and 9.5 years of follow up. [93] The first study included 681 volunteers aged 50 to 79 years and assessed the risk of falls after five years based on different muscle mass only definitions. [6] In males, ALM adjusted for height, weight, and the regression technique were all associated with the falls risk score (assessed using the physiological profile assessment [94]) at follow up, whereas in women, only ALM adjusted

for weight was associated with the falls risk score at follow up. The study also assessed the change in the fall risks score over five years. ALM adjusted for height, weight, and the residual technique were associated with change in the falls risk score in males, but only the ALM adjusted using the residual technique was associated with change in falls risk in females. Sim et al. investigated the association between sarcopenia and falls-related hospitalization risk over five and 9.5 years in 903 Australian women aged 70 years and over at baseline. [93] Sarcopenia was defined using the FNIH and original EWGSOP definitions using the cut offs recommended by the expert group consensus definitions as well as cut offs specifically developed for Australians. [19, 21] In this study, none of the definitions were associated with fall-related hospitalization after five or 9.5 years. It is plausible that the different methods of operationalizing falls for these studies compared to the other studies in the litearture is the reason for the discrepant findings.

The inconclusive findings of the association between sarcopenia and falls is not surprising given the wide range of prevalence estimates and limited agreement between sarcopenia definitions. [23, 24, 27–30, 32–34, 76] The systematic review and meta-analyses by Yeung et al. attempted to account for the differences in methods of operationalizing sarcopenia by stratifying the studies by definition. However, this makes the erroneous assumption that each definition is applied the same way by different studies. Of the 14 studies that used the EWGSOP definition for sarcopenia, no two studies used identical techniques for operationalizing the variables. Four different methods of measuring muscle mass were utilized, DXA [34, 35, 95–100], BIA [8, 101, 102], the Lee equation based on anthropometric measures [103, 104], and mid upper arm muscle circumference. [7] Of the

studies using DXA, six adjusted muscle mass for height^2 [34, 35, 97–100], one adjusted for weight [96], and the last adjusted using the regression technique. [95] Physical function was measured using gait speed by all but three studies, two of which utilized the SPPB [101, 104] and one which used the timed up and go. [96] The 11 studies that used gait speed to operationalize physical function included different course lengths; three meters [35, 97], four meters [7, 103], 15 feet [34], five meters [8, 99, 100], six meters, [95, 98] and ten meters. [102] Nine of the studies used a cut off of 0.8 meters per second, [7, 34, 35, 95, 97–99, 102, 103], while one used cut offs stratified by BMI [100] and the other considered the lowest quartile of the study population to have limited physical performance. [8] In addition to the differences in how sarcopenia was operationalized in each study, the studies also utilized different designs (cross-sectional versus longitudinal), had different study populations (community-dwelling, hospital inpatients, nursing home, or outpatient clinics), and were conducted in different countries. Yeung et al. stratified by study design (cross-sectional and prospective), study population (community-dwelling, hospital, nursing home, and outpatient clinic), continent (Asia, Australia, Europe, North America, and South America) and found that the only groups for which the association between sarcopenia and falls did not hold was for nursing home residents, outpatient clinics, and studies conducted in South America. [31] The point estimates for the studies conducted in nursing home residents (two studies, pooled odds ratio 1.37, 95% CI 0.60 – 1.30) and studies conducted in South America (4 studies, pooled odds ratio 1.45, 95% CI 0.90 – 2.32) were only marginally lower compared to the other subgroups, but had wider confidence intervals.

Another consideration regarding the association between sarcopenia and falls is clinical utility of diagnosing sarcopenia. Based on the results of the systematic review and meta-analyses assessing the association between sarcopenia and falls, the odds of falling pooled across all cross-sectional studies was 1.60 (95% CI 1.37-1.86) and the odds of falling pooled across all prospective cohort studies was 1.89 (95% CI 1.33-2.68). The odds ratios were statistically significant ($p< 0.05$) as well as clinically relevant given that between approximately 6% of adults aged 65 years and older report an injury caused by a fall in the past 12 months. [105] However, odds ratios have limited clinical utility based on how they are calculated. Odds ratios compare the odds of falling if a participant is sarcopenic compared to the odds of falling if they are not sarcopenic. For outcomes with a low odds in the unexposed population, even a modest odds in the exposed group may result in a large odds ratio. Only one study has used area under the curve (AUC) to better understand the utility of sarcopenia clinically. [32] The study did not report AUC estimates for sarcopenia and falls, but rather the change in the AUC of a model including sarcopenia versus a model with age alone for the outcome of recurrent falls. The study observed that even for sarcopenia definitions that were significantly associated with falls with odds ratios between 2.24 and 2.38, the AUC changed by 0.010 or less. This can be interpreted as compared to a model containing only age, knowing if a participant is sarcopenic only improves the classification of fall status by 1%. This study indicates that the cost associated with measuring sarcopenia clinically may not be justified based on the minimal improvement in AUC values.

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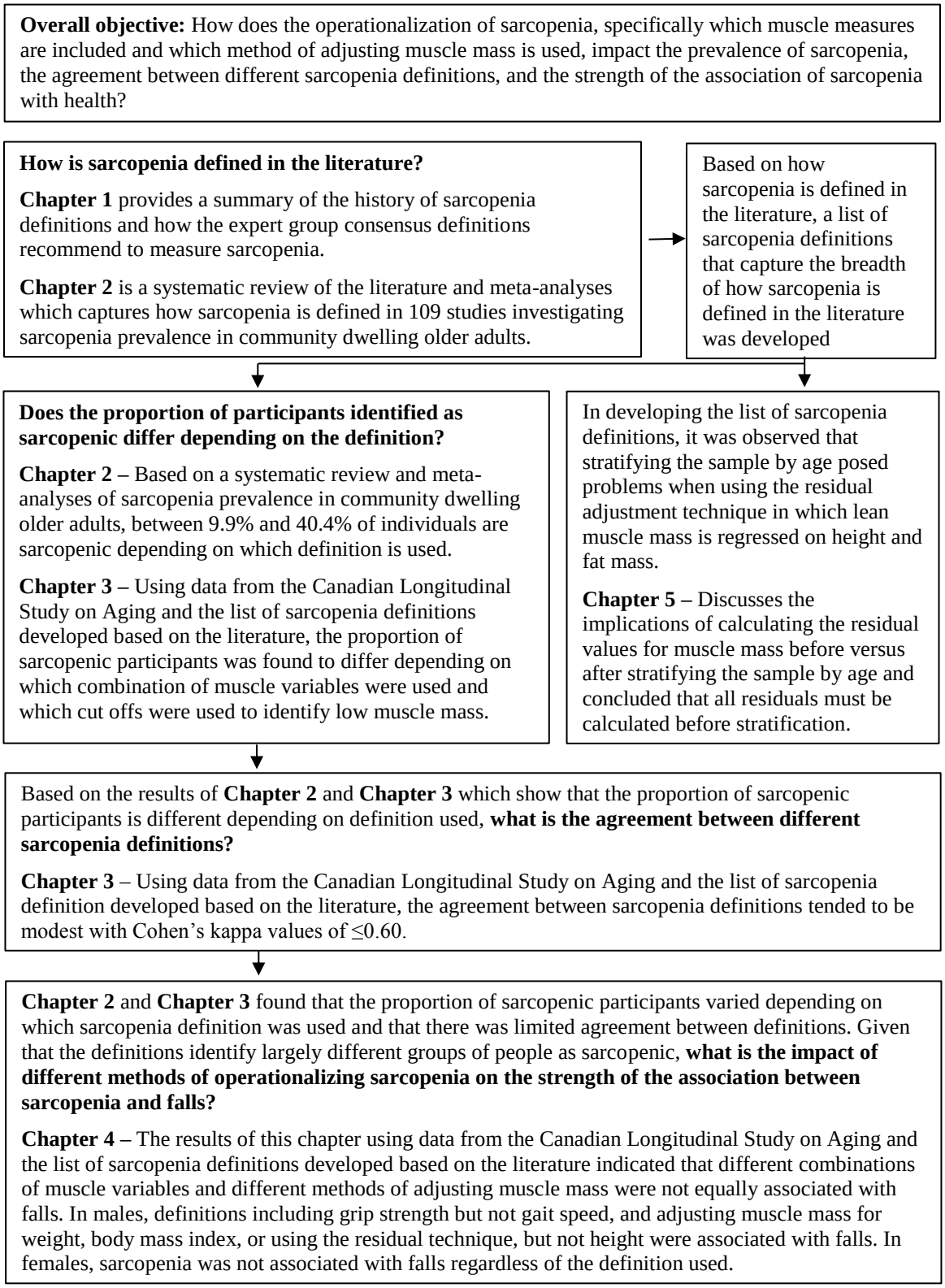
Table 1. Measures included in the sarcopenia expert group consensus definitions

Definition	Muscle Mass				Muscle strength				Physical performance			
	Bioelectrical impedance analyses (BIA)	Dual-energy x-ray absorptiometry (DXA)	Cat scan (CT)	Magnetic resonance imaging (MRI)	Grip strength	Chair rise	Knee flexion	Peak expiratory flow	Short physical performance battery	Timed up and go	Stair climb test	Gait speed
EWGSOP	⊕	⊕	⊕	⊕	⊕		⊕	⊕	⊕	⊕	⊕	⊕
EWGSOP (revised 2019)	⊕	⊕	⊕	⊕	⊕	⊕			⊕	⊕		⊕
IWGS		⊕										⊕
FNIH		⊕			⊕							
AWGS	⊕	⊕			⊕							⊕

Figure 1. Overview of how individual chapters support overall thesis objectives



Chapter 2: A systematic review and meta-analyses of sarcopenia prevalence

This chapter is published in *Age and Ageing*, 2019; 48(1), 48-56. doi: 10.1093/ageing/afy106. Alexandra Mayhew and Parminder Raina conceived the research question and designed the review protocol with input from Stuart Phillips, Russell de Souza, Paul McNicholas, Gianni Parise, and Lehana Thabane. Donna Fitzpatrick Lewis provided support for the design of the systematic review search strategy and development of the study eligibility criteria and data extraction forms. Krystal Amog completed study screening, data extraction, and risk of bias assessment in duplicate with Alexandra Mayhew. Thesis committee members, Russell de Souza, Paul McNicholas, Gianni Parise, and Lehana Thabane, as well as Stuart Phillips provided feedback throughout the project. All authors contributed to manuscript revisions. All authors approved the version of the manuscript before submission. Age and Ageing provided permission for the manuscript to be included in this thesis.

Context and background

Previous studies have observed a wide range of prevalence estimates for sarcopenia between studies as well as within the same study using different definitions. However, based on the existing literature it was unclear how much of the variability in prevalence estimates was due to the operationalization of sarcopenia, the use of different cut points for measures of muscle mass, muscle strength, and muscle function and differences in study methodologies and participant populations. The purpose of this study was to identify the definitions used in the literature to measure sarcopenia in community-dwelling older adults and to assess the similarities and differences in prevalence estimates by definition. By capturing the range of definitions used in the literature for sarcopenia, this study set the foundation for the development of a list of sarcopenia definitions that would allow for the impact of changing each of the three components of sarcopenia to be investigated individually in the following chapters.

Chapter 2: A systematic review and meta-analyses of sarcopenia prevalence

Title: The prevalence of sarcopenia in community dwelling older adults, an exploration of differences between studies and within definitions: A systematic review and meta-analyses

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Abstract

Background: Sarcopenia in aging is a progressive decrease in muscle mass, strength and/or physical function. This review aims to summarize the definitions of sarcopenia in community-dwelling older adults and explore similarities and differences in prevalence estimates by definition.

Methods: A systematic review was conducted to identify articles which estimated sarcopenia prevalence in older populations using search terms for sarcopenia and muscle mass. Overall prevalence for each sarcopenia definition was estimated stratified by sex and ethnicity. Secondary analyses explored differences between studies and within definitions, including participant age, muscle mass measurement techniques, and thresholds for muscle mass and gait speed.

Results: In 109 included articles, eight definitions of sarcopenia were identified. The lowest pooled prevalence estimates came from the European Working Group on Sarcopenia/Asian Working Group on Sarcopenia (12.9%, 95% confidence interval: 9.9-15.9%), International Working Group on Sarcopenia (9.9%, 3.2-16.6%), and Foundation for the National Institutes of Health (18.6%, 11.8-25.5%) definitions. The highest prevalence estimates were for the appendicular lean mass (ALM)/weight (40.4%, 19.5-61.2%), ALM/height (30.4%, 20.4-40.3%), ALM regressed on height and weight (30.4%, 20.4-40.3%), and ALM / body mass index (24.2%, 18.3-30.1%) definitions. Within definitions, the age of study participants and the muscle mass cut-points used were substantive sources of between-study differences.

Conclusion: Estimates of sarcopenia prevalence vary from 9.9 to 40.4%, depending on the definition used. Significant differences in prevalence exist within definitions across populations. This lack of agreement between definitions needs to be better understood before sarcopenia can be appropriately used in a clinical context.

Introduction

Sarcopenia is a progressive decrease in muscle mass, strength, and physical function that occurs with age. Beginning in approximately the fifth decade of life, muscle mass and strength decline at annual rates of 0.8% and 1-3%, respectively. Functional declines, culminating in a loss of independence in self-care abilities, are not evident until later in life, but are related to decreases in strength and physical function. Sarcopenia is associated with a significantly greater risk for poor health outcomes including disability and functional impairments [5], increased risk of falls [6], longer hospital stays [7], and an increased risk of mortality. [8,9] In 2000, it was estimated that the United States incurred $18.5 billion in direct health care costs related to sarcopenia alone. [10]

Sarcopenia was first defined by Baumgartner using appendicular lean mass (ALM) adjusted for height (kg/m^2). [11] Subsequent definitions of sarcopenia include measures of either muscle strength or function because muscle strength declines more rapidly than muscle mass during aging [2] and muscle strength and function are more strongly associated with outcomes such as mortality. [12] The International Working Group on Sarcopenia (IWGS) defined sarcopenia as a combination of low muscle mass and low muscle function [13], while the European Working Group on Sarcopenia in Older People (EWGSOP) suggested that low muscle mass and either low muscle strength or low physical performance must be present. [14]

Depending on the definition used, sarcopenia is estimated to affect between 1% and 29% of community-dwelling older adults [15] though some estimates are as high was 60%. [16] The

wide range of prevalence estimates suggest that different sarcopenia definitions are not measuring the same underlying construct. Studies using the same population have found that sarcopenia estimates vary up to 40% by definition. [17-19] It is unclear how much of the prevalence variability is due to the operationalization of sarcopenia, the use of different cut-points, and/or the different techniques used for muscle measurement, study methodologies and participant populations. However, the lack of a standardized sarcopenia definition makes it challenging to accurately estimate the burden of the disease, thus limits the clinical usefulness of a sarcopenia diagnosis. With the introduction of sarcopenia into the International Classification of Disease [20], there is an even greater urgency to arrive at a unified definition for sarcopenia. The aims of this review are: 1) to identify definitions currently used to characterize sarcopenia in community-dwelling older adults; and 2) to document the similarities and difference between prevalence estimates by definition.

Methods

This review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (**Supporting Information S1**). Ethics approval was not required for this research. The protocol for this systematic review has been published on PROSPERO (ID: CRD42016043777).

Data sources and searches - An electronic search strategy was developed to identify human studies with estimates of sarcopenia prevalence in community-dwelling older adults without specific health conditions. No restrictions on study design were imposed. Studies were limited to original English language articles. MEDLINE, EMBASE, CINAHL,

AgeLine, and SPORTDiscus were searched from inception to 19 December 2016 (**Supporting Information S2**). The bibliographies of the retrieved articles were reviewed for additional studies.

Study selection - The title, abstract, and full-text screenings were performed in duplicate by two independent reviewers. Discrepancies were resolved by discussion. A third author was consulted to reach consensus when necessary. Studies were excluded if they were a review, meeting abstract, commentary, letter to the editor, study protocol without data, exclusively used animal models, were not English language, had participants exclusively under the age of 60, or if the mean age minus one standard deviation was below 55 years. Other exclusion criteria include participants living in hospitals, long-term care facilities, nursing homes, or retirement homes, the use of convenience sampling to recruit participants, sarcopenia measured at only a specific area of the body such as the thigh or tongue, and sarcopenia exclusively defined as a change in muscle parameter(s).

Data extraction and quality assessment - Two authors independently extracted details of the study design, country the study was conducted in, sarcopenia definition including details of measures of muscle mass, muscle strength and physical function, and participant characteristics such as age, sex, and ethnicity. For each study, prevalence was calculated as the number of participants with sarcopenia divided by the entire sample size. If this information was not provided, the prevalence reported in the paper was extracted**.** Discrepancies were resolved by discussion.

The *Joanna Briggs Institute Prevalence Critical Appraisal Tool* [22] was used to assess risk of bias (ROB). Manuscripts and additional documentation referenced by the study were reviewed for the ROB assessment. Studies were categorized as low, moderate, high or very high ROB. Studies at low ROB scored all responses as either "yes" or "not applicable" with an allowance for one "unclear" response for a total score of 8.5 or 9. Moderate ROB studies could have three "unclear" responses or one response of "no" and one response of "unclear" for a score of 7.5 or 8.0.ROB. High ROB studies had scores between 5.0 and 7.5 and very high ROB studies had scores of less than 5.0.

Data synthesis and analysis - All studies were stratified by ethnicity and, when possible, by sex. Ethnicity was categorized as European if the study took place in North America, Europe, or Australia/New Zealand or non-European. For all analyses, the EWGSOP/AWGS were included together because they used identical algorithms for determining sarcopenia status. In cases where at least two studies provided combinable data, a DerSimonian and Laird's random effects meta-analysis was performed which yields conservative confidence intervals (CI) around the prevalence estimates in the presence of heterogeneity. Heterogeneity was detected using Cochran's *Q* test (significant at $P<0.10$) and quantified using the I^2 statistic (ranging from 0 to 100%). All analyses were completed using Review Manager (version 5).

In the primary analyses, overall prevalence for each sarcopenia definition was estimated, stratified by sex and ethnicity. A subgroup analyses was conducted after removing studies that were poor or very poor quality. Four sensitivity analyses were conducted to assess the impact of age, muscle mass cut-offs, the method of measuring muscle mass, and gait

speed/course length on sarcopenia prevalence. Studies were first stratified by sarcopenia definition, sex, and ethnicity, then further categorized by the sensitivity analyses variable. For age and muscle mass cut offs, studies were categorized by approximate tertiles for each sex and ethnicity group and the results of groups were pooled together. The method of muscle mass determination was categorized as DXA, BIA, or other. Only the EWGSOP/AWGS definitions had sufficient data on gait speed/course length. Categories included all possible combinations of speed and length. For each sensitivity analysis, prevalence estimates for each of the sensitivity analyses categories within each age/ethnicity strata were calculated. These estimates were then pooled together to determine the overall prevalence for that category across all age/ethnicity strata for a given definition.

Results

Literature Flow **-** Of the 13,191 potentially eligible articles, 777 remained after removing duplicates and screening the titles and abstracts, and 109 after the full-text review (**Supporting Information S3**).

Study Characteristics - **Table 1** summarizes the characteristics and results of the 109 articles categorized by definition. The articles represented 58 unique cohorts from 26 countries with 656 individual estimates of sarcopenia prevalence. Across all studies, the minimum age was 55 years, and the earliest year of data collection was 1988. Sarcopenia estimates were available for eight common definitions-ALM/body mass index (BMI), AWGS, ALM divided by weight, ALM regressed on height and weight, ALM divided by

height, EWGSOP, FNIH, and IWGS-and three uncommon definitions that measured sarcopenia using absolute muscle mass, fat mass, handgrip strength, or knee extensor strength (**Supporting Information S4**).

Risk of Bias Assessment - According to the *Joanna Briggs Institute Prevalence Critical Appraisal Tool*, 10.6% (n=10) of studies were at low ROB, 20.4% (n=29) were at moderate risk, 52.8% (n=75) of studies were at high risk, and 16.2% (n=23) were at very high risk.

Overall sarcopenia prevalence estimates - After merging studies where two or more manuscripts provided an estimate for sarcopenia using identical measurement methods in the same population, 227 individual prevalence estimates remained. The most frequently used definitions were the EWGSOP/AWGS criteria (n=83), ALM/height (n=68), and ALM/weight (n=27). The remaining definitions had fewer than 20 estimates. The lowest pooled prevalence estimates were for the EWGSOP/AWGS (12.9%, 95% CI: 9.9, 15.9%), IWGS (9.9%, 95% CI: 3.2, 16.6%), and FNIH (18.6%, 95% CI: 11.8, 25.5%) definitions. The highest prevalence estimates were for the ALM/weight (40.4%, 95% CI: 19.5, 61.2%), ALM/height (30.4%, 95% CI: 20.4, 40.3%), ALM regressed on height and weight (30.4%, 95% CI: 20.4, 40.3%), and ALM/BMI (24.2%, 18.3, 30.1%) definitions. All definitions except for IWGS had a significant between study heterogeneity (I^2 > 87%, Cochrane's Q, *P*-value <0.00001) (**Supporting Information S5**).

Prevalence estimates varied between males and females. In Europeans and non-Europeans, prevalence was higher in males for EWGSOP/AWGS, ALM/height, and ALM/BMI. For FNIH, ALM/weight, and ALM/BMI, sarcopenia prevalence was higher in females. For

ALM regression, prevalence was higher in European males than European females, but equal in non-European males and females. When comparing Europeans versus non-Europeans, sarcopenia prevalence was similar (<5% difference) for EWGSOP/AWGS and ALM/BMI in males and females. Compared to non-Europeans, prevalence was higher in Europeans for ALM/height, ALM/weight, and ALM regression and lower for FNIH. For IWGS, sarcopenia prevalence was higher in European males compared to non-European males but lower in European females compared to non-European females. When studies with high or very high ROB were removed, 76 studies remained. Prevalence estimates decreased for the EWGSOP/AWGS, FNIH, ALM/height, ALM/weight, ALM regression and other definitions and increased for IWGS (5.5%) and ALM/BMI (1.1%).

Prevalence estimates stratified by age groups - After including all age categories, there were 363 unique estimates of sarcopenia prevalence. Prevalence increased across age groups from youngest to oldest for EWGSOP/AWGS, FNIH and ALM/BMI. For the ALM/height, ALM/weight and ALM/regression definitions, prevalence estimates differed by 10% between age groups, but did not increase across increasing age groups. The prevalence of IWGS varied by 13.8% between age groups but did not demonstrate an increase with age (**Table 3**).

Prevalence estimates stratified by muscle mass threshold - 123 estimates of sarcopenia from the EWGSOP/AWGS, IWGS, ALM/height, and ALM/weight definitions were included in this analysis. Definitions with less than three cut-points were excluded. Two definitions (EWGSOP/AWGS and ALM/height) had studies in different muscle mass groups depending on whether the prevalence was ranked according to the cut offs in males

or females for the pooled analyses. When groups were based on female cut-points, EWGSOP/AWGS and ALM/height as well as ALM/weight showed trends for sarcopenia prevalence increasing as muscle mass increased ALM (**Table 4).**

Comparison of gait speed, length of gait speed test - Only the EWGSOP/AWGS definitions provided sufficient data for gait speed analysis. For European males and females, a gait speed cut off of 0.8m/s was used for course lengths of 3m, 4m and 6m. Prevalence was lowest for the 3m distance (12.1% (95% CI: 0.0, 24.3%) males, 4.8% (95% CI: 0.0, 9.9%), females) and highest for the 4m distance (20.4% (95% CI: 17.3, 23.4% males, 32.1% (26.8, 37.4%, females). Pooled estimates for European males and females used a cut-point of 0.8m/s with course lengths of 3m, 4m, 6m, and 10m. Prevalence ranged from 4.5% (95% CI: 3.3, 5.6%) for the 10m course to 21.5% (95% CI: 17.5, 25.5%) for the 6m course. In non-Europeans, the shortest course length was 2.4m and the longest course length was 20m and gait speed cut offs were between 0.8m/s and 1.26m/s. As the course length increased for a given cut-point, the prevalence of sarcopenia decreased in both sex strata with the exceptions of the 20m walk course in males and females and the 4.0m to 4.572m/s gait speed for females only**.**

Comparison of methods of measuring muscle mass - Across all definitions, 158 sarcopenia estimates used DXA to measure muscle mass, 39 used BIA, and 21 used methods such as muscle circumference or a formula based estimate of muscle mass. Of the definitions using both BIA and DXA, the prevalence of sarcopenia was between 2.0% (EWGSOP/AWGS) and 8.5% (IWGS) higher when measured by BIA than DXA.

Discussion

Recognizing and screening for sarcopenia and developing steps for its treatment has become an important public health challenge in light of the recent development of the International Classification of Disease code. This review critically evaluated 656 individual estimates of sarcopenia from 109 articles, representing 58 unique cohorts from 26 countries. Eight common definitions of sarcopenia used in community-dwelling older adults (ALM/BMI, AWGS, ALM/weight, ALM regressed on height and weight, ALM divided by height, EWGSOP, FNIH, and IWGS) were identified. Surprisingly, sarcopenia prevalence was markedly dependant on the operationalized definition, ranging from 9.9% to 40.4%. This more than fourfold difference suggests that there are crucially important differences between the definitions of sarcopenia in regard to muscle parameters, the operationalization of variables, and study populations. We explored some of these differences in this review.

The clinical implications of a lack of standardized definition for sarcopenia are of particular concern with the introduction of the International Classification of Disease code for sarcopenia in 2016. [20] With issuance of the code came no guidance for clinicians about which definition to use or how to treat individuals identified as sarcopenic, which appears to encompass many different phenotypic presentations and pursuant treatment strategies. [24] It is also unknown if the participant characteristics vary in those considered sarcopenic and if different treatment strategies may be more or less effective based on the sarcopenia definitions used. Understanding which interventions to employ for composite definitions is further complicated by the inclusion of multiple variables and an absence of an outcome

for treatment. From a public health perspective, the lack of a standard definition makes it impossible to understand the burden of sarcopenia.

A key difference between definitions was whether sarcopenia was operationalized using a single measure of muscle mass (ALM/BMI, ALM/weight, ALM regressed on height and weight, and ALM/height) or a composite measure of muscle mass and muscle strength and/or physical function (AWGS, EWGSOP, FNIH, IWGS). Sarcopenia prevalence was between 24.2 and 40.4% for single measure definitions and 9.9 and 18.6% using composite definitions (**Table 3**). This suggests that there are more people with lower indices of muscle mass but fewer with lower muscle mass in conjunction with poor strength or function. However, people with low muscle mass and poor strength or function are more likely to experience disability compared to those with low muscle mass alone. [25,26]

Within definitions, muscle mass thresholds and the use of BIA versus DXA may explain some of the difference in prevalence estimates. For most definitions, prevalence increased across increasing age groups indicating studies including older participants are likely to report a higher prevalence. Twenty of the 22 studies with different age groups within the same population reported increased prevalence in the older age groups. However, it is unlikely that potential differences in age distribution of participants by definition explains the difference in prevalence estimates between definitions. The difference in prevalence within definition by age tertiles tended to be smaller than the difference between definitions for the same age tertile. Prevalence also increased as muscle mass cut offs increased within definitions. The same trend was found in studies that used multiple cut-points. For all definitions with both BIA and DXA measures, BIA yielded higher prevalence estimates

than DXA. Conclusions about gait speed and course length were less clear due to lack of evidence. However, the results suggested that for a given gait speed, prevalence of sarcopenia generally increases with increasing course length. However, the cause of this trend is unclear and may be attributable to differences in methods of measurement such as when timers are started or the speed at which participants are instructed to walk.

A challenge encountered in this review was that subsets of the same population were used to estimate sarcopenia in multiple publications. This occurred when either a single study such as National Health and Nutrition Examination Survey or the Korean National Health and Nutrition Examination Survey had multiple publications using overlapping but not identical participant populations. Whenever possible, sample size estimates were adjusted to better reflect the number of unique estimates contributing to the pooled data.

Our review provides a comprehensive synthesis of the literature, building upon previous systematic reviews which have only included a subset of definitions, have been restricted to specific diseases, or looked at sarcopenia in relation to another outcome. This is the first systematic review that has investigated prevalence estimates for sarcopenia definitions in community-dwelling older adults, which allows for comparisons to be made between and within definitions. Our subgroup analyses revealed factors that may contribute to differences in prevalence estimates within studies including the age distribution of the study population, muscle mass cut-points, the use of BIA versus DXA, and gait speed cut offs that require further investigation.

Our study has limitations. First, the literature search was last updated in December 2016 and does not reflect the most recent literature. Secondly, though this review highlights variables that potentially contribute to differences in prevalence, it is impossible to isolate the unique contribution of these variables due to other between-study differences including variables not investigated in this review such as study inclusion and exclusion criteria for physical performance tasks. Another limitation is the use of sex and ethnicity specific tertiles for muscle mass cut points and age opposed to the same cut points for each sarcopenia definition. This was done to allow for internal comparisons to be made for these variables within a definition by maximizing the number of studies included in each of the groups. More primary research is required to better understand what drives the differences in study prevalence. In addition to the current literature [27,28], more studies are required to empirically test which sarcopenia definitions are predictive of future health status. There is also a need for further exploration of the effect of different methods of adjusting lean mass for body size on sarcopenia. Four methods of adjustment were captured in this review, ALM/height, ALM/weight, ALM regression and ALM/BMI. Adjustment of muscle parameters for body size has been shown to increase the strength of the association between muscle with function and disability, but it is unknown which of the four adjustment techniques is most appropriate. This review provides evidence that the prevalence of sarcopenia is also impacted by the method of adjustment with prevalence estimates ranging from 24.2% to 40.4%. This research will provide the information necessary for researchers and clinicians to determine what the standard definition of sarcopenia might be.

Conclusions

In this review, the pooled prevalence of sarcopenia pooled ranged between 9.9% and 40.4%, depending on the definition used. The differences in sarcopenia prevalence suggests that the definitions are not measuring the same underlying construct. In general, definitions that include measures of muscle function or physical performance in addition to muscle mass provide lower estimates of sarcopenia compared to measures of muscle mass only. Our findings also suggest that, within definitions, there are multiple sources of between study differences including participant age, the muscle mass cut-points used in definitions, and the use of DXA versus BIA. Most importantly, this review emphasizes the need for further development and refinement of the definition of sarcopenia to allow for greater comparability between future studies examining sarcopenia and its treatment.

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Table 1. Summary of study characteristics

Definition, year that definition was developed	Cohorts included	Countries represented	Number of unique estimates	Years of data collection	Range of ages included	Number of participants, total number, (lowest – highest)	Range of measures of sarcopenia	Range of measures of sarcopenia prevalence
EWGSOP, 2009	AGES Reykjavik [1]	Iceland	210	1998 - 2014	50+	58,442 (70 – 17,655)	Muscle mass: thigh muscle surface area (<116.5cm^2 males, <83.2cm^2 females), mid arm muscle circumference area (lowest 40% of participants at risk for sarcopenia, or <21.1cm males and <19.2cm in females), calf circumference (31 - 34cm males, 31 - 33cm females), skinfold thickness (lowest third), ALM/height^2 measured with DXA and BIA (5.58 – 10.75kg/m^2 males, 4.32 - 6.75kg/m^2 females), ALM/BMI (country specific lowest quintile), unadjusted lean body mass (lowest	Males: 0% - 36.7% Females: 0% - 62.2%
	BEFRAIL [2]	Belgium						
	BRHS [3] EPIC [4] Hertfordshire Cohort Study [5,6] Hertfordshire Sarcopenia Study [5] HSHD [7] Sumukadas, 2015 – Scotland [8]	Great Britain						
	COMO VAI? [9,10] Quilombola Elderly [11] Lafaiete Coutinho-BA [12] SABE – Brazil [13,14]							
	COURAGE/SAGE [15,16]	China Ghana India						

		Mexico Poland Russia South Africa Spain					tertile), ALM/body weight (< 27.1% - 29.9% males, <22.3% - 25.1% females), ALM regressed on height and weight (lowest tertile), total ASM (<19.75kg males). Muscle strength: HGS (< 25 - 30kg males, < 16 - 20kg females or <33nm, or BMI based cut points, or <0.75Nm males, <0.79 Nm females, or lowest quantiles,). Physical performance: Walk speed (<0.8m/s, <1.0m/s, 1.26m/s, age/sex or height specific cut offs, course distance of 2.44 – 10m) or SPPB (score of less than 8)	
	EPIDOS [17]	France						
	I-Lan [18] Lin, 2014 – Taiwan [19] Taichung Community Health [20,21] TOP Study [22]	Taiwan						
	IlSirente [23-27] InCHIANTI Study [28,29]	Italy						
	Kashiwa Cohort Study [30-33] Japan Murakami [34] OSHPE [35] ROAD Study [36]	Japan						
	KLoSHA [37,38]	Korea						
	MaSS [39-41]	Netherlands						
	Wen, 2015 – China [42]	China						
	Mexico City [43,44]	Mexico						
	MrOS and SOF [45]	United States						

	SABE – Colombia [46]	Colombia						
	SARIR [47,48]	Iran						
	SMAS [49] CHAMP [50]	Australia						
	The FORMoSA Project [51,52]	Germany						
AWGS, 2014	Chinese Elderly Study [53] No-Name China [42]	China	30	2010 – 2013	60+	2835 (286 – 1149)	Muscle mass: calf circumference (cut off of 31cm), DXA measured ALM/height (cut offs of 7.0kg/m^2 for males, 5.4kg/m^2) for females. Muscle strength: Handgrip strength (cut offs of 28kg for males and 16kg for females) Physical function: gait speed (cut offs of 0.8m/s (n=3 cohorts), and 1.0m/s (1 cohort).	Males: 0% - 27.0% Females: 0% – 23.9%
	I-Lan [54]	Taiwan						
	ROAD Study, (n=2) [36, 55]	Japan						
IWGS, 2009	EPIDOS [17]	France	37	1988 – 2015	60+	10,383 (285 – 4425)	Muscle mass: DXA or BIA measured ALM/height^2 (<7.23kg/m^2 <10.76kg/m^2 males, <5.67kg/m^2 – 6.75kg/m^2 females), ALM/BMI	Males: 0% - 35.9% Females: 0% - 24.2%
	Hertfordshire Cohort Study [6]	Britain						
	NHANES (1988 – 1994) [56]	United States						
	Wen, 2015 – China [42]	China						

	Tramontano – Peru [57]	Peru					(<0.789 males, <0.512 females). Muscle strength: handgrip strength (<26kg males, <12kg females) Physical function: gait speed (<0.8m/s or 1.0m/s, course length 4m, 6m, 10m, or 50 feet)	
	FORMoSA Project [52]	Germany						
	Gouveia, 2016 - Portugal [58]	Portugal						
FNIH, 2014	Hertfordshire Cohort Study [6] HSHD [7]	Britain	85	1999 – 2013	60 +	10,979 (290 – 4984)	Muscle mass: DXA measured ALM/height^2 (7.23kg/m^2 males, 5.67kg/m^2 females), unadjusted ALM (<19.75kg males, <15.02kg females), ALM/BMI (<0.789 males, <0.512 females). Muscle strength: handgrip strength <26kg males, <16kg females. Physical function: gait speed (<0.8m/s or <1.0m/s)	Males: 3.1% - 72.8% Females: 0% - 63.6%
	NHANES (1999 – 2004) [59, 60]	United States						
	CHAMP [50, 61]	Australia						
	SMAS [49]	Australia	147	1988 – 2013	50+	32,732	Muscle mass: measured by DXA or BIA with cut	Males: 9.9% - 70.7%

ASM divided by height, 1998						(70 – 4652)[a]	points ranging from 6.52kg/m^2 to 10.65kg/m^2 for males and 4.59kg/m^2 to 8.5kg/m^2 for females.	Females: 0.7% - 58.1%
	NHANES (1988 – 1994) [62, 63] NHANES (1999 – 2000) [64] Cardiovascular Health Study [65, 66] Health ABC [67, 68] NMAPS [59] Buehring, 2013 - US [70] STORM [71] The Framingham Study [72] New Mexico Elder Health [73] WHAS II [74]	United States						
	KNHANES (2008 – 2009) [75-78] KHNAES (2008 – 2010) KNHANS (2008 – 2011) [82, 83] KLoSHA [37, 84]	Korea						

[a] Assumed that the 2008 – 2010 KNHANES study included all participants in the 2008 – 2009 grouping. The sample size for KNHANES 2008 – 2011 was disregarded (n=463) because of the small sample size an impossibility of knowing which participants were included in other samples. Therefore this is an underestimation of the sample size.

