Sarcopenia in Older People (EWGSOP) published the first consensus on sarcopenia that recognized muscle mass function as a mainstay of its diagnosis, gaining immediate international acceptance (Cruz-Jentoft et al., 2010).

Since then, much has been stressed over the importance of skeletal muscle function assessment for accurately determining sarcopenia. A couple of additional formal guidelines and societal official positions have followed similar recommendations after the EWGSOP's (Studenski et al., 2014; Chen et al., 2014; Chumlea et al., 2011). In addition, original observational studies have been published analyzing to which degree skeletal muscle function can predict hard outcomes, such as quality of life (QoL), falls, hospitalizations and, most importantly, overall mortality (Cesari et al., 2009; Gale et al., 2007; Legrand et al., 2014; Newman et al., 2006; Wickham et al., 1989). In those studies, skeletal muscle function has been routinely measured by either muscle strength or muscle performance. The first is usually assessed by hand-grip strength and the latter by one of many different muscle performance tests available, among which Timed Up and Go (TUG) and Short Physical Performance Battery (SPPB) are likely the most common ones (Cruz-Jentoft et al., 2019).

1. Introduction

Sarcopenia is a pathologic syndrome which comprises a concomitant loss of muscle mass and muscle function (Sanchez-Rodriguez et al., 2020). It affects predominantly older adults and its prevalence steadily increases after the age of 60 (Cruz-Jentoft et al., 2014). As the world population grows older and overall survival improves, it is expected for sarcopenia to have a greater impact on health systems (Ethgen et al., 2017). Hence, precise knowledge about sarcopenia pathogenesis, diagnosis and management is crucial for those health professionals who routinely care for older adults.

For the last three decades, definitions on sarcopenia have undergone substantial changes (Sanchez-Rodriguez et al., 2020). When first coined in 1989 by Rosenberg, the term was considered a mere synonymous of low muscle mass (LMM) (Rosenberg, 1997) and, for a long time, no particular emphasis was devoted to the muscle functional compromise, which usually accompanies and antedates loss of muscle mass (Larsson et al., 2019). It was only in 2010 that the European Working Group on Sarcopenia in Older People (EWGSOP) published the first consensus on sarcopenia that recognized muscle mass function as a mainstay of its diagnosis, gaining immediate international acceptance (Cruz-Jentoft et al., 2010).
Recent clinical research on sarcopenia has considerably focused on the undeniable role of skeletal muscle function on the higher morbidity and mortality in older adults (Chainani et al., 2016; Denk et al., 2018; García-Hermoso et al., 2018; Pavasini et al., 2016). Both decreased skeletal muscle strength and muscle performance have been shown to independently predict higher morbidity and mortality, even after appropriate adjustment for LMM (Cesari et al., 2009; Gale et al., 2007; Legrand et al., 2014; Newman et al., 2006; Wickham et al., 1989). Moreover, it has been hypothesized that the association between LMM and higher mortality in older adults is primarily driven by low skeletal muscle function (LMF), whether by low skeletal muscle strength (LMS) or low skeletal muscle performance (LMP) (Li et al., 2018). Consistent with that, Newman et al. found that a reduced skeletal muscle strength as assessed by handgrip dynamometry or knee extension was independently associated with a higher mortality in individuals aged between 70 and 79 years, while no association for LMM assessed by DXA or CT was found (Newman et al., 2006).

Several systematic reviews with meta-analysis have assessed the association between sarcopenia, comprising the combination of LMM and LMF, and mortality (Beaudart et al., 2017; Liu et al., 2017a; Chang and Lin, 2016; Zhang et al., 2018). All of these studies found an association between the presence of sarcopenia and mortality. They have in common the use of operational definitions of sarcopenia and predefined cut-off points. Although these meta-analyses provide consistent answers about the ability of the operational definitions of sarcopenia to predict mortality, they did not assess the question of whether muscle mass itself would be associated with this outcome. Besides, none of these meta-analyses performed meta-regression, including data on muscle mass and muscle strength measurements.

Although it is now clear that the association between LMM and a higher mortality in older adults can be partly explained by confounding due to compromised muscle strength and performance, caution must be exercised to not overlook its genuine importance. For instance, lack of statistical significance for this association might simply be a result of underpowered studies. In this issue, meta-analytical approaches could be helpful in increasing one's power to detect such an association. Systematic reviews and meta-analysis to date, however, have mostly focused on the combined definition of sarcopenia (LMM + LMF) as the primary exposure, hampering their ability to conclude on isolated LMM as independent risk factor for mortality (Chang and Lin, 2016; Liu et al., 2017b; Yeung et al., 2019).