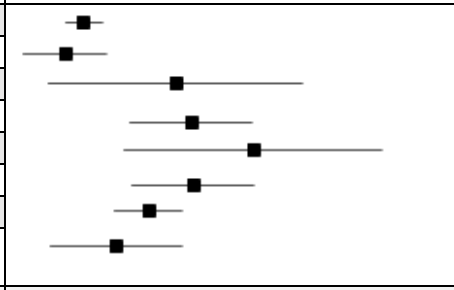
	Ansan Geriatric Study [85]							
	No-Name China [42]	China						
	Taichung Community Health [86]	Taiwan						
	MINOS [87] EPIDOS	France						
	Portuguese centenarians [91]	Portugal						
	No-Name Germany [92]	Germany						
	EXERNET [93]	Spain						
	NuAge [94]	Canada						
	Quilombola Elderly [11] SPAH [95, 96]	Brazil						
ASM/weight, 2002	KLoSHA [37, 84] KNHANES (2008 – 2009) KNHANES (2008 – 2010) [37,99,100] KNHANES (2008 – 2011) [83] KHNAES (2009 – 2010) [99] KHANES (2009 - 2011) [101]	Korea	56	1988 - 2013	60+	21,219[b] (286 – 6949)	Muscle mass: ASM measured using DXA, BIA, or densitometry divided by total weight. Cut points range from 25.72% to 27.6% in males and 19.43% to 37.0% in females.	Males: 3.1% - 56.1% Females: 3.2% - 52.3%

[b] Assumes that the 6949 participants reported for KNHANES (2008 – 2011) encompasses the participants from all KNHANES studies using a subset of that data. This will be resulted in an underestimation of the number of participants

	KNHANES (2009) [102] KNHAES (2010 – 2011) [103] KNHANES (2010) [104]							
	NHANES (1999 – 2004) [105] NHANES (1988 – 1994) [106]	United States						
	Wen, 2015 – China [42]	China						
	SMAS [49]	Australia						
ASM regressed on height and weight, 2003	EPIDOS [17]	France	31	1992 – 2011	65+	15,289 (419 – 5993)	Muscle mass: measured by DXA and regressed on weight and height. Lowest quintile considered sarcopenic.	Males: 8.2% - 27.1% Females: 8.1% - 30.5%
	Health ABC [67, 68] Mr OS [107] The Framingham Study [72]	United States (n=4)						
	SMAS [49] TASOAC [108]	Australia						
	SPAH (n=2) [95, 96]	Brazil						
ALM/BMI, 2014	NHANES 1999 – 2004 [60]	United States	60	1999 – 2004	60 +	3880	Muscle mass: ALM/BMI. Cut off of <0.789 for males and <0.512 for females.	Males: 4.0% - 47.3% Females: 3.6% - 51.2%

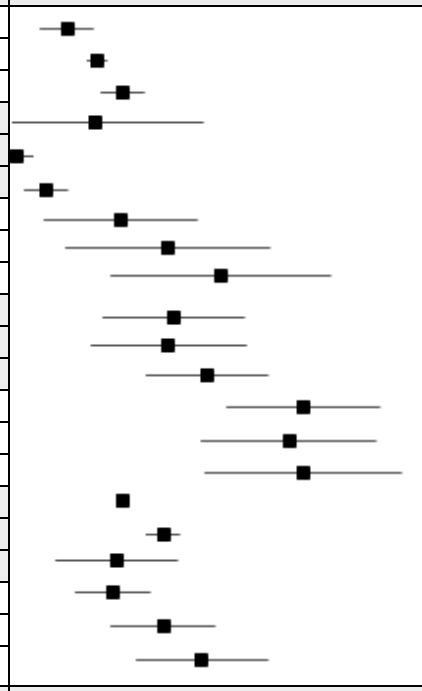
Other	Cardiovascular Health Study [65] Rancho Bernardo Study [109]	United States	6	1988 – 2011	55+	8,824 (733 – 3366)	Muscle mass: BIA fat free mass of <47.9kg for men and <34.7kg for women. Muscle strength: Handgrip strength adjusted for height using regression (lowest tertile), handgrip strength only (<30kg males, <20kg females), knee extensor strength (<23.64 males, <15.24 females)	Males: 6.2,% no upper estimate Females: 5.9%, no upper estimate
	EPIDOS [17]	France						
	SMAS [49]	Australia						

Table 2. Overall sarcopenia prevalence estimates

Definition	Number of studies	Participants (n)	Forest plot	Prevalence estimate	95% CI	Heterogeneity
EWGSOP/AWGS	83	58283		12.9%	9.9, 15.9%	93% (*P*<0.001)
IWGS	12	10381		9.9%	3.2, 16.6%	52% (*P* =0.100)
FNIH	16	6467		18.6%	11.8, 25.5%	75% (*P* =0.003)
ALM/height	68	39135		30.4%	20.4%, 40.3%	87% (*P* <0.001)
ALM/weight	27	18985		40.4%	19.5, 61.2%	100% (*P* <0.001)
ALM regression	6	16899		30.4%	20.4, 40.3%	87% (*P* <0.001)
ALM/BMI	8	4984		24.2%	18.3, 30.1%	92% (*P* <0.001)
Other	6	9243		18.0%	7.3, 28.8%	100% (*P* <0.001)
			0% 40% 80%			

Abbreviations: ALM – appendicular lean mass; ALM – appendicular skeletal mass; AWGS – Asian Working Group on Sarcopenia; EWGSOP – European Working Group on Sarcopenia; FNIH – Foundation for the National Institutes of Health; IWGS – International Working Group on Sarcopenia

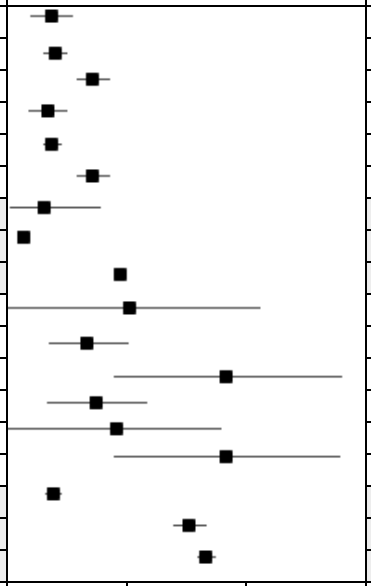
Table 3. Sarcopenia prevalence stratified by definition and age groups

Definition	Age Group	Number of studies	Number of participants	Forest Plot	Prevalence Estimate	95% CI	Heterogeneity
EWGSOP/ AWGS	Youngest	48	24244		9.9%	5.4, 14.4%	94%, (*P*<0.001)
	Middle	47	35553		15.1%	13.5, 16.7%	8%, (*P*=0.370)
	Oldest	46	12393		19.4%	15.6, 23.2%	70%, (*P*=0.006)
IWGS	Youngest	5	3143		14.8%	3.7, 33.2%	0%, (*P*=0.360)
	Middle	6	4493		1.0%	0.0, 3.3%	88%, (*P*=0.004)
	Oldest	5	3553		6.7%	3.1, 10.3%	0%, (*P*=0.500)
FNIH	Youngest	15	8208		12.5%	7.6, 17.4%	0%, (*P*=0.650)
	Middle	15	4129		25.3%	11.3, 39.3%	79%, (*P*<0.001)
	Oldest	15	2911		29.0%	14.9, 43.0%	92%, (*P*<0.001)
ALM/height	Youngest	33	14079		28.9%	16.8, 41.0%	87%, (*P*<0.001)
	Middle	31	24697		27.9%	14.7, 41.2%	92%, (*P*<0.001)
	Oldest	32	15183		34.5%	24.0, 45.0%	30%, (*P*=0.220)
ALM/weight	Youngest	11	8735		51.1%	38.0, 64.3%	94%, (*P*<0.001)
	Middle	11	5113		48.5%	33.6, 63.5%	96%, (*P*<0.001)
	Oldest	11	4266		51.1%	34.3, 67.8%	97%, (*P*<0.001)
ALM regression	Youngest	4	8976		20%	19.1, 20.9%	0%, (*P*=0.330)
	Middle	2	1401		27%	24.2, 19.9%	0%, (*P*=0.750)
	Oldest	2	3299		19.1%	8.8, 29.3%	94%, (*P*<0.001)
ALM/BMI	Youngest	8	2129		18.4%	12.0, 24.8%	98%, (*P*<0.001)
	Middle	8	1635		27%	18.1, 35.8%	92%, (*P*<0.001)
	Oldest	8	1173		33.6%	22.5, 44.8%	71%, (*P*<0.020)
				0% 40% 80%			

Abbreviations: ALM – appendicular lean mass; ALM – appendicular skeletal mass; AWGS – Asian Working Group on Sarcopenia; EWGSOP – European Working Group on Sarcopenia; FNIH – Foundation for the National Institutes of Health; IWGS – International Working Group on Sarcopenia

Table 4. Sarcopenia prevalence stratified by definition and muscle mass measure groups

Definition	Muscle mass group	Number of studies	Number of participants	Forest Plot	Prevalence Estimate	95% CI	Heterogeneity
EWGSOP/ AWGS[a]	Lowest	14	6573		9.4%	4.6, 14.1%	93%, (*P* <0.001)
	Middle	18	6763		10.2%	7.5, 12.9%	65%, (*P* =0.020)
	Highest	18	10644		18.4%	14.7, 22.1%	23%, (*P* =0.260)
EWGSOP/ AWGS[b]	Lowest	16	11355		8.7%	4.2, 13.2%	92%, (*P* <0.001)
	Middle	18	10642		9.5%	7.2, 11.9%	65%, (*P* =0.020)
	Highest	15	18045		18.4%	14.7, 22.1%	23%, (*P* =0.260)
IWGS	Lowest	2	3427		7.9%	0.0, 20.3%	100%, (*P* <0.001)
	Middle	1	1325		3.3%	2.3, 4.3%	N/A
	Highest	1	2500		24.2%	22.5, 25.9%	N/A
ALM/height[c]	Lowest	15	12334		26.3%	0.0, 55.1%	100%, (*P* <0.001)
	Middle	19	11619		17.2%	8.2, 26.2%	85%, (*P* <0.001)
	Highest	15	18045		47.3%	22.1, 72.6%	93%, (*P* <0.001)
ALM/height[d]	Lowest	15	6797		8.7%	4.2, 13.2%	92%, (*P* <0.001)
	Middle	17	6572		9.5%	7.2, 11.9%	61%, (*P* =0.020)
	Highest	18	10611		18.4%	14.7, 22.1%	23%, (*P* =0.260)
ALM/weight	Lowest	7	6949		9.9%	8.0, 11.8%	0%, (*P* =0.390)
	Middle	9	3984		39.3%	35.4, 43.1%	0%, (*P* =0.640)
	Highest	4	3718		43%	40.8, 45.1%	93%, (*P* <0.001)
				0% 40% 80%			



Abbreviations: ALM – appendicular skeletal mass; AWGS – Asian Working Group on Sarcopenia; EWGSOP – European Working Group on Sarcopenia; IWGS – International Working Group on Sarcopenia

[a] Male ordered cut points were used.
[b] Female ordered cut points were used.
[c] Male ordered cut points were used.
[d] Female ordered cut points were used.

Supplementary Appendices

Supplementary appendices are available online at:

https://academic.oup.com/ageing/article/48/1/48/5058979#supplementary-data

Chapter 3: Proportion of sarcopenic participants and agreement between sarcopenia definitions

This chapter has been submitted to *Journals of Gerontology – Medical Sciences*. Alexandra Mayhew was responsible for developing the research question and study protocols, applying for data, analyzing data, writing and revising the drafts of the manuscripts. The work is primarily the undertaking of Alexandra Mayhew with guidance from Drs. Parminder Raina and Stuart Phillips throughout the project. Dr. Nazmul Sohel assisted with coding for the data analyses. Thesis committee members, Drs. Russell de Souza, Paul McNicholas, Gianni Parise, and Lehana Thabane provided feedback throughout the project. As an author generated version of a submitted manuscript, no copyright license documentation is required.

Context and background

The results of **Chapter 2** of this thesis, A Systematic Review and Meta-Analyses of Sarcopenia Prevalence showed that sarcopenia prevalence varied from 9.9% to 40.4% in community dwelling older adults depending on the definition used for sarcopenia. Due to the differences in study populations and methods of operationalizing sarcopenia, it was impossible to determine what components of the sarcopenia definitions were driving the differences in prevalence estimates. The objective of this study was to better understand the impact of the method of operationalizing sarcopenia on the proportion of sarcopenic participants and to assess the agreement between definitions. To accomplish this objective, this study identified participants from the Canadian Longitudinal Study on Aging as sarcopenic. A list of sarcopenia definitions was developed that not only captured the range of definitions in the literature, but also allowed for the impact of each sarcopenia component on the proportion of sarcopenic participants and agreement to be individually examined. By using the same sample for all analyses, differences in prevalence were attributable to the definitions rather than to differences in the study population.

Chapter 3: Proportion of sarcopenic participants and agreement between sarcopenia definitions

Title: Sarcopenia in the Canadian Longitudinal Study on Aging: The impact of diagnostic criteria on the proportion of sarcopenic participants and the agreement between criteria

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Abstract

Background: Definitions for sarcopenia incorporate different combinations of muscle mass, strength, and function and utilize different methods of adjusting muscle mass. It is unclear how these operational differences impact prevalence and the agreement between definitions.

Methods: Appendicular lean mass, grip strength, and usual gait speed were measured in 25,399 participants from the Canadian Longitudinal Study on Aging. Sarcopenia was operationalized as muscle mass alone, muscle mass and grip strength, and muscle mass and gait speed. Muscle mass was adjusted for height^2, weight, body mass index (BMI), and regressing muscle mass on height and fat mass. The sex-specific 20th percentile muscle mass values of participants aged ≥65 years were used as the threshold for low muscle mass. The proportion of sarcopenic participants was calculated for each definition and Cohen's kappa was used to measure agreement between definitions.

Results: The mean age was 62.9 ± 10.2 years and 49.9% of the sample was male. The agreement between definitions including muscle mass and grip strength and muscle mass and gait speed were modest with Cohen's kappa values of ≤0.41. Limited agreement was observed between the methods of adjusting muscle mass with Cohen's kappa values of <0.35 with the exception of ALM/weight and ALM/BMI with values of 0.60 in both males and females and ALM/height^2 and ALM/residuals with kappa values of 0.63 in males and 0.46 in females.

Conclusions: Sarcopenia defined using different muscle variables and muscle mass adjustment techniques have insufficient agreement to be used interchangeably.

Introduction

Sarcopenia is the progressive decrease in muscle mass, strength, and physical function that occurs with age. (1) The timing of the onset of sarcopenia is not known, but is usually measurable at approximately the fifth decade of life, from which time muscle mass typically declines 0.8% and strength 1% to 3% annually. (2–4) The consequences of sarcopenia such as functional declines, culminating in a loss of independence in self-care abilities, are not evident until later in life. Sarcopenia is associated with a significantly greater risk for poor health outcomes including disability and functional impairments (5), increased risk of falls (6–8), longer hospital stays (9), and an increased risk of mortality. (10,11) In 2000, it was estimated that the United States incurred $18.5 billion in direct health care costs due to sarcopenia alone. (12)

Definitions of sarcopenia have evolved from the original measures including muscle mass only, measured using appendicular lean mass (ALM). (13–16) The inclusion of strength and function in the definition of sarcopenia recognizes the strong and important association these variables have with outcomes such as disability and mortality. (17) The International Working Group on Sarcopenia (IWGS) defines sarcopenia using low muscle mass and low muscle function (15) whereas both the revised European Working Group on Sarcopenia (EWGSOP) and the Foundation for the National Institute of Health (FNIH) recommend considering both low muscle mass and low muscle strength. (16,18) The various definitions, in addition to recommending the inclusion of different variables, recommend different method of adjusting muscle mass including dividing ALM by height

in meters squared (height^2), weight in kilograms, body mass index (BMI), and using the residuals from a linear regression model adjusting ALM for fat mass and height. (13–16)

The use of different definitions and methods of adjusting ALM result in varying estimates of sarcopenia prevalence. A recent systematic review and meta-analyses showed that sarcopenia prevalence estimates varied widely between 9.9 to 40.4% in community dwelling older adults. (19) Studies assessing different sarcopenia definitions in the same population have similarly found a wide range of prevalence estimates as well as low to modest agreement between definitions. (20–27) This likely reflects variation across the components of each operationalized definition of sarcopenia. Consequently, the impact of changing a single sarcopenia definition criterion (e.g., the combination of muscle variables or the methods of adjusting ALM) impacts sarcopenia prevalence and agreement. The method used to develop muscle mass cut points further complicates comparisons. Cut points for the different adjustment techniques are recommended based on comparisons to healthy young reference populations, clinical evidence, or the lowest sex-specific quintile of the study population. (13–16) The choice of cut point will determine the proportion of participants classified as having low muscle mass. When cut points differ, the comparability between muscle mass adjustment techniques across studies is limited.

Understanding how combinations of muscle mass, muscle strength, and/or muscle function as well the muscle mass adjustment techniques impact sarcopenia prevalence and agreement is vital for interpreting and comparing results between studies using

different sarcopenia definitions. Using data from the Canadian Longitudinal Study on Aging (CLSA), the objectives of this study were to assess 1) the impact of different sarcopenia definitions on the prevalence of sarcopenia; and 2) the agreement between different sarcopenia definitions.

Methods

Setting and study population

The CLSA is a national, longitudinal research platform that includes 51,338 participants aged 45 to 85 years at baseline from the ten Canadian provinces. Details on the study design have been described elsewhere. (28) Participants had to be physically and cognitively able to participate on their own and not living in institutions such as long term care. Of these participants, there are 21,241 participants in the Tracking cohort who were randomly selected from all ten provinces and were interviewed by phone. The remaining 30,097 participants are a part of the Comprehensive cohort and were randomly selected from participants living within 25 to 50 km of one of 11 Data Collection Sites located in seven provinces. The Comprehensive cohort participants are interviewed in-person and complete in-depth physical assessments at the Data Collection Sites as well as provide blood and urine samples. The present study uses data from the 30,907 participants in the Comprehensive cohort who provided physical assessment data and identified as European between 2011 and 2015. We limited our analysis to Europeans only, because standards for muscle mass, muscle strength, and physical function have been derived from this population. (29–31) De-identified data was provided by the Canadian Longitudinal Study

on Aging. Ethics approval for this study was provided by the Hamilton Integrated Research Ethics Boards (#2686).

Clinical measurements

Trained research assistants conducted all measurements. Height was measured with a stadiometer, taking the mean value of two measurements; and weight using a digital scale (Rice Lake, Model 140-10-7). BMI was calculated as weight in kilograms divided by height squared. Muscle mass was measured by Dual Energy X-ray Absorptiometry (DXA) using Hologic Discovery A^{TM}, which was calibrated daily using a spine phantom, weekly using a whole body step phantom, and yearly using a gold standard phantom. DXA provides an estimates of ALM which measures the amount of lean mass which includes water and all other non-bone and non-fat soft tissues in the arms and legs. (32,33) We measured hand grip strength with the Tracker Freedom® Wireless Grip Dynamometer. Participants performed three repetitions with their dominant hand, the highest value of which was used in the analyses. Grip strength measured using a dynamometer has been shown to have excellent reliability and is predictive of falls, disability, and impaired health-related quality of life. (34) Gait speed was measured using a four meter walk course with participants instructed to walk at their normal walking speed. The four meter walk test has excellent test-re-test reliability and is associated with self-rated health and performance on chair rise and balance tests. (35,36)

Sarcopenia definitions

Sarcopenia was defined as 1) low muscle mass alone; 2) low muscle mass and low muscle strength; and 3) low muscle mass and low muscle function. Grip strength was chosen as the measure of muscle strength, and gait speed as the measure of muscle function because they are recommended by all consensus definitions and available in the CLSA. (13–16) We selected cut offs for grip strength (30kg for males and 20kg for females) and gait speed (0.8m/s) recommended by the original EWGSOP guidelines. (14) We used four techniques to adjust muscle mass: 1) height (in meters squared); 2) weight (kg); 3) BMI (kg/m^2); 4) residuals of ALM regressed on fat mass (kg) and height (m). To optimize the comparison of prevalence and agreement across definitions, we standardized the proportion of participants with low muscle mass according to each adjustment technique. To do this, cut points corresponding to the lowest sex-specific quintiles of muscle mass in CLSA participants aged 65 years and older were selected. The sample for cut point development was limited to those aged 65 years and older as most previous reference populations have a minimum age of between 60 and 70 years. (14) In total, we assessed 12 sarcopenia definitions. Sensitivity analyses using thresholds corresponding to the lowest sex-specific 10^{th} and 40^{th} percentiles of muscle mass in CLSA participants aged 65 years and older were conducted.

Statistical analyses

We determined the percentage of sex-stratified participants categorized as sarcopenic by each of the 12 definitions, and calculated bootstrap percentile confidence intervals for each estimate. We used Cohen's Kappa to assess the agreement between sex-stratified

participants identified as sarcopenic using different muscle mass adjustment techniques as well as different combinations of muscle mass with grip strength and gait speed. Specifically, we assessed agreement for sarcopenia between muscle mass techniques (height^2, weight, BMI, residuals) within definitions of sarcopenia using 1) muscle mass alone; 2) muscle mass and grip strength; and 3) muscle mass and gait speed. Agreement for identifying sarcopenia between different combination of sarcopenia variables (muscle mass, grip strength, gait speed) was assessed within each muscle mass adjustment technique (height^2, weight, BMI, residuals). All analyses were stratified by sex. Due to prevalence of sarcopenia increasing with age, age stratified analyses (45-54, 55-64, 65-74, and 75-85 years) were conducted. We used SAS (version 12.3) for all analyses. The manuscript is reported according to the STROBE statement.

Results

Participant characteristics

After excluding participants who identified as non-European (n=1324), or who were missing muscle mass, grip strength, gait speed, or BMI data (n= 3356), there were 25,399 participants included in the analyses. **Table 1** displays the characteristics of the included participants by age group (younger than 65 years and 65 years and older) and sex. The mean age of the participants was 62.8 ± 10.2 years and 49.9% of the sample were males. Younger males and females had greater ALM (28.8kg ± 4.4 and 19.0kg ± 3.5), grip strength (47.3kg ± 9.1 and 28.6kg ± 5.6), and gait speed (1.03m/s ± 0.18 and 1.02m/s ± 0.19) compared to older males and females (ALM: 25.9kg ± 3.8 and 17.4kg ± 3.0, grip

strength: 39.4kg ± 8.5 and 23.6kg ± 5.2, and gait speed: 0.94m/s ± 0.19 and 0.90m/s ± 0.19).

Muscle mass cut offs

The muscle mass thresholds for the 10th, 20th, and 40th percentiles were 7·29, 7·68, 8·23 for ALM/height^2, 26.96, 28.33, 30.12 for ALM/weight, 0.78, 0.83, 0.90 for ALM/BMI and -4.75, -3.61, and -1.97 for ALM residuals for males. For females, the muscle mass thresholds for the 10th, 20th, and 40th, percentiles were 5.58, 5.93, and 6.42 for ALM/height^2, 21.40, 22.36, and 23.81 for ALM/weight, 0.52, 0.55, 0.60 for ALM/BMI and -2.95, -2.20, and -1.14 for the ALM residuals.

Combination of variables

Regardless of sex, age, and method of adjusting for muscle mass, the proportion of participants considered sarcopenic was highest when sarcopenia was operationalized as muscle mass alone, followed by muscle mass and gait speed and then muscle mass and grip strength. In males 45 to 85, for the four different methods of adjusting muscle mass, the proportion of participants with sarcopenia was between 12.5% and 13.8% for muscle mass only, 2.7% and 3.8% for muscle mass and gait speed, and 2.3% and 3.0% for muscle mass and grip strength. Values were similar in females, 13.0% to 15.3%, 2.9% to 4.9% and 3.2% to 3.6%. The proportion of participants that were sarcopenic increased with age for all age and sex strata for all methods of adjusting muscle mass and all

combinations of muscle variables (**Figure 1, Figure 2, Supplementary Table 1, and Supplementary Table 2**).

Cohen's kappa, the measure of agreement between muscle mass and grip strength and muscle mass and gait speed, was between 0.32 and 0.35 for all methods of adjusting muscle mass in males and between 0.37 and 0.41 for all methods of adjusting muscle mass in females. Agreement was not significantly different across age groups in males (**Supplementary Table 3**), but tended to be significantly higher in females aged 75 to 85 compared to the younger age groups for all muscle mass adjustment techniques.

Muscle mass adjustment

For all four muscle mass adjustment techniques (height^2, weight, BMI, and residuals), between 13.0% and 13.8% of males (**Figure 1**) and 13.0% to 15.3% of females (**Figure 2**) aged 45 to 85 years were sarcopenic when sarcopenia was defined as only muscle mass. For muscle mass and grip strength, between 2.3% and 3.0% of males and 3.2% to 3.6% of females were sarcopenic. For muscle mass and gait speed between 2.7% and 3.8% of males and 2.9% and 4.9% of females were sarcopenic. For all methods of adjusting muscle mass, the proportion of participants categorized as sarcopenic increased with age (**Supplementary Tables 1 and 2**).

Defining sarcopenia as muscle mass only, the agreement between different methods of adjusting muscle mass using Cohen's kappa was generally poor with values of less than 0.35 with the exception of 1) ALM/weight and ALM/BMI with kappa values of 0.60 in

both males and females and 2) ALM/height^2 and ALM/residuals with kappa values of 0.63 in males and 0.46 in females (**Figures 3 and 4**). In both males and females, agreement between muscle mass adjustment techniques improved when low muscle mass was combined with grip strength or gait speed, though the agreement was still limited. The level of agreement did not tend to vary with age in males (**Supplementary Table 4**) or females (**Supplementary Table 5**).

Sensitivity analyses

For males and females of all ages and for all methods of muscle mass adjustment, sarcopenia prevalence increased when the low muscle mass threshold was increased from 10% to 20% and from 20% to 40% (**Supplementary Figures 1 to 4**). The difference in sarcopenia prevalence between thresholds was greatest when sarcopenia was defined as just muscle mass. All trends in the primary prevalence analyses using the 20th percentile as a threshold were observed using the 10th and 40th percentile thresholds. Generally, the agreement between sarcopenia definitions when comparing muscle mass and grip strength and muscle mass and gait speed was higher when the 10th percentile threshold was used and lower when the 40th percentile threshold was used (**Supplementary Table 3**). When comparing agreement between methods of adjusting muscle mass, agreement tended to increase from the 10th to the 40th percentile thresholds (**Supplementary Tables 4 and 5**).

Discussion

This study is, to the best of our knowledge, the first to determine the extent to which different combinations of muscle variables and methods of adjusting muscle mass contribute to the differences in sarcopenia prevalence and the agreement between sarcopenia definitions reported in the literature. (20–27,37) We report that the differences in sarcopenia prevalence are highly dependent on whether sarcopenia is measured as muscle mass only or in combination with either grip strength or gait speed; however, even in circumstances where sarcopenia prevalence was similar, the agreement between muscle mass combinations and most methods of adjusting muscle mass was low.

Previous studies have shown that the prevalence of sarcopenia differs by definition and that the agreement between definitions ranges from poor to substantial. (20–27,37) These studies used various sarcopenia definitions. (13–16,38–40) Nonetheless, we view this approach as problematic as most sarcopenia definitions have more than one difference in how they are operationalized. For example, Dam et al found that 5.3% of males and 13.3% of females were sarcopenic based on the EWGSOP definition while 1.3% of males and 2.3% of females were sarcopenic based on the FNIH definition. The agreement (Cohen's kappa) was 0.53 in males and 0.14 in females. (26) The EWGSOP definition included low muscle mass adjusted for height^2 and one of low grip strength or low gait speed, while the FNIH definition included low muscle mass adjusted for BMI and low grip strength. Due to the multiple differences in the definitions, it is unclear to what extent changing each of the variables contributed to the difference in prevalence and the

limited agreement. Another problem with comparing sarcopenia prevalence and agreement for existing definitions found in the literature is the range of cut points for what would be considered low muscle mass. Within the same population, the recommended cut points identify anywhere between 0 and 60% of participants as having low muscle mass making it difficult to compare the prevalence between methods that have operationalized sarcopenia. (20,23)

We used a novel method of operationalizing sarcopenia to understand the factors that impact the prevalence of sarcopenia and the agreement between sarcopenia definitions. The sample for cut point development was limited to those aged 65 years and older as most previous reference populations have a minimum age of between 60 and 70 years. (14) To capture the spectrum of cut points found in the literature, a sensitivity analyses using cut offs corresponding to the lowest 10^{th} and 40^{th} percentiles of participants was conducted. By using the same method to determine cut points for each muscle mass adjustment technique, the comparability between sarcopenia definitions was improved. Differences in prevalence once combined with muscle strength and muscle function and agreement between definitions did not reflect underlying differences in the proportion of individuals with low muscle mass for each adjustment technique.

The major important finding of our study is that differences in sarcopenia prevalence are highly dependent on whether sarcopenia is measured as muscle mass only or in combination with either grip strength or gait speed. Operationalizing sarcopenia as muscle mass only identified around 14% of participants as sarcopenic regardless of

muscle mass adjustment technique, while including grip strength or gait speed reduced the proportion sarcopenic to between 2 and 5%, respectively. Our systematic review and meta-analyses of sarcopenic prevalence had similar results. (37) Sarcopenia prevalence was between 24.2% and 40.4% when sarcopenia was operationalized as muscle mass only, but only between 9.9% and 18.6% when the definition included muscle strength and/or muscle function. (37)

The second key finding of this study is that there was generally poor agreement between sarcopenia definitions. The agreement (Cohen's kappa) comparing muscle mass and grip strength versus muscle mass and gait speed was only fair (0.21 to 0.40) for all methods of adjusting muscle mass (**Table 1**). Agreement was limited (<0.40) between the different methods of adjusting muscle mass when sarcopenia was operationalized as muscle mass only with two exceptions; 1) ALM/height^2 versus ALM residuals and 2) ALM weight versus ALM/BMI for which agreement was moderate (0.41 to 0.60) to substantial (0.61 – 0.80) (**Figures 3 and 4**). Despite the relatively high agreement for these comparisons, the percent positive agreement was less than 55% meaning that few participants were considered sarcopenic according to both definitions. Though, agreement improved when grip strength and/or gait speed were included in the sarcopenia definition, the degree of improvement did not result in any other comparisons of muscle mass adjustment techniques exceeding a kappa value of 0.60. Our findings are similar to previous studies that have found that agreement tends to be below 0.50 for different methods of adjusting muscle mass, regardless of what combination of muscle variables are used to operationalize sarcopenia. (23–26) Previous studies have generally found modestly higher

agreement (0.40 to 0.60) between combinations of muscle variables compared to our study, which may reflect the older age groups included in their analyses. (22,25,26)

While the approach taken to operationalizing sarcopenia in this study allowed for a novel investigation of what factors impact the prevalence of and the agreement between sarcopenia definitions, it does have some important limitations. Firstly, the results of this study are not specific to existing sarcopenia definitions. While the combinations of muscle variables and methods of muscle mass adjustment suggested by the consensus definitions are included, we did not use their cut points for muscle variables. Using the suggested muscle mass thresholds would not alter the conclusions of this study as our sensitivity analyses using the 10^{th} and 40^{th} percentiles as low muscle mass thresholds find similar results as our primary cut points. These cut points encompass the spectrum of values recommended by consensus definitions. We did not explore alternative cut offs for grip strength (26kg for males, 16kg for females) or gait speed (1.0m/s) because these cut points identify 2.7% of males and 3.4% of females as having low strength and 64.9% of males and 71.5% of females as having low gait speed. Previous studies have similarly found that these grip strength and gait speed cut off values identify too few and too many people as having low value respectively. (42,43) Another limitation of this study is that the primary analyses were limited to people of European decent. Muscle mass, grip strength, and gait speed have been shown to differ by ethnicity and the CLSA does not have the required sample size for ethnicity-specific analyses. (29–31)

Conclusions

We found that sarcopenia prevalence was substantially higher when measured using muscle mass only, but relatively similar regardless of whether muscle mass was combined with grip strength or gait speed. The method of adjusting muscle mass did not have a large impact on sarcopenia prevalence. However, agreement tended be limited when comparing muscle mass adjustment techniques and poor for comparing muscle mass and grip strength versus muscle mass and gait speed. These results highlight the need to work towards a single consensus definition for sarcopenia, one that hopefully has a strong association with future health problems, as the existing definitions have limited comparability.

Author contributions

AJM, SMP, and PR were responsible for designing this project with feedback from NS, LT, PDM, RJd, and GP. AJM, NS, and PR were responsible for the acquisition, analysis, and preliminary interpretation of the data. AJM and PR drafted the manuscript and all other authors critically reviewed the manuscript for intellectual content. All authors have approved this paper for publication and agree to be accountable for all aspects of the work.

Conflict of interest

None declared

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Table 1. Participant characteristics

	Aged <65 years				Aged ≥65 years			
	Males		Females		Males		Females	
	Mean or N	SE or %	Mean or N	SE or %	Mean or N	SE or %	Mean or N	SE or %
Total population	7286	48.7	7677	51.3	5376	51.5	5060	48.5
Age, years	55.8	5.4	55.5	5.4	73.0	5.6	73.0	5.7
Height, cm	176.6	6.7	163.1	6.3	173.9	6.7	159.9	6.3
Weight, kg	89.0	16.5	74.1	16.9	84.6	14.1	70.9	14.3
BMI, kg/m2	28.5	5.0	27.8	6.3	28.0	4.2	27.8	5.5
Total body fat mass, %	25.5	9.5	29.8	11.0	25.5	8.0	29.6	9.4
Appendicular lean mass, %	28.8	4.4	19.0	3.5	25.9	3.8	17.4	3.0
ALM/height^2	9.23	1.19	7.14	1.17	8.56	1.06	6.78	1.04
ALM/weight	32.72	3.37	26.09	3.25	30.90	3.12	24.75	2.86
ALM/BMI	1.02	0.14	0.70	0.11	0.94	0.12	0.63	0.10
Gait speed, meters per second	1.03	0.18	1.02	0.19	0.94	0.19	0.90	0.19
Grip strength, kg	47.3	9.1	28.6	5.6	39.4	8.5	23.6	5.2
Chronic conditions								
Heart disease[7]	648	9.0	375	4.9	1403	26.6	772	15.5
Cardiovascular disease[8]	151	2.1	147	1.9	416	7.8	332	6.6
Diabetes	1108	15.3	1011	13.2	1296	24.2	876	17.4
COPD	259	3.6	341	4.5	348	6.5	408	8.1
Cataracts or glaucoma	707	9.9	984	13.1	2652	50.9	3027	61.7
Osteoarthritis	1070	14.9	1632	21.7	1379	26.4	2060	42.2
Depression	937	12.9	1325	17.4	527	10.0	888	17.9
Dementia/Alzheimer's Disease	7	0.1	9	0.1	22	0.4	17	0.3
Neurological conditions[9]	648	8.9	1678	21.9	376	7.0	864	17.2
Osteoporosis	82	1.1	616	8.1	202	3.8	1223	24.5
Hypertension	2212	30.5	1884	24.6	2626	49.2	2463	48.9

[7] Heart disease includes angina, myocardial infarction, and heart disease

[8] Cardiovascular disease includes stroke and transient ischemic attack

[9] Neurological conditions include multiple sclerosis, epilepsy, migraine headaches, and Parkinson's Disease

Peripheral vascular disease	214	3.0	309	4.0	380	7.1	386	7.7
Kidney disease	2011	27.7	1960	25.6	1516	28.3	1444	28.6
Cancer	478	6.6	768	10.0	1205	22.5	975	19.3
Poor or fair self-rated health (%)	635	8.7	572	7.5	454	8.5	417	8.3
Smoking (%)								
Never	6483	89.4	6811	89.1	5056	94.7	4763	95.0
Former	160	2.2	157	2.1	45	0.8	42	0.8
Current	611	8.4	673	8.8	237	4.4	211	4.2
Household income (%)								
< $20,000	242	3.4	329	4.5	179	3.5	423	9.4
≥ $20,000 < $50,000	770	10.9	1200	16.5	1309	25.9	1872	41.8
≥ $50,000 <$100,000	2114	30.0	2496	34.3	2235	44.2	1579	35.2
≥ $100,000 < $150,000	1862	26.5	1661	22.8	866	17.1	423	9.4
≥ 150,000	2051	29.1	1593	21.9	472	9.3	185	4.1
PASE score	172.6	80.3	150.9	74.4	125.5	60.4	107.8	53.2

Table 2. Agreement between low muscle mass and grip strength versus low muscle mass and gait speed for different methods of adjusting muscle mass

Method of adjusting muscle mass	Males	Females
	Cohen's Kappa (95% CI)	**Cohen's Kappa (95% CI)**
ALM adjusted for height^2	0.35 (0.30 - 0.40)	0.38 (0.33 - 0.42)
ALM adjusted for weight	0.32 (0.28 - 0.36)	0.37 (0.34 - 0.41)
ALM adjusted for BMI	0.33 (0.29 - 0.37)	0.41 (0.37 - 0.45)
ALM residuals	0.34 (0.30 - 0.39)	0.37 (0.33 - 0.41)

Figure 1. Percentage of males with sarcopenia using 20th percentile cut offs

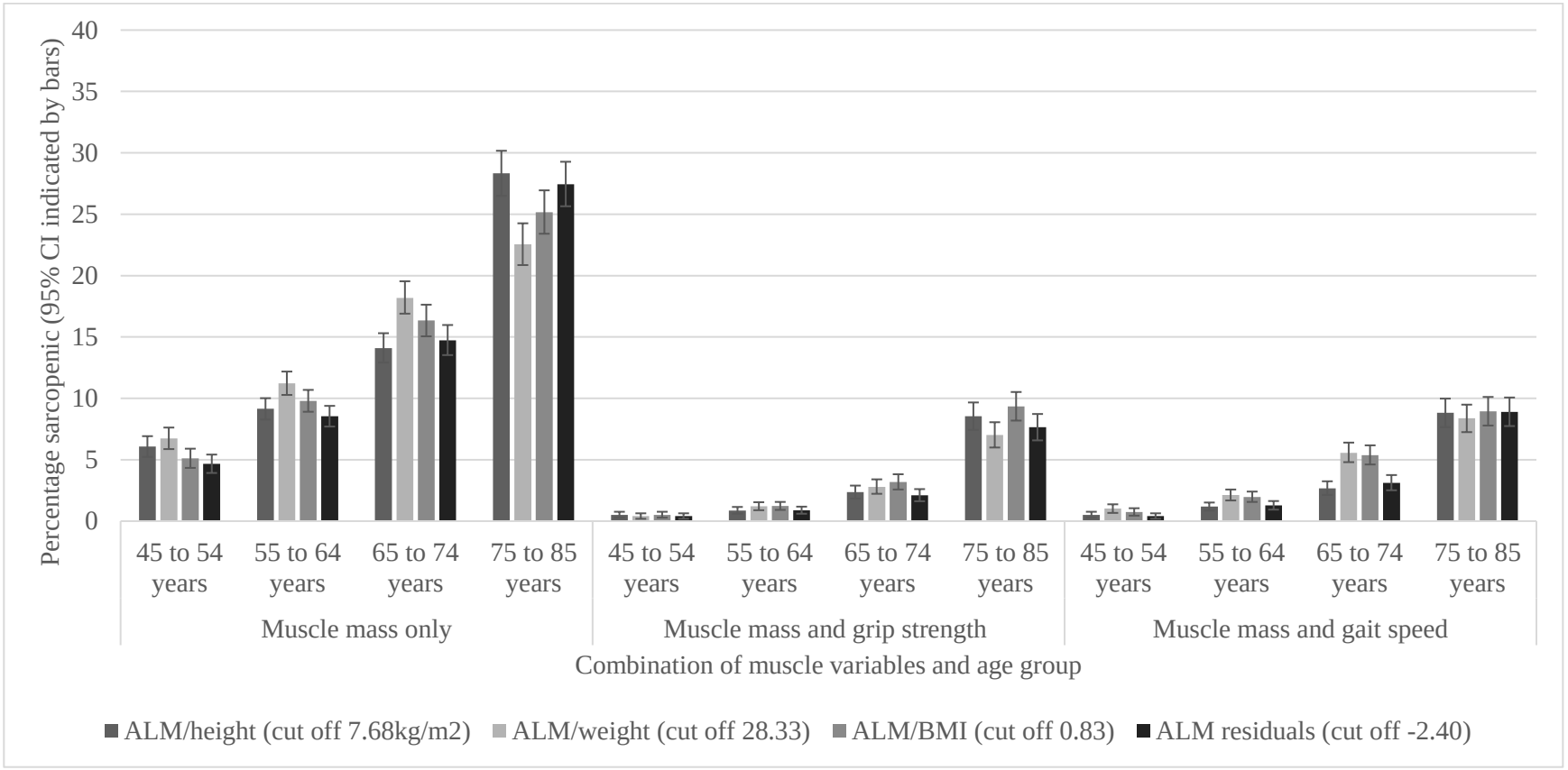


Fig 1 the percentage of males identified as sarcopenic based on muscle mass only, muscle mass and grip strength, and muscle mass and gait speed using the four muscle mass adjustment techniques. The cut offs for the muscle mass adjustment techniques are 7.68kg/m^2 for ALM/height, 28.33 for ALM adjusted for weight, 0.83 for ALM adjusted for BMI, and -2.40 for the ALM residual technique. Percentage of sarcopenia is reported stratified by age (45 to 54 years, 55 to 64 years, 65 to 74 years, and 75 to 85 years)

Figure 2. Percentage of females with sarcopenia using 20th percentile cut offs

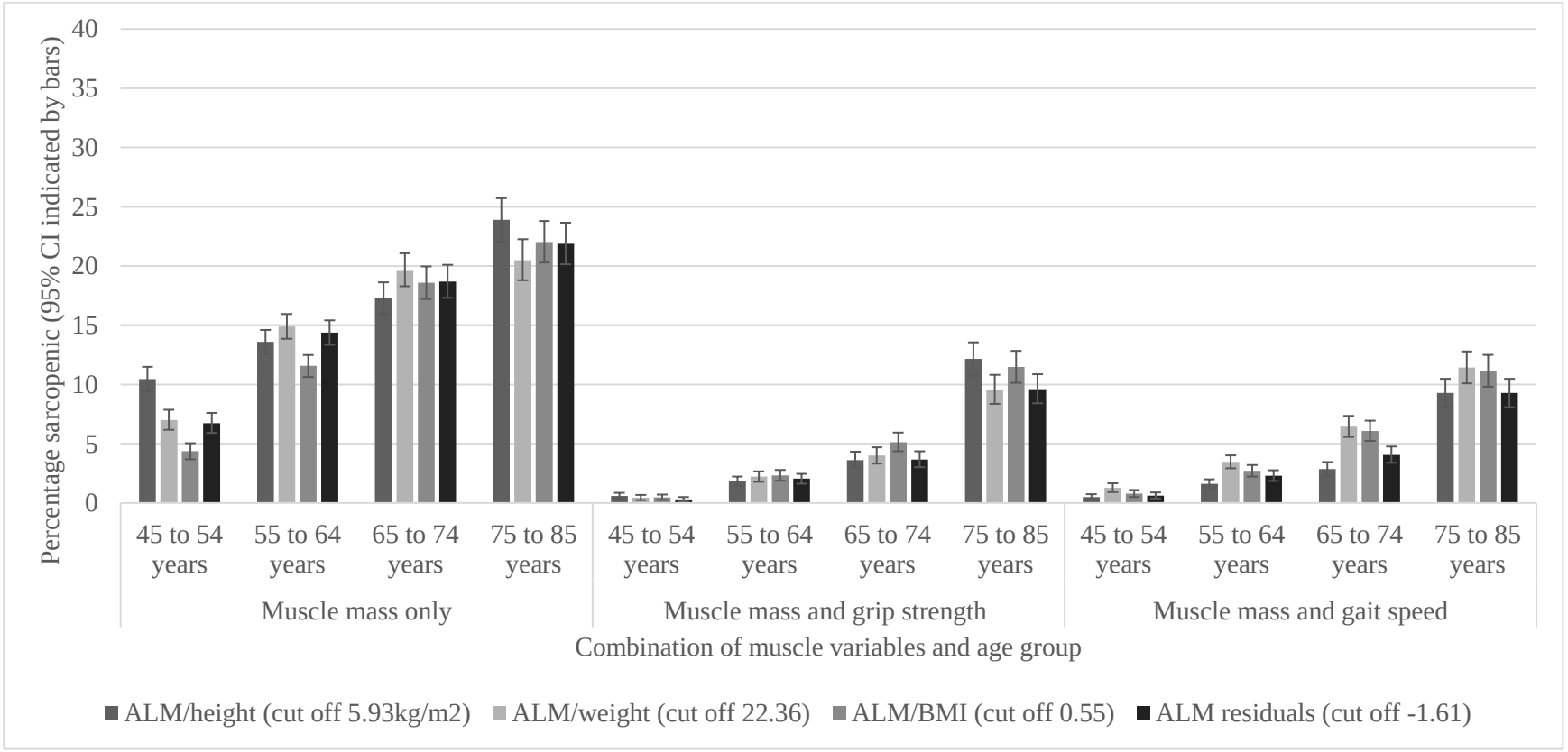


Fig 2 the percentage of females identified as sarcopenic based on muscle mass only, muscle mass and grip strength, and muscle mass and gait speed using the four muscle mass adjustment techniques. The cut offs for the muscle mass adjustment techniques are 5.93kg/m^2 for ALM/height, 22.36 for ALM adjusted for weight, 0.55 for ALM adjusted for BMI, and -1.61 for the ALM residual technique. Percentage of sarcopenia is reported stratified by age (45 to 54 years, 55 to 64 years, 65 to 74 years, and 75 to 85 years)

Figure 3. Agreement between methods of adjusting muscle mass for different combinations of muscle mass variables in males

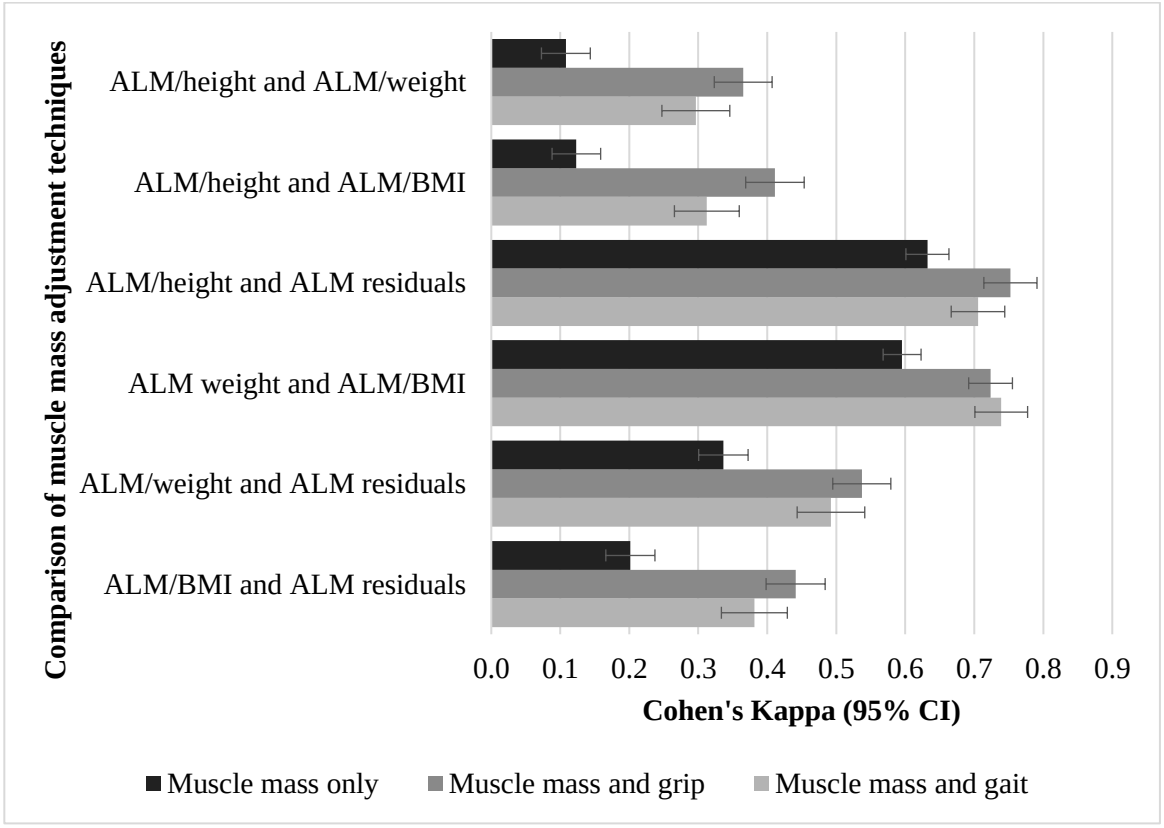


Fig 3 the agreement between methods of adjusting muscle mass for different combinations of muscle mass variables in males. Cohen's kappa statistics are provided for the agreement between the four methods of adjusting muscle mass (ALM/height, ALM/weight, ALM/BMI, and the ALM residuals)

Figure 4. Agreement between methods of adjusting muscle mass for different combinations of muscle mass variables in females

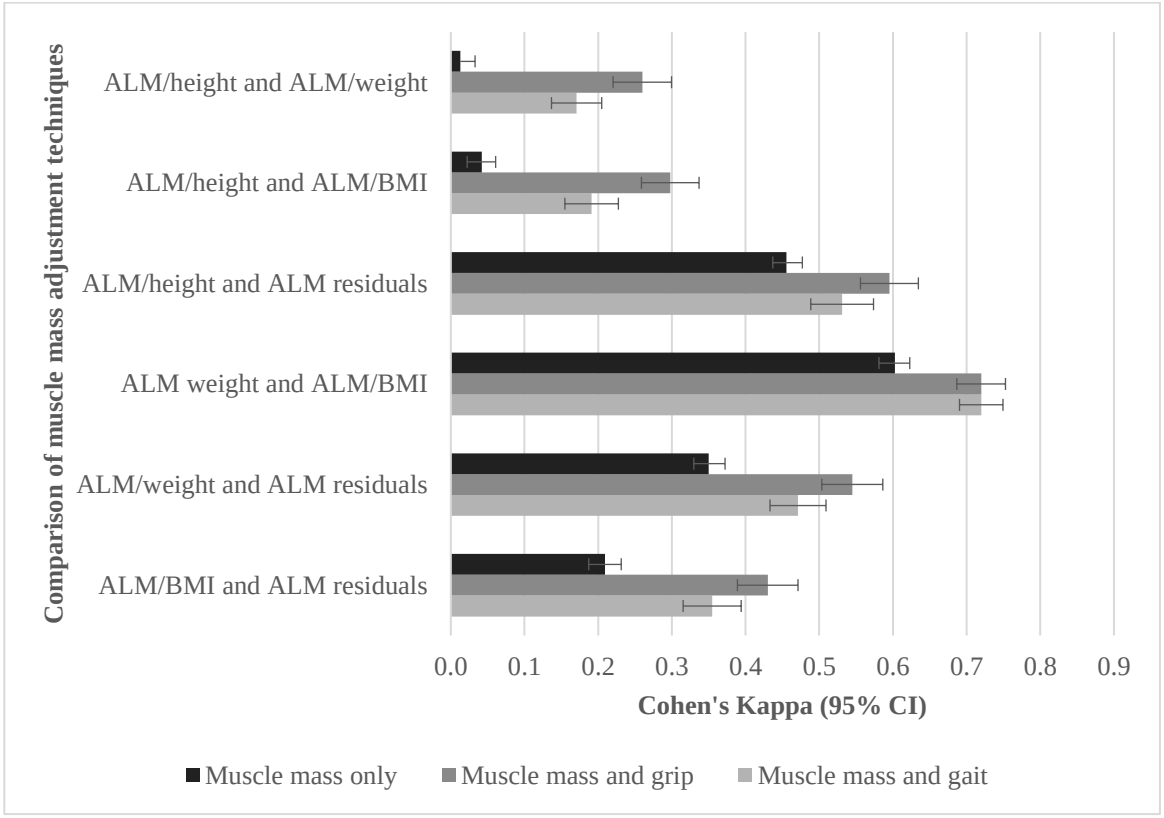


Fig 4 the agreement between methods of adjusting muscle mass for different combinations of muscle mass variables in females. Cohen's kappa statistics are provided for the agreement between the four methods of adjusting muscle mass (ALM/height, ALM/weight, ALM/BMI, and the ALM residuals)

Supplementary Material

Supplementary Table 1. The percentage of male participants identified as sarcopenic for each combination of muscle variables, adjustment techniques for muscle mass, and the 10th, 20th, and 40th percentile cut offs, stratified by age group

Muscle mass adjustment technique	Age group (years)	Muscle mass only			Muscle mass and grip strength			Muscle mass and gait speed		
		Number sarcopenic	Number without sarcopenia	Percentage sarcopenic (95% CI)	Number sarcopenic	Number without sarcopenia	Percentage sarcopenic (95% CI)	Number sarcopenic	Number without sarcopenia	Percentage sarcopenic (95% CI)
10th percentile cut points										
ALM/height	**45 - 54**	82	3048	2.6 (2.1 - 3.2)	6	3124	0.2 (0.1 - 0.4)	9	3121	0.3 (0.1 - 0.5)
	55 - 64	196	3957	4.7 (4.1 - 5.4)	31	4122	0.7 (0.5 – 1.0)	31	4122	0.7 (0.5 – 1.0)
	65 - 74	210	2934	6.7 (5.8 - 7.6)	44	3100	1.4 (1.0 - 1.8)	49	3095	1.6 (1.1 – 2.0)
	75 - 85	328	1906	14.7 (13.2 - 16.2)	109	2125	4.9 (4.0 - 5.8)	116	2118	5.2 (4.3 - 6.1)
	45 - 85	816	11845	6.4 (6.0 - 6.9)	190	12471	1.5 (1.3 - 1.7)	205	12456	1.6 (1.4 - 1.8)
ALM/weight	**45 - 54**	118	3012	3.8 (3.1 - 4.5)	9	3121	0.3 (0.1 - 0.5)	18	3112	0.6 (0.3 - 0.9)
	55 - 64	244	3909	5.9 (5.2 - 6.6)	35	4118	0.8 (0.6 - 1.1)	49	4104	1.2 (0.9 - 1.5)
	65 - 74	273	2871	8.7 (7.7 - 9.7)	51	3093	1.6 (1.2 - 2.1)	98	3046	3.1 (2.5 - 3.8)
	75 - 85	265	1969	11.9 (10.5 - 13.2)	92	2142	4.1 (3.3 – 5.0)	105	2129	4.7 (3.8 - 5.6)
	45 - 85	900	11761	7.1 (6.7 - 7.5)	187	12474	1.5 (1.3 - 1.7)	270	12391	2.1 (1.9 - 2.4)
ALM/BMI	**45 - 54**	76	3054	2.4 (1.9 – 3.0)	9	3121	0.3 (0.1 - 0.5)	12	3118	0.4 (0.2 - 0.6)
	55 - 64	192	3961	4.6 (4.0 - 5.3)	34	4119	0.8 (0.6 - 1.1)	44	4109	1.1 (0.7 - 1.4)
	65 - 74	255	2889	8.1 (7.2 - 9.1)	65	3079	2.1 (1.6 - 2.6)	98	3046	3.1 (2.5 - 3.8)
	75 - 85	283	1951	12.7 (11.3 - 14)	118	2116	5.3 (4.4 - 6.2)	116	2118	5.2 (4.3 - 6.1)
	45 - 85	806	11855	6.4 (5.9 - 6.8)	226	12435	1.8 (1.6 – 2.0)	270	12391	2.1 (1.9 - 2.4)
ALM residuals	**45 - 54**	60	3070	1.9 (1.4 - 2.4)	5	3125	0.2 (0.0 - 0.3)	7	3123	0.2 (0.1 - 0.4)
	55 - 64	172	3981	4.1 (3.5 - 4.7)	21	4132	0.5 (0.3 - 0.7)	25	4128	0.6 (0.4 - 0.8)
	65 - 74	210	2934	6.7 (5.8 - 7.6)	33	3111	1.0 (0.7 - 1.4)	55	3089	1.7 (1.3 - 2.2)

	75 - 85	328	1906	14.7 (13.2 - 16.2)	102	2132	4.6 (3.7 - 5.5)	117	2117	5.2 (4.3 - 6.2)
	45 - 85	770	11891	6.1 (5.7 - 6.5)	161	12500	1.3 (1.1 - 1.5)	204	12457	1.6 (1.4 - 1.8)
20th percentile cut points										
ALM/height	**45 - 54**	190	2940	6.1 (5.2 - 6.9)	16	3114	0.5 (0.3 - 0.8)	16	3114	0.5 (0.3 - 0.8)
	55 - 64	380	3773	9.2 (8.3 – 10.0)	36	4117	0.9 (0.6 - 1.2)	49	4104	1.2 (0.9 - 1.5)
	65 - 74	443	2701	14.1 (12.9 - 15.3)	74	3070	2.4 (1.8 - 2.9)	84	3060	2.7 (2.1 - 3.2)
	75 - 85	633	1601	28.3 (26.5 - 30.2)	191	2043	8.5 (7.4 - 9.7)	197	2037	8.8 (7.7 – 10.0)
	45 - 85	1646	11015	13 (12.4 - 13.6)	317	12344	2.5 (2.2 - 2.8)	346	12315	2.7 (2.5 – 3.0)
ALM/weight	**45 - 54**	211	2919	6.7 (5.9 - 7.6)	13	3117	0.4 (0.2 - 0.6)	32	3098	1.0 (0.7 - 1.4)
	55 - 64	466	3687	11.2 (10.3 - 12.2)	50	4103	1.2 (0.9 - 1.5)	88	4065	2.1 (1.7 - 2.6)
	65 - 74	572	2572	18.2 (16.9 - 19.5)	88	3056	2.8 (2.2 - 3.4)	175	2969	5.6 (4.8 - 6.4)
	75 - 85	504	1730	22.6 (20.9 - 24.3)	157	2077	7.0 (6.0 - 8.1)	187	2047	8.4 (7.3 - 9.5)
	45 - 85	1753	10908	13.8 (13.2 - 14.4)	308	12353	2.4 (2.2 - 2.7)	482	12179	3.8 (3.5 - 4.1)
ALM/BMI	**45 - 54**	160	2970	5.1 (4.3 - 5.9)	16	3114	0.5 (0.3 - 0.8)	23	3107	0.7 (0.4 - 1.1)
	55 - 64	407	3746	9.8 (8.9 - 10.7)	51	4102	1.2 (0.9 - 1.6)	82	4071	2.0 (1.6 - 2.4)
	65 - 74	514	2630	16.3 (15.1 - 17.6)	100	3044	3.2 (2.6 - 3.8)	169	2975	5.4 (4.6 - 6.2)
	75 - 85	562	1672	25.2 (23.4 - 26.9)	209	2025	9.4 (8.2 - 10.5)	200	2034	9.0 (7.8 - 10.1)
	45 - 85	1643	11018	13 (12.4 - 13.6)	376	12285	3.0 (2.7 - 3.3)	474	12187	3.7 (3.4 - 4.1)
ALM residuals	**45 - 54**	146	2984	4.7 (3.9 - 5.4)	13	3117	0.4 (0.2 - 0.6)	13	3117	0.4 (0.2 - 0.6)
	55 - 64	355	3798	8.5 (7.7 - 9.4)	37	4116	0.9 (0.6 - 1.2)	53	4100	1.3 (0.9 - 1.6)
	65 - 74	463	2681	14.7 (13.5 - 16)	66	3078	2.1 (1.6 - 2.6)	98	3046	3.1 (2.5 - 3.8)
	75 - 85	613	1621	27.4 (25.6 - 29.3)	171	2063	7.7 (6.6 - 8.7)	199	2035	8.9 (7.7 - 10.1)
	45 - 85	1577	11084	12.5 (11.9 - 13)	287	12374	2.3 (2.0 - 2.5)	363	12298	2.9 (2.6 - 3.2)
40th percentile cut points										
ALM/height	**45 - 54**	493	2637	15.8 (14.5 – 17.0)	25	3105	0.8 (0.5 - 1.1)	32	3098	1.0 (0.7 - 1.4)
	55 - 64	857	3296	20.6 (19.4 - 21.9)	50	4103	1.2 (0.9 - 1.5)	82	4071	2.0 (1.6 - 2.4)
	65 - 74	986	2158	31.4 (29.8 – 33.0)	119	3025	3.8 (3.1 - 4.5)	162	2982	5.2 (4.4 – 6.0)
	75 - 85	1165	1069	52.1 (50.0 - 54.3)	304	1930	13.6 (12.2 - 15)	351	1883	15.7 (14.2 - 17.2)
	45 - 85	3501	9160	27.7 (26.9 - 28.4)	498	12163	3.9 (3.6 - 4.3)	627	12034	5.0 (4.6 - 5.3)

ALM/weight	**45 - 54**	503	2627	16.1 (14.8 - 17.4)	29	3101	0.9 (0.6 - 1.3)	44	3086	1.4 (1.0 - 1.8)
	55 - 64	1023	3130	24.6 (23.3 - 25.9)	77	4076	1.9 (1.4 - 2.3)	147	4006	3.5 (3.0 - 4.1)
	65 - 74	1142	2002	36.3 (34.7 – 38.0)	136	3008	4.3 (3.6 - 5.1)	261	2883	8.3 (7.4 - 9.3)
	75 - 85	1009	1225	45.2 (43.1 - 47.3)	274	1960	12.3 (10.9 - 13.6)	356	1878	15.9 (14.4 - 17.4)
	45 - 85	3677	8984	29.0 (28.2 - 29.8)	516	12145	4.1 (3.7 - 4.4)	808	11853	6.4 (6.0 - 6.8)
ALM/BMI	**45 - 54**	471	2659	15.0 (13.8 - 16.3)	28	3102	0.9 (0.6 - 1.2)	48	3082	1.5 (1.1 – 2.0)
	55 - 64	918	3235	22.1 (20.9 - 23.4)	86	4067	2.1 (1.6 - 2.5)	144	4009	3.5 (2.9 – 4.0)
	65 - 74	1091	2053	34.7 (33.1 - 36.4)	147	2997	4.7 (4.0 - 5.4)	270	2874	8.6 (7.6 - 9.6)
	75 - 85	1060	1174	47.4 (45.4 - 49.6)	312	1922	14 (12.5 - 15.4)	360	1874	16.1 (14.6 - 17.6)
	45 - 85	3540	9121	28.0 (27.2 - 28.7)	573	12088	4.5 (4.2 - 4.9)	822	11839	6.5 (6.1 - 6.9)
ALM residuals	**45 - 54**	441	2689	14.1 (12.9 - 15.3)	31	3099	1.0 (0.7 - 1.3)	33	3097	1.1 (0.7 - 1.4)
	55 - 64	829	3324	20.0 (18.8 - 21.2)	63	4090	1.5 (1.2 - 1.9)	106	4047	2.6 (2.1 – 3.0)
	65 - 74	1024	2120	32.6 (31.0 - 34.2)	133	3011	4.2 (3.5 – 5.0)	199	2945	6.3 (5.5 - 7.2)
	75 - 85	1127	1107	50.4 (48.4 - 52.6)	283	1951	12.7 (11.3 - 14)	360	1874	16.1 (14.6 - 17.6)
	45 - 85	3421	9240	27.0 (26.2 - 27.8)	510	12151	4.0 (3.7 - 4.4)	698	11963	5.5 (5.1 - 5.9)

Supplementary Table 2. The percentage of female participants identified as sarcopenic for each combination of muscle variables, adjustment techniques for muscle mass, and the 10th, 20th, and 40th percentile cut offs, stratified by age group

Muscle mass adjustment technique	Age group (years)	Muscle mass only			Muscle mass and grip strength			Muscle mass and gait speed		
		Number sarcopenic	Number without sarcopenia	Percentage sarcopenic (95% CI)	Number sarcopenic	Number without sarcopenia	Percentage sarcopenic (95% CI)	Number sarcopenic	Number without sarcopenia	Percentage sarcopenic (95% CI)
10th percentile cut points										
ALM/height	**45 - 54**	129	3239	3.1 (2.4 - 3.5)	8	3360	0.3 (0.1 - 0.5)	7	3361	0.7 (0.5 – 1.0)
	55 - 64	251	4054	7.7 (7.0 - 8.4)	44	4261	1.2 (0.9 - 1.6)	29	4276	2.2 (2.0 - 2.6)
	65 - 74	257	2724	10.0 (9.0 – 11.0)	58	2923	2.5 (2.0 - 3.1)	41	2940	4.0 (3.5 - 4.7)
	75 - 85	249	1831	10.0 (8.6 - 11.3)	131	1949	5.3 (4.3 - 6.4)	103	1977	5.8 (4.9 - 6.9)
	45 - 85	886	11849	7.0 (6.6 - 7.4)	241	12494	1.9 (1.7 - 2.1)	180	12555	1.4 (1.2 - 1.6)
ALM/weight	**45 - 54**	104	3264	3.1 (2.4 - 3.5)	9	3359	0.3 (0.1 - 0.5)	24	3344	0.7 (0.5 – 1.0)
	55 - 64	332	3973	7.7 (7.0 - 8.4)	53	4252	1.2 (0.9 - 1.6)	95	4210	2.2 (2.0 - 2.6)
	65 - 74	298	2683	10.0 (9.0 – 11.0)	75	2906	2.5 (2.0 - 3.1)	118	2863	4.0 (3.5 - 4.7)
	75 - 85	208	1872	10.0 (8.6 - 11.3)	111	1969	5.3 (4.3 - 6.4)	121	1959	5.8 (4.9 - 6.9)
	45 - 85	942	11793	7.4 (7.0 - 7.8)	248	12487	1.9 (1.7 - 2.1)	358	12377	2.8 (2.5 - 3.1)
ALM/BMI	**45 - 54**	57	3311	1.7 (1.1 - 2.3)	11	3357	1.1 (0.8 - 1.4)	16	3352	2.1 (1.5 - 2.5)
	55 - 64	224	4081	5.2 (4.4 - 5.9)	55	4250	3.9 (3.4 - 4.5)	63	4242	5.2 (1.5 - 2.5)
	65 - 74	276	2705	9.3 (8.2 - 10.3)	80	2901	8.2 (7.3 - 9.1)	112	2869	10.6 (9.5 - 11.6)
	75 - 85	230	1850	11.1 (9.8 - 12.4)	143	1937	20.9 (19.3 - 22.5)	130	1950	21.8 (20.1 - 23.4)
	45 - 85	787	11948	6.2 (5.8 - 6.6)	289	12446	2.3 (2.0 - 2.6)	321	12414	2.5 (2.2 - 2.8)
ALM residuals	**45 - 54**	98	3270	2.9 (2.3 - 3.5)	6	3362	0.2 (0.0 - 0.3)	13	3355	0.4 (0.1 - 0.6)
	55 - 64	311	3994	7.2 (6.4 – 8.0)	48	4257	1.1 (0.8 - 1.4)	55	4250	1.3 (0.8 - 1.6)
	65 - 74	281	2700	9.4 (8.4 - 10.5)	64	2917	2.1 (1.6 - 2.7)	67	2914	2.2 (1.5 - 2.8)
	75 - 85	225	1855	10.8 (9.6 - 12.2)	109	1971	5.2 (4.3 - 6.2)	110	1970	5.3 (4.3 - 6.3)
	45 - 85	915	11820	7.2 (6.8 - 7.6)	227	12508	1.8 (1.6 – 2.0)	245	12490	1.9 (1.7 - 2.1)

20th percentile cut points										
ALM/height	**45 - 54**	352	3016	10.5 (9.4 - 11.5)	20	3348	0.6 (0.4 - 0.9)	17	3351	0.5 (0.3 - 0.7)
	55 - 64	585	3720	13.6 (12.6 - 14.6)	79	4226	1.8 (1.4 - 2.2)	70	4235	1.6 (1.3 – 2.0)
	65 - 74	515	2466	17.3 (15.9 - 18.6)	108	2873	3.6 (3.0 - 4.3)	85	2896	2.9 (2.3 - 3.5)
	75 - 85	497	1583	23.9 (22.1 - 25.7)	253	1827	12.2 (10.8 - 13.6)	193	1887	9.3 (8.1 - 10.5)
	45 - 85	1949	10785	15.3 (14.7 - 15.9)	460	12274	3.6 (3.3 - 3.9)	365	12369	2.9 (2.6 - 3.2)
ALM/weight	**45 - 54**	236	3132	7.0 (6.2 - 7.9)	15	3353	0.4 (0.2 - 0.7)	43	3325	1.3 (0.9 - 1.7)
	55 - 64	641	3664	14.9 (13.9 - 15.9)	96	4209	2.2 (1.8 - 2.7)	149	4156	3.5 (2.9 – 4.0)
	65 - 74	586	2395	19.7 (18.3 - 21.1)	119	2862	4.0 (3.3 - 4.7)	192	2789	6.4 (5.6 - 7.3)
	75 - 85	426	1654	20.5 (18.8 - 22.3)	199	1881	9.6 (8.4 - 10.8)	238	1842	11.4 (10.1 - 12.8)
	45 - 85	1889	10845	14.8 (14.2 - 15.5)	429	12305	3.4 (3.1 - 3.7)	622	12112	4.9 (4.5 - 5.3)
ALM/BMI	**45 - 54**	147	3221	4.4 (3.7 – 5.0)	16	3352	0.5 (0.3 - 0.7)	27	3341	0.8 (0.5 - 1.1)
	55 - 64	498	3807	11.6 (10.6 - 12.5)	100	4205	2.3 (1.9 - 2.8)	117	4188	2.7 (2.2 - 3.2)
	65 - 74	554	2427	18.6 (17.2 – 20.0)	153	2828	5.1 (4.4 - 5.9)	181	2800	6.1 (5.2 - 6.9)
	75 - 85	458	1622	22.0(20.3 - 23.8)	239	1841	11.5 (10.1 - 12.8)	232	1848	11.2 (9.8 - 12.5)
	45 - 85	1657	11077	13.0 (12.4 - 13.6)	508	12226	4.0 (3.7 - 4.3)	557	12177	4.4 (4.0 - 4.7)
ALM residuals	**45 - 54**	227	3141	6.7 (5.9 - 7.6)	10	3358	0.3 (0.1 - 0.5)	21	3347	0.6 (0.4 - 0.9)
	55 - 64	619	3686	14.4 (13.3 - 15.4)	88	4217	2.0 (1.6 - 2.5)	99	4206	2.3 (1.9 - 2.8)
	65 - 74	557	2424	18.7 (17.3 - 20.1)	109	2872	3.7 (3.0 - 4.4)	121	2860	4.1 (3.4 - 4.8)
	75 - 85	455	1625	21.9 (20.1 - 23.7)	200	1880	9.6 (8.4 - 10.9)	193	1887	9.3 (8.1 - 10.5)
	45 - 85	1858	10876	14.6 (14.0 - 15.2)	407	12327	3.2 (2.9 - 3.5)	434	12300	3.4 (3.1 - 3.7)
40th percentile cut points										
ALM/height	**45 - 54**	824	2544	24.5 (23 - 25.9)	40	3328	1.2 (0.8 - 1.5)	47	3321	1.4 (1.0 - 1.8)
	55 - 64	1323	2982	30.7 (29.4 - 32.1)	140	4165	3.3 (2.7 - 3.8)	153	4152	3.6 (3.0 - 4.1)
	65 - 74	1087	1894	36.5 (34.8 - 38.2)	195	2786	6.5 (5.7 - 7.4)	182	2799	6.1 (5.3 – 7.0)
	75 - 85	937	1143	45.0 (42.9 - 47.2)	404	1676	19.4 (17.7 - 21.2)	335	1745	16.1 (14.6 - 17.6)
	45 - 85	4171	8563	32.8 (31.9 - 33.6)	779	11955	6.1 (5.7 - 6.5)	717	12017	5.6 (5.2 – 6.0)
ALM/weight	**45 - 54**	588	2780	17.5 (16.2 - 18.7)	41	3327	1.2 (0.9 - 1.6)	94	3274	2.8 (2.2 - 3.4)
	55 - 64	1371	2934	31.8 (30.5 - 33.3)	157	4148	3.6 (3.1 - 4.2)	267	4038	6.2 (5.5 - 6.9)

	65 - 74	1174	1807	39.4 (37.7 - 41.1)	218	2763	7.3 (6.4 - 8.3)	340	2641	11.4 (10.3 - 12.5)
	75 - 85	850	1230	40.9 (38.8 - 43)	359	1721	17.3 (15.6 - 18.8)	429	1651	20.6 (18.9 - 22.4)
	45 - 85	3983	8751	31.3 (30.5 - 32.1)	775	11959	6.1 (5.7 - 6.5)	1130	11604	8.9 (8.4 - 9.4)
ALM/BMI	**45 - 54**	421	2947	12.5 (11.4 - 13.6)	38	3330	1.1 (0.8 - 1.5)	70	3298	2.1 (1.6 - 2.6)
	55 - 64	1153	3152	26.8 (25.5 - 28.1)	169	4136	3.9 (3.4 - 4.5)	222	4083	5.2 (4.5 - 5.8)
	65 - 74	1120	1861	37.6 (35.9 - 39.3)	245	2736	8.2 (7.3 - 9.2)	317	2664	10.6 (9.5 - 11.7)
	75 - 85	904	1176	43.5 (41.3 - 45.6)	435	1645	20.9 (19.2 - 22.7)	453	1627	21.8 (20.0 - 23.6)
	45 - 85	3598	9136	28.3 (27.5 – 29.0)	887	11847	7.0 (6.5 - 7.4)	1062	11672	8.3 (7.9 - 8.8)
ALM residuals	**45 - 54**	625	2743	18.6 (17.3 - 19.9)	30	3338	0.9 (0.6 - 1.2)	58	3310	1.7 (1.3 - 2.2)
	55 - 64	1342	2963	31.2 (29.8 - 32.6)	149	4156	3.5 (2.9 – 4.0)	187	4118	4.3 (3.8 - 4.9)
	65 - 74	1137	1844	38.1 (36.4 - 39.9)	200	2781	6.7 (5.8 - 7.6)	240	2741	8.1 (7.1 – 9.0)
	75 - 85	887	1193	42.6 (40.5 - 44.8)	376	1704	18.1 (16.4 - 19.7)	368	1712	17.7 (16.1 - 19.3)
	45 - 85	3991	8743	31.3 (30.5 - 32.1)	755	11979	5.9 (5.5 - 6.3)	853	11881	6.7 (6.3 - 7.1)

Supplementary Table 3. Agreement (Cohen's kappa) between sarcopenia definitions including muscle mass and grip strength and muscle mass and gait speed by each muscle mass adjustment technique

Comparison	Threshold percentile	Males							
		45 - 54 years		55 - 64 years		65 - 74 years		75 - 85 years	
		kappa	95% CI	kappa	95% CI	kappa	95% CI	kappa	95% CI
Grip strength of <30kg and gait speed <0.8m/s		0.13	(0.07 - 0.2.0)	0.08	(0.04 - 0.12)	0.18	(0.13 - 0.22)	0.11	(0.07 - 0.15)
ALM height and grip strength versus ALM height and gait speed	**10**	0.40	(0.08 - 0.71)	0.28	(0.14 - 0.43)	0.44	(0.32 - 0.57)	0.33	(0.25 - 0.41)
	20	0.37	(0.16 - 0.59)	0.23	(0.11 - 0.35)	0.38	(0.28 - 0.47)	0.33	(0.26 - 0.39)
	40	0.20	(0.06 - 0.35)	0.14	(0.05 - 0.22)	0.30	(0.23 - 0.38)	0.27	(0.21 - 0.32)
ALM weight and grip strength versus ALM weight and gait speed	**10**	0.29	(0.07 - 0.52)	0.21	(0.09 - 0.32)	0.36	(0.26 - 0.46)	0.41	(0.32 - 0.50)
	20	0.31	(0.13 - 0.48)	0.18	(0.09 - 0.26)	0.32	(0.24 - 0.39)	0.35	(0.28 - 0.42)
	40	0.29	(0.16 - 0.43)	0.19	(0.11 - 0.26)	0.24	(0.18 - 0.30)	0.27	(0.22 - 0.32)
ALM BMI and grip strength versus ALM BMI and gait speed	**10**	0.47	(0.21 - 0.74)	0.17	(0.06 - 0.29)	0.41	(0.32 - 0.51)	0.39	(0.30 - 0.47)
	20	0.36	(0.16 - 0.55)	0.20	(0.11 - 0.29)	0.33	(0.26 - 0.40)	0.33	(0.27 - 0.39)
	40	0.23	(0.10 - 0.36)	0.19	(0.12 - 0.26)	0.26	(0.20 - 0.32)	0.26	(0.21 - 0.31)
ALM residuals and grip strength versus ALM residuals and gait speed	**10**	0.30	(0.07 - 0.54)	0.26	(0.14 - 0.38)	0.35	(0.25 - 0.44)	0.32	(0.26 - 0.39)
	20	0.33	(0.18 - 0.49)	0.20	(0.11 - 0.29)	0.31	(0.23 - 0.38)	0.27	(0.22 - 0.33)
	40	0.22	(0.10 - 0.33)	0.16	(0.09 - 0.22)	0.26	(0.20 - 0.32)	0.21	(0.16 - 0.26)
Comparison	**Threshold percentile**	**Females**							
		45 - 54 years		**55 - 64 years**		**65 - 74 years**		**75 - 85 years**	
		kappa	**95% CI**	**kappa**	**95% CI**	**kappa**	**95% CI**	**kappa**	**95% CI**
Grip strength of <20kg and gait speed <0.8m/s		0.09	(0.04 - 0.14)	0.13	(0.09 - 0.17)	0.12	(0.08 - 0.16)	0.17	(0.12 - 0.21)
ALM height and grip strength versus ALM height and gait speed	**10**	0.00	(0.00 – 0.00)	0.27	(0.13 - 0.4.0)	0.21	(0.10 - 0.32)	0.54	(0.46 - 0.62)
	20	0.05	(-0.05 - 0.15)	0.26	(0.16 - 0.35)	0.21	(0.13 - 0.29)	0.48	(0.42 - 0.54)
	40	0.13	(0.03 - 0.23)	0.22	(0.15 - 0.29)	0.22	(0.15 - 0.28)	0.42	(0.37 - 0.47)
ALM weight and grip strength versus ALM weight and gait speed	**10**	0.12	(-0.03 - 0.27)	0.29	(0.19 - 0.38)	0.30	(0.21 - 0.39)	0.61	(0.53 - 0.68)
	20	0.20	(0.06 - 0.34)	0.23	(0.16 - 0.31)	0.23	(0.17 - 0.30)	0.55	(0.49 - 0.61)
	40	0.15	(0.06 - 0.23)	0.19	(0.13 - 0.24)	0.22	(0.17 - 0.27)	0.45	(0.40 - 0.50)