In this study, we conducted a systematic review and subsequent meta-analysis in the current literature to test whether LMM assessed by different methods is independently associated with increased mortality in community-dwelling, non-frail older adults. This meta-analysis complied with the recommended steps in the checklist from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (Moher et al., 2016) and was previously registered in the PROSPERO database (registration number CRD4201946511).

2. Material and methods

2.1. Published literature search and selection

From February 2019 to August 2020 (last search August 10th, 2020), we systematically searched the medical literature in two databases (the National Library of Medicine (PubMed®) and the Excerpta Medica database (Embase®)) for articles on the association between LMM and mortality in older adults. Inclusion criteria consisted of cohort or case-control studies reporting on the association of muscle mass and mortality and enrolling community-dwelling older adults aged 65 years or more. Cross-sectional, case-control, animal, in-vitro, and other study designs were excluded. Studies focusing on individuals suffering from specific diseases known to significantly impact mortality, such as chronic kidney disease (CKD), heart failure (HF) and cancer, were excluded. Studies enrolling older adults living in nursing home facilities or frail individuals were also excluded. The terms used for the search protocol are detailed in the attached Supplementary data (S1).

Two researchers performed the screening and selection of the articles (FMS and MOP), independently. Possible differences were resolved among the evaluators. Retrieved articles were first screened for eligibility criteria based on titles and subsequently on abstracts. Duplicates were then excluded. Remaining studies were further analyzed based on the full manuscript to confirm whether all inclusion and exclusion criteria were met. Studies remaining at this point included those missing some interest data (e.g. appendicular lean mass) which were considered potentially accessible by further contact to authors. These incomplete articles whose authors did not respond our contact or were unable to provide us with the interest data were finally excluded.

2.2. Data extraction

Data were extracted from each study by three independent protocol members (FMS, MOP, NYT). Where any disagreement in extracted data emerged, all three protocol members discussed the divergent data to a consensus. If no consensus was reached, a fourth member (RMRP) settled the issue. Extracted data included: study authors, year of publication, study design (whether cohort or case-control), study site (continent), sex (percentage of women included in the study), mean age and BMI of participants, number of deaths during follow-up, number of individuals who survived follow-up, mean and standard deviation (SD) for appendicular skeletal muscle mass index (ASMI), method used to estimate ASMI and, finally, mean and SD for handgrip strength (GS). ASMI estimates muscle mass dividing the appendicular muscle mass for height in meters squared (ASM/h²). Since ASMI measured by DXA is commonly reported as appendicular lean mass index (ALMI) these terms were considered interchangeable. Only GS estimated by handgrip dynamometry (kg) was extracted.

2.3. Study quality assessment

Included studies were assessed for design quality by the Newcastle-Ottawa Scale (NOS) (Lo et al., 2014). Briefly, this instrument scores stars to observational studies ranging from 0 to 9. Assessment is performed in three different domains: selection, comparability, and outcome. Studies scoring ≥7 stars were considered of high quality. The GRADE approach was used to evaluate the quality of evidence of the pooled results (Guyatt et al., 2008).

2.4. Statistical analysis

Summary results and covariates of interest from each included study were tabulated for analysis. The principal effect size was calculated as the standardized mean difference (SMD) between mean ASMI of individuals who survived follow-up and those who died (ASMI SMD). SMD takes into account the difference between the mean of two groups adjusting it for the SD of the entire cohort (difference of means between groups/SD among groups). This way, SMD makes it comparable between studies that might otherwise have differed in measurement methodologies (Takeshima et al., 2014). A random effect meta-analysis (REM) and a fixed effect meta-analysis (FEM) were computed from the data. REM was performed with DerSimonian and Laird as variance estimator (DerSimonian and Laird, 2015). Statistical heterogeneity among studies was assessed by Cochran’s Q and inconsistency I² test (Higgins et al., 2009). Both REM and FEM outputs were retained in the final model so potential differences found, if any, between them could additionally facilitate the reader to understand the degree to which the true effect size diverged between included studies. Publication bias was assessed both by qualitative inspection of funnel plots and by Egger test (Rothstein et al., 2005).