ALM BMI and grip strength versus ALM BMI and gait speed	**10**	0.14	(-0.04 - 0.33)	0.33	(0.22 - 0.44)	0.34	(0.26 - 0.43)	0.64	(0.58 - 0.71)
	20	0.18	(0.02 - 0.34)	0.31	(0.22 - 0.39)	0.28	(0.22 - 0.35)	0.54	(0.48 - 0.60)
	40	0.17	(0.07 - 0.27)	0.23	(0.17 - 0.29)	0.24	(0.18 - 0.29)	0.43	(0.38 - 0.47)
ALM residuals and grip strength versus ALM residuals and gait speed	**10**	0.19	(0.00 - 0.38)	0.25	(0.16 - 0.35)	0.25	(0.17 - 0.33)	0.51	(0.44 - 0.58)
	20	0.12	(0.01 - 0.23)	0.22	(0.15 - 0.30)	0.24	(0.17 - 0.30)	0.48	(0.42 - 0.53)
	40	0.09	(0.01 - 0.17)	0.20	(0.14 - 0.26)	0.19	(0.14 - 0.24)	0.39	(0.35 - 0.44)

Supplementary Table 4. Agreement between muscle mass adjustment techniques in males stratified by age and muscle variables used to operationalize sarcopenia

Muscle mass adjustment comparison	Combination of muscle variables	45 - 54 years		55 to 64 years		65 to 74 years		75 and older	
		10th percentile threshold							
ALM/height vs ALM/weight	Mass only	0.02	(-0.02 - 0.06)	0.02	(-0.02 - 0.05)	0.03	(-0.01 - 0.07)	0.11	(0.06 - 0.15)
	Mass + grip	0.26	(-0.03 - 0.56)	0.18	(0.05 - 0.30)	0.24	(0.12 - 0.36)	0.26	(0.17 - 0.34)
	Mass + gait	0.22	(0.01 - 0.43)	0.04	(-0.03 - 0.11)	0.17	(0.09 - 0.26)	0.26	(0.18 - 0.34)
ALM/height vs ALM/BMI	Mass only	0.01	(-0.03 - 0.06)	0.04	(0.00 - 0.08)	0.06	(0.01 - 0.10)	0.10	(0.05 - 0.14)
	Mass + grip	0.26	(-0.03 - 0.56)	0.24	(0.10 - 0.38)	0.21	(0.10 - 0.31)	0.25	(0.17 - 0.33)
	Mass + gait	0.19	(-0.04 - 0.41)	0.04	(-0.03 - 0.12)	0.19	(0.10 - 0.28)	0.27	(0.19 - 0.35)
ALM/height vs ALM residuals	Mass only	0.49	(0.41 - 0.57)	0.58	(0.53 - 0.63)	0.47	(0.42 - 0.51)	0.52	(0.48 - 0.56)
	Mass + grip	0.63	(0.38 - 0.88)	0.72	(0.60 - 0.84)	0.70	(0.60 - 0.80)	0.68	(0.62 - 0.74)
	Mass + gait	0.73	(0.52 - 0.94)	0.57	(0.45 - 0.70)	0.58	(0.49 - 0.68)	0.64	(0.58 - 0.70)
ALM/weight vs ALM/BMI	Mass only	0.59	(0.50 - 0.67)	0.59	(0.53 - 0.64)	0.56	(0.51 - 0.61)	0.54	(0.49 - 0.60)
	Mass + grip	0.89	(0.74 - 1.00)	0.75	(0.64 - 0.87)	0.75	(0.67 - 0.84)	0.65	(0.57 - 0.73)
	Mass + gait	0.67	(0.47 - 0.86)	0.64	(0.53 - 0.76)	0.64	(0.56 - 0.72)	0.62	(0.55 - 0.70)
ALM/weight vs ALM residuals	Mass only	0.21	(0.15 - 0.28)	0.22	(0.17 - 0.27)	0.30	(0.25 - 0.34)	0.31	(0.27 - 0.36)
	Mass + grip	0.36	(0.10 - 0.62)	0.38	(0.24 - 0.52)	0.45	(0.33 - 0.56)	0.50	(0.42 - 0.57)
	Mass + gait	0.38	(0.17 - 0.60)	0.32	(0.21 - 0.44)	0.47	(0.38 - 0.56)	0.44	(0.37 - 0.51)
ALM/BMI vs ALM residuals	Mass only	0.09	(0.03 - 0.15)	0.14	(0.09 - 0.18)	0.16	(0.12 - 0.21)	0.14	(0.10 - 0.19)
	Mass + grip	0.27	(0.03 - 0.52)	0.33	(0.19 - 0.47)	0.35	(0.24 - 0.46)	0.36	(0.29 - 0.44)
	Mass + gait	0.32	(0.08 - 0.55)	0.26	(0.15 - 0.38)	0.33	(0.24 - 0.41)	0.30	(0.23 - 0.37)
		20th percentile threshold							
ALM/height vs ALM/weight	Mass only	0.00	(-0.04 - 0.03)	0.03	(0.00 - 0.07)	0.05	(0.02 - 0.09)	0.17	(0.13 - 0.22)
	Mass + grip	0.27	(0.06 - 0.49)	0.25	(0.13 - 0.37)	0.27	(0.17 - 0.36)	0.42	(0.35 - 0.49)
	Mass + gait	0.24	(0.08 - 0.41)	0.12	(0.04 - 0.20)	0.25	(0.18 - 0.32)	0.37	(0.30 - 0.43)

ALM/height vs ALM/BMI	**Mass only**	0.03	(-0.01 - 0.07)	0.06	(0.02 - 0.09)	0.07	(0.03 - 0.11)	0.13	(0.09 - 0.17)
	Mass + grip	0.37	(0.16 - 0.59)	0.29	(0.17 - 0.42)	0.35	(0.26 - 0.44)	0.43	(0.37 - 0.50)
	Mass + gait	0.30	(0.11 - 0.49)	0.14	(0.06 - 0.22)	0.27	(0.20 - 0.35)	0.36	(0.30 - 0.43)
ALM/height vs ALM residuals	**Mass only**	0.55	(0.50 - 0.60)	0.58	(0.54 - 0.61)	0.52	(0.48 - 0.55)	0.59	(0.56 - 0.62)
	Mass + grip	0.71	(0.56 - 0.86)	0.76	(0.66 - 0.86)	0.68	(0.60 - 0.76)	0.73	(0.69 - 0.78)
	Mass + gait	0.56	(0.39 - 0.73)	0.65	(0.56 - 0.74)	0.59	(0.52 - 0.66)	0.68	(0.63 - 0.73)
ALM/weight vs ALM/BMI	**Mass only**	0.54	(0.48 - 0.61)	0.60	(0.56 - 0.64)	0.58	(0.54 - 0.62)	0.58	(0.54 - 0.62)
	Mass + grip	0.62	(0.41 - 0.83)	0.75	(0.65 - 0.84)	0.75	(0.68 - 0.82)	0.70	(0.64 - 0.75)
	Mass + gait	0.76	(0.64 - 0.89)	0.72	(0.65 - 0.80)	0.76	(0.71 - 0.81)	0.71	(0.66 - 0.76)
ALM/weight vs ALM residuals	**Mass only**	0.22	(0.17 - 0.27)	0.25	(0.21 - 0.29)	0.27	(0.24 - 0.31)	0.34	(0.3 - 0.37)
	Mass + grip	0.47	(0.29 - 0.66)	0.50	(0.38 - 0.62)	0.50	(0.42 - 0.59)	0.59	(0.53 - 0.65)
	Mass + gait	0.58	(0.43 - 0.72)	0.41	(0.31 - 0.50)	0.53	(0.46 - 0.60)	0.53	(0.47 - 0.58)
ALM/BMI vs ALM residuals	**Mass only**	0.13	(0.08 - 0.18)	0.17	(0.13 - 0.21)	0.13	(0.09 - 0.17)	0.18	(0.14 - 0.22)
	Mass + grip	0.44	(0.26 - 0.62)	0.44	(0.32 - 0.56)	0.45	(0.37 - 0.54)	0.54	(0.49 - 0.60)
	Mass + gait	0.52	(0.36 - 0.69)	0.38	(0.28 - 0.47)	0.38	(0.31 - 0.44)	0.42	(0.36 - 0.48)
		40th percentile threshold							
ALM/height vs ALM/weight	**Mass only**	0.04	(0.00 - 0.07)	0.02	(-0.01 - 0.05)	0.07	(0.03 - 0.10)	0.15	(0.11 - 0.20)
	Mass + grip	0.36	(0.20 - 0.53)	0.37	(0.26 - 0.48)	0.51	(0.44 - 0.59)	0.64	(0.59 - 0.69)
	Mass + gait	0.28	(0.15 - 0.42)	0.28	(0.20 - 0.36)	0.37	(0.31 - 0.43)	0.48	(0.43 - 0.53)
ALM/height vs ALM/BMI	**Mass only**	0.06	(0.02 - 0.10)	0.01	(-0.02 - 0.04)	0.04	(0.00 - 0.07)	0.10	(0.06 - 0.14)
	Mass + grip	0.45	(0.28 - 0.62)	0.46	(0.36 - 0.57)	0.54	(0.46 - 0.61)	0.67	(0.63 - 0.72)
	Mass + gait	0.32	(0.18 - 0.45)	0.27	(0.20 - 0.35)	0.38	(0.32 - 0.44)	0.47	(0.42 - 0.52)
ALM/height vs ALM residuals	**Mass only**	0.62	(0.59 - 0.66)	0.60	(0.57 - 0.62)	0.60	(0.57 - 0.63)	0.60	(0.57 - 0.63)
	Mass + grip	0.82	(0.71 - 0.92)	0.66	(0.56 - 0.75)	0.80	(0.75 - 0.85)	0.89	(0.86 - 0.92)
	Mass + gait	0.71	(0.60 - 0.82)	0.67	(0.60 - 0.74)	0.70	(0.66 - 0.75)	0.80	(0.77 - 0.83)
ALM/weight vs ALM/BMI	**Mass only**	0.61	(0.57 - 0.65)	0.62	(0.59 - 0.65)	0.61	(0.58 - 0.64)	0.57	(0.54 - 0.61)
	Mass + grip	0.81	(0.69 - 0.92)	0.86	(0.80 - 0.91)	0.83	(0.78 - 0.87)	0.84	(0.81 - 0.87)
	Mass + gait	0.74	(0.63 - 0.84)	0.82	(0.77 - 0.87)	0.79	(0.75 - 0.83)	0.77	(0.73 - 0.81)

ALM/weight vs ALM residuals	**Mass only**	0.26	(0.22 - 0.29)	0.25	(0.22 - 0.28)	0.33	(0.30 - 0.37)	0.33	(0.30 - 0.37)
	Mass + grip	0.61	(0.47 - 0.75)	0.67	(0.58 - 0.75)	0.73	(0.67 - 0.79)	0.74	(0.70 - 0.79)
	Mass + gait	0.56	(0.44 - 0.68)	0.56	(0.49 - 0.62)	0.64	(0.59 - 0.69)	0.64	(0.60 - 0.68)
ALM/BMI vs ALM residuals	**Mass only**	0.18	(0.14 - 0.22)	0.14	(0.11 - 0.17)	0.18	(0.15 - 0.22)	0.15	(0.11 - 0.19)
	Mass + grip	0.56	(0.41 - 0.70)	0.68	(0.60 - 0.76)	0.70	(0.64 - 0.76)	0.75	(0.71 - 0.79)
	Mass + gait	0.47	(0.35 - 0.59)	0.49	(0.42 - 0.56)	0.56	(0.51 - 0.62)	0.57	(0.52 - 0.61)

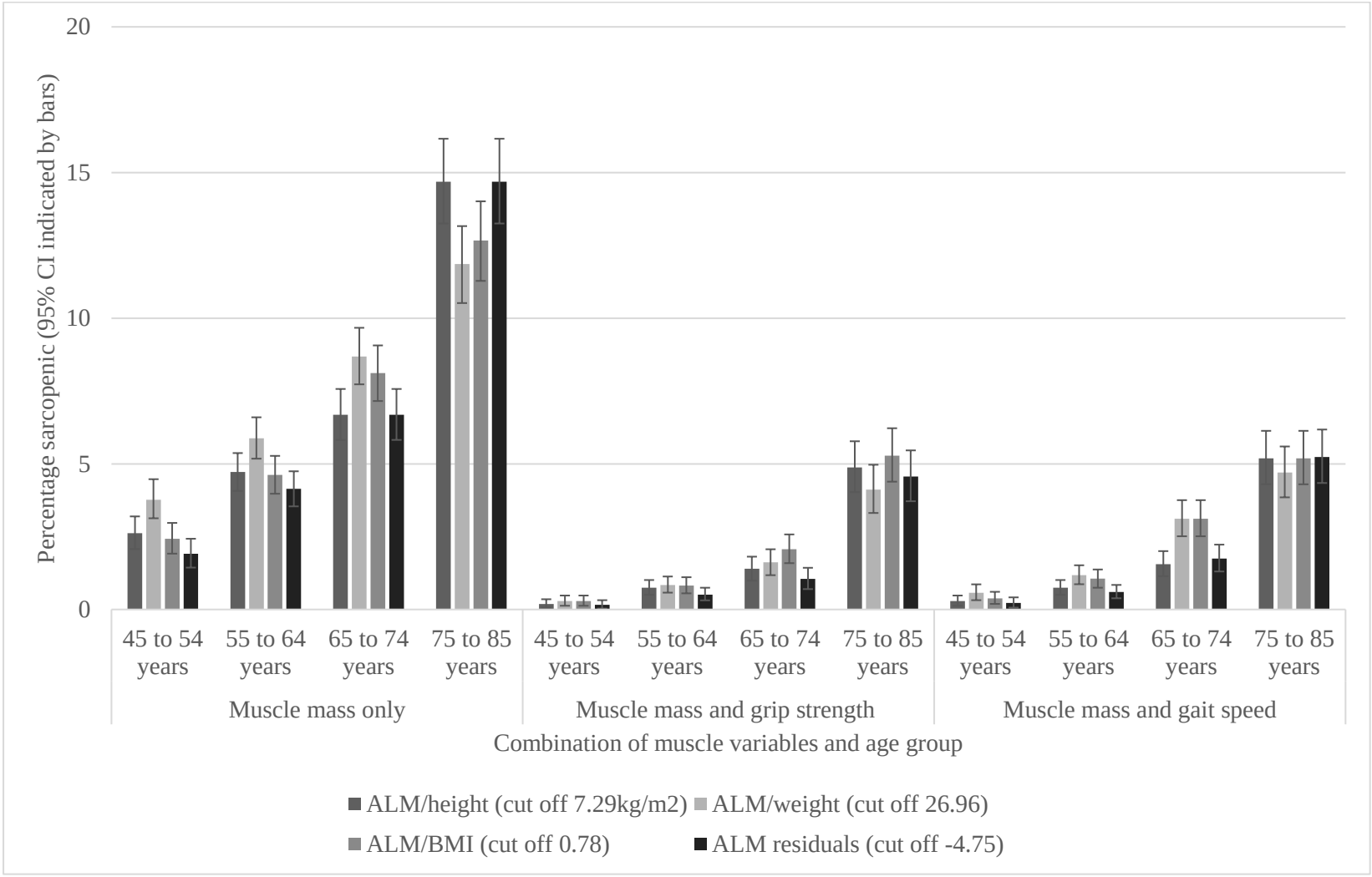
Supplementary Table 5. Agreement between muscle mass adjustment techniques in females stratified by age and muscle variables used to operationalize sarcopenia

Muscle mass adjustment comparison	Combination of muscle variables	45 - 54 years		55 to 64 years		65 to 74 years		75 and older	
		10th percentile threshold							
ALM/height vs ALM/weight	Mass only	0.00	(-0.03 - 0.03)	0.01	(-0.02 - 0.04)	0.02	(-0.02 - 0.06)	0.09	(0.04 - 0.14)
	Mass + grip	0.00	(0.00 - 0.00)	0.16	(0.05 - 0.26)	0.15	(0.06 - 0.23)	0.17	(0.10 - 0.24)
	Mass + gait	0.06	(-0.06 - 0.18)	0.05	(-0.01 - 0.11)	0.06	(0.00 - 0.11)	0.13	(0.06 - 0.20)
ALM/height vs ALM/BMI	Mass only	0.00	(-0.03 - 0.03)	0.04	(0.00 - 0.08)	0.03	(-0.01 - 0.06)	0.11	(0.05 - 0.16)
	Mass + grip	0.10	(-0.09 - 0.29)	0.17	(0.07 - 0.28)	0.15	(0.07 - 0.24)	0.17	(0.10 - 0.24)
	Mass + gait	0.00	(0.00 - 0.00)	0.10	(0.01 - 0.19)	0.09	(0.02 - 0.15)	0.18	(0.10 - 0.25)
ALM/height vs ALM residuals	Mass only	0.42	(0.35 - 0.49)	0.35	(0.30 - 0.39)	0.38	(0.33 - 0.43)	0.43	(0.37 - 0.48)
	Mass + grip	0.33	(0.05 - 0.61)	0.46	(0.35 - 0.58)	0.50	(0.40 - 0.60)	0.50	(0.43 - 0.57)
	Mass + gait	0.36	(0.13 - 0.58)	0.35	(0.24 - 0.47)	0.39	(0.29 - 0.49)	0.52	(0.43 - 0.60)
ALM/weight vs ALM/BMI	Mass only	0.50	(0.40 - 0.59)	0.56	(0.51 - 0.61)	0.58	(0.53 - 0.63)	0.55	(0.49 - 0.61)
	Mass + grip	0.50	(0.23 - 0.77)	0.76	(0.67 - 0.85)	0.60	(0.50 - 0.69)	0.61	(0.53 - 0.68)
	Mass + gait	0.65	(0.48 - 0.82)	0.66	(0.58 - 0.75)	0.67	(0.59 - 0.74)	0.57	(0.50 - 0.65)
ALM/weight vs ALM residuals	Mass only	0.19	(0.13 - 0.26)	0.26	(0.22 - 0.31)	0.32	(0.27 - 0.37)	0.36	(0.31 - 0.42)
	Mass + grip	0.31	(0.04 - 0.59)	0.51	(0.40 - 0.61)	0.50	(0.41 - 0.60)	0.48	(0.39 - 0.56)
	Mass + gait	0.49	(0.31 - 0.67)	0.35	(0.26 - 0.44)	0.40	(0.32 - 0.49)	0.47	(0.40 - 0.55)
ALM/BMI vs ALM residuals	Mass only	0.11	(0.05 - 0.17)	0.16	(0.12 - 0.20)	0.16	(0.12 - 0.21)	0.19	(0.14 - 0.24)
	Mass + grip	0.09	(-0.08 - 0.27)	0.45	(0.35 - 0.56)	0.32	(0.23 - 0.42)	0.31	(0.24 - 0.38)
	Mass + gait	0.38	(0.18 - 0.57)	0.31	(0.21 - 0.40)	0.27	(0.19 - 0.35)	0.28	(0.21 - 0.35)
		20th percentile threshold							
ALM/height vs ALM/weight	Mass only	-0.01	(-0.04 - 0.03)	-0.02	(-0.04 - 0.01)	-0.03	(-0.06 - 0.01)	0.05	(0.00 - 0.09)
	Mass + grip	0.05	(-0.06 - 0.16)	0.27	(0.18 - 0.36)	0.25	(0.18 - 0.33)	0.22	(0.16 - 0.28)
	Mass + gait	0.09	(-0.01 - 0.20)	0.14	(0.07 - 0.20)	0.12	(0.06 - 0.17)	0.19	(0.13 - 0.24)

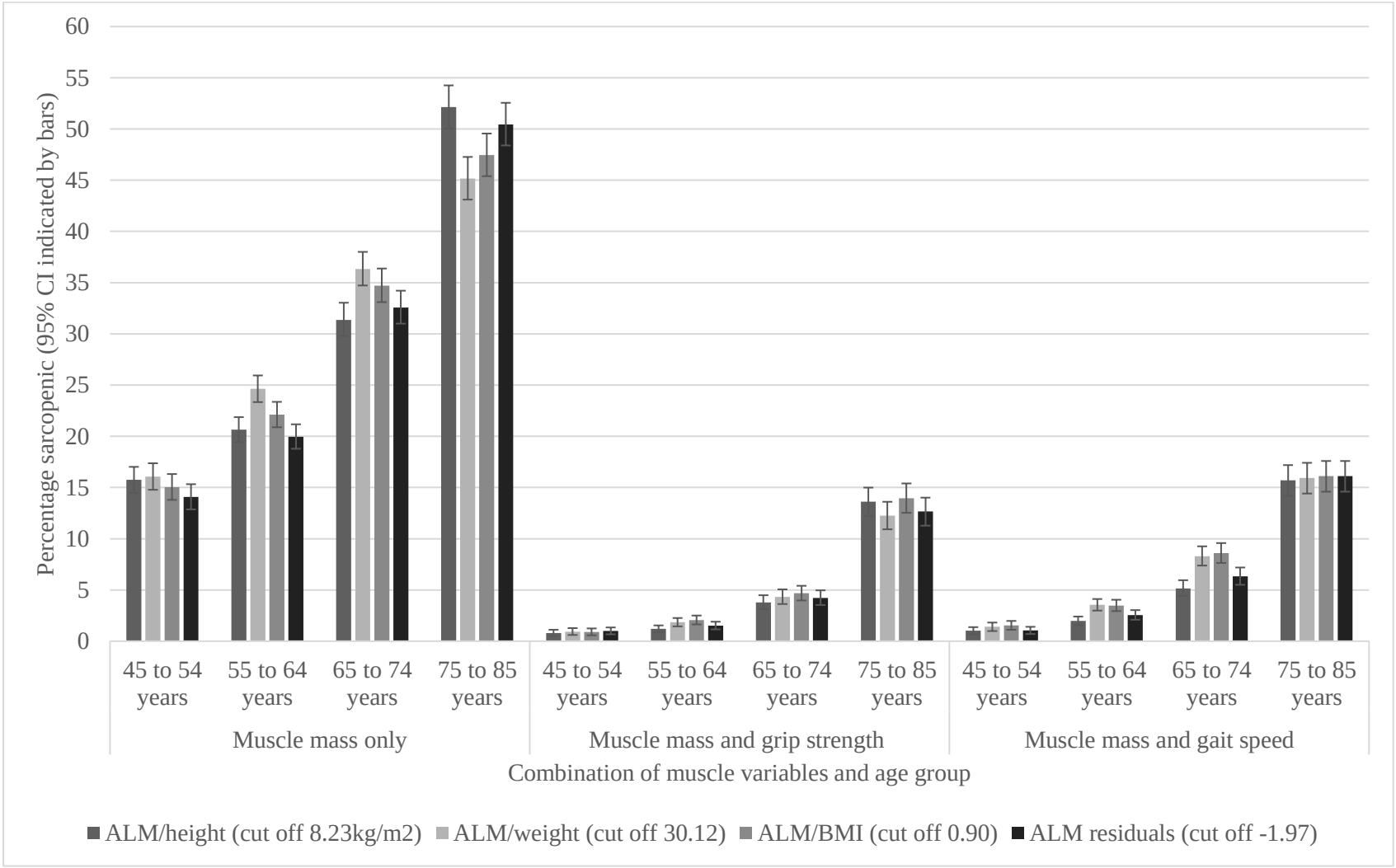
ALM/height vs ALM/BMI	**Mass only**	0.00	(-0.03 - 0.03)	0.01	(-0.02 - 0.04)	0.02	(-0.02 - 0.05)	0.05	(0.01 - 0.1)
	Mass + grip	0.16	(0.00 - 0.33)	0.29	(0.20 - 0.38)	0.32	(0.25 - 0.40)	0.24	(0.18 - 0.3)
	Mass + gait	-0.01	(-0.01 – 0.00)	0.14	(0.07 - 0.21)	0.18	(0.11 - 0.24)	0.19	(0.13 - 0.25)
ALM/height vs ALM residuals	**Mass only**	0.52	(0.48 - 0.57)	0.45	(0.42 - 0.48)	0.44	(0.40 - 0.48)	0.45	(0.41 - 0.49)
	Mass + grip	0.66	(0.50 - 0.83)	0.66	(0.58 - 0.74)	0.61	(0.54 - 0.67)	0.61	(0.56 - 0.66)
	Mass + gait	0.40	(0.24 - 0.56)	0.54	(0.46 - 0.62)	0.48	(0.40 - 0.55)	0.59	(0.53 - 0.66)
ALM/weight vs ALM/BMI	**Mass only**	0.51	(0.44 - 0.57)	0.59	(0.55 - 0.63)	0.62	(0.58 - 0.65)	0.61	(0.56 - 0.65)
	Mass + grip	0.45	(0.23 - 0.67)	0.79	(0.73 - 0.85)	0.73	(0.67 - 0.79)	0.68	(0.63 - 0.73)
	Mass + gait	0.62	(0.49 - 0.76)	0.73	(0.67 - 0.79)	0.73	(0.68 - 0.78)	0.70	(0.65 - 0.75)
ALM/weight vs ALM residuals	**Mass only**	0.21	(0.16 - 0.26)	0.30	(0.26 - 0.33)	0.34	(0.30 - 0.37)	0.38	(0.34 - 0.42)
	Mass + grip	0.21	(0.03 - 0.39)	0.56	(0.48 - 0.65)	0.59	(0.52 - 0.66)	0.52	(0.46 - 0.59)
	Mass + gait	0.51	(0.38 - 0.64)	0.46	(0.39 - 0.54)	0.48	(0.41 - 0.54)	0.52	(0.47 - 0.58)
ALM/BMI vs ALM residuals	**Mass only**	0.12	(0.08 - 0.16)	0.17	(0.14 - 0.21)	0.19	(0.15 - 0.23)	0.20	(0.15 - 0.24)
	Mass + grip	0.15	(0.00- 0.31)	0.50	(0.42 - 0.59)	0.51	(0.44 - 0.58)	0.39	(0.33 - 0.44)
	Mass + gait	0.34	(0.20 - 0.49)	0.39	(0.31 - 0.47)	0.39	(0.32 - 0.46)	0.37	(0.31 - 0.43)
		40th percentile threshold							
ALM/height vs ALM/weight	**Mass only**	-0.06	(-0.09 - -0.03)	-0.07	(-0.1 - -0.04)	-0.06	(-0.1 - -0.03)	0.02	(-0.02 - 0.07)
	Mass + grip	0.24	(0.11 - 0.36)	0.40	(0.32 - 0.47)	0.41	(0.35 - 0.48)	0.36	(0.31 - 0.41)
	Mass + gait	0.15	(0.07 - 0.24)	0.27	(0.21 - 0.33)	0.23	(0.18 - 0.29)	0.35	(0.3 - 0.40)
ALM/height vs ALM/BMI	**Mass only**	-0.01	(-0.04 - 0.02)	-0.07	(-0.1 - -0.04)	-0.06	(-0.09 - -0.02)	-0.02	(-0.07 - 0.02)
	Mass + grip	0.30	(0.17 - 0.43)	0.41	(0.34 - 0.48)	0.43	(0.37 - 0.49)	0.39	(0.34 - 0.44)
	Mass + gait	0.21	(0.11 - 0.31)	0.24	(0.18 - 0.30)	0.24	(0.19 - 0.30)	0.35	(0.30 - 0.40)
ALM/height vs ALM residuals	**Mass only**	0.54	(0.51 - 0.57)	0.48	(0.46 - 0.51)	0.47	(0.44 - 0.50)	0.52	(0.48 - 0.55)
	Mass + grip	0.65	(0.53 - 0.78)	0.74	(0.68 - 0.79)	0.73	(0.68 - 0.78)	0.72	(0.68 - 0.76)
	Mass + gait	0.59	(0.48 - 0.69)	0.65	(0.59 - 0.71)	0.62	(0.57 - 0.67)	0.70	(0.66 - 0.74)
ALM/weight vs ALM/BMI	**Mass only**	0.60	(0.56 - 0.63)	0.63	(0.60 - 0.65)	0.64	(0.61 - 0.67)	0.65	(0.62 - 0.68)
	Mass + grip	0.65	(0.53 - 0.78)	0.84	(0.80 - 0.88)	0.86	(0.82 - 0.89)	0.78	(0.74 - 0.81)
	Mass + gait	0.75	(0.68 - 0.82)	0.77	(0.73 - 0.81)	0.82	(0.79 - 0.85)	0.80	(0.77 - 0.83)

ALM/weight vs ALM residuals	**Mass only**	0.26	(0.22 - 0.30)	0.32	(0.29 - 0.34)	0.34	(0.30 - 0.37)	0.37	(0.34 - 0.41)
	Mass + grip	0.49	(0.36 - 0.63)	0.64	(0.58 - 0.70)	0.66	(0.61 - 0.72)	0.61	(0.57 - 0.66)
	Mass + gait	0.52	(0.43 - 0.62)	0.59	(0.54 - 0.64)	0.60	(0.55 - 0.65)	0.62	(0.58 - 0.66)
ALM/BMI vs ALM residuals	**Mass only**	0.18	(0.15 - 0.22)	0.17	(0.14 - 0.20)	0.19	(0.15 - 0.22)	0.23	(0.19 - 0.27)
	Mass + grip	0.41	(0.27 - 0.55)	0.58	(0.52 - 0.65)	0.63	(0.57 - 0.68)	0.59	(0.55 - 0.63)
	Mass + gait	0.52	(0.42 - 0.62)	0.49	(0.44 - 0.55)	0.51	(0.46 - 0.56)	0.56	(0.52 - 0.60)

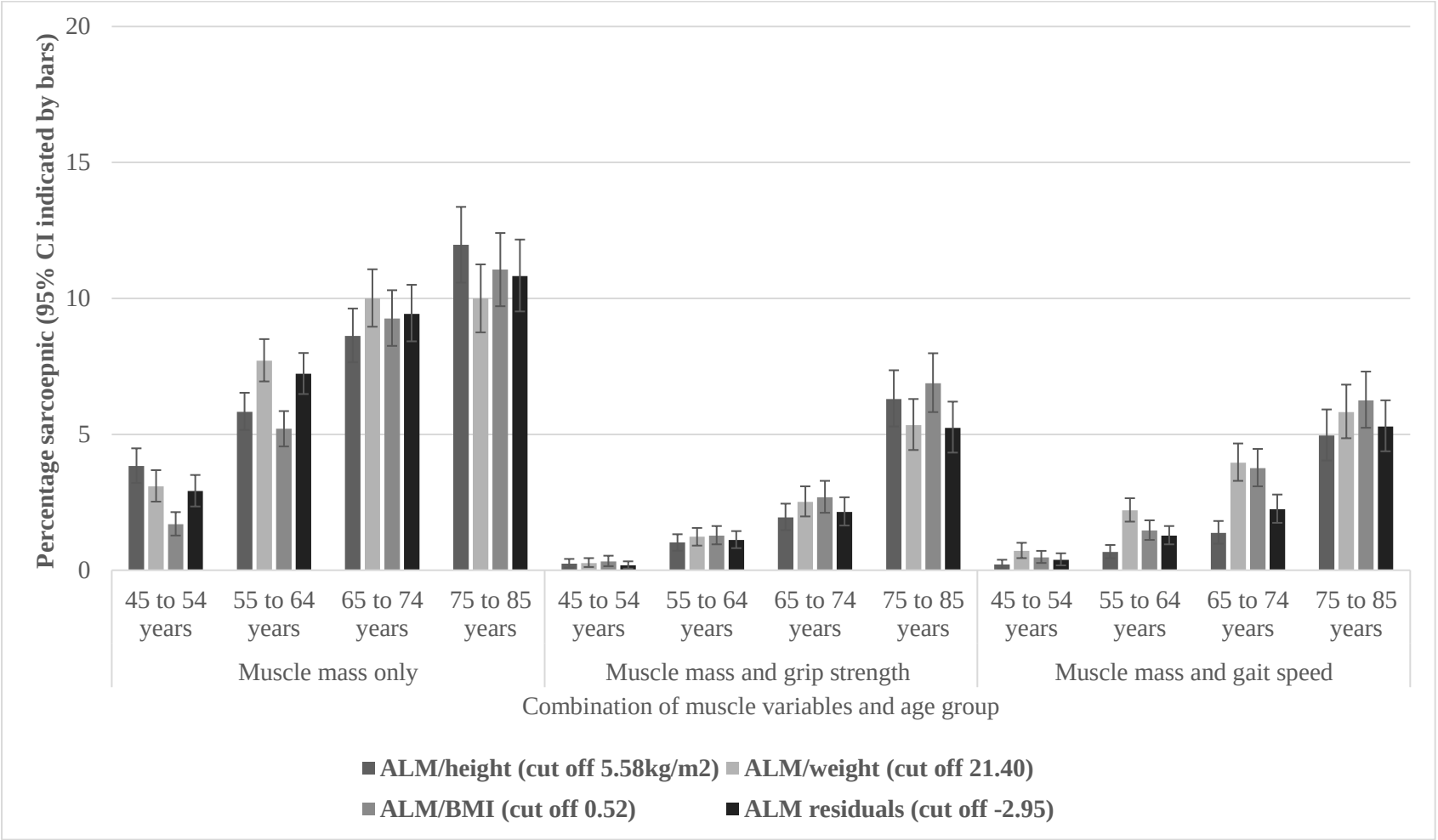
Supplementary Figure 1. Percentage of males with sarcopenia using 10th percentile cut offs



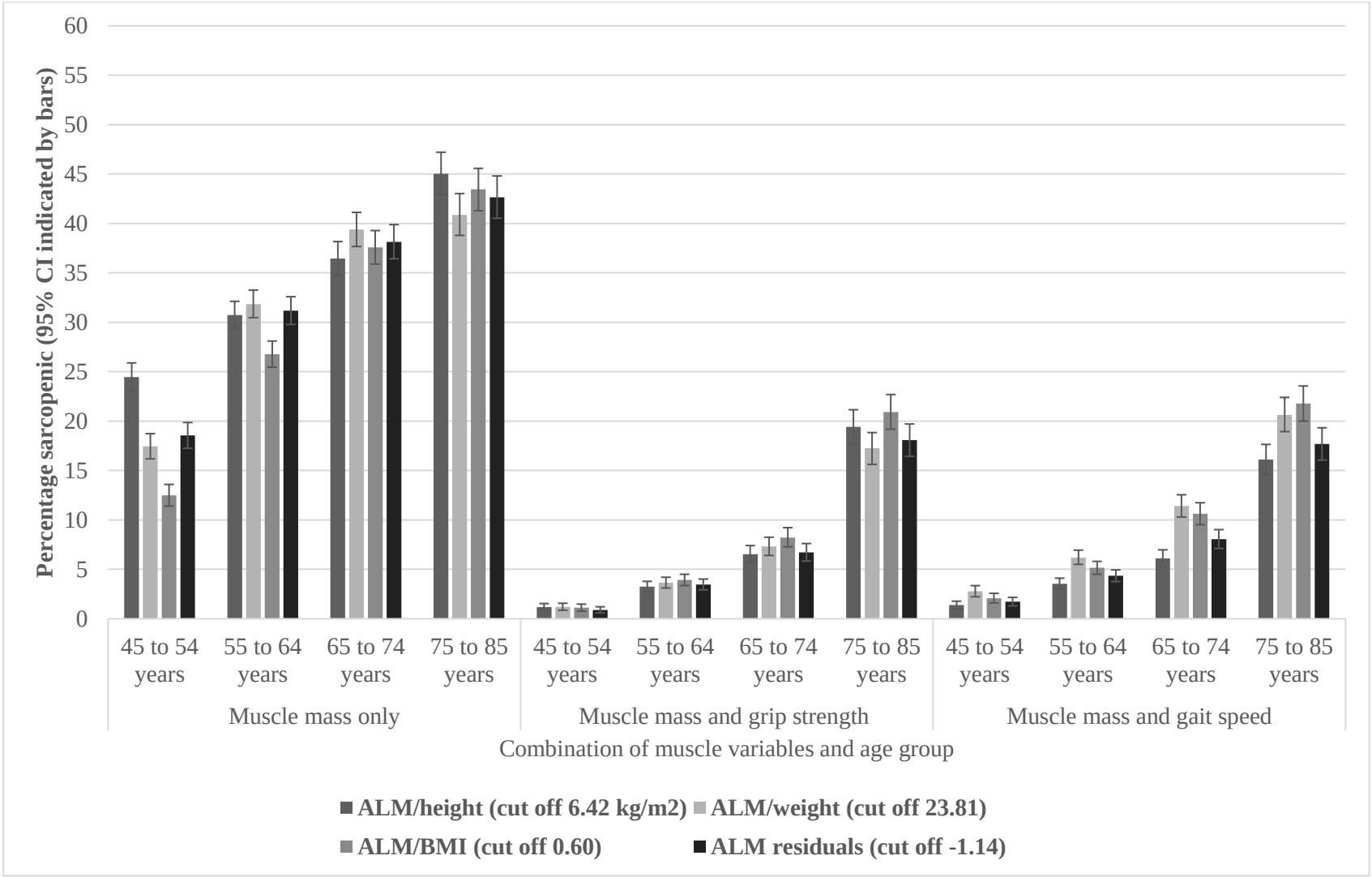
Supplementary Figure 2. Percentage of males with sarcopenia using 40th percentile cut offs



Supplementary Figure 3. Percentage of females with sarcopenia using 10th percentile cut offs



Supplementary Figure 4. Percentage of females with sarcopenia using 40th percentile cut offs



Chapter 4: The association of sarcopenia with falls

This chapter has been submitted to the *Journal of Cachexia, Sarcopenia and Muscle.* Alexandra Mayhew was responsible for developing the research question and study protocols, applying for data, analyzing data, writing and revising the drafts of the manuscripts. The work is primarily the undertaking of Alexandra Mayhew with guidance from Drs. Parminder Raina and Stuart Phillips throughout the project. Dr. Nazmul Sohel assisted with coding for the data analyses. Thesis committee members, Drs. Russell de Souza, Paul McNicholas, Gianni Parise, and Lehana Thabane provided feedback throughout the project. As an author generated version of a submitted manuscript, no copyright license documentation is required.

Context and background

Chapters 2 and 3 of this thesis showed that different methods of operationalizing sarcopenia resulted in differences in the proportion of participants considered sarcopenic, as well **Chapter 3** finding that the agreement between the vast majority of sarcopenia definitions was limited. However, based on the literature, it was not clear if the difference in proportion of sarcopenic participants and poor agreement translate in differences in the association of sarcopenia with health. One of the primary goals of the sarcopenia research community is decide on a unified definition of sarcopenia. To do this, information is required regarding the construct validity of sarcopenia definitions. The sarcopenia definition(s) which best identify participants with outcomes thought to be associated with sarcopenia are candidates for the unified definition. Therefore, the objective of this study was to apply the sarcopenia definitions developed in **Chapter 3** to assess the association between sarcopenia and falls was assessed. Falls was selected as an outcome because of their biological connection to sarcopenia and overall relevance to health in aging adults.

Chapter 4: The association of sarcopenia with falls

Title: Exploring the impact of different diagnostic criteria on the association between sarcopenia and falls in the CLSA

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Abstract

Background: Sarcopenia definitions recommend different combinations of muscle mass, strength, and function as well as different methods of adjusting muscle mass. It is unclear how these differences in definitions impact the association between sarcopenia and falls. The objective of this study was to assess how differences in the operationalization of sarcopenia impact the association between sarcopenia and falls.

Methods: Participants from the Canadian Longitudinal Study on Aging who were ≥65 years at baseline (2012-2015), had complete data for muscle mass, grip strength, gait speed, body mass index, and falls (n=10,008) were included in the analyses. Sarcopenia was defined using all combinations of muscle variables (muscle mass, grip strength and gait speed) and methods of adjusting muscle mass (height, weight, BMI, and regressing on height and fat mass) recommended by the expert group sarcopenia definitions. A range of cut off values for all muscle measures were explored. Proportional odds regression models were used to assess the relationship between sarcopenia and incident falls (0, 1, or 2+ falls) measured 18 months after baseline data collection.

Results: In males, the sarcopenia definitions including muscle mass adjusted for weight, BMI, and using the residual technique, each identifying approximately 20% of participants as having low muscle mass, in combination with a grip strength of <26kg were associated with a between 2.10 and 2.28 greater odds of having a higher level of falling (1 or more falls versus 0 falls, 2 or more falls versus 0 or 1 falls). In females, none of the sarcopenia definition explored were associated with a significant increase in the risk of falling.

However, the results should be interpreted cautiously as only a small number of participants with sarcopenia experienced falls.

Conclusions: Sarcopenia definitions based on different combinations of muscle variables and methods of adjusting muscle mass are not equally associated with falls. In males, definitions including grip strength but not gait speed, and adjusting muscle mass for weight, BMI, or using the residual technique but not height, were associated with falls. In females, sarcopenia was not associated with falls regardless of the definition used.

Introduction

Sarcopenia refers to the decline in muscle mass, strength, and function that occurs during ageing. The earliest definitions of sarcopenia were based on muscle mass alone and used low appendicular lean mass (ALM) adjusted for height or weight. [1,2] More recent expert group definitions have included measures of muscle strength or function in addition to muscle mass based on evidence that muscle strength and muscle function are more strongly associated with outcomes including disability and mortality compared to muscle mass [3–7] However, the variables included vary by definition as do the techniques recommended for adjusting muscle mass.

It appears that the different sarcopenia definitions are not equivalent. Depending on the definition used, between 9.9% and 40.4% of community-dwelling older adults are sarcopenic. [8] Agreement between most definitions is limited with Cohen's kappa values of less than 0.60. [9–14] Efforts have been taken to move towards a more unified sarcopenia definition by comparing the ability of the definitions to predict relevant health outcomes. [15] Falls are one of the outcomes of greatest interest for sarcopenia due the biological link between muscle strength and function with falls [16], because approximately one third of adults aged 65 years and older fall each year [17], and because falls and injuries related to falls are one of the largest contributors to a loss of independence in older adults. [18]

Studies investigating the association between sarcopenia and falls have yielded inconsistent results. In a meta-analyses of studies assessing the association between sarcopenia and falls, certain definitions such as muscle mass adjusted for height and

weight and some of the expert group definitions were associated with a greater risk of falling. [19] In studies comparing definition in the same population, generally only definitions including muscle strength and/or muscle function were significantly associated with falls. [15,20,21] In addition to odds ratios or hazard ratios, one study calculated the area under the curve (AUC) for sarcopenia and falls and found that compared to a model with age alone, the AUC improved by less than 0.01 for all of the included sarcopenia definitions, despite some of them being associated with a more than two times greater odds of falling. [15]

To understand why sarcopenia has been inconsistently associated with falls, it is necessary to systematically examine differences in how sarcopenia is operationalized. All sarcopenia definitions are made up of three components; 1) combination of muscle variables; 2) methods of adjusting muscle mass; and 3) cut points for all muscle variables. Most definitions differ based on more than one of these components, making it impossible to determine to what extent each component contributes to differences in the strength of the relationship between sarcopenia and falls.

Understanding how combinations of muscle mass, muscle strength, and/or muscle function as well the muscle mass adjustment techniques impact the relationship between sarcopenia and health outcomes such as falls is a critical step towards finding a unified sarcopenia definition. A single definition would benefit researchers by increasing the comparability of results across studies, as well as clinicians who are given little, if any, guidance on how to diagnose or treat sarcopenia despite it being included in the International Classification of disease. [22] The objective of this study was to assess the

impact of different methods of operationalizing sarcopenia on the strength of the relationship between sarcopenia and falls.

Methods

Setting and study population

The Canadian Longitudinal Study on Aging (CLSA) is a national, longitudinal research platform that includes 51,338 participants aged 45 to 85 years at baseline from the ten Canadian provinces. To be eligible for the study, participants had to be physically and cognitively able to participant on their own and not living in institutions such as long term care. Participants were recruited in the Tracking cohort (n=21,241) and the Comprehensive cohort (n=30,097). Tracking cohort participants were randomly selected from all ten provinces and completed interviews by phone. The participants in the Comprehensive cohort were randomly selected from within 25 to 50km of one of 11 Data Collection Sites which are located in seven provinces. In addition to being interviewed in-person, Comprehensive cohort participants completed in-depth physical assessments and provided blood and urine samples. Details on the study design have been described elsewhere. [23] The analyses for this study was limited to participants aged 65 years and older in the Comprehensive cohort due to requiring physical assessment data and to those identifying as European as muscle mass, muscle strength, and physical function have shown to vary by ethnicity. [24–26] This project uses data collected during baseline (September 2011 to May 2015) as well as data collected during a Maintaining Contact Questionnaire administered approximately 18 months after baseline data collection.

Clinical measurements

All data were collected by trained research assistants. Height was measured using a stadiometer. The mean value of two measurements was used for analyses. Weight was measured using a digital scale. BMI was calculated as weight in kilograms divided by height squared. Muscle mass was measured by Dual Energy X-ray Absorptiometry (DXA) using Hologic Discovery A^{TM}. The Hologic Discovery A^{TM} DXA machine was calibrated daily using a spine phantom, weekly using a whole body step phantom, and yearly using a gold standard phantom. DXA provides an estimate of ALM which refers to the amount of lean mass in the arms and legs. Lean mass includes muscle mass, organs, water, and all other non-bone and non-fat soft tissues. [27,28] Hand grip strength was measured using the Tracker Freedom ® Wireless Grip Dynamometer. Three repetitions were performed with the dominant hand, the highest of which was used in the analyses. Grip strength measured using a dynamometer has been shown to have excellent reliability and is predictive of falls, disability, and impaired health-related quality of life. [29] Gait speed was measured using a four meter walk course with participants instructed to walk at their normal walking speed. The four meter walk test has been shown to have excellent test re-test reliability and is significantly associated with self-rated health and performance on chair rise and balance tests. [30,31]

Falls assessment

Falls were assessed during the maintaining contact interview that occurred appropriately 18 months after participants visited the data collection site. Participants were asked if they had experienced a fall where they were hurt enough to limit some of their normal

activities in the past 12 months, and if they had a fall, how many times they had fallen. Participants were categorized as having not fallen, fallen once, or fallen two or more times.

Sarcopenia operationalization

Sarcopenia definitions include three components; 1) combination of muscle variables; 2) methods of adjusting muscle mass; and 3) cut offs of each variable. [1,2,4–8,32]. We defined sarcopenia based on the recommendation of the expert-group definitions. [4–7] ALM was used to measure muscle mass and was adjusted by height, weight, BMI, or regressing ALM on fat mass and height. [4–7] Muscle strength was measured using grip strength with cut offs of 30kg, 27kg, and 26kg for males and 20kg and 16kg for females. Muscle function was measured using gait speed using cut offs of 0.8m/s and 1.0m/s. [4–6,32] Cut offs corresponding to the lowest sex-specific 10^{th}, 20^{th}, and 40^{th} percentiles of muscle mass values for the CLSA were utilized (**Table 1**). Each combination of muscle variables, methods of adjusting muscle mass, and cut offs were used to define sarcopenia. The cut off of 27kg of grip strength for males, 1.0m/s for gait speed, and the muscle mass thresholds corresponding to the 10^{th} and 40^{th} percentiles were included as secondary analyses.

Statistical analyses

Of the 30,097 participants at baseline, 12,646 were ≥65 years. Participants were excluded for being non-European (n=436), missing data on muscle mass, grip strength, gait speed or BMI (n=1764), and missing data on falls (n=438). Data from 10,008 participants was available for analyses. Multiple imputation (ten imputations) using the predictive mean

matching technique was used for missing data. [33] The percentage of missing data for any variable was <6.5%. The CLSA provides inflation weights and analytical weights, which were used for prevalence estimates and regression modeling respectively, that allow the results to reflect the population of Canada. [34] All statistical analyses were completed using SAS (version 12.3).

A proportional odds model [35] was used to estimate the odds ratios and 95% confidence intervals for the outcome of falls categorized as no falls, one fall, or two or more falls in the previous year. The proportional odds model takes the ordinal nature of the falls data into consideration. The proportionality assumption was tested and was not found to be violated. Potential covariates were identified in the literature based on their relevance to falls and sarcopenia. [36] The univariate association between each variable and falls was assessed; any variable with a Wald statistic p-value of less than or equal to 0.25 was considered a candidate for the model. Age was automatically included in the model and other potential covariates were added in one at a time based on statistical significance. Variables for which the deviance statistic was statistically significant (Chi-square test p-value of <0.05) were kept in the model or those which impacted the strength of the relationship between sarcopenia and falls. [37] The final model included age (65 to 74 years, 75 years and older), urinary incontinence, the use of mobility devices, general health (fair or poor versus excellent, very good, or good), and the presence of pain or discomfort for which the deviance was significant reduced ($p < 0.05$) as well as diabetes and osteoarthritis which had p-values of 0.054 and 0.072 respectively and impacted the strength of the association between sarcopenia and falls. Analyses were stratified by sex.

The discriminative ability of each sarcopenia definition for the outcome of one or more falls and two or more falls was assessed using area under the receiver operator curve (AUC) analyses. The direction of the misclassification was assessed by calculating sensitivity and specificity. These analyses were unadjusted.

Results

Participant characteristics

The mean age of the participants was 73.0 ± 5.7 years and 51.4% of the sample was male (**Table 2**). Males had greater ALM (26.0 ± 3.8kg) compared to females (17.4 ± 3.0kg), faster gait speed (0.94 ± 0.12 versus 0.91m/s +/- 0.19, all m/s), and greater grip strength (39.6 ± 8.5kg versus 23.7 ± 5.2kg). Falls were more common in females than in males with 13.0% of females and 9.5% of males reporting falling at least once in the previous 12 months. Weighted results are available in **Supplementary Table 1**.

Sarcopenia – Primary analyses

The proportional odds model provides one odds ratio for each exposure variable which refers to the increase in risk of the outcome from one level to the next. The difference in risk between the levels of the outcome are provided by y-intercepts for each of the non-reference categories of the outcome variable.

In males using the 20th percentile cut offs for muscle mass, definitions including muscle mass adjusted for weight, BMI, and using the residual technique in combination with low grip strength (cut offs of either 30kg or 26kg) were significantly associated with falls with odds ratios of between 1.66 and 2.33 (**Table 3**). The y-intercepts for having one or more

falls versus no falls were between -4.29 and -4.34 and for having two or more falls versus zero or one falls were between -2.67 and -2.72. Regardless of the definition of sarcopenia, the AUC values ranged from 0.51 to 0.55 for having at least one fall and 0.51 to 0.56 for having two or more falls (**Supplementary Table 2**). Compared to age alone, the AUC values improved by only 0.01 to 0.04 for having at least one fall and 0.04 to 0.09 for having two or more falls.

In females, none of the sarcopenia definitions were significantly associated with an increased risk of falls (**Table 4**). The y-intercepts for having one or more falls versus no falls were between -3.86 and -3.89 and the y-intercepts for having two or more falls versus zero or one falls were between -2.24 and -2.29.The AUC values ranged from 0.50 to 0.52 for having at least one fall to 0.51 to 0.55 for having two or more falls (**Supplementary Table 2**). Compared to age alone, the AUC values improved by only 0.01 to 0.02 for having at least one fall and 0.01 to 0.05 for having two or more falls.

Sarcopenia – Secondary analyses

In males, using definitions including the 10^{th} or 40^{th} percentile cut offs for muscle mass typically changed the odds of falling by <0.30 with a trend towards definitions using the 40^{th} percentile cut offs to become statistically significant (**Supplementary Table 3**). Most notable of the changes was that muscle mass adjusted for height combined with grip strength using cut offs of 30kg or 27kg were significantly associated with falls using the 40^{th} but not the 20^{th} percentiles. In females, using the alternative cut offs for muscle mass and gait speed did not meaningfully change the interpretation of the results (**Supplementary Table 4**). For males, the minimum and maximum AUC values

including the alternative cut offs were 0.51 and 0.55 for having at least one fall and 0.51 and 0.60 for having at least two falls. For females, the minimum and maximum AUC values were 0.50 and 0.54 for having at least one fall and 0.51 to 0.55 for having two or more falls (**Supplementary Table 2**).

Multiple imputation

The results were not meaningfully changed when completers only analyses was conducted (**Supplementary Tables 5 and 6**).

Discussion

This study systematically explored the impact of different combinations of muscle variables and different cut points on the relationship between sarcopenia and falls. In males, sarcopenia defined as the combination of low muscle mass and low grip strength was significantly associated with falls with odds ratios between 1.65 and 2.76 for all grip strength cut points and for all methods of muscle mass adjustment besides height^2. In females, sarcopenia was not significantly associated with increased falls for any of the included definitions. Regardless of the strength of the association between sarcopenia and falls, the clinical utility was limited with AUC values of less than 0.60 for all definitions.

The association of sarcopenia with falls in males, but not in females, has previously been observed. Only two other studies have conducted sex-stratified analyses and both found that the odds of falling were higher in sarcopenic males than in females but neither attempted to explain the finding. [21,38] The reason for this apparent difference is unclear. We explored if the association in males was stronger than in females due to a lower percentage of males having low grip strength and gait speed compared to females. We

created sex-specific cut offs for grip strength and gait speed corresponding to the lowest 5th, 10th, 15th, and 20th percentiles. Identifying the same percentage of males and females with low grip strength and gait speed did not alter the results. Previous studies have noted that there are sex differences in older adults for the risk factors for falls with males with physical function limitations being at higher risk of injurious falls compared to females. [39,40] This may reflect that males who generally have greater muscle mass and strength compared to females rely more greatly on strength to avoid falling while females do not which may translate into the presence of sarcopenia having a greater impact in males than females.[41] Other non-function related risk factors such as urinary incontinence are strong risk factors for falls in females but not in males. [40] Our study joins the growing body of evidence showing that the risk factors of falls differ in males and females and highlights the importance of conducting analyses which takes sex into account.

In males, definitions including ALM adjusted for height^2 and grip strength were not significantly associated with falls while definitions including ALM adjusted for weight, BMI, or using the residual technique and grip strength were. Few studies have compared the different muscle mass adjustment techniques. One study observed that sarcopenia defined as unadjusted ALM, but not height^2 adjusted ALM, was associated with falls [20] and one found significant associations using height^2 adjusted definitions but not BMI adjusted definitions. [21]A potential explanation for the attenuated association of sarcopenia when ALM is adjusted for height^2 is because the ALM technique identifies more individuals with normal BMI values (between 18.5kg/m^2 and 24.9kg/m^2) as having low muscle mass whereas the other techniques tend to identify more obese (BMI values of >30kg/m^2) individuals as having low muscle mass (**Supplementary Table 7**).

Sarcopenia in the presence of obesity, called sarcopenic obesity, is associated with a greater risk of falling compared to either sarcopenia or obesity alone. [42,43] Therefore adjusting ALM for height^2 may be less strongly associated with falls compared to the other definitions since these individuals on average have a healthier weight. Additionally, in our analyses, the same grip strength cut offs were applied regardless of BMI. Given that BMI is associated with increased grip strength in males, obese sarcopenic males with low grip strength may have experienced more decline compared to normal weight males. [44] Further investigation of how muscle mass adjustment techniques impact the association of muscle mass with health outcomes is required.

Though many sarcopenia in definitions in males were associated with a two or more times greater odds of falling, the maximum AUC value for all definitions was 0.59 (95% CI 0.57 – 0.60). AUC are interpreted as the probability that a person who had fallen at least once was sarcopenic versus not sarcopenic. Therefore, sarcopenic status provided little information about the risk of falls over chance alone. To understand the direction of the misclassification, the sensitivity and specificity of each definition for detecting falls was assessed. For one or more falls, the sensitivity for all definitions ranged from 0.09 to 0.24 and the specificity was between 0.87 and 0.92. Therefore all the sarcopenia definitions classified the participants not at risk for falling well, but had a limited ability to identify those that would fall (**Supplementary Tables 8 and 9**). The modest AUC values may in part reflect the issues of using DXA to estimate muscle mass. Though considered by many to be the reference standard for measuring muscle mass for sarcopenia, DXA does not actually measure muscle mass but rather lean mass which includes organ tissue, water, and all other non-bone and non-fat soft tissues in addition to muscle mass. [27,28]

Muscle mass directly measured using D_3-creatine is significantly associated with falls, performance, and mobility limitations. [45] DXA measured lean mass is not associated with these outcomes. Therefore, if muscle mass were more accurately measured, sarcopenia may better identify those at risk of falling.

A strength of our study was the list of sarcopenia definitions used which allowed us to examine how individual components of sarcopenia definitions impacted the association between sarcopenia and falls. This allowed for important findings such as how adjusting ALM for height^2 resulted in attenuated relationships with falls compared to other adjustment techniques in males. Additionally, our method allowed us to explore how using alternative cut offs impacted the association of sarcopenia with falls. This strengthens our conclusion that sarcopenia is not associated with falls in females as we excluded the potential that an association would be found using alternative cut offs. Including the AUC analyses also provided insight about the clinical usefulness of diagnosing sarcopenia in order to identify potential fallers.

There are several limitations to our study. The results of our study may have limited generalizability. Our sample was limited to participants of European ethnicity. Muscle mass, grip strength, and gait speed have been shown to differ by ethnicity and the CLSA does not have the required sample size for ethnicity-specific analyses. [24–26] Though our sample size was larger compared to most previous studies investigating sarcopenia and falls [19], only a small percentage of participants experienced falls and our analyses were therefore under powered (**Supplementary Tables 8 and 9**). Therefore, the results of this study should be interpreted with caution as the estimates for the odds ratios and AUC values may be unstable. In order to more definitively assess the association between sarcopenia

and health, individual participant data from multiple studies should be pooled to provide the required sample size.

Conclusions

We found that sarcopenia operationalized as low muscle mass adjusted for weight, BMI, or using the residual adjustment technique in combination with low grip strength was significantly associated with falling in males across a range of cut offs for low muscle mass and low grip strength. Sarcopenia was not significantly associated with increased odds of falling in females. In both males and females, the AUC analyses estimates for all definitions were less than 0.60 suggesting that sarcopenia may have limited utility in identifying potential fallers. These results highlight the need for future studies to conduct sex-stratified analyses and to explore the individual components to sarcopenia definitions to best identify people at risk of poor health. Future studies should also consider the use of AUC analyses to better understand the clinical relevance of sarcopenia for identifying people at risk of poor health.

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opinions expressed in this manuscript are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging. The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle. [46]

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Table 1. Low muscle mass cut offs

Method of adjusting muscle mass	Percentile	Low muscle mass cut offs	
		Males	Females
ALM/height	10th	7.29	5.58
	20th	7.68	5.93
	40th	8.23	6.42
ALM/weight	10th	26.96	21.4
	20th	28.33	22.36
	40th	30.12	23.81
ALM/BMI	10th	0.78	0.52
	20th	0.83	0.55
	40th	0.9	0.6
ALM residuals	10th	-4.75	-2.95
	20th	-3.61	-2.2
	40th	-1.97	-1.14

Table 2. Participant characteristics

Characteristic	Males (n=5147)		Females (N=4861)	
	Mean or N	SD or %	Mean or N	SD or %
Age, years	73.0	5.6	72.9	5.7
Height, cm	174	6.7	160	6.3
Weight, kg	84.7	14.0	71.0	14.3
BMI, kg/m2	28.0	4.2	27.7	5.5
Total body fat mass, %	25.5	8.0	29.6	9.4
Appendicular lean mass, kg	26.0	3.8	17.4	3.0
ALM/height^2	8.58	1.05	6.78	1.05
ALM/weight	30.9	3.1	24.8	2.9
ALM/BMI	0.94	0.12	0.64	0.10
Gait speed, meters per second	0.94	0.19	0.91	0.19
Grip strength, kg	39.6	8.5	23.7	5.2
Number of falls in previous year (%)				
Zero	4659	90.5	4231	87.0
One	381	7.4	479	9.9
Two or more	107	2.1	151	3.1
Self-rated general health (%)				
Fair or poor	404	7.8	381	7.8
Good, very good, or excellent	4743	92.2	4480	92.2
Presence of pain or discomfort (%)	3476	67.5	2071	42.6
Self-rated hearing (%)				
Fair or poor	926	18.0	4321	88.9
Good, very good, or excellent	4221	82.0	540	11.1
Urinary incontinence (%)	407	7.9	721	14.8
Household income (%)				
< $20,000	175	3.4	460	9.5
≥ $20,000 < $50,000	1315	25.5	2000	41.1
≥ $50,000 <$100,000	2279	44.3	1723	35.4
≥ $100,000 < $150,000	892	17.3	467	9.6
≥ 150,000	487	9.5	212	4.4
Smoking status (%)				
Current	265	5.2	239	4.9
Never or former	4882	94.8	4622	95.1
COPD (%)	329	6.4	389	8.0
Depression (%)	519	10.1	873	17.9
Neurological conditions (%)	357	6.9	837	17.2
Arthritis (%)	1389	27.0	2074	42.7
Diabetes (%)	1228	23.9	837	17.2
Stroke (%)	393	7.6	323	6.6
Osteoporosis (%)	191	3.7	1193	24.5

Table 3. Association between sarcopenia and falls in males using different methods of operationalizing sarcopenia

Sarcopenia definition		Number of participants with sarcopenia (%)	Y-intercept for one or more falls versus no falls	Y-intercept for two or more falls versus zero or one falls	Odds of falling	95% Confidence interval	p-value
Combination of muscle variables	**Method of adjusting muscle mass**						
Muscle mass only (20th percentile)	**Height**	1007 (19.6)	-4.31	-2.69	1.13	0.83 - 1.53	0.428
	Weight	999 (19.4)	-4.34	-2.72	1.51	1.13 – 2.00	0.005
	BMI	1008 (19.6)	-4.30	-2.68	1.15	0.86 - 1.54	0.359
	Residuals	1009 (19.6)	-4.33	-2.71	1.28	0.96 - 1.71	0.099
Grip strength only <30kg		655 (12.7)	-4.31	-2.69	1.43	1.02 - 1.99	0.036
Grip strength only <26kg		253 (4.9)	-4.30	-2.67	1.80	1.13 - 2.86	0.013
Gait speed only <0.8m/s		1136 (22.1)	-4.31	-2.69	1.28	0.96 - 1.70	0.095
Muscle mass (20th percentile) and grip strength <30kg	**Height**	243 (4.7)	-4.29	-2.67	1.27	0.75 - 2.14	0.375
	Weight	224 (4.4)	-4.29	-2.67	1.60	0.97 - 2.63	0.065
	BMI	285 (5.5)	-4.29	-2.67	1.66	1.06 - 2.59	0.026
	Residuals	218 (4.2)	-4.29	-2.67	1.66	1.01 - 2.74	0.046
Muscle mass (20th percentile) and grip strength <26kg	**Height**	106 (2.1)	-4.29	-2.67	1.41	0.67 - 2.99	0.364
	Weight	104 (2.0)	-4.29	-2.67	2.14	1.11 - 4.13	0.024
	BMI	122 (2.4)	-4.29	-2.67	2.33	1.28 - 4.26	0.006
	Residuals	95 (1.8)	-4.29	-2.67	2.14	1.08 - 4.25	0.029
Muscle mass (20th percentile) and gait speed <0.8m/s	**Height**	258 (5.0)	-4.29	-2.67	1.18	0.70 - 1.98	0.707
	Weight	344 (6.7)	-4.29	-2.67	1.54	1.01 - 2.36	0.164
	BMI	357 (6.9)	-4.29	-2.67	1.20	0.77 - 1.87	0.812
	Residuals	274 (5.3)	-4.29	-2.67	1.33	0.82 - 2.16	0.385

Table 4. Association between sarcopenia and falls in females using different methods of operationalizing sarcopenia

Sarcopenia definition		Number of participants with sarcopenia (%)	Y-intercept for one or more falls versus no falls	Y-intercept for two or more falls versus zero or one falls	Odds of falling	95% Confidence interval	p-value
Combination of muscle variables	**Method of adjusting muscle mass**						
Muscle mass only (20th percentile)	**Height**	972 (20.0)	-3.89	-2.29	1.12	0.87 - 1.44	0.367
	Weight	963 (19.8)	-3.85	-2.24	0.89	0.70 - 1.15	0.377
	BMI	961 (19.8)	-3.86	-2.26	1.01	0.79 - 1.29	0.947
	Residuals	969 (19.9)	-3.88	-2.28	1.10	0.87 - 1.41	0.419
Grip strength only <20kg		1125 (23.1)	-3.86	-2.26	1.00	0.78 - 1.27	0.990
Grip strength only <16kg		338 (7.0)	-3.86	-2.26	0.93	0.62 - 1.38	0.701
Gait speed only <0.8m/s		1414 (29.1)	-3.88	-2.28	1.15	0.92 - 1.45	0.219
Muscle mass (20th percentile) and grip strength <20kg	**Height**	340 (7.0)	-3.86	-2.26	1.07	0.73 - 1.58	0.722
	Weight	296 (6.1)	-3.86	-2.25	0.54	0.33 - 0.87	0.011
	BMI	366 (7.5)	-3.86	-2.25	0.73	0.49 - 1.09	0.125
	Residuals	291 (6.0)	-3.86	-2.26	0.93	0.61 - 1.42	0.740
Muscle mass (20th percentile) and grip strength <16kg	**Height**	117 (2.4)	-3.86	-2.26	1.15	0.64 - 2.07	0.647
	Weight	83 (1.7)	-3.86	-2.26	0.50	0.2 - 1.28	0.148
	BMI	126 (2.6)	-3.86	-2.26	0.69	0.35 - 1.35	0.278
	Residuals	88 (1.8)	-3.86	-2.26	0.79	0.36 - 1.73	0.550
Muscle mass (20th percentile) and gait speed <0.8m/s	**Height**	264 (5.4)	-3.87	-2.27	1.28	0.85 - 1.93	0.235
	Weight	411 (8.5)	-3.86	-2.26	0.94	0.66 - 1.34	0.734
	BMI	396 (8.1)	-3.86	-2.26	1.13	0.81 - 1.59	0.467
	Residuals	304 (6.3)	-3.87	-2.27	1.40	0.97 - 2.01	0.075

Supplementary Material

Supplementary Table 1. Participant characteristics – weighted data

Characteristic	Males (n=5147)		Females (N=4861)	
	Mean or N	SE or %	Mean or N	SE or %
Age, years	72.6	5.78	72.5	5.84
Height, cm	174	6.94	160	6.48
Weight, kg	84.8	14.8	71.0	15.1
BMI, kg/m2	28.0	4.5	27.8	5.8
Total body fat mass, %	25.5	8.6	29.7	9.9
Appendicular lean mass	26.1	4.0	17.3	3.1
ALM/height^2	8.60	1.10	6.76	1.09
ALM/weight	31.0	3.3	24.7	2.9
ALM/BMI	0.94	0.13	0.63	0.10
Gait speed, meters per second	0.95	0.20	0.91	0.21
Grip strength, kg	39.9	9.1	23.9	5.5
Number of falls in previous year (%)				
Zero	361815	90.3	381393	86.7
One	30329	7.6	44458	10.1
Two or more	8522	2.1	13970	3.2
Self-rated general health (%)				
Fair or poor	30374	7.6	35400	8.0
Good, very good, or excellent	370293	92.4	404421	92.0
Presence of pain or discomfort (%)	134030	33.5	191131	43.5
Self-rated hearing (%)				
Fair or poor	68955	17.2	49554	11.3
Good, very good, or excellent	331712	82.8	390267	88.7
Urinary incontinence (%)	29424	7.3	67165	15.3
Household income (%)				
< $20,000	12324	3.1	40809	9.3
≥ $20,000 < $50,000	107245	26.8	175956	40.0
≥ $50,000 <$100,000	174030	43.4	157127	35.7
≥ $100,000 < $150,000	68468	17.1	45669	10.4
≥ 150,000	38600	9.6	20261	4.6
Smoking status (%)				
Current	19979	5.0	20480	4.7
Never or former	380687	95.0	419341	95.3
COPD (%)	24132	6.0	32793	7.5

Depression (%)	39073	9.8	77297	17.6
Neurological conditions (%)	29368	7.3	75426	17.1
Arthritis (%)	109767	27.4	183637	41.8
Diabetes (%)	95406	23.8	74616	17.0
Stroke (%)	27642	6.9	29190	6.6
Osteoporosis (%)	15275	3.8	108571	24.7

Supplementary Table 2. Area under the curve statistics for sarcopenia definitions using the outcomes of one or more falls and two or more falls

Sarcopenia definition			Males				Females			
			1+ Fall		2+ falls		1+ Fall		2+ falls	
Muscle mass percentile	Combination of muscle variables	Method of adjusting muscle mass	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI
Grip strength <30kg males, <20kg females			0.54	0.53 - 0.54	0.57	0.56 - 0.59	0.51	0.51 - 0.52	0.54	0.53 - 0.54
Grip strength <26kg males, <16kg females			0.52	0.52 - 0.53	0.54	0.53 - 0.55	0.50	0.50 - 0.51	0.52	0.52 - 0.53
Grip strength <27kg males			0.53	0.53 - 0.54	0.54	0.53 - 0.55	0.50	0.50 - 0.51	0.53	0.53 - 0.54
Gait speed <0.8m/s			0.54	0.54 - 0.55	0.60	0.58 - 0.61	0.54	0.53 - 0.55	0.54	0.54 - 0.55
Gait speed <1.0m/s			0.51	0.51 - 0.52	0.55	0.53 - 0.56	0.52	0.51 - 0.52	0.51	0.51 - 0.52
10th	**Muscle mass only**	**Height**	0.51	0.51 - 0.52	0.53	0.52 - 0.54	0.50	0.50 - 0.51	0.51	0.51 - 0.52
		Weight	0.53	0.52 - 0.53	0.52	0.51 - 0.53	0.50	0.50 - 0.51	0.53	0.52 - 0.53
		BMI	0.52	0.52 - 0.53	0.55	0.53 - 0.56	0.50	0.50 - 0.51	0.52	0.52 - 0.53
		Residuals	0.53	0.52 - 0.53	0.53	0.52 - 0.54	0.50	0.50 - 0.50	0.53	0.52 - 0.53
	Muscle mass and grip strength <30kg males, <20kg females	**Height**	0.51	0.51 - 0.51	0.51	0.51 - 0.52	0.50	0.50 - 0.50	0.51	0.51 - 0.51
		Weight	0.51	0.51 - 0.52	0.51	0.50 - 0.52	0.50	0.50 - 0.50	0.51	0.51 - 0.52
		BMI	0.51	0.51 - 0.52	0.54	0.53 - 0.55	0.51	0.50 - 0.51	0.51	0.51 - 0.52
		Residuals	0.51	0.51 - 0.52	0.52	0.51 - 0.52	0.50	0.50 - 0.50	0.51	0.51 - 0.52
	Muscle mass and grip strength <26kg males, <16kg females	**Height**	0.51	0.50 - 0.51	0.51	0.50 - 0.51	0.50	0.50 - 0.50	0.51	0.50 - 0.51
		Weight	0.51	0.51 - 0.51	0.51	0.50 - 0.51	0.50	0.50 - 0.50	0.51	0.51 - 0.51
		BMI	0.51	0.51 - 0.51	0.53	0.52 - 0.54	0.50	0.50 - 0.50	0.51	0.51 - 0.51
		Residuals	0.51	0.50 - 0.51	0.51	0.50 - 0.51	0.50	0.50 - 0.50	0.51	0.50 - 0.51
	Muscle mass and grip	**Height**	0.51	0.51 - 0.51	0.51	0.51 - 0.52	0.50	0.50 - 0.50	0.51	0.51 - 0.51
		Weight	0.51	0.51 - 0.51	0.51	0.50 - 0.51	0.50	0.50 - 0.50	0.51	0.51 - 0.51
		BMI	0.52	0.51 - 0.52	0.53	0.52 - 0.54	0.50	0.50 - 0.50	0.52	0.51 - 0.52

	strength <27kg males	**Residuals**	0.51	0.51 - 0.51	0.51	0.5 - 0.51	0.50	0.50 - 0.50	0.51	0.51 - 0.51
	Muscle mass and gait speed <0.8m/s	**Height**	0.51	0.50 - 0.51	0.52	0.51 - 0.53	0.50	0.50 - 0.51	0.51	0.50 - 0.51
		Weight	0.52	0.51 - 0.52	0.51	0.50 - 0.52	0.51	0.50 - 0.51	0.52	0.51 - 0.52
		BMI	0.51	0.51 - 0.51	0.52	0.51 - 0.53	0.50	0.50 - 0.50	0.51	0.51 - 0.51
		Residuals	0.51	0.51 - 0.52	0.52	0.51 - 0.53	0.51	0.51 - 0.51	0.51	0.51 - 0.52
	Muscle mass and gait speed <1.0m/s	**Height**	0.51	0.51 - 0.52	0.52	0.51 - 0.53	0.50	0.50 - 0.51	0.51	0.51 - 0.52
		Weight	0.52	0.52 - 0.53	0.52	0.51 - 0.53	0.51	0.50 - 0.51	0.52	0.52 - 0.53
		BMI	0.52	0.51 - 0.52	0.54	0.53 - 0.55	0.50	0.50 - 0.50	0.52	0.51 - 0.52
		Residuals	0.52	0.52 - 0.53	0.53	0.52 - 0.54	0.50	0.50 - 0.51	0.52	0.52 - 0.53
20th	**Muscle mass only**	**Height**	0.52	0.51 - 0.52	0.53	0.52 - 0.54	0.51	0.50 - 0.51	0.52	0.51 - 0.52
		Weight	0.55	0.54 - 0.56	0.53	0.52 - 0.55	0.50	0.50 - 0.51	0.55	0.54 - 0.56
		BMI	0.53	0.52 - 0.54	0.56	0.55 - 0.58	0.51	0.51 - 0.52	0.53	0.52 - 0.54
		Residuals	0.53	0.53 - 0.54	0.53	0.52 - 0.54	0.51	0.50 - 0.51	0.53	0.53 - 0.54
	Muscle mass and grip strength <30kg males, <20kg females	**Height**	0.51	0.51 - 0.52	0.52	0.51 - 0.53	0.50	0.50 - 0.51	0.51	0.51 - 0.52
		Weight	0.52	0.52 - 0.52	0.53	0.52 - 0.53	0.50	0.50 - 0.51	0.52	0.52 - 0.52
		BMI	0.53	0.52 - 0.53	0.55	0.54 - 0.56	0.50	0.50 - 0.50	0.53	0.52 - 0.53
		Residuals	0.52	0.52 - 0.52	0.52	0.51 - 0.53	0.50	0.50 - 0.51	0.52	0.52 - 0.52
	Muscle mass and grip strength <26kg males, <16kg females	**Height**	0.51	0.51 - 0.51	0.51	0.51 - 0.52	0.50	0.50 - 0.50	0.51	0.51 - 0.51
		Weight	0.52	0.51 - 0.52	0.53	0.52 - 0.54	0.50	0.50 - 0.50	0.52	0.51 - 0.52
		BMI	0.52	0.52 - 0.52	0.54	0.53 - 0.55	0.50	0.50 - 0.50	0.52	0.52 - 0.52
		Residuals	0.51	0.51 - 0.52	0.51	0.51 - 0.52	0.50	0.50 - 0.50	0.51	0.51 - 0.52
	Muscle mass and grip strength <27kg males	**Height**	0.51	0.51 - 0.52	0.52	0.51 - 0.52	0.50	0.50 - 0.50	0.51	0.51 - 0.52
		Weight	0.52	0.52 - 0.52	0.53	0.52 - 0.53	0.50	0.50 - 0.50	0.52	0.52 - 0.52
		BMI	0.52	0.52 - 0.53	0.54	0.53 - 0.55	0.50	0.50 - 0.50	0.52	0.52 - 0.53
		Residuals	0.52	0.51 - 0.52	0.51	0.51 - 0.52	0.50	0.50 - 0.50	0.52	0.51 - 0.52
		Height	0.51	0.51 - 0.51	0.52	0.51 - 0.53	0.51	0.51 - 0.51	0.51	0.51 - 0.51
		Weight	0.52	0.52 - 0.53	0.53	0.52 - 0.54	0.51	0.50 - 0.51	0.52	0.52 - 0.53