To assess for covariates that could potentially explain ASMI SMD
In REM, we performed a meta-regression analysis sequentially including the following summary variables: handgrip strength standardized mean difference between dead and living individuals (GS SMD), mean age, mean BMI, sex (percentage of women in the study), geographic site from the study (continent), which body composition method was used (BIA or DXA) and study design quality. A sensitivity analysis was then performed to assess the influence on heterogeneity of grouping studies according to covariates. For quantitative covariates (GS SMD, age, BMI, sex and design quality), we proceeded in categorizing studies in two or more subgroups. For this purpose, we relied on medians among studies for subgroup allocation. We also performed sensitivity analyses for categorical covariates (site and body composition method). To ascertain that no single study was responsible for the summary effect size and for the between-studies heterogeneity, we performed a Leave-One-Out Meta-analysis (LOOM), sequentially excluding from the model each study at a time. This way we could visualize the degree to which each study was responsible for the summary effect size and for the between-studies heterogeneity.

All analyses were performed using the computing environment R (R Development Core Team, 2020). This meta-analysis protocol was previously registered in the PROSPERO database (CRD42019146531) just after its conception.

3. Results

A total of 6722 and 3841 results were initially retrieved from Pubmed® and Embase®, respectively. Following the stepwise process of selection, nine articles were considered eligible for the study and were then included for analysis (Bianchi et al., 2016; De Buyser et al., 2016; de Santana et al., 2019; Kruse et al., 2018; Moon et al., 2016; Nakamura et al., 2020; Seino et al., 2020; von Berens et al., 2020; Woo and Leung, 2018) (Table 1). These comprised a pooled sample of 10,028 older adults. A detailed flowchart of the selection process is shown in Fig. 1.

Mean ASMI across studies in individuals who died during the follow-up ranged from 6.46kg/m² to 10.25kg/m² (arithmetic non-weighted mean = 7.37kg/m²) while in those who survived follow-up ranged from 6.57kg/m² to 10.74kg/m² (arithmetic non-weighted mean = 7.57kg/m²). Mean age and BMI of participants were 76 years and 25.5kg/m², respectively. Forty nine percent (49%) of included individuals were women (n = 4860). Forty five percent (45%) of included studies took place in Asia (n = 4); an additional 45% (45%), in Europe (n = 4) and 10% (10%), in Latin America (n = 1). Fifty six percent (56%) of the included studies assessed muscle mass by DXA (n = 5) while the remainder (44%) assessed muscle mass by BIA (n = 4). Details on these variables for each included study can be found in Supplementary data (S2).

Quality assessment by means of NOS resulted in a median quality score of eight stars. All but one study were considered of high quality (>7 stars). Table 3 shows, for each included study, the assessment of its overall quality and according to its specific domains.

Pooled results from meta-analysis including all nine studies showed a reduced ASMI in individuals who died during the follow-up as compared to those who survived (ASMI SMD = −0.18, CI95%: −0.23 to −0.12, REM). Meta-analysis by both REM and FEM yielded very similar statistically significant results, with a very small nominal difference between confidence intervals. However, inconsistency measured by I² test was found to be moderate and we found a statistically significant heterogeneity between included studies (I² = 61%, p < 0.01 for Cochran’s Q test) (Higgins et al., 2003). Results of this ASMI SMD meta-analysis can be found in Fig. 2.

To better account for potential confounding factors that could explain heterogeneity between studies, we performed a meta-regression including ASMI SMD, GS SMD, BMI, sex, study quality, method used to assess ASMI, site of study and age. Both ASMI and GS were assessed by SMD between dead and living individuals (ASMI SMD and GS SMD, respectively). Sex was assessed by percentage of women included in the study. The results can be found in Table 2. BMI and site of study were found to be significantly associated with ASMI SMD among studies. Studies which included individuals whose BMI were higher on average tended to be associated with more profound differences in ASMI between dead and living individuals (Fig. 3). As for the site of the study, those which included Asian individuals found a more discrete difference in ASMI between dead and living individuals as compared to those in Europe and Latin America (Fig. 4).

As was pre-planned, a sensitivity analysis was subsequently performed to account for the contribution of each included study to the moderate heterogeneity found between studies (LOOM). The study from Nakamura 2020 was found to be responsible for one third (1/3) of the heterogeneity in the ASMI SMD meta-analysis, reducing inconsistency between studies from 60% to 40% in the LOOM (Fig. 5).