	Muscle mass and gait speed <0.8m/s	**BMI**	0.51	0.51 - 0.52	0.55	0.54 - 0.56	0.51	0.51 - 0.52	0.51	0.51 - 0.52
		Residuals	0.52	0.51 - 0.52	0.53	0.52 - 0.53	0.52	0.51 - 0.52	0.52	0.51 - 0.52
	Muscle mass and gait speed <1.0m/s	**Height**	0.52	0.51 - 0.52	0.52	0.51 - 0.53	0.51	0.51 - 0.51	0.52	0.51 - 0.52
		Weight	0.54	0.54 - 0.55	0.53	0.52 - 0.54	0.50	0.50 - 0.51	0.54	0.54 - 0.55
		BMI	0.53	0.52 - 0.54	0.56	0.55 - 0.58	0.51	0.51 - 0.52	0.53	0.52 - 0.54
		Residuals	0.53	0.52 - 0.53	0.51	0.50 - 0.53	0.51	0.50 - 0.51	0.53	0.52 - 0.53
40th	**Muscle mass only**	**Height**	0.53	0.52 - 0.54	0.56	0.54 - 0.57	0.51	0.50 - 0.52	0.53	0.52 - 0.54
		Weight	0.54	0.54 - 0.55	0.55	0.54 - 0.57	0.51	0.50 - 0.51	0.54	0.54 - 0.55
		BMI	0.54	0.53 - 0.55	0.58	0.57 - 0.60	0.52	0.51 - 0.52	0.54	0.53 - 0.55
		Residuals	0.54	0.53 - 0.54	0.55	0.53 - 0.56	0.52	0.51 - 0.53	0.54	0.53 - 0.54
	Muscle mass and grip strength <30kg males, <20kg females	**Height**	0.53	0.53 - 0.54	0.56	0.55 - 0.57	0.51	0.51 - 0.52	0.53	0.53 - 0.54
		Weight	0.53	0.53 - 0.54	0.55	0.54 - 0.56	0.50	0.50 - 0.51	0.53	0.53 - 0.54
		BMI	0.53	0.53 - 0.54	0.56	0.55 - 0.57	0.51	0.50 - 0.51	0.53	0.53 - 0.54
		Residuals	0.53	0.53 - 0.54	0.55	0.54 - 0.56	0.51	0.51 - 0.51	0.53	0.53 - 0.54
	Muscle mass and grip strength <26kg males, <16kg females	**Height**	0.52	0.51 - 0.52	0.54	0.53 - 0.55	0.51	0.51 - 0.51	0.52	0.51 - 0.52
		Weight	0.52	0.52 - 0.52	0.54	0.53 - 0.55	0.50	0.50 - 0.50	0.52	0.52 - 0.52
		BMI	0.52	0.52 - 0.53	0.54	0.53 - 0.55	0.50	0.50 - 0.50	0.52	0.52 - 0.53
		Residuals	0.52	0.52 - 0.53	0.54	0.53 - 0.55	0.51	0.50 - 0.51	0.52	0.52 - 0.53
	Muscle mass and grip strength <27kg males	**Height**	0.52	0.52 - 0.53	0.54	0.53 - 0.55	0.51	0.51 - 0.51	0.52	0.52 - 0.53
		Weight	0.53	0.52 - 0.53	0.54	0.53 - 0.55	0.50	0.50 - 0.50	0.53	0.52 - 0.53
		BMI	0.53	0.52 - 0.53	0.54	0.53 - 0.54	0.50	0.50 - 0.50	0.53	0.52 - 0.53
		Residuals	0.53	0.52 - 0.53	0.54	0.53 - 0.55	0.51	0.50 - 0.51	0.53	0.52 - 0.53
	Muscle mass and gait speed <0.8m/s	**Height**	0.52	0.52 - 0.53	0.55	0.54 - 0.56	0.53	0.52 - 0.53	0.52	0.52 - 0.53
		Weight	0.53	0.53 - 0.54	0.57	0.56 - 0.58	0.52	0.51 - 0.52	0.53	0.53 - 0.54
		BMI	0.53	0.53 - 0.54	0.58	0.57 - 0.60	0.52	0.52 - 0.53	0.53	0.53 - 0.54
		Residuals	0.53	0.52 - 0.53	0.56	0.55 - 0.57	0.53	0.52 - 0.53	0.53	0.52 - 0.53
		Height	0.54	0.53 - 0.55	0.57	0.55 - 0.58	0.52	0.51 - 0.52	0.54	0.53 - 0.55

	Muscle mass and gait speed <1.0m/s	**Weight**	0.54	0.53 - 0.55	0.56	0.55 - 0.57	0.51	0.51 - 0.52	0.54	0.53 - 0.55
		BMI	0.54	0.53 - 0.55	0.59	0.57 - 0.60	0.52	0.52 - 0.53	0.54	0.53 - 0.55
		Residuals	0.54	0.54 - 0.55	0.56	0.55 - 0.58	0.52	0.52 - 0.53	0.54	0.54 - 0.55

Supplementary Table 3. Association between sarcopenia and falls in males using different methods of operationalizing sarcopenia

Sarcopenia definition			Number of participants with sarcopenia (%)	Intercept 1	Intercept 2	Odds of falling	95% Confidence interval	p-value
Muscle mass percentile	**Combination of muscle variables**	**Method of adjusting muscle mass**						
Not applicable	**Grip strength <30kg**		655 (12.7)	-4.31	-2.69	1.43	1.02 - 1.99	0.036
	Grip strength <26kg		253 (4.9)	-4.30	-2.67	1.80	1.13 - 2.86	0.013
	Grip strength <27kg		322 (6.3)	-4.30	-2.68	1.81	1.19 - 2.73	0.005
	Gait speed <0.8m/s		1136 (22.1)	-4.31	-2.69	1.28	0.96 - 1.70	0.095
	Gait speed <1.0m/s		3340 (64.9)	-4.22	-2.60	0.88	0.68 - 1.15	0.357
10th	**Muscle mass only**	**Height**	499 (9.7)	-4.30	-2.68	1.18	0.80 - 1.75	0.394
		Weight	503 (9.8)	-4.30	-2.68	1.24	0.85 - 1.81	0.256
		BMI	500 (9.7)	-4.30	-2.68	1.30	0.90 - 1.87	0.164
		Residuals	504 (9.8)	-4.32	-2.70	1.48	1.03 - 2.13	0.033
	Muscle mass and grip strength <30kg	**Height**	139 (2.7)	-4.29	-2.67	1.55	0.83 - 2.90	0.171
		Weight	131 (2.5)	-4.29	-2.67	1.47	0.77 - 2.78	0.239
		BMI	168 (3.3)	-4.29	-2.67	1.60	0.91 - 2.80	0.103
		Residuals	124 (2.4)	-4.29	-2.67	1.65	0.87 - 3.13	0.128
	Muscle mass and grip strength <26kg	**Height**	60 (1.2)	-4.29	-2.67	1.69	0.67 - 4.26	0.263
		Weight	64 (1.2)	-4.29	-2.67	1.80	0.76 - 4.22	0.179
		BMI	80 (1.6)	-4.29	-2.67	2.08	0.98 - 4.39	0.056
		Residuals	61 (1.2)	-4.29	-2.67	1.65	0.67 - 4.03	0.273
	Muscle mass and grip strength <27kg	**Height**	76 (1.5)	-4.29	-2.67	2.25	1.06 - 4.76	0.034
		Weight	76 (1.5)	-4.29	-2.67	1.97	0.93 - 4.17	0.075
		BMI	92 (1.8)	-4.29	-2.67	2.37	1.22 - 4.60	0.011

		Residuals	75 (1.5)	-4.29	-2.67	1.93	0.89 - 4.16	0.095
	Muscle mass and gait speed <0.8m/s	**Height**	144 (2.8)	-4.29	-2.67	1.10	0.56 - 2.14	0.788
		Weight	194 (3.8)	-4.29	-2.67	1.26	0.72 - 2.19	0.417
		BMI	205 (4.0)	-4.29	-2.67	1.08	0.62 - 1.89	0.780
		Residuals	161 (3.1)	-4.29	-2.67	1.41	0.78 - 2.54	0.257
	Muscle mass and gait speed <1.0m/s	**Height**	355 (6.9)	-4.30	-2.68	1.21	0.78 - 1.89	0.394
		Weight	407 (7.9)	-4.29	-2.67	1.14	0.75 - 1.74	0.531
		BMI	405 (7.9)	-4.29	-2.67	1.16	0.77 - 1.75	0.485
		Residuals	369 (7.2)	-4.30	-2.68	1.40	0.92 - 2.12	0.113
20th	**Muscle mass only**	**Height**	1007 (19.6)	-4.31	-2.69	1.13	0.83 - 1.53	0.428
		Weight	999 (19.4)	-4.34	-2.72	1.51	1.13 – 2.00	0.005
		BMI	1008 (19.6)	-4.30	-2.68	1.15	0.86 - 1.54	0.359
		Residuals	1009 (19.6)	-4.33	-2.71	1.28	0.96 - 1.71	0.099
	Muscle mass and grip strength <30kg	**Height**	243 (4.7)	-4.29	-2.67	1.27	0.75 - 2.14	0.375
		Weight	224 (4.4)	-4.29	-2.67	1.60	0.97 - 2.63	0.065
		BMI	285 (5.5)	-4.29	-2.67	1.66	1.06 - 2.59	0.026
		Residuals	218 (4.2)	-4.29	-2.67	1.66	1.01 - 2.74	0.046
	Muscle mass and grip strength <26kg	**Height**	106 (2.1)	-4.29	-2.67	1.41	0.67 - 2.99	0.364
		Weight	104 (2.0)	-4.29	-2.67	2.14	1.11 - 4.13	0.024
		BMI	122 (2.4)	-4.30	-2.67	2.33	1.28 - 4.26	0.006
		Residuals	95 (1.8)	-4.29	-2.67	2.14	1.08 - 4.25	0.029
	Muscle mass and grip strength <27kg	**Height**	129 (2.5)	-4.29	-2.67	1.68	0.88 - 3.21	0.113
		Weight	124 (2.4)	-4.29	-2.67	2.29	1.28 - 4.13	0.006
		BMI	147 (2.9)	-4.30	-2.68	2.48	1.45 - 4.24	0.001
		Residuals	119 (2.3)	-4.29	-2.67	2.20	1.20 - 4.04	0.011
		Height	258 (5.0)	-4.29	-2.67	1.11	0.65 - 1.87	0.707

	Muscle mass and gait speed <0.8m/s	**Weight**	344 (6.7)	-4.29	-2.67	1.36	0.88 - 2.08	0.164
		BMI	357 (6.9)	-4.29	-2.67	1.06	0.67 - 1.65	0.812
		Residuals	274 (5.3)	-4.29	-2.67	1.24	0.76 - 2.02	0.385
	Muscle mass and gait speed <1.0m/s	**Height**	694 (13.5)	-4.30	-2.68	1.11	0.79 - 1.58	0.542
		Weight	760 (14.8)	-4.31	-2.69	1.36	0.99 - 1.86	0.059
		BMI	789 (15.3)	-4.30	-2.68	1.14	0.83 - 1.57	0.425
		Residuals	723 (14.0)	-4.30	-2.68	1.18	0.85 - 1.65	0.327
40th	**Muscle mass only**	**Height**	2033 (39.5)	-4.36	-2.74	1.21	0.94 - 1.55	0.138
		Weight	2022 (39.3)	-4.35	-2.73	1.24	0.97 - 1.60	0.091
		BMI	2020 (39.2)	-4.34	-2.72	1.19	0.93 - 1.52	0.177
		Residuals	2019 (39.2)	-4.35	-2.73	1.20	0.94 - 1.54	0.142
	Muscle mass and grip strength <30kg	**Height**	390 (7.6)	-4.30	-2.68	1.54	1.03 - 2.32	0.036
		Weight	379 (7.4)	-4.30	-2.67	1.60	1.07 - 2.39	0.022
		BMI	426 (8.3)	-4.30	-2.68	1.63	1.11 - 2.40	0.013
		Residuals	382 (7.4)	-4.30	-2.68	1.67	1.12 - 2.49	0.011
	Muscle mass and grip strength <26kg	**Height**	164 (3.2)	-4.29	-2.67	1.67	0.94 - 2.98	0.082
		Weight	153 (3.0)	-4.29	-2.67	2.09	1.20 - 3.65	0.010
		BMI	175 (3.4)	-4.29	-2.67	2.08	1.22 - 3.53	0.007
		Residuals	155 (3.0)	-4.29	-2.67	2.24	1.30 - 3.87	0.004
	Muscle mass and grip strength <27kg	**Height**	205 (4.0)	-4.30	-2.67	1.85	1.11 - 3.07	0.017
		Weight	194 (3.8)	-4.29	-2.67	2.22	1.36 - 3.61	0.001
		BMI	221 (4.3)	-4.30	-2.67	2.15	1.35 - 3.44	0.001
		Residuals	194 (3.8)	-4.30	-2.68	2.34	1.44 - 3.80	0.001
	Muscle mass and gait speed <0.8m/s	**Height**	489 (9.5)	-4.30	-2.68	1.24	0.84 - 1.82	0.287
		Weight	595 (11.6)	-4.29	-2.67	1.24	0.87 - 1.78	0.229
		BMI	604 (11.7)	-4.30	-2.68	1.28	0.90 - 1.82	0.164

		Residuals	528 (10.3)	-4.30	-2.68	1.28	0.88 - 1.84	0.196
	Muscle mass and gait speed <1.0m/s	**Height**	1358 (26.4)	-4.33	-2.71	1.27	0.96 - 1.66	0.089
		Weight	1465 (28.5)	-4.31	-2.69	1.14	0.87 - 1.49	0.339
		BMI	1494 (29.0)	-4.31	-2.69	1.13	0.87 - 1.48	0.364
		Residuals	1401 (27.2)	-4.34	-2.72	1.27	0.97 - 1.66	0.080

Supplementary Table 4. Association between sarcopenia and falls in females using different methods of operationalizing sarcopenia

Sarcopenia definition			Number of participants with sarcopenia (%)	Intercept 1	Intercept 2	Odds of falling	95% Confidence interval	p-value
Muscle mass percentile	Combination of muscle variables	Method of adjusting muscle mass						
Not applicable	Grip strength <20kg		1125 (23.1)	-3.86	-2.26	1.00	0.78 - 1.27	0.990
	Grip strength <16kg		338 (7.0)	-3.86	-2.26	0.93	0.62 - 1.38	0.701
	Gait speed <0.8m/s		1414 (29.1)	-3.88	-2.28	1.15	0.92 - 1.45	0.219
	Gait speed <1.0m/s		3474 (71.5)	-3.82	-2.22	0.94	0.74 - 1.18	0.575
10th	Muscle mass only	Height	484 (10.0)	-3.88	-2.27	1.13	0.81 - 1.57	0.467
		Weight	484 (10.0)	-3.86	-2.26	1.00	0.72 - 1.38	0.991
		BMI	475 (9.8)	-3.86	-2.25	0.90	0.65 - 1.25	0.529
		Residuals	490 (10.1)	-3.86	-2.26	0.97	0.70 - 1.34	0.854
	Muscle mass and grip strength <20kg	Height	176 (3.6)	-3.86	-2.26	0.89	0.51 - 1.56	0.689
		Weight	173 (3.6)	-3.86	-2.25	0.60	0.33 - 1.10	0.096
		BMI	205 (4.2)	-3.86	-2.26	0.44	0.24 - 0.80	0.008
		Residuals	164 (3.4)	-3.86	-2.25	0.74	0.41 - 1.34	0.322
	Muscle mass and grip strength <16kg	Height	59 (1.2)	-3.86	-2.26	0.94	0.38 - 2.31	0.899
		Weight	53 (1.1)	-3.86	-2.26	0.44	0.13 - 1.46	0.180
		BMI	74 (1.5)	-3.86	-2.26	0.56	0.23 - 1.39	0.214
		Residuals	43 (0.9)	-3.86	-2.26	0.59	0.18 - 1.91	0.381
	Muscle mass and gait speed <0.8m/s	Height	135 (2.8)	-3.86	-2.26	1.12	0.63 - 2.02	0.694
		Weight	229 (4.7)	-3.86	-2.26	1.14	0.75 - 1.75	0.534
		BMI	230 (4.7)	-3.86	-2.26	0.82	0.51 - 1.30	0.388
		Residuals	169 (3.5)	-3.87	-2.26	1.46	0.92 - 2.33	0.112

	Muscle mass and gait speed <1.0m/s	**Height**	344 (7.1)	-3.87	-2.27	1.1	0.75 - 1.61	0.629
		Weight	409 (8.4)	-3.86	-2.26	1.01	0.72 - 1.42	0.954
		BMI	406 (8.4)	-3.86	-2.25	0.81	0.56 - 1.16	0.252
		Residuals	385 (7.9)	-3.86	-2.26	0.99	0.69 - 1.41	0.935
20th	**Muscle mass only**	**Height**	972 (20.0)	-3.89	-2.29	1.12	0.87 - 1.44	0.367
		Weight	963 (19.8)	-3.85	-2.24	0.89	0.70 - 1.15	0.377
		BMI	961 (19.8)	-3.86	-2.26	1.01	0.79 - 1.29	0.947
		Residuals	969 (19.9)	-3.88	-2.28	1.10	0.87 - 1.41	0.419
	Muscle mass and grip strength <20kg	**Height**	340 (7.0)	-3.86	-2.26	1.07	0.73 - 1.58	0.722
		Weight	296 (6.1)	-3.86	-2.25	0.54	0.33 - 0.87	0.011
		BMI	366 (7.5)	-3.86	-2.25	0.73	0.49 - 1.09	0.125
		Residuals	291 (6.0)	-3.86	-2.26	0.93	0.61 - 1.42	0.740
	Muscle mass and grip strength <16kg	**Height**	117 (2.4)	-3.86	-2.26	1.15	0.64 - 2.07	0.647
		Weight	83 (1.7)	-3.86	-2.26	0.50	0.20 - 1.28	0.148
		BMI	126 (2.6)	-3.86	-2.26	0.69	0.35 - 1.35	0.278
		Residuals	88 (1.8)	-3.86	-2.26	0.79	0.36 - 1.73	0.550
	Muscle mass and gait speed <0.8m/s	**Height**	264 (5.4)	-3.87	-2.27	1.28	0.85 - 1.93	0.235
		Weight	411 (8.5)	-3.86	-2.26	0.94	0.66 - 1.34	0.734
		BMI	396 (8.1)	-3.86	-2.26	1.13	0.81 - 1.59	0.467
		Residuals	304 (6.3)	-3.87	-2.27	1.40	0.97 - 2.01	0.075
	Muscle mass and gait speed <1.0m/s	**Height**	689 (14.2)	-3.87	-2.27	1.08	0.82 - 1.44	0.576
		Weight	800 (16.5)	-3.85	-2.25	0.87	0.66 - 1.13	0.296
		BMI	784 (16.1)	-3.86	-2.26	0.99	0.76 - 1.30	0.968
		Residuals	722 (14.9)	-3.87	-2.27	1.08	0.82 - 1.42	0.581
40th	**Muscle mass only**	**Height**	1948 (40.1)	-3.93	-2.32	1.15	0.93 - 1.41	0.195
		Weight	1937 (39.8)	-3.83	-2.23	0.90	0.73 - 1.11	0.323

		BMI	1930 (39.7)	-3.85	-2.25	0.96	0.78 - 1.17	0.674
		Residuals	1947 (40.1)	-3.92	-2.32	1.15	0.94 - 1.4	0.176
	Muscle mass and grip strength <20kg	**Height**	565 (11.6)	-3.87	-2.27	1.15	0.85 - 1.56	0.378
		Weight	544 (11.2)	-3.85	-2.25	0.79	0.57 - 1.10	0.159
		BMI	644 (13.2)	-3.85	-2.25	0.82	0.60 - 1.11	0.193
		Residuals	545 (11.2)	-3.86	-2.26	1.02	0.74 - 1.39	0.924
	Muscle mass and grip strength <16kg	**Height**	186 (3.8)	-3.87	-2.26	1.32	0.82 - 2.11	0.247
		Weight	154 (3.2)	-3.86	-2.26	0.73	0.40 - 1.34	0.309
		BMI	204 (4.2)	-3.86	-2.26	0.77	0.46 - 1.30	0.329
		Residuals	167 (3.4)	-3.86	-2.26	1.19	0.72 - 1.98	0.503
	Muscle mass and gait speed <0.8m/s	**Height**	498 (10.2)	-3.88	-2.28	1.37	1.01 - 1.86	0.040
		Weight	741 (15.2)	-3.86	-2.26	1.00	0.76 - 1.32	0.982
		BMI	746 (15.3)	-3.86	-2.26	1.07	0.82 - 1.41	0.617
		Residuals	589 (12.1)	-3.88	-2.28	1.38	1.04 - 1.83	0.024
	Muscle mass and gait speed <1.0m/s	**Height**	1321 (27.2)	-3.89	-2.29	1.13	0.90 - 1.41	0.302
		Weight	1542 (31.7)	-3.84	-2.24	0.91	0.73 - 1.13	0.405
		BMI	1531 (31.5)	-3.86	-2.26	0.98	0.79 - 1.22	0.878
		Residuals	1424 (29.3)	-3.89	-2.29	1.12	0.91 - 1.39	0.283

Supplementary Table 5. Association between sarcopenia and falls in males using different methods of operationalizing sarcopenia – males, completers only anaylses without multiple imputation

Sarcopenia definition			Number of participants with sarcopenia (%)	Intercept 1	Intercept 2	Odds of falling	95% Confidence interval	p-value
Muscle mass percentile	**Combination of muscle variables**	**Method of adjusting muscle mass**						
Not applicable	**Grip strength <30kg**		655 (14.1)	-4.31	-2.68	1.49	1.06 - 2.09	0.023
	Grip strength <26kg		253 (5.4)	-4.29	-2.67	1.83	1.14 - 2.94	0.012
	Grip strength <27kg		322 (6.9)	-4.30	-2.67	1.86	1.22 - 2.83	0.004
	Gait speed <0.8m/s		1133 (24.4)	-4.31	-2.69	1.29	0.96 - 1.73	0.092
	Gait speed <1.0m/s		3337 (71.7)	-4.25	-2.63	0.94	0.72 - 1.23	0.648
10th	**Muscle mass only**	**Height**	499 (10.7)	-4.30	-2.68	1.22	0.82 - 1.81	0.335
		Weight	501 (10.8)	-4.29	-2.67	1.25	0.85 - 1.85	0.252
		BMI	500 (10.8)	-4.30	-2.67	1.33	0.91 - 1.94	0.143
		Residuals	503 (10.8)	-4.31	-2.69	1.51	1.05 - 2.19	0.028
	Muscle mass and grip strength <30kg	**Height**	139 (3.0)	-4.29	-2.67	1.67	0.88 - 3.17	0.114
		Weight	131 (2.8)	-4.28	-2.66	1.44	0.75 - 2.77	0.278
		BMI	168 (3.6)	-4.29	-2.66	1.60	0.90 - 2.86	0.112
		Residuals	124 (2.7)	-4.28	-2.66	1.74	0.90 - 3.35	0.098
	Muscle mass and grip strength <26kg	**Height**	60 (1.3)	-4.28	-2.66	1.71	0.66 - 4.45	0.268
		Weight	64 (1.4)	-4.28	-2.66	1.63	0.67 - 4.00	0.282
		BMI	80 (1.7)	-4.29	-2.66	1.90	0.87 - 4.17	0.109
		Residuals	61 (1.3)	-4.28	-2.66	1.66	0.66 - 4.19	0.279
	Muscle mass and grip strength <27kg	**Height**	76 (1.6)	-4.29	-2.66	2.31	1.07 - 4.98	0.032
		Weight	76 (1.6)	-4.29	-2.66	1.84	0.85 - 4.00	0.121
		BMI	92 (2.0)	-4.29	-2.66	2.23	1.12 - 4.45	0.022

		Residuals	75 (1.6)	-4.28	-2.66	1.97	0.89 - 4.32	0.093
	Muscle mass and gait speed <0.8m/s	**Height**	144 (3.1)	-4.28	-2.66	1.13	0.56 - 2.26	0.733
		Weight	193 (4.1)	-4.28	-2.66	1.17	0.65 - 2.09	0.599
		BMI	205 (4.4)	-4.28	-2.66	1.05	0.59 - 1.87	0.880
		Residuals	161 (3.5)	-4.29	-2.66	1.46	0.79 - 2.68	0.225
	Muscle mass and gait speed <1.0m/s	**Height**	355 (7.6)	-4.29	-2.67	1.25	0.79 - 1.96	0.343
		Weight	406 (8.7)	-4.29	-2.67	1.16	0.75 - 1.78	0.500
		BMI	405 (8.7)	-4.29	-2.67	1.19	0.78 - 1.82	0.416
		Residuals	369 (7.9)	-4.30	-2.68	1.46	0.96 - 2.23	0.078
20th	**Muscle mass only**	**Height**	1006 (21.6)	-4.30	-2.68	1.12	0.82 - 1.52	0.485
		Weight	996 (21.4)	-4.34	-2.72	1.53	1.14 - 2.05	0.004
		BMI	1006 (21.6)	-4.30	-2.68	1.15	0.85 - 1.56	0.370
		Residuals	1008 (21.7)	-4.33	-2.71	1.32	0.98 - 1.77	0.066
	Muscle mass and grip strength <30kg	**Height**	243 (5.2)	-4.29	-2.67	1.30	0.76 - 2.23	0.329
		Weight	224 (4.8)	-4.29	-2.66	1.60	0.96 - 2.67	0.073
		BMI	285 (6.1)	-4.29	-2.67	1.68	1.06 - 2.66	0.026
		Residuals	218 (4.7)	-4.29	-2.67	1.78	1.07 - 2.95	0.027
	Muscle mass and grip strength <26kg	**Height**	106 (2.3)	-4.28	-2.66	1.36	0.62 - 2.96	0.439
		Weight	104 (2.2)	-4.29	-2.66	2.10	1.06 - 4.14	0.032
		BMI	122 (2.6)	-4.29	-2.67	2.28	1.22 - 4.24	0.010
		Residuals	95 (2.0)	-4.29	-2.66	2.21	1.10 - 4.44	0.026
	Muscle mass and grip strength <27kg	**Height**	129 (2.8)	-4.29	-2.66	1.65	0.85 - 3.21	0.137
		Weight	124 (2.7)	-4.29	-2.66	2.27	1.24 - 4.14	0.008
		BMI	147 (3.2)	-4.30	-2.67	2.44	1.41 - 4.24	0.002
		Residuals	119 (2.6)	-4.29	-2.66	2.26	1.22 - 4.20	0.010
		Height	257 (5.5)	-4.28	-2.66	1.04	0.60 - 1.81	0.878

	Muscle mass and gait speed <0.8m/s	**Weight**	342 (7.4)	-4.29	-2.67	1.29	0.82 - 2.02	0.264
		BMI	355 (7.6)	-4.28	-2.66	0.98	0.61 - 1.58	0.943
		Residuals	274 (5.9)	-4.29	-2.67	1.27	0.77 - 2.09	0.344
	Muscle mass and gait speed <1.0m/s	**Height**	693 (14.9)	-4.29	-2.67	1.09	0.77 - 1.57	0.621
		Weight	758 (16.3)	-4.31	-2.69	1.38	1.00 - 1.91	0.053
		BMI	787 (16.9)	-4.29	-2.67	1.14	0.82 - 1.58	0.442
		Residuals	723 (15.5)	-4.30	-2.68	1.23	0.88 - 1.73	0.227
40th	**Muscle mass only**	**Height**	2030 (43.6)	-4.35	-2.73	1.20	0.93 - 1.55	0.170
		Weight	2019 (43.4)	-4.36	-2.74	1.27	0.99 - 1.65	0.065
		BMI	2016 (43.3)	-4.33	-2.71	1.19	0.93 - 1.54	0.173
		Residuals	2016 (43.3)	-4.36	-2.73	1.23	0.95 - 1.58	0.115
	Muscle mass and grip strength <30kg	**Height**	390 (8.4)	-4.30	-2.67	1.60	1.06 - 2.42	0.025
		Weight	379 (8.1)	-4.29	-2.67	1.63	1.08 - 2.46	0.020
		BMI	426 (9.2)	-4.30	-2.67	1.67	1.13 - 2.48	0.010
		Residuals	382 (8.2)	-4.30	-2.68	1.75	1.17 - 2.63	0.007
	Muscle mass and grip strength <26kg	**Height**	164 (3.5)	-4.29	-2.67	1.65	0.91 – 3.00	0.100
		Weight	153 (3.3)	-4.28	-2.66	2.06	1.16 - 3.66	0.014
		BMI	175 (3.8)	-4.29	-2.66	2.08	1.21 - 3.60	0.009
		Residuals	155 (3.3)	-4.29	-2.66	2.23	1.27 - 3.92	0.005
	Muscle mass and grip strength <27kg	**Height**	205 (4.4)	-4.29	-2.67	1.85	1.10 - 3.11	0.020
		Weight	194 (4.2)	-4.29	-2.66	2.21	1.34 - 3.63	0.002
		BMI	221 (4.8)	-4.29	-2.67	2.16	1.34 - 3.50	0.002
		Residuals	194 (4.2)	-4.30	-2.67	2.38	1.44 - 3.91	0.001
	Muscle mass and gait speed <0.8m/s	**Height**	488 (10.5)	-4.29	-2.67	1.21	0.81 - 1.81	0.355
		Weight	593 (12.7)	-4.29	-2.67	1.23	0.85 - 1.78	0.272
		BMI	601 (12.9)	-4.29	-2.67	1.22	0.85 - 1.77	0.279

		Residuals	526 (11.3)	-4.29	-2.67	1.25	0.86 - 1.83	0.245
	Muscle mass and gait speed <1.0m/s	**Height**	1357 (29.2)	-4.34	-2.71	1.30	0.99 - 1.72	0.064
		Weight	1463 (31.5)	-4.31	-2.69	1.18	0.89 - 1.55	0.246
		BMI	1491 (32.1)	-4.31	-2.68	1.14	0.87 - 1.50	0.340
		Residuals	1399 (30.1)	-4.34	-2.72	1.30	0.99 - 1.71	0.058

Supplementary Table 6. Association between sarcopenia and falls in males using different methods of operationalizing sarcopenia, completers only anaylses without multiple imputation

Sarcopenia definition			Number of participants with sarcopenia (%)	Intercept 1	Intercept 2	Odds of falling	95% Confidence interval	p-value
Muscle mass percentile	Combination of muscle variables	Method of adjusting muscle mass						
Not applicable	Grip strength <20kg		1124 (23.3)	-3.87	-2.27	1.01	0.79 - 1.30	0.927
	Grip strength <16kg		337 (7.0)	-3.87	-2.26	0.89	0.59 - 1.35	0.586
	Gait speed <0.8m/s		1412 (29.3)	-3.89	-2.28	0.89	0.59 - 1.35	0.586
	Gait speed <1.0m/s		3472 (71.9)	-3.83	-2.23	1.16	0.92 - 1.46	0.224
10th	Muscle mass only	Height	483 (9.9)	-3.88	-2.28	1.09	0.78 - 1.53	0.608
		Weight	482 (9.9)	-3.87	-2.26	0.93	0.67 - 1.31	0.691
		BMI	473 (9.7)	-3.86	-2.26	0.86	0.61 - 1.22	0.394
		Residuals	489 (10.1)	-3.86	-2.26	0.96	0.68 - 1.34	0.795
	Muscle mass and grip strength <20kg	Height	175 (3.6)	-3.87	-2.26	0.93	0.74 - 1.18	0.565
		Weight	173 (3.6)	-3.87	-2.26	0.91	0.51 - 1.60	0.738
		BMI	205 (4.2)	-3.87	-2.26	0.55	0.29 - 1.05	0.070
		Residuals	164 (3.4)	-3.86	-2.26	0.38	0.20 - 0.75	0.005
	Muscle mass and grip strength <16kg	Height	58 (1.2)	-3.87	-2.27	0.74	0.40 - 1.36	0.329
		Weight	53 (1.1)	-3.87	-2.26	0.86	0.33 - 2.21	0.747
		BMI	74 (1.5)	-3.87	-2.26	0.36	0.09 - 1.43	0.148
		Residuals	43 (0.9)	-3.87	-2.26	0.46	0.16 - 1.29	0.139
	Muscle mass and gait speed <0.8m/s	Height	134 (2.8)	-3.87	-2.27	0.64	0.20 - 2.08	0.463
		Weight	228 (4.7)	-3.87	-2.27	1.18	0.65 - 2.15	0.591
		BMI	229 (4.7)	-3.87	-2.27	1.07	0.69 - 1.67	0.751
		Residuals	168 (3.5)	-3.87	-2.27	0.75	0.46 - 1.23	0.250

	Muscle mass and gait speed <1.0m/s	**Height**	343 (7.1)	-3.88	-2.27	1.45	0.89 - 2.35	0.133
		Weight	408 (8.4)	-3.87	-2.26	1.10	0.74 - 1.63	0.639
		BMI	405 (8.3)	-3.86	-2.26	0.96	0.67 - 1.37	0.811
		Residuals	384 (7.9)	-3.87	-2.26	0.78	0.54 - 1.14	0.204
20th	**Muscle mass only**	**Height**	971 (20.0)	-3.89	-2.29	0.97	0.67 - 1.40	0.855
		Weight	961 (19.8)	-3.85	-2.25	0.86	0.67 - 1.12	0.268
		BMI	959 (19.7)	-3.87	-2.26	0.97	0.75 - 1.25	0.808
		Residuals	967 (19.9)	-3.88	-2.28	1.08	0.84 - 1.38	0.544
	Muscle mass and grip strength <20kg	**Height**	339 (7.0)	-3.87	-2.27	1.09	0.74 - 1.61	0.670
		Weight	296 (6.1)	-3.87	-2.26	0.50	0.30 - 0.84	0.008
		BMI	366 (7.5)	-3.86	-2.26	0.70	0.46 - 1.06	0.094
		Residuals	290 (6.0)	-3.87	-2.26	0.91	0.59 - 1.41	0.678
	Muscle mass and grip strength <16kg	**Height**	116 (2.4)	-3.87	-2.27	1.08	0.58 – 2.00	0.806
		Weight	83 (1.7)	-3.87	-2.26	0.44	0.16 - 1.22	0.113
		BMI	126 (2.6)	-3.87	-2.26	0.62	0.30 - 1.28	0.199
		Residuals	87 (1.8)	-3.87	-2.26	0.69	0.29 - 1.65	0.409
	Muscle mass and gait speed <0.8m/s	**Height**	263 (5.4)	-3.88	-2.27	1.32	0.87 - 2.01	0.192
		Weight	410 (8.4)	-3.87	-2.27	0.90	0.63 - 1.29	0.570
		BMI	395 (8.1)	-3.87	-2.27	1.08	0.76 - 1.54	0.665
		Residuals	302 (6.2)	-3.88	-2.27	1.35	0.92 - 1.97	0.125
	Muscle mass and gait speed <1.0m/s	**Height**	688 (14.2)	-3.88	-2.28	1.07	0.80 - 1.43	0.655
		Weight	799 (16.5)	-3.86	-2.25	0.84	0.64 - 1.11	0.219
		BMI	783 (16.1)	-3.87	-2.26	0.95	0.73 - 1.25	0.736
		Residuals	720 (14.8)	-3.88	-2.27	1.05	0.80 - 1.39	0.713
40th	**Muscle mass only**	**Height**	1946 (40.1)	-3.93	-2.33	1.14	0.92 - 1.40	0.237
		Weight	1934 (39.8)	-3.83	-2.22	0.87	0.71 - 1.08	0.212

		BMI	1927 (39.7)	-3.85	-2.25	0.95	0.77 - 1.17	0.641
		Residuals	1945 (40.0)	-3.92	-2.32	1.13	0.92 - 1.39	0.232
	Muscle mass and grip strength <20kg	**Height**	564 (11.6)	-3.88	-2.28	1.15	0.84 - 1.57	0.379
		Weight	543 (11.2)	-3.86	-2.26	0.78	0.55 - 1.09	0.148
		BMI	643 (13.2)	-3.86	-2.26	0.81	0.59 - 1.12	0.198
		Residuals	544 (11.2)	-3.87	-2.27	1.01	0.73 - 1.39	0.953
	Muscle mass and grip strength <16kg	**Height**	185 (3.8)	-3.87	-2.27	1.20	0.73 - 1.98	0.468
		Weight	153 (3.2)	-3.87	-2.26	0.63	0.33 - 1.22	0.174
		BMI	203 (4.2)	-3.87	-2.26	0.71	0.41 - 1.24	0.232
		Residuals	166 (3.4)	-3.87	-2.27	1.08	0.63 - 1.87	0.771
	Muscle mass and gait speed <0.8m/s	**Height**	497 (10.2)	-3.89	-2.29	1.41	1.03 - 1.92	0.031
		Weight	739 (15.2)	-3.87	-2.27	0.97	0.73 - 1.29	0.856
		BMI	744 (15.3)	-3.87	-2.27	1.06	0.80 - 1.40	0.686
		Residuals	587 (12.1)	-3.89	-2.28	1.38	1.03 - 1.84	0.030
	Muscle mass and gait speed <1.0m/s	**Height**	1320 (27.2)	-3.90	-2.29	1.12	0.89 - 1.40	0.349
		Weight	1540 (31.7)	-3.85	-2.24	0.88	0.70 - 1.10	0.267
		BMI	1529 (31.5)	-3.86	-2.26	0.97	0.78 - 1.22	0.818
		Residuals	1422 (29.3)	-3.90	-2.29	1.11	0.89 - 1.39	0.343

Supplementary Table 7. Percentage of underweight, normal weight, overweight, and obese participants for each method of adjusting for low muscle mass using the 20th percentile cut offs

Males					
Body mass index	**Number of participants in body mass index category (%)**				
	ALM/height	**ALM/weight**	**ALM/BMI**	**ALM Residuals**	**All participants**
Underweight (<18.5kg/m2)	13 (1.3)	0 (0)	0 (0)	12 (1.2)	14 (0.3)
Normal weight (18.5 - 24.9 kg/m2)	628 (62.4)	44 (4.4)	79 (7.8)	401 (39.7)	1218 (23.7)
Overweight (25.0 - 29.9kg/m2)	334 (33.2)	255 (25.5)	401 (39.8)	437 (43.3)	2558 (49.7)
Obese (≥30kg/m2)	32 (3.2)	600 (60.1)	528 (52.4)	159 (15.8)	1357 (26.4)
Females					
	Number of participants in body mass index category (%)				
Body mass index	**ALM/height**	**ALM/weight**	**ALM/BMI**	**ALM Residuals**	**All participants**
Underweight (<18.5kg/m2)	54 (5.6)	0 (0)	0 (0)	17 (1.8)	63 (1.3)
Normal weight (18.5 - 24.9 kg/m2)	731 (75.2)	58 (6.0)	97 (10.1)	386 (39.8)	1563 (32.2)
Overweight (25.0 - 29.9kg/m2)	178 (18.3)	281 (29.2)	303 (31.5)	370 (38.2)	1820 (37.4)
Obese (≥30kg/m2)	9 (0.9)	624 (64.8)	561 (58.4)	196 (20.2)	1415 (29.1)

Supplementary Table 8. Number of male participants with zero, one, or two or more falls stratified by sarcopenia status

		Sarcopenia No			Sarcopenia yes			1 or more falls		2 or more falls	
		0 Falls	1 Fall	2+ Falls	0 Falls	1 Fall	2+ Falls	Sensitivity	Specificity	Sensitivity	Specificity
Muscle mass only (10th percentile)	ALM/height	4219	339	90	440	42	17	0.12	0.91	0.03	0.98
	ALM/weight	4227	325	92	432	56	15	0.14	0.91	0.03	0.98
	ALM/BMI	4228	332	87	431	49	20	0.14	0.91	0.04	0.98
	ALM regression	4226	327	90	433	54	17	0.14	0.91	0.03	0.98
Muscle mass only (20th percentile)	ALM/height	3762	298	80	897	83	27	0.11	0.91	0.03	0.98
	ALM/weight	3799	270	79	860	111	28	0.14	0.92	0.03	0.98
	ALM/BMI	3774	292	73	885	89	34	0.12	0.91	0.03	0.98
	ALM regression	3774	284	80	885	97	27	0.12	0.91	0.03	0.98
Muscle mass only (40th percentile)	ALM/height	2847	214	53	1812	167	54	0.11	0.91	0.03	0.98
	ALM/weight	2868	203	54	1791	178	53	0.11	0.92	0.03	0.98
	ALM/BMI	2867	212	48	1792	169	59	0.11	0.92	0.03	0.98
	ALM regression	2863	210	55	1796	171	52	0.11	0.92	0.03	0.98
Grip strength	30kg	4100	314	78	559	67	29	0.15	0.91	0.04	0.98
	26kg	4452	349	93	207	32	14	0.18	0.91	0.06	0.98
	27kg	4395	338	92	264	43	15	0.18	0.91	0.05	0.98
Gait speed	1.0 mps	3669	279	63	990	102	44	0.13	0.91	0.04	0.98
	0.80 mps	1647	132	28	3012	249	79	0.10	0.91	0.02	0.98
10th percentile - Muscle mass and grip strength (30kg)	ALM/height	4543	364	101	116	17	6	0.17	0.91	0.04	0.98
	ALM/weight	4551	363	102	108	18	5	0.18	0.91	0.04	0.98
	ALM/BMI	4520	363	96	139	18	11	0.17	0.91	0.07	0.98
	ALM regression	4558	364	101	101	17	6	0.19	0.91	0.05	0.98
10th percentile - Muscle mass and grip strength (26kg)	ALM/height	4610	373	104	49	8	3	0.18	0.91	0.05	0.98
	ALM/weight	4609	370	104	50	11	3	0.22	0.91	0.05	0.98
	ALM/BMI	4597	371	99	62	10	8	0.23	0.91	0.10	0.98
	ALM regression	4610	372	104	49	9	3	0.20	0.91	0.05	0.98

10th percentile - Muscle mass and grip strength (27kg)	**ALM/height**	4600	368	103	59	13	4	0.22	0.91	0.05	0.98
	ALM/weight	4600	367	104	59	14	3	0.22	0.91	0.04	0.98
	ALM/BMI	4589	367	99	70	14	8	0.24	0.91	0.09	0.98
	ALM regression	4600	368	104	59	13	3	0.21	0.91	0.04	0.98
10th percentile - Muscle mass and gait speed (0.8m/s)	**ALM/height**	4535	368	100	124	13	7	0.14	0.91	0.05	0.98
	ALM/weight	4497	355	101	162	26	6	0.16	0.91	0.03	0.98
	ALM/BMI	4481	363	98	178	18	9	0.13	0.91	0.04	0.98
	ALM regression	4526	361	99	133	20	8	0.17	0.91	0.05	0.98
10th percentile - Muscle mass and gait speed (1.0m/s)	**ALM/height**	4349	348	95	310	33	12	0.13	0.91	0.03	0.98
	ALM/weight	4310	335	95	349	46	12	0.14	0.91	0.03	0.98
	ALM/BMI	4309	342	91	350	39	16	0.14	0.91	0.04	0.98
	ALM regression	4345	339	94	314	42	13	0.15	0.91	0.04	0.98
20th percentile - Muscle mass and grip strength (30kg)	**ALM/height**	4451	356	97	208	25	10	0.14	0.91	0.04	0.98
	ALM/weight	4474	352	97	185	29	10	0.17	0.91	0.04	0.98
	ALM/BMI	4424	348	90	235	33	17	0.18	0.91	0.06	0.98
	ALM regression	4479	352	98	180	29	9	0.17	0.91	0.04	0.98
20th percentile - Muscle mass and grip strength (26kg)	**ALM/height**	4570	369	102	89	12	5	0.16	0.91	0.05	0.98
	ALM/weight	4579	365	99	80	16	8	0.23	0.91	0.08	0.98
	ALM/BMI	4566	363	96	93	18	11	0.24	0.91	0.09	0.98
	ALM regression	4585	365	102	74	16	5	0.22	0.91	0.05	0.98
20th percentile - Muscle mass and grip strength (27kg)	**ALM/height**	4553	364	101	106	17	6	0.18	0.91	0.05	0.98
	ALM/weight	4564	360	99	95	21	8	0.23	0.91	0.06	0.98
	ALM/BMI	4547	357	96	112	24	11	0.24	0.91	0.07	0.98
	ALM regression	4566	360	102	93	21	5	0.22	0.91	0.04	0.98
20th percentile - Muscle mass and gait speed (0.8m/s)	**ALM/height**	4435	357	97	224	24	10	0.13	0.91	0.04	0.98
	ALM/weight	4369	340	94	290	41	13	0.15	0.91	0.04	0.98
	ALM/BMI	4349	352	89	310	29	18	0.13	0.91	0.05	0.98
	ALM regression	4426	351	96	233	30	11	0.15	0.91	0.04	0.98

20th percentile - Muscle mass and gait speed (1.0m/s)	**ALM/height**	4045	320	88	614	61	19	0.11	0.91	0.03	0.98
	ALM/weight	4008	294	85	651	87	22	0.14	0.91	0.03	0.98
	ALM/BMI	3971	310	77	688	71	30	0.13	0.91	0.04	0.98
	ALM regression	4028	307	89	631	74	18	0.13	0.91	0.02	0.98
40th percentile - Muscle mass and grip strength (30kg)	**ALM/height**	4333	338	86	326	43	21	0.16	0.91	0.05	0.98
	ALM/weight	4343	337	88	316	44	19	0.17	0.91	0.05	0.98
	ALM/BMI	4302	334	85	357	47	22	0.16	0.91	0.05	0.98
	ALM regression	4342	334	89	317	47	18	0.17	0.91	0.05	0.98
40th percentile - Muscle mass and grip strength (26kg)	**ALM/height**	4525	362	96	134	19	11	0.18	0.91	0.07	0.98
	ALM/weight	4539	360	95	120	21	12	0.22	0.91	0.08	0.98
	ALM/BMI	4520	357	95	139	24	12	0.21	0.91	0.07	0.98
	ALM regression	4538	358	96	121	23	11	0.22	0.91	0.07	0.98
40th percentile - Muscle mass and grip strength (27kg)	**ALM/height**	4493	354	95	166	27	12	0.19	0.91	0.06	0.98
	ALM/weight	4507	351	95	152	30	12	0.22	0.91	0.06	0.98
	ALM/BMI	4483	348	95	176	33	12	0.20	0.91	0.05	0.98
	ALM regression	4508	350	95	151	31	12	0.22	0.91	0.06	0.98
40th percentile - Muscle mass and gait speed (0.8m/s)	**ALM/height**	4236	336	86	423	45	21	0.13	0.91	0.04	0.98
	ALM/weight	4148	324	80	511	57	27	0.14	0.91	0.05	0.98
	ALM/BMI	4140	326	77	519	55	30	0.14	0.91	0.05	0.98
	ALM regression	4207	328	84	452	53	23	0.14	0.91	0.04	0.98
40th percentile - Muscle mass and gait speed (1.0m/s)	**ALM/height**	3464	260	65	1195	121	42	0.12	0.92	0.03	0.98
	ALM/weight	3368	250	64	1291	131	43	0.12	0.92	0.03	0.98
	ALM/BMI	3342	253	58	1317	128	49	0.12	0.92	0.03	0.98
	ALM regression	3429	252	65	1230	129	42	0.12	0.92	0.03	0.98

Supplementary Table 9. Number of female participants with zero, one, or two or more falls stratified by sarcopenia status

		Sarcopenia No			Sarcopenia yes			1 or more falls		2 or more falls	
		0 Falls	1 Fall	2+ Falls	0 Falls	1 Fall	2+ Falls	Sensitivity	Specificity	Sensitivity	Specificity
Muscle mass only (10th percentile)	ALM/height	3814	430	133	417	49	18	0.14	0.87	0.04	0.97
	ALM/weight	3815	433	129	416	46	22	0.14	0.87	0.05	0.97
	ALM/BMI	3820	434	132	411	45	19	0.13	0.87	0.04	0.97
	ALM regression	3805	435	131	426	44	20	0.13	0.87	0.04	0.97
Muscle mass only (20th percentile)	ALM/height	3393	380	116	838	99	35	0.14	0.87	0.04	0.97
	ALM/weight	3396	392	110	835	87	41	0.13	0.87	0.04	0.97
	ALM/BMI	3407	387	106	824	92	45	0.14	0.87	0.05	0.97
	ALM regression	3395	383	114	836	96	37	0.14	0.87	0.04	0.97
Muscle mass only (40th percentile)	ALM/height	2545	283	85	1686	196	66	0.13	0.87	0.03	0.97
	ALM/weight	2553	287	84	1678	192	67	0.13	0.87	0.03	0.97
	ALM/BMI	2569	284	78	1662	195	73	0.14	0.88	0.04	0.97
	ALM regression	2557	272	85	1674	207	66	0.14	0.88	0.03	0.97
Grip strength	20kg	3266	362	108	965	117	43	0.14	0.87	0.04	0.97
	16kg	3941	441	141	290	38	10	0.14	0.87	0.03	0.97
Gait speed	1.0 mps	3045	325	77	1186	154	74	0.16	0.88	0.05	0.98
	0.80 mps	1228	127	32	3003	352	119	0.14	0.89	0.03	0.98
10th percentile - Muscle mass and grip strength (20kg)	ALM/height	4077	463	145	154	16	6	0.12	0.87	0.03	0.97
	ALM/weight	4078	466	144	153	13	7	0.12	0.87	0.04	0.97
	ALM/BMI	4046	465	145	185	14	6	0.10	0.87	0.03	0.97
	ALM regression	4087	468	142	144	11	9	0.12	0.87	0.05	0.97
10th percentile - Muscle mass and grip strength (16kg)	ALM/height	4180	473	149	51	6	2	0.12	0.87	0.03	0.97
	ALM/weight	4183	475	150	48	4	1	0.09	0.87	0.02	0.97
	ALM/BMI	4166	472	149	65	7	2	0.12	0.87	0.03	0.97
	ALM regression	4192	476	150	39	3	1	0.09	0.87	0.02	0.97
	ALM/height	4180	473	149	51	6	2	0.12	0.87	0.03	0.97

10th percentile - Muscle mass and grip strength (16kg)	**ALM/weight**	4183	475	150	48	4	1	0.09	0.87	0.02	0.97
	ALM/BMI	4166	472	149	65	7	2	0.12	0.87	0.03	0.97
	ALM regression	4192	476	150	39	3	1	0.09	0.87	0.02	0.97
10th percentile - Muscle mass and gait speed (0.8m/s)	**ALM/height**	4118	469	139	113	10	12	0.16	0.87	0.09	0.97
	ALM/weight	4039	457	136	192	22	15	0.16	0.87	0.07	0.97
	ALM/BMI	4033	458	140	198	21	11	0.14	0.87	0.05	0.97
	ALM regression	4094	463	135	137	16	16	0.18	0.87	0.10	0.97
10th percentile - Muscle mass and gait speed (1.0m/s)	**ALM/height**	3937	445	135	294	34	16	0.14	0.87	0.05	0.97
	ALM/weight	3882	438	132	349	41	19	0.14	0.87	0.05	0.97
	ALM/BMI	3878	442	135	353	37	16	0.13	0.87	0.04	0.97
	ALM regression	3899	445	132	332	34	19	0.14	0.87	0.05	0.97
20th percentile - Muscle mass and grip strength (20kg)	**ALM/height**	3939	444	138	292	35	13	0.14	0.87	0.04	0.97
	ALM/weight	3968	456	141	263	23	10	0.11	0.87	0.03	0.97
	ALM/BMI	3913	444	138	318	35	13	0.13	0.87	0.04	0.97
	ALM regression	3983	449	138	248	30	13	0.14	0.87	0.04	0.97
20th percentile - Muscle mass and grip strength (16kg)	**ALM/height**	4132	464	148	99	15	3	0.15	0.87	0.03	0.97
	ALM/weight	4157	471	150	74	8	1	0.11	0.87	0.01	0.97
	ALM/BMI	4122	466	147	109	13	4	0.13	0.87	0.03	0.97
	ALM regression	4155	470	148	76	9	3	0.13	0.87	0.03	0.97
20th percentile - Muscle mass and gait speed (0.8m/s)	**ALM/height**	4013	452	132	218	27	19	0.17	0.87	0.07	0.97
	ALM/weight	3881	445	124	350	34	27	0.15	0.87	0.07	0.97
	ALM/BMI	3901	440	124	330	39	27	0.16	0.87	0.07	0.97
	ALM regression	3983	447	127	248	32	24	0.18	0.87	0.08	0.97
20th percentile - Muscle mass and gait speed (1.0m/s)	**ALM/height**	3642	409	121	589	70	30	0.14	0.87	0.04	0.97
	ALM/weight	3538	407	116	693	72	35	0.13	0.87	0.04	0.97
	ALM/BMI	3562	403	112	669	76	39	0.15	0.87	0.05	0.97
	ALM regression	3612	406	121	619	73	30	0.14	0.87	0.04	0.97
	ALM/height	3752	415	129	479	64	22	0.15	0.87	0.04	0.97

40th percentile - Muscle mass and grip strength (20kg)	**ALM/weight**	3762	426	129	469	53	22	0.14	0.87	0.04	0.97
	ALM/BMI	3677	414	126	554	65	25	0.14	0.87	0.04	0.97
	ALM regression	3768	419	129	463	60	22	0.15	0.87	0.04	0.97
40th percentile - Muscle mass and grip strength (16kg)	**ALM/height**	4079	452	144	152	27	7	0.18	0.87	0.04	0.97
	ALM/weight	4098	462	147	133	17	4	0.13	0.87	0.03	0.97
	ALM/BMI	4055	455	147	176	24	4	0.13	0.87	0.02	0.97
	ALM regression	4093	457	144	138	22	7	0.17	0.87	0.04	0.97
40th percentile - Muscle mass and gait speed (0.8m/s)	**ALM/height**	3825	419	119	406	60	32	0.18	0.88	0.06	0.97
	ALM/weight	3605	406	109	626	73	42	0.15	0.88	0.06	0.97
	ALM/BMI	3609	401	105	622	78	46	0.16	0.88	0.06	0.97
	ALM regression	3749	411	112	482	68	39	0.18	0.88	0.07	0.97
40th percentile - Muscle mass and gait speed (1.0m/s)	**ALM/height**	3100	339	101	1131	140	50	0.14	0.88	0.04	0.97
	ALM/weight	2903	324	92	1328	155	59	0.14	0.88	0.04	0.97
	ALM/BMI	2924	318	88	1307	161	63	0.15	0.88	0.04	0.97
	ALM regression	3017	324	96	1214	155	55	0.15	0.88	0.04	0.97

Chapter 5: Age stratification using the residual adjustment technique for muscle mass

This chapter has been submitted to *Gerontology*. Alexandra Mayhew was responsible for developing the research question and study protocols, applying for data, analyzing data, writing and revising the drafts of the manuscripts. The work is primarily the undertaking of Alexandra Mayhew with guidance from Drs. Parminder Raina and Stuart Phillips throughout the project. Dr. Nazmul Sohel assisted with coding for the data analyses. Thesis committee members, Drs. Russell de Souza, Paul McNicholas, Gianni Parise, and Lehana Thabane provided feedback throughout the project. As an author generated version of a submitted manuscript, no copyright license documentation is required.

Context and background

In **Chapter 3**, the proportion of sarcopenic participants according to different sarcopenia definitions was assessed for four age groups, 45 to 54, 55 to 64, 65 to 74, and 75 to 85 years. To develop the cut offs for low muscle mass, the sample was restricted to participants aged 65 years and older and the lowest sex-specific 10^{th}, 20^{th}, and 40^{th} percentile values were determined. These cut offs were then applied to each age and sex strata. For muscle mass adjusted by height, weight, and body mass index, the proportion of participants with low muscle mass was approximately equal. For the residual adjustment technique which involves regressing appendicular lean mass on fat mass and height, the proportion of participants with low muscle mass was similar to the other adjustment techniques pooled across all age groups. However, the proportion of participants with low muscle mass was highest in the younger participants and lowest in the oldest participants which was contrary to what was expected. Based on these findings, further analyses were conducted stratifying for age before versus after the residual values were calculated for the purpose of developing the low muscle mass cut offs and for subgroup analyses.

The analyses showed that calculating the residuals in the whole sample before stratifying by age for the cut offs or subgroup analyses resulted in a similar proportion of participants having low muscle mass compared to the other muscle mass adjustment techniques for each age and sex strata. This method of handling age stratification was used for the analyses included in **Chapter 3** and there was not sufficient space for discussion of why the alternative strategies for handling age stratification were inappropriate. Furthermore, there was no guidance available in the literature regarding stratification for age or any other variable using the regression technique for adjusting muscle mass. Therefore, the purpose

of this paper was to discuss the methodological challenges of age stratification when using the residual adjustment technique for muscle mass and justify the method selected in **Chapter 3**.

Chapter 5: Age stratification using the residual adjustment technique for muscle mass

Title: Methodological issues and the impact of age stratification on the proportion of participants with low muscle mass when adjusting for height and fat mass using linear regression in the Canadian Longitudinal Study on Aging

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Abstract

Background: Regressing appendicular lean muscle mass (ALM) on fat mass and height is one of several suggested strategies for adjusting ALM for body size. However, special consideration is required when using this technique in different subgroups in order to capture the correct individuals as sarcopenic.

Objectives: To provide guidance about how to conduct stratified analyses for the regression adjustment technique using age groups as an example.

Methods: Using baseline data from the Canadian Longitudinal Study on Aging, sex-specific residuals were calculated in participants before and after stratifying participants by age group (45-54, 55-64, 65-74, 75-85 years). Cut offs corresponding to the 20th percentile sex-specific residual values in participants ≥65 years were determined first in the residuals calculated in all participants and residuals calculated in only those aged ≥65 years. For each set of cut offs, the percentage of age and sex-stratified participants with low muscle mass were compared for the residuals calculated in all participants and the residuals calculated after stratifying by age.

Results: In 12,622 males and 12,737 females, regardless of the cut off used, the percentage of participants with low muscle mass decreased with age when residuals were calculated after age stratification. When the residuals were calculated in all participants, the percentage of participants with sarcopenia increased from the youngest to the oldest age groups.

Conclusions: Sex-specific residuals in all participants should be calculated prior to stratifying the sample by age group for the purposes of developing muscle mass cut offs or subgroup analyses.

Background

Sarcopenia refers to the decline in muscle mass, muscle strength, and muscle function that occurs with age. [1] It is associated with an increased risk of falls and fractures, an inability to perform activities of daily living, and mortality. [2–5] Given the profound costs of sarcopenia to individuals as well as society, there has been substantial interest in finding ways to prevent and treat sarcopenia. However, the field of sarcopenia research has been hindered by the lack of a clear definition and standardized diagnostic criteria. [6]

Since 2010, four expert group consensus definitions on sarcopenia have been released. [6–10] All the definitions consider sarcopenia the combination of low muscle mass with either low muscle strength or impaired physical performance. There is a consensus among the definitions that muscle mass should be adjusted for body size due to the strong correlation between these variables, however there is little agreement about which measure of body size should be utilized. [6,11] Four techniques are recommended; dividing by height squared, body mass, body mass index (BMI), and regressing muscle mass on height and fat mass. [6–10] Of these methods, regressing muscle mass on height and fat mass has the greatest face validity as it simultaneously adjusts for height and fat mass. [12] Though BMI includes height and body mass, it is considered a crude measure of body composition as it is unable to differentiate between lean mass and fat mass. [13] Despite having the greatest face validity, the regression adjustment technique is not commonly used which may be related to the challenges of using the technique. [14]

Adjusting muscle mass by height, weight, or BMI can be done at the individual level and values are not influenced by other participants. Therefore, the adjusted values refer to the

same amount of muscle mass relative to the anthropometric measure adjusted for regardless of the person or sample. Consequently, cut points validated in one sample can be appropriately used in another comparable sample. In contrast, the regression adjustment technique involves creating a regression model (appendicular lean mass (ALM) = intercept + height (m^2) + fat mass (kg)) in a sample of people. The residual value calculated as the actual ALM value minus the model-estimated ALM value is then used to determine if a person has low muscle mass. The residual value for each person is dependent on the regression equation which in turn is dependent on the distribution of the variables in the sample. As a result, even if low muscle cut points are developed in a random, population-based sample, they cannot be appropriately applied to another population unless the two samples have identical joint distributions of ALM, fat mass, and height. Due to the unavailability of cut points, studies that have investigated sarcopenia using the regression adjustment technique considered the lowest quintile of sex-specific residual values as sarcopenic. [15–21] However, a consequence of using the lowest quintile is that sarcopenia prevalence is the same (20%) for all studies, regardless of age, which is problematic for a condition for which the prevalence increases with age.

In order to evaluate how the regression technique identifies those with clinically relevant low muscle mass compared to the other muscle mass adjustment techniques, better understanding of how to use the regression adjustment technique is required. We aimed to provide the necessary guidance for how to handle age stratification when using the regression technique to adjust muscle mass.

Methods

Setting and study population **-** We used data from the Canadian Longitudinal Study on Aging (CLSA), a national longitudinal research platform. There were 51,338 participants aged 45 to 85 years recruited from the ten Canadian provinces at baseline. Participants had to be physically and cognitively able to participate on their own as well as not living in institutions such as long term care to be eligible for the study. The participants were recruited in to one of two cohorts, the Tracking cohort and the Comprehensive cohort. Participants from all 10 provinces were randomly selected for the Tracking cohort (n=21,241) and were interviewed by telephone. The Comprehensive cohort participants (n=30,097) lived within 25-50km of one of 11 Data Collection Sites located in seven provinces. The Comprehensive cohort participants were interviewed in-person and also completed in-depth physical assessments and provided blood and urine samples. Details on the study design have been described elsewhere. [22] Only participants from the Comprehensive cohort (n=30,097) were included in these analyses as the physical assessment data was required. The sample was further limited to those identifying as European as muscle mass, muscle strength, and physical function have shown to vary by ethnicity. [23–25] This project uses data collected during baseline (September 2011 to May 2015).

Clinical measurements **-** Trained research assistants collected data on height, weight, and muscle mass. Height was measured twice using a stadiometer and the mean value of the two measurements was used in the analyses. Weight was measured in light clothing using a digital scale. BMI was calculated as weight in kilograms divided by height squared. Dual Energy X-ray Absorptiometry (DXA) was used to measure muscle mass. The Hologic

Discovery A^{TM} DXA machine was calibrated daily using a spine phantom, weekly using a whole body step phantom, and yearly using a gold standard phantom. DXA provides a valid measure of ALM when compared to the gold standards of computerized tomography (CT) and magnetic resonance imaging (MRI) scans. [26]

Operationalizing low muscle mass adjusted for height and fat mass - All analyses were stratified by sex. To identify participants as having low muscle mass adjusted for height and fat mass, individual residual values of ALM regressed on height and fat mass must be available for each participant as well as a cut point that categorizes participants as having low ALM relative to their height and fat mass. We explored the impact of stratifying the sample by age for the 1) individual residual values and 2) the cut points.

For the individual residual values, multiple linear regression was used to calculate the residual value for each participant. The model included ALM as the outcome variable and fat mass (kg) and height (m) as the predictor variables. The first set of models included all participants without age stratification. The second model stratified participants by age (45 to 54, 55 to 64, 65 to 74, and 75 to 85 years) before calculating the residuals.

For the muscle mass cut points, the original EWGSOP guidelines recommend that the lowest 20th percentile of residual values be used to identify people with low muscle mass. [7] In order to be consistent with the literature in which muscle mass cut points are typically developed in those with a minimum age of between 60 and 70 years [7], cut points were determined in participants aged 65 years and older. The first set of models calculated in the residuals in all participants without age stratification. After calculating the residuals, the sample was then limited to those aged 65 years and older and the 20th percentile residual

values were determined to be the cut points. The second set of models calculated the residuals in only participants aged 65 years and older. The residual values corresponding to the 20th percentile residual values were determined to be the cut points.

The cut-points using the non-age stratified residuals and the residuals calculated in just participants aged 65 years and older were applied to the residuals calculated in the whole sample and the age-stratified residual residuals. Therefore, there were four different strategies used to identify participants with low muscle mass relative to their height and fat mass (**Table 1**).

Muscle mass adjusted for height^2 (meters), weight (kilograms), and body mass index (BMI, kilograms/meters^2 was assessed by dividing ALM by each of the measures. Participants were considered to have low muscle mass if their adjusted value was below the sex-specific 20th percentile in participants aged 65 years and older.

Statistical anaylses - Of the 30,097 participants at baseline, 1324 were excluded as they were non-European, 3356 were excluded for missing muscle mass, grip strength, gait speed, or BMI data resulting in a final sample size of 25,399 participants. All statistical analyses were completed using SAS (version 12.3).

The percentage of age and sex-stratified participants categorized as having low muscle mass by each of the four strategies for handling age-stratification for the development of cut points and individual residual values were determined. Bootstrap percentile confidence intervals were calculated for each estimate. This technique involves resampling with replacement and calculating the proportion of participants with sarcopenia for each resample. [27] We resampled 10,000 times and identified the values corresponding to the 2.5th

and 97.5th percentiles of the 10,000 resamples in order to estimate the 95% confidence interval. This technique has the advantage of only including valid values of parameter estimates in the confidence interval. [27]

Results

Participant characteristics **- Table 2** displays the characteristics of the included participants by age group (younger than 65 years and 65 years and older) and sex. The mean age of the participants was 62.8 ± 10.2 years and 49.9% of the sample were males. Younger males and females had greater ALM (28.8kg ± 4.4 and 19.0kg ± 3.5), grip strength (47.3kg ± 9.1 and 28.6kg ± 5.6), and gait speed (1.03m/s ± 0.18 and 1.02m/s ± 0.19) compared to older males and females (ALM: 25.9kg ± 3.8 and 17.4kg ± 3.0, grip strength: 39.4kg ± 8.5 and 23.6kg ± 5.2, and gait speed: 0.94m/s ± 0.19 and 0.90m/s ± 0.19).

Distribution of residuals **-** For males and females, the overall distribution of the residual values was calculated in all participants versus calculating the residuals in age-stratified groups. In males, the mean for all participants was 0 with a standard deviation of 3.22, while the mean of the residuals for all age-stratified residuals pooled together was 0 with a standard deviation of 3.00. The same values were 0 ± 2.22 and 0 ± 2.13 in females. However, the distribution of the data within each age group was markedly different (**Figures 1 through 4**). In both males and females, when the residuals were calculated after stratifying the sample by age, the residuals of each age group had a mean of 0. In contrast, when the residuals were calculated in the whole sample, there was a gradient of mean values when stratified by age group. The mean residual value for males 45 to 54 years was 1.36

and for females was 0.89 which decreased to -1.93 in males and -0.68 in females aged 75 to 85 years.

Muscle mass cut point estimates **-** When the sex-specific linear regression models were run in participants of all ages and the residual values were then limited to participants aged 65 years and older, the lowest 20th percentile corresponded to -1.61 for males and -2.20 for females. When the sex-specific linear regression models were limited to only participants aged 65 years and older and those residual values were used to determine the lowest 20th percentile, the values corresponded to -2.40 for males and -3.61 for females.

Low muscle mass prevalence **-** The lower cut points determined using the non-age stratified residual values of -3.61 for males and -2.20 for females identified fewer participants as having low muscle mass compared to the age-stratified residual values of -2.40 for males and -2.20 for females (**Figure 5**). Using the non-age stratified residual cut points, the prevalence of low muscle mass was 12.4% for males and 10.3% for females when the individual residuals were not age stratified (**Strategy 1**) and 14.6% for males and 13.6% for females when the individual residuals were age stratified (**Strategy 3**). In contrast, when using the cut points developed using residual values calculated in only participants aged 65 years and older, 22.4% of males and 23.1% of females were identified as having low muscle mass when the non-age stratified residual values (**Strategy 2**) and 20.5% of males and 21.8% of females were identified as having low muscle mass when the age-stratified values were used (**Strategy 4**). The percentage of participants with low muscle mass after adjustment for height^2, weight, and BMI was between 13.0% and 13.8% in males and 13.0% and 15.3% in females (**Table 3**).

When looking at the percentage of people with low muscle mass within each age group, the percentage of males and females with low muscle mass increased with age when the individual residuals were not age-stratified, regardless of the cut points used (**Strategy 1** and **Strategy 2**). In contrast, the percentage of males and females with low muscle mass decreased with age when the age-stratified residuals were used (**Strategy 3** and **Strategy 4**).

Discussion

This study is, to the best of our knowledge, the first to investigate the implications of age stratification when determining muscle mass cut points and in calculating residual values for a sample using linear regression to adjust ALM for height and fat mass. We found that the most appropriate method of handling age stratification was to calculate the residuals in the whole sample, then stratify the residuals by age to determine cut points and to conduct analyses by age group (**Strategy 1**). Using this message, the percentage of participants with low muscle mass were within approximately 2% of the estimates when ALM was adjusted for height^2, weight, or BMI for each age and sex strata (**Table 3**).

Stratifying the sample by age prior to calculating residuals for the purpose of subgroup analyses based on age or for developing cut points proved problematic. When the sample was stratified by age before calculating the residuals (**Strategy 3** and **Strategy 4**), the percentage of participants with low muscle mass decreased from the youngest to the oldest age groups (**Table 3**). Muscle mass values are expected to decrease with age indicating that this technique is not appropriate. [1] When cut points were based off of residuals calculated in participants aged 65 years and older versus the residuals calculated in the whole sample

(**Strategy 2** and **Strategy 4**), the overall prevalence of sarcopenia was higher than expected with over 30% of males and females aged 65 years and older having low muscle mass. In comparison, previous studies have found that between 14.1% and 33.2% of community-dwelling adults aged 65 years and older have low muscle mass. [15,16,18,21,28–30] Based on these observations, participants should not be stratified by age prior to calculating residuals regardless of if the purpose of age stratification is for subgroup analyses or developing low muscle mass cut points.

Stratifying by age before calculating the residuals was problematic because of how residuals are calculated. The maximum likelihood estimation technique used in linear regression to calculate the residuals requires that the sum of the residuals for the sample to equal zero. When the sample was stratified by age, the mean value of the residuals for each age group was zero. However, the standard deviation decreased with age (**Figures 1 through 4**). The greater the standard deviation for the age group, the more participants were below the low muscle mass cut off and therefore the higher the percentage of people with low muscle mass. Similarly, when the sample was limited to participants aged 65 years and older before calculating the residuals, the mean residual value was zero. When the data from all participants was used to calculate the residuals, the mean values were -1.17 for males and -0.56 for females as these participants had lower predicted lean mass compared to the younger participants. This resulted in more extreme values for the 20^{th} percentile and the greater percentage of participants with low muscle mass.

The problems we encountered stratifying our sample by age before calculating the residuals extend to any situation in which residuals calculated in one sample are combined or applied to another sample. Residual values are sample dependent and therefore unless two groups

of participants have identical joint distributions of ALM, height, and fat mass, the residuals from one study will not identify people with the same amount of ALM relative to height and fat mass. This means that cut points for the residual technique, even if developed in a population-based random sample with cut points validated against relevant health outcomes, cannot be meaningfully applied to another sample. Another problem with the residual adjustment technique is that it requires a sample of people in order to run a regression model and calculate residuals which is not practical for clinical settings.

To our knowledge, only one study has assessed the relationship between low muscle mass operationalized using the residual adjustment technique with health. [12,31] Cawthon et al. observed that low muscle mass adjusted for height and fat mass was significantly associated with risk of functional limitations and mortality, but not recurrent falls or hip fractures. [12] Studies operationalizing sarcopenia as low muscle mass only often do not find significant associations with health, therefore the associations found with functional limitations and mortality are particularly notable. [12,32,33] Given this evidence as well as the strong face validity for adjusting ALM simultaneously for height and fat mass, future studies are required to determine if adjusting ALM for height and fat mass, alone and in combination with muscle strength or function, better identifies people at poor risk for health compared to the other adjustment techniques.

To resolve the issue of the residual adjustment technique requiring a sample of people for the regression model and the lack of comparability of residual values between studies, prediction equations, similar to those that have been used for lung function can be developed. [34] A sample of healthy older adults could be used to create sex-specific prediction equations for ALM based on height and fat mass. Variables such as age and

ethnicity could be explored for inclusion in the equation. To use the prediction equations in clinical or research settings, ALM would be measured using DXA for an individual. The prediction equation would be used to determine the predicted ALM based on height and fat mass. Subtracting their predicted ALM from actual ALM provides the residual value. Then, this residual value could be compared to a pre-determined cut point to categorize the person as having low or normal muscle mass relative to their height and fat mass. Ideally, cut points for the low muscle mass residuals would be determined by assessing which cut points best predict health outcomes relevant to sarcopenia. In the absence of clinically relevant cut points, the residual value corresponding to the desired percentage of healthy older adults being considered to have low muscle mass relative to height and fat mass could be used.

Conclusions

There is a general consensus amongst sarcopenia researchers that muscle mass should be adjusted for at least one other anthropometric measure, but there is no agreement about which measure should be used. Of the suggested options, using linear regression to adjust ALM simultaneously for height and fat mass has the greatest face validity. However, this technique is rarely used, likely due to the lack of comparability of residual values between different samples making standard cut points for low muscle mass unavailable and leading to challenges in handling age-stratification within a sample. Given the high face validity of the regression adjustment technique, more research is needed to understand how this technique compares to adjusting for height, weight, or BMI. One of the barriers to studies using the regression adjustment technique is the lack of guidance on how to handle age-stratification. In our analyses, we explored multiple techniques of handling age-

stratification and determined that the best method of handling age stratification was to run linear regression models in participants of all ages and then stratify the residual values by age to determine appropriate low muscle mass cut points or to conduct subgroup analyses.

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Table 1. Strategies for operationalizing low muscle mass adjusted for height and fat mass

	Residuals for cut points developed in all participants	**Residuals for cut points developed in participants aged 65 years and older**
Residuals calculated in all participants	Strategy 1	Strategy 2
Residuals calculated after stratifying by age	Strategy 3	Strategy 4

Table 2. Participant characteristics

	Aged <65 years				Aged ≥65 years			
	Males		Females		Males		Females	
	Mean or N	SE or %	Mean or N	SE or %	Mean or N	SE or %	Mean or N	SE or %
Total population	7286	48.7	7677	51.3	5376	51.5	5060	48.5
Age, years	55.8	5.4	55.5	5.4	73.0	5.6	73.0	5.7
Height, cm	176.6	6.7	163.1	6.3	173.9	6.7	159.9	6.3
Weight, kg	89.0	16.5	74.1	16.9	84.6	14.1	70.9	14.3
BMI, kg/m2	28.5	5.0	27.8	6.3	28.0	4.2	27.8	5.5
Total body fat mass, %	25.5	9.5	29.8	11.0	25.5	8.0	29.6	9.4
Appendicular lean mass, %	28.8	4.4	19.0	3.5	25.9	3.8	17.4	3.0
ALM/height^2	9.23	1.19	7.14	1.17	8.56	1.06	6.78	1.04
ALM/weight	32.72	3.37	26.09	3.25	30.90	3.12	24.75	2.86
ALM/BMI	1.02	0.14	0.70	0.11	0.94	0.12	0.63	0.10
Gait speed, meters per second	1.03	0.18	1.02	0.19	0.94	0.19	0.90	0.19
Grip strength, kg	47.3	9.1	28.6	5.6	39.4	8.5	23.6	5.2
Chronic conditions								
Heart disease[10]	648	9.0	375	4.9	1403	26.6	772	15.5
Cardiovascular disease[11]	151	2.1	147	1.9	416	7.8	332	6.6
Diabetes	1108	15.3	1011	13.2	1296	24.2	876	17.4
COPD	259	3.6	341	4.5	348	6.5	408	8.1
Cataracts or glaucoma	707	9.9	984	13.1	2652	50.9	3027	61.7
Osteoarthritis	1070	14.9	1632	21.7	1379	26.4	2060	42.2
Depression	937	12.9	1325	17.4	527	10.0	888	17.9
Dementia/Alzheimer's Disease	7	0.1	9	0.1	22	0.4	17	0.3
Neurological conditions[12]	648	8.9	1678	21.9	376	7.0	864	17.2
Osteoporosis	82	1.1	616	8.1	202	3.8	1223	24.5
Hypertension	2212	30.5	1884	24.6	2626	49.2	2463	48.9
Peripheral vascular disease	214	3.0	309	4.0	380	7.1	386	7.7
Kidney disease	2011	27.7	1960	25.6	1516	28.3	1444	28.6
Cancer	478	6.6	768	10.0	1205	22.5	975	19.3

[10] Heart disease includes angina, myocardial infarction, and heart disease

[11] Cardiovascular disease includes stroke and transient ischemic attack

[12] Neurological conditions include multiple sclerosis, epilepsy, migraine headaches, and Parkinson's Disease

Poor or fait self-rated health (%)	635	8.7	572	7.5	454	8.5	417	8.3
Smoking (%)								
Never	6483	89.4	6811	89.1	5056	94.7	4763	95.0
Former	160	2.2	157	2.1	45	0.8	42	0.8
Current	611	8.4	673	8.8	237	4.4	211	4.2
Household income (%)								
< $20,000	242	3.4	329	4.5	179	3.5	423	9.4
≥ $20,000 < $50,000	770	10.9	1200	16.5	1309	25.9	1872	41.8
≥ $50,000 <$100,000	2114	30.0	2496	34.3	2235	44.2	1579	35.2
≥ $100,000 < $150,000	1862	26.5	1661	22.8	866	17.1	423	9.4
≥ 150,000	2051	29.1	1593	21.9	472	9.3	185	4.1
PASE score	172.6	80.3	150.9	74.4	125.5	60.4	107.8	53.2

Figure 1. Residual values of muscle mass regressed on height^2 and fat mass in males by age group when the residuals are calculated in all participants

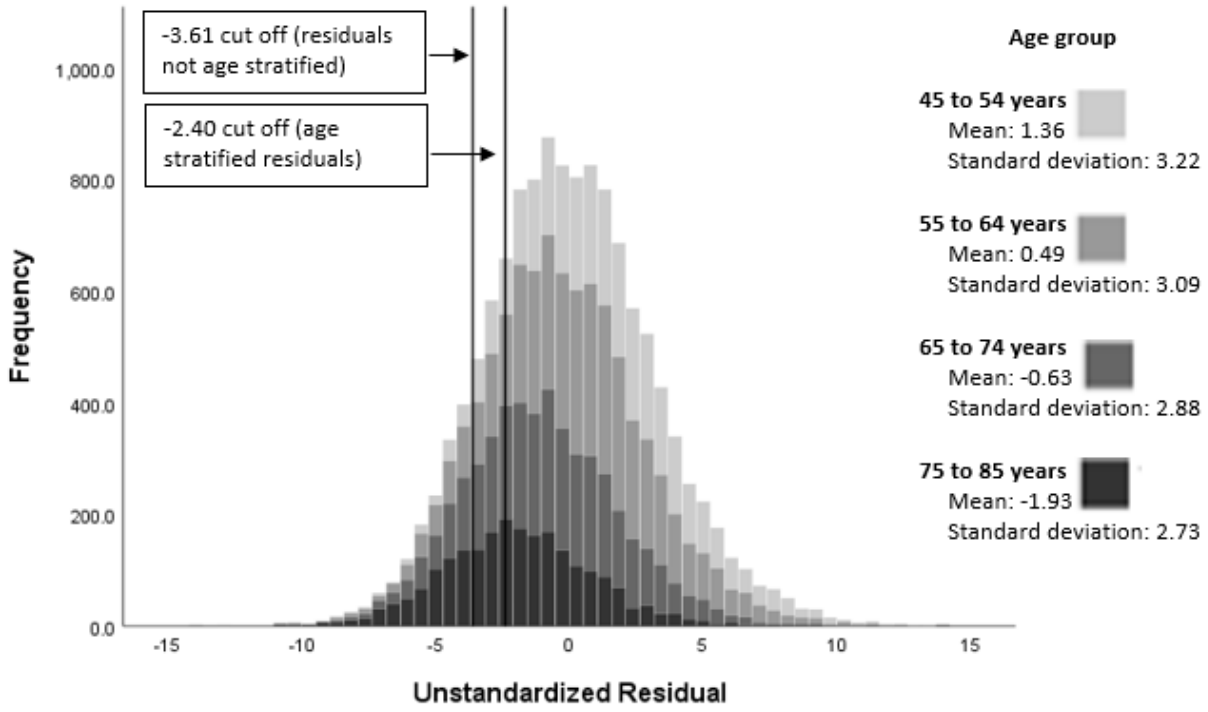


Figure 2. Residual values of muscle mass regressed on height^2 and fat mass in males by age group when the residuals are calculated after age stratification

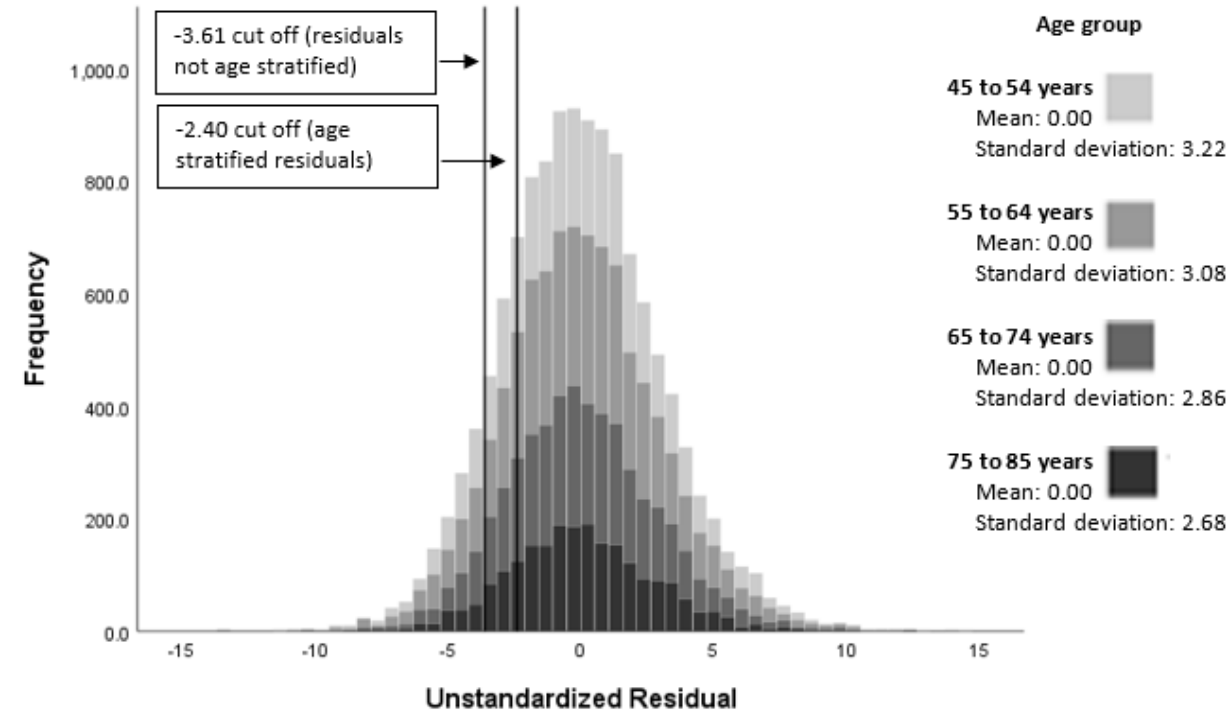


Figure 3. Residual values of muscle mass regressed on height^2 and fat mass in females by age group when the residuals are calculated in all participants

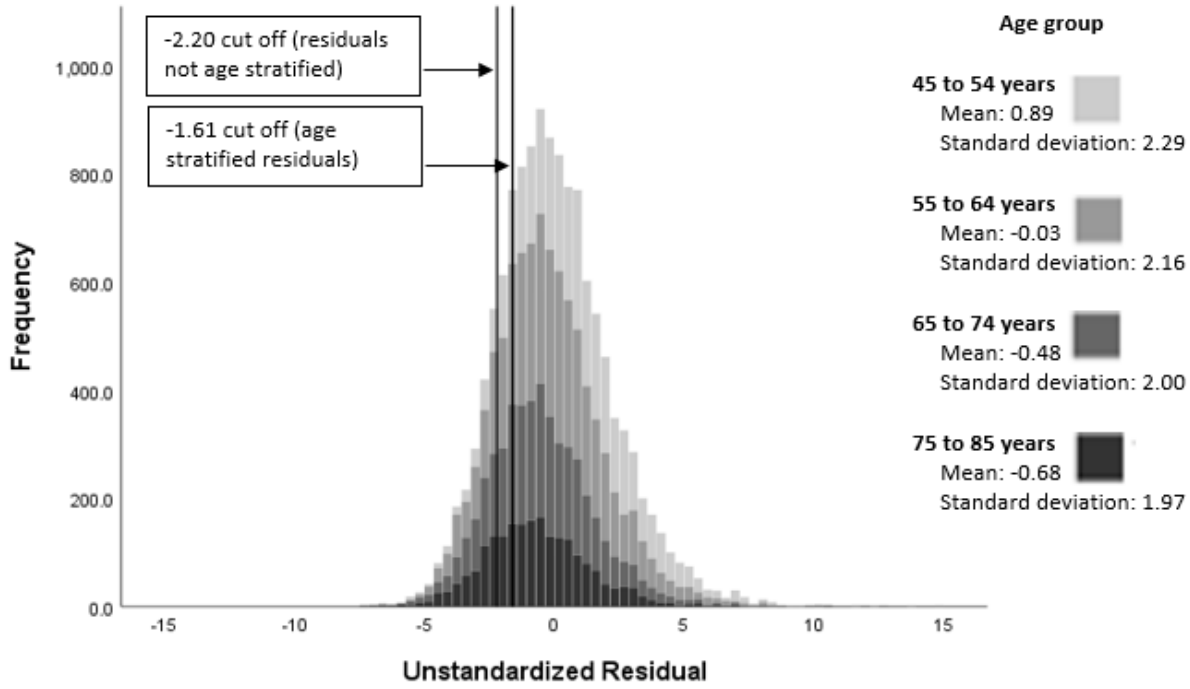


Figure 4. Residual values of muscle mass regressed on height^2 and fat mass in females by age group when the residuals are calculated after age stratification

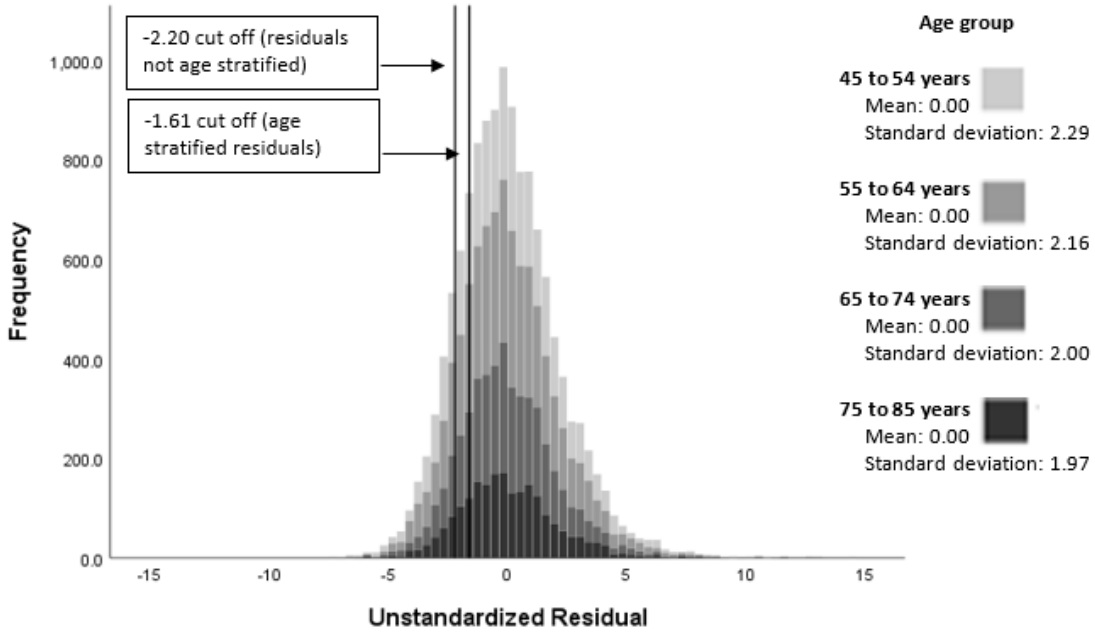
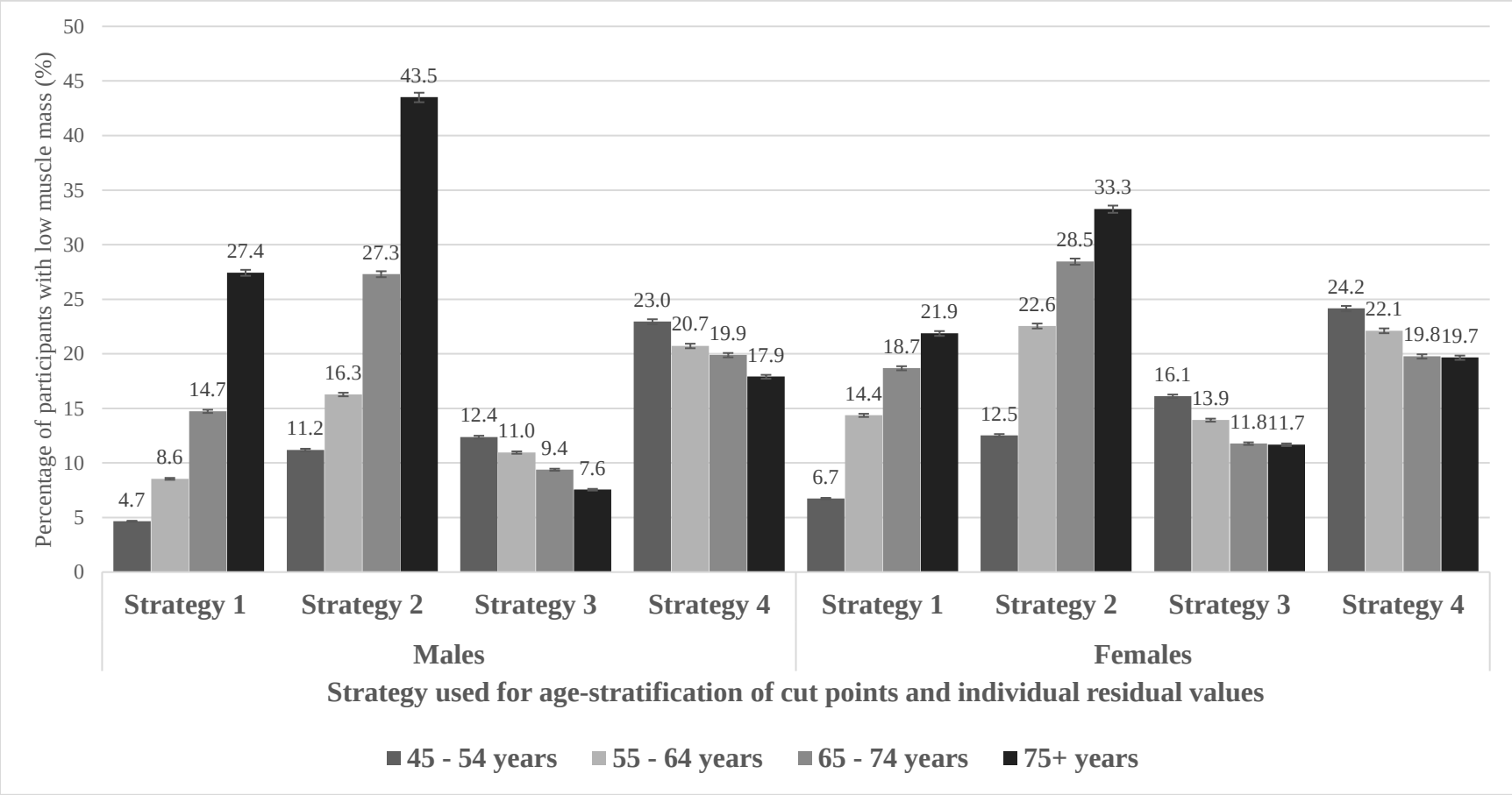


Figure 5. Percentage of participants with low muscle mass adjusted for height and fat mass



Strategy 1 – individual residuals calculated in all participants, residuals for cut points calculated in all participants
Strategy 2 – individual residuals calculated in all participants, residuals for cut points calculated in participants aged 65 years and older
Strategy 3 – individual residuals calculated after age stratification, residuals for cut points calculated in all participants
Strategy 4 – individual residuals calculated after age stratification, residuals for cut points calculated in participants aged 65 years and older

Chapter 6: Conclusions

Overview

This thesis explored how the individual components of sarcopenia definitions including the combination of muscle variables used, the technique used to adjust muscle mass, and the cut offs for the muscle variables, impact the proportion of participants with sarcopenia, the agreement between definitions, and the association between sarcopenia and falls.

Chapter 1 served as an introduction to the history of sarcopenia, how the expert group consensus definitions operationalize sarcopenia, and a literature review of previous studies investigating the prevalence of sarcopenia, agreement between sarcopenia definitions, and the association between sarcopenia and falls. **Chapter 2** is a systematic review and meta-analyses of studies assessing the prevalence of sarcopenia in community-dwelling older adults in population-based studies. The results showed that the prevalence of sarcopenia was markedly different depending on which definition of sarcopenia was used and inspired the research objectives of **Chapter 3** which investigates how using different sarcopenia definitions impacts the proportion of participants identified as sarcopenic and the agreement between definitions.

The details of how each of the studies operationalized sarcopenia collected as a part of **Chapter 2** was instrumental in creating the list of sarcopenia definitions that were used in **Chapters 3 and 4**. Several of the measurement strategies recommended by the expert group definitions were never or rarely used by the studies included in the systematic review and therefore were not incorporated into our list of sarcopenia definitions creating a more

parsimonious set of definitions. The systematic review revealed that a wide range of cut offs for low muscle mass were utilized which typically categorized between 10% and 40% of participants as having low muscle mass. Therefore, we used cut offs corresponding to the 10^{th}, 20^{th}, and 40^{th} percentile of sex-specific muscle mass for participants aged 65 years and older.

Chapter 3 showed that there was poor agreement between nearly all sarcopenia definitions. However, as there is no criterion standard for sarcopenia, it was impossible to compare the validity of the various sarcopenia definitions. In the absence of a criterion standard, construct validity is the best method of assessing the validity of the different sarcopenia definitions. To test the construct validity of the different sarcopenia definitions, we hypothesised that individuals with sarcopenia are likely to have an increased risk of falls in **Chapter 4**. While developing the low muscle mass cut offs using the residual technique in which appendicular lean mass is regressed on height and fat mass for our list of sarcopenia definitions for **Chapters 3 and 4**, we encountered problems with the percentage of participants with low muscle mass decreasing with age. A further investigation of the data revealed that when using the residual technique, the sample should not be stratified by age or other variables until after the residuals are calculated. To our knowledge, there is no guidance in the literature on how to handle stratification when using the residual technique. **Chapter 5** provides a detailed discussion of the statistical rationale supporting our conclusion that residuals should be calculated prior to stratifying the sample by age.

This concluding chapter includes a discussion of the sarcopenia definitions included in the analyses, the key findings, clinical implications, strengths and limitations, and opportunities for future research.

Selection of sarcopenia definitions

Previous studies have investigated how the use of different sarcopenia definitions impacts the prevalence of sarcopenia, the association of sarcopenia with health, as well as assessing the agreement between definitions. However, these studies are limited by the selection of sarcopenia definitions. Each sarcopenia definition is made up of three components; 1) the combination of muscle variables; 2) the technique used to adjust muscle mass; and 3) the cut offs for each of the included variables. In most cases, existing sarcopenia definitions from the literature, including the expert group consensus definitions, vary based on more than one component. Therefore, in the previous studies it has been impossible to determine which of the three components is responsible for any observed differences in prevalence, the magnitude of the association of sarcopenia with health, and poor agreement between definitions. To accomplish the objectives of this thesis, we required a list of sarcopenia definitions that would allow for the impact of changing each of the three components of sarcopenia to be investigated individually. To understand how sarcopenia is defined in the literature, we reviewed the recommendations of the consensus definitions released by the four expert groups, as well as conducted a systematic review of studies investigating sarcopenia prevalence conducted in population-based samples of community dwelling older adults. [1–5]

Combination of muscle variables - Based on our review of the expert group consensus definitions and systematic review of the literature, three combinations of variables were identified as defining sarcopenia; 1) muscle mass only; 2) muscle mass and muscle strength; and 3) muscle mass and muscle function. The original European Working Group on Sarcopenia (EWGSOP) definition also included the combination of muscle mass with *either* muscle strength *or* muscle function. However, the revised EWGSOP definition recommends against this combination and it was therefore not included in our list of definitions. Three of the four expert group consensus definitions for sarcopenia recommend operationalizing muscle strength using grip strength and muscle function using gait speed. The original and the revised EWGSOP include a list of variables that can be used to operationalize muscle strength (grip strength, chair rise test, and knee strength) and muscle function (gait speed, Short Physical Performance Battery, Timed up and Go, and stair climb test). The measures other than grip strength and gait speed are rarely used in the literature with two or fewer studies included in our systematic review reporting using any of the variables and were therefore not incorporated in our list of sarcopenia definitions.

Method of adjusting muscle mass – Four different techniques for adjusting muscle mass are recommended by the expert group consensus definitions for sarcopenia and have been used in the literature. Three involve dividing appendicular lean mass by an anthropometric measure, either height squared, weight, or body mass index. The fourth technique calculates the residual values of appendicular lean mass regressed on height and fat mass. Appendicular lean mass was measured using dual-energy x-ray absorptiometry (DXA).

Cut offs for muscle variables – Based on the expert group definitions, grip strength cut offs for males include 30kg, 27kg, and 26kg, and for females 20kg and 16kg. For gait speed, the recommended cut offs are 1.0 meters per second or 0.8 meters per second. These cut offs were also used by the majority of studies included in our systematic review and meta-analyses and therefore were all incorporated into our list of sarcopenia definitions. There is less consensus on what cut offs are relevant for low muscle mass. Though many of the expert group consensus definitions for sarcopenia reference cut offs based on previous analyses, there is also a recommendation for studies to choose their own cut offs, often the lowest quintile of sex-specific values of the sample. In our systematic review of the literature, we observed that a wide range of cut off values are used. In the absence of any clear guidance about which cut offs are most appropriate for muscle mass, we chose to create three sets of low muscle mass cut offs for each method of adjusting muscle mass. The cut offs correspond to the 10^{th}, 20^{th}, and 40^{th} sex-specific percentile values. These cut offs captured the range of cut offs referenced by the expert group consensus definitions and what is used in the literature.

Creating the list of sarcopenia definitions – Our final list of sarcopenia definitions fit into three categories based on which variables were used in the model; 1) muscle mass only; 2) muscle mass and grip strength; and 3) muscle mass and gait speed. Within each of these categories, sarcopenia was operationalized using each of the four techniques of adjusting muscle mass (height, weight, body mass index, and the residual techniques), using the 10^{th}, 20^{th}, and 40^{th} percentile cut offs. For the definitions including grip strength, the 30kg, 27kg, and 26kg cut offs for males and the 20kg and 16kg cut offs were included for females. The

definitions including gait speed included the cut offs of 1.0 meters per second and 0.8 meters per second. The final list included 72 definitions for males and 60 for females that captured the range of methods of operationalizing sarcopenia recommended by the expert group consensus definitions.

Key findings

The results of this thesis showed that differences in both the combination of muscle variables used to define sarcopenia and the technique to adjust muscle mass resulted in limited agreement between sarcopenia definitions. In some cases, the differences in operationalizing sarcopenia changed the magnitude of the association between sarcopenia and falls. In males, sarcopenia definitions including grip strength were usually significantly associated with falls, but not definitions including gait speed. Of the definitions including grip strength, those that adjusted muscle mass for weight, BMI, and using the residual technique were associated with falls, but not those that adjusted muscle mass for height. The combination of poor agreement and differences in the strength of relationship of different sarcopenia definitions and health indicate that different sarcopenia definitions should not be used interchangeably as they often are in the literature.

There were several important findings based on the analyses of the strength of the association of sarcopenia with falls. Numerous definitions of sarcopenia were associated with falls in males, but none of the sarcopenia definitions were associated with falls in females. Two other studies that have conducted sex-stratified analyses have had similar findings showing no association between sarcopenia and falls in women. [6,7] A key sex-

based difference hypothesized to influence sarcopenia is the menopausal transition in females. The timing of menopause coincides with increases in sarcopenia and it is hypothesized that the hormonal changes associated with menopause are responsible for the changes in muscle mass. [19] However, a recent systematic review and meta-analyses found that hormone therapy during menopause did not attenuate muscle mass loss regardless of type and dose of hormone therapy, time since menopause that hormone therapy was given, and duration of hormone therapy. [20] This suggests that menopause alone is unlikely to be the cause of differences in males and females. There is also evidence that the mechanisms leading to sarcopenia are different in males and females and may therefore impact the association of sarcopenia with health. Several studies have observed that reduced insulin-like growth factor 1 (IGF1) is associated with sarcopenia components in females but not males. [21–23] IGF1 has anabolic properties and therefore and helps the body to synthesize muscle protein in response to stimuli like exercise. [24] However, at least one study has observed that IGF1 is associated with sarcopenia in males but not females [25] There is also evidence that the effects of catabolic cytokines leading to increased muscle breakdown such as interleukin IL6 may have a greater impact in males than in females. [26]

In addition to potential biological differences in males and females that may impact the relationship of sarcopenia on falls, it is also essential to explore gender differences. Being female is a well-documented risk factor for falls. [27] In the CLSA sample, a greater percentage of females fell (13.0%) compared to males (9.5%). However, on average across all sarcopenia definitions, the percentage of fallers in the non-sarcopenic group was 9.0% for males and 12.7% for females, while the percentage of fallers in the sarcopenic group

was 16.4% for males and 14.1% for females. This shows that factors other than sarcopenia, appear to increase the risk of falls more greatly in females than in males. Examples of potential factors include physical activity and socioeconomic status. Across the lifespan, females are generally less physically active compared to males due a number of psychosocial factors which is associated with lower levels of physical function which may increase the risk of falls. [28] Females are also more likely to have lower household incomes, which was observed in our sample with 29.9% of males and 49.3% of females aged 65 years and older reporting household incomes of less than $50,000. Lower income is associated with poorer living conditions, less access to health care services, and fewer healthy lifestyle behaviours which are associated with an increased risk of falling. [27] In our models assessing the relationship between sarcopenia and falls, we considered gender-based variables by adjusting for physical activity level and income. In addition to conducting sex-stratified analyses, future studies should carefully consider what other gender-based variables may be relevant to sarcopenia.

Our results also show that sarcopenia operationalized using muscle mass adjusted for height squared, was not significantly associated with falls or had a more modest relationship with falls compared to adjusting for weight, BMI, or using the residual technique in males when grip strength was included in the sarcopenia definition. [1,3,5] We hypothesize that this result is explained by appendicular lean mass adjusted for height mostly identifying individuals with normal body mass index values (between 18.5kg/m^2 and 24.9kg/m^2) as sarcopenic. In contrast, adjusting for weight and body mass index, and the residual technique identified more obese individuals with body mass index values of 30kg/m^2 and greater as sarcopenic.

The co-existence of sarcopenia and obesity is called sarcopenic obesity and has previously been found to be associated with a greater risk of falling than sarcopenia or obesity alone. [8,9] Therefore, because individuals identified as sarcopenic using height adjusted muscle mass have on average a healthier body weight compared to the other muscle mass adjustment techniques, they have an attenuated risk of falling. Interestingly, we did not observe the same attenuation when sarcopenia was defined using muscle mass and gait speed instead of grip strength. A potential explanation is that body mass index is associated with increased grip strength in males. [10] Sarcopenia definitions capturing mostly obese sarcopenic males may identify individuals at higher risk of falling due to a larger difference in their actual versus expected grip strength compared to their normal weight peers. The attenuation effect was not observed in females. This may be because unlike in males, grip strength was not associated with falls in females. Therefore, selecting primarily normal weight versus obese participants based on the muscle mass adjustment technique does not have the same impact on the results as in males. Additionally, increased body mass index is not associated with increased grip strength in females which means that a single cut off for low muscle mass identifies the same extent of muscle loss in obese females as it does in normal weight females. [10]

Finding relationships between definitions utilizing the residual adjustment technique was of particular interest as this adjustment technique has the greatest face validity. [12] The sarcopenia research community agrees that muscle mass should be adjusted for body size due to the strong correlation between these variables and the residual adjustment technique in may be the most appropriate as it simultaneously adjust for height and fat mass. [1,13]

Applying the residual adjustment technique is challenging, particularly when stratifying by age group, as the residuals developed in one group are not applicable to another unless the distribution of ALM, height, and fat mass are identical. Therefore, it is difficult to determine which cut points are appropriate for identifying low muscle mass. The results of this thesis provide guidance about how to apply this adjustment technique by showing that the residuals should be calculated prior to stratifying the sample by any variable. This allows for the residuals in each subgroup to be interpreted in the context of the whole sample. The odds of falling in males with sarcopenia was more than two times higher for many sarcopenia definitions compared to non-sarcopenic males. Though the magnitude of the odds ratio appeared clinically important, the AUC values were 0.56 and lower which indicated that knowing if a participant was sarcopenic had little value for identifying fallers. Compared to models with age only, including sarcopenia only improved the AUC values by less than 0.04 for identifying people with at least one fall, further supporting that diagnosing sarcopenia has limited utility in identifying fallers.

Clinical implications

One of the primary goals of the sarcopenia research community is to have physicians to routinely diagnosis and treat sarcopenia. [14] The findings of this thesis highlight two important considerations that should be made before measuring sarcopenia becomes standard practice. Firstly, given the poor agreement between nearly all sarcopenia definitions observed in this thesis, it is unlikely that a treatment shown to effectively manage sarcopenia based on one definition would have the same effectiveness when an alternative definition of sarcopenia is utilized. It is unrealistic to expect clinicians to

understand the nuances of each expert group consensus definition and choose treatment plans accordingly. Secondly, the results of this thesis indicate that more work is required to determine the value of diagnosing sarcopenia clinically. Sarcopenia, regardless of how it was defined, was not significantly associated with falls in females. In males, several definitions were associated with a more than two times greater odds of falling. However, the AUC analyses revealed that at best, males who had fallen at least twice had a 0.56 probability of being sarcopenic. Given the modest AUC values and that sarcopenia is a relatively expensive diagnosis to make due to the cost of the technology required to validly measure muscle mass, analyses studying the cost-effectiveness of diagnosing sarcopenia as a prevention strategy for falls is required. Additionally, more studies assessing the AUC using the outcome of falls should be conducted to replicate the results of this thesis, as well as studies assessing the AUC for other health outcomes related to sarcopenia.

Strengths and limitations

The key strength of the projects included in this thesis was the technique used to develop the sarcopenia definitions. By reviewing the sarcopenia consensus definitions published by the four expert groups as well as conducting a systematic review of which sarcopenia definitions were used in prevalence studies of community-dwelling older adults, we developed a list of sarcopenia definitions that allowed us to systematically examine each of the individual components making up common sarcopenia definitions. The selection of cut offs for grip strength and gait speed were directly guided by the expert group consensus definitions. However, selecting cut offs for low muscle mass was challenging due to the wide range of values recommended by the expert group consensus definitions and that are

observed in the literature. Given the large sample size of community-dwelling older adults available in the CLSA, we were able to create three sets of low muscle mass cut offs for each method of adjusting muscle mass corresponding to the 10th, 20th, and 40th percentile sex-specific values of adults aged 65 years and older in the CLSA. This technique offered two main advantages. Firstly, the cut offs capture the range of values recommended by the expert group consensus definitions and that are used in the literature. This translates into our results being generalizable to other studies. Secondly, this technique identified the same proportion of participants as having low muscle mass across the various adjustment techniques.

The use of data from the CLSA was another strength of this thesis. The CLSA is a national, longitudinal study that includes 51,338 community dwelling participants from the ten Canadian provinces. The 30,097 participants from the Comprehensive cohort who provided in-depth physical assessments at one of 11 Data Collection Sites located in seven provinces were eligible for the analyses. Comprehensive cohort participants were randomly selected from within 25 to 50km of each Data Collection Site. The randomly selected, community-dwelling sample increases the generalizability of the findings. In the analyses assessing the association between sarcopenia and falls, weighted data was utilized which further improves the generalizability of the findings to the Canadian population. Weighted data was not utilized for the agreement analyses as it would have resulted in altering the proportion of participants considered sarcopenic from the standardized values of 10%, 20%, and 40% and may have negatively impacted the agreement. The large sample sizes available for analyses, in particular for exploring the association between sarcopenia and

falls (n=10,008), was advantageous as it allowed for the analyses to be stratified by sex revealing that sarcopenia is associated with falls in males but not in females. Only two previous studies have stratified their analyses by sex, likely due to most studies having insufficient sample sizes. [6,7] The majority of sarcopenia definitions (n=22/26) studying the association between sarcopenia and falls in a recent meta-analyses were associated with an increased odds of falling, however, only 12 were statistically significant. [15] This is likely due to the small sample sizes available with most studies including fewer than 1000 participants. The small sample sizes and low event rates result in large confidence intervals which included an odds ratio of one. Though our sample was larger compared to previous studies, the number of participants with sarcopenia experiencing falls was small for some definitions and results for definitions using the 10th percentile cut offs for muscle mass should be interpreted with caution.

A major limitation of the projects in this thesis is that our results are only generalizable to participants of European ancestry. The literature has previously reported that muscle mass, muscle strength, and physical function vary by ethnicity, which was confirmed in the CLSA sample. [16–18] Males and females of European ancestry had significantly greater percent appendicular lean mass, faster gait speed, and greater grip strength compared to non-Europeans (**Table 1**). Due to the small sample size of adults aged 65 years and older that were not of European ancestry (n=235 males, n=139 females), it was not possible to further stratify the non-European ancestry group into more specific ancestry groups. Due to the differences in muscle mass, grip strength, and gait speed, Non-European participants were excluded from our analyses which limits the generalizability of our findings. A second

limitation is that our assessment of the construct validity of sarcopenia was limited to falls. We found that only certain sarcopenia definitions were associated with falls in males and that none of the definitions were associated with falls in females. While the results demonstrate that different sarcopenia definitions are not equally associated with falls and that there are important sex differences to take into consideration, a single project using one outcome is insufficient to establish construct validity. Falls are thought to be one of the most relevant health outcomes related to sarcopenia, but to fully assess construct validity, other important health outcomes such as function and disability also need to be assessed.

Opportunities for future research

The original objective of this thesis was to advance the goal of identifying a standard definition of sarcopenia that would be applicable to clinical settings. Though we feel this work has been an important step towards developing a unified definition, the results of the analyses also revealed that there may be limited clinical utility for diagnosing sarcopenia which requires further investigation.

The results of assessing the agreement between different sarcopenia definitions robustly showed that for almost all definitions, there is limited agreement and that both the muscle variables included in the definition as well as the techniques used to adjust muscle mass are sources of poor agreement. Several of the expert group consensus definitions recommend either multiple measures for the same muscle variable or two different muscle mass adjustment techniques. [1,2,4] The results of this thesis show that this practice results in poor agreement between definitions as well as differences in the strength of the association

of sarcopenia with falls in some cases. Therefore, any efforts to develop a standard definition of sarcopenia should be limited to definitions with only one method of operationalization.

The analyses of the association between sarcopenia with falls has several implications for future research. Most sarcopenia definitions including grip strength were strongly associated with falls in males, however none of the sarcopenia definitions were associated with falls in females. Based on these results, all future sarcopenia studies should conduct sex-stratified analyses in order to detect potential between sex differences. It is unclear why sarcopenia was associated with falls in males and not in females, though two previous studies have had similar findings. [6,7] To better understand the discrepancy of results in males and females for falls, future studies should focus on both sex and gender.

It is unclear if the difference in risk for males with sarcopenia versus females is specific to falls, or if sarcopenia is less strongly associated with multiple health outcomes in females. Similarly to falls, few studies have conducted sex-stratified analyses looking at outcomes such as functional disability which one study found decreased and one found similar odds of disability in females versus males, and only one study looked at sex-stratified analyses for mortality risk and found similar odds in males and females. [29,30] Further studies evaluating outcomes important to sarcopenia incorporating sex-stratified analyses are required to understand if sarcopenia is associated with health. Additionally, studies should be conducted in other ethnic groups to determine if different sarcopenia definitions better identify risk in participants of different ethnic backgrounds.

Future studies assessing the relationship between different sarcopenia definitions with other health outcomes are vital to developing a standard sarcopenia definition. In the context of sarcopenia, there is no criterion standard to measure sarcopenia against and therefore the definition with the strongest association with priority health outcomes should be considered the standard definition. Ideally, longitudinal analyses should be used. It would be more beneficial to predict people that will experience poor health caused by sarcopenia in the future allowing for early interventions to take place. For all analyses looking at the association between sarcopenia and health, the technique of looking at all combinations of sarcopenia variables and muscle mass adjustment techniques across a range of cut points should be utilized. This technique allows for an understanding of how changes in each of the individual components of the sarcopenia definition impacts the relationship between sarcopenia and health and allows the definition with the best construct validity to be identified.

Though several sarcopenia definitions were significantly associated with falls in males, conducting AUC analyses revealed that little knowledge about falls risk was gained by knowing the sarcopenia status of a participant. To our knowledge, only one previous study has assessed AUC values in the context of sarcopenia and the risk of falls. This study reported the change in AUC values of a model with just age predicting recurrent falls versus age and sarcopenia predicting recurrent falls. When sarcopenia was added to the model, the AUC improved between 0 and 0.01, depending on which definition of sarcopenia was used. [12] Similarly to our study, this shows that knowing if someone was sarcopenic provided little information about if they would fall or not. . All future studies assessing the

relationship between sarcopenia and any health outcome should calculate AUC values. If other studies show similarly low AUC values for a variety of health outcomes, the value of developing a standard sarcopenia definition for clinical settings should be assessed.

As the sarcopenia literature continues to evolve, if there are a subset of sarcopenia definitions which demonstrate adequate construct validity, efforts should be made to develop clinically relevant cut offs for muscle mass, grip strength, and gait speed. Previous studies have developed cut offs for grip strength which best categorized participants with limited physical function and muscle mass cut offs for muscle mass which categorize participants with low grip strength. [4] It is unclear if physical function is the correct outcome to use to develop cut offs, or if outcomes such as falls, disability, or mortality may be more appropriate. The sarcopenia research community should work towards a consensus of which outcomes should be used for developing cut offs. Consideration should also be given to developing cut offs using longitudinal data to determine values that predict poor outcomes rather than are associated with poor outcomes.

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Table 1. Mean values for anthropometric measures, grip strength, and gait speed in European and non-European males and females

	Males				
	European (n=5376)		Non-European (n = 235)		p-value for t-test comparing European versus non-European males
	Mean	Standard deviation	Mean	Standard deviation	
Height, cm	173.9	6.7	169.4	6.7	<0.0001
Weight, kg	84.6	14.1	76.9	14.9	<0.0001
BMI, kg/m2	28.0	4.2	26.7	4.6	<0.0001
Total body fat mass, %	25.5	8.0	22.9	8.0	<0.0001
Appendicular lean mass, %	25.9	3.8	24.1	4.2	<0.0001
ALM/height2	8.56	1.06	8.36	1.21	0.0050
ALM/weight	30.9	3.1	31.6	3.4	0.0011
ALM/BMI	0.94	0.12	0.91	0.13	0.0166
Gait speed, meters per second	0.94	0.19	0.89	0.21	<0.0001
Grip strength, kg	39.4	8.5	35.8	8.1	<0.0001
	Females				
	European (n=5060)		Non-European (n = 139)		p-value for t-test comparing European versus non-European females
	Mean	Standard deviation	Mean	Standard deviation	
Height, cm	159.9	6.3	156.3	6.5	<0.0001
Weight, kg	70.9	14.3	67.5	14.9	0.0029
BMI, kg/m2	27.8	5.5	27.6	5.8	0.3364
Total body fat mass, %	29.6	9.4	28.0	9.4	0.0248
Appendicular lean mass, %	17.4	3.0	16.7	3.4	0.0088
ALM/height2	6.78	1.04	6.82	1.24	0.3536
ALM/weight	24.8	2.86	25.0	2.9	0.1587
ALM/BMI	0.63	0.10	0.61	0.10	0.0100
Gait speed, meters per second	0.90	0.19	0.83	0.21	<0.0001
Grip strength, kg	23.6	5.2	22.6	5.1	0.0120