Sensitivity analysis grouping studies according to relevant covariates were also performed. These covariates were the same as those included in the meta-regression model mentioned above. Sensitivity analysis for BMI grouped studies into upper and lower BMI. Sensitivity analysis for age classified studies into two different groups, according to mean age (>75 years and <75 years). Sensitivity analysis for body composition method grouped studies according to whether DXA or BIA was used. Sensitivity analysis for GS SMD grouped studies into upper and lower GS SMD. Sensitivity analysis for quality was performed according to the number of stars awarded by NOS. Finally, studies were grouped according to site (Asia, Europe and Latin America). Details on these analyses can be found in Supplementary data (S4). In summary, studies which included individuals whose BMI were higher on average showed no degree of heterogeneity (I² = 0%) between them. The same trend was found for studies which included older individuals as compared to those which included younger individuals and for studies which took place in

### Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Study population</th>
<th>Country</th>
<th>No. of participants</th>
<th>No. of deaths</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moon et al</td>
<td>2016</td>
<td>Korean Longitudinal Study on Health and Aging (KLoSHA)</td>
<td>South Korea</td>
<td>560</td>
<td>61</td>
<td>6.0</td>
</tr>
<tr>
<td>De Buyser et al</td>
<td>2016</td>
<td>Belgium community population</td>
<td>Belgium</td>
<td>191</td>
<td>165</td>
<td>12.0</td>
</tr>
<tr>
<td>Bianchi et al</td>
<td>2016</td>
<td>InCHIANTI Study</td>
<td>Italy</td>
<td>538</td>
<td>55</td>
<td>4.6</td>
</tr>
<tr>
<td>Woo et al</td>
<td>2018</td>
<td>Mr. and Ms. Os Cohort</td>
<td>Hong Kong (China)</td>
<td>4000</td>
<td>972</td>
<td>10.2</td>
</tr>
<tr>
<td>Kruse et al</td>
<td>2018</td>
<td>Belgium community population</td>
<td>Belgium</td>
<td>264</td>
<td>56</td>
<td>5.0</td>
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<tr>
<td>de Santana et al</td>
<td>2019</td>
<td>Sao Paulo Ageing &amp; Health Study (SPA)</td>
<td>Brazil</td>
<td>839</td>
<td>132</td>
<td>4.1</td>
</tr>
<tr>
<td>Seino et al</td>
<td>2020</td>
<td>Kanazawa Longitudinal Study and Hatoyama Cohort Study</td>
<td>Japan</td>
<td>1977</td>
<td>203</td>
<td>5.3</td>
</tr>
<tr>
<td>von Berens et al</td>
<td>2020</td>
<td>Gothenburg H70 Birth Cohort Studies and Uppsala Longitudinal</td>
<td>Sweden</td>
<td>809</td>
<td>147</td>
<td>10.0 and 4.0¹</td>
</tr>
<tr>
<td>Nakamura et al</td>
<td>2020</td>
<td>Study of Adult Men (ULSAM)</td>
<td>Japan</td>
<td>1371</td>
<td>87</td>
<td>4.3</td>
</tr>
</tbody>
</table>

* Gothenburg H70 Birth Cohort Studies and Uppsala Longitudinal Study of Adult Men were followed-up for, respectively, 10 and 4 years.
Asia as compared to those which did not. Publication bias for the ASMI SMD meta-analytic model was assessed by inspection of funnel plot, which resulted in a symmetrical pattern around the mean (Fig. 6). Egger test for publication bias was also not significant ($p = 0.80$).

4. Discussion

The present meta-analysis uncovered a significant pooled difference in appendicular skeletal muscle mass, as measured by ASMI, between older adults who died as compared to those who survived across follow-up cohort studies. This difference was just partly attenuated by known mortality risk factors after meta-regressing them. Noteworthy, handgrip strength differences between groups were unable to explain the higher mortality found in lower ASMI individuals as compared to those with higher ASMI. These results emerge as an invaluable reminder that not only skeletal muscle quality matters, as has been recently the focus of most studies, but also its quantity.

Currently, several different methods can be used to estimate skeletal muscle mass (DXA, BIA, MRI, CT, anthropometry, etc.), each of them relying on their own techniques (Rubbieri et al., 2014). Hence, skeletal muscle mass is often reported in a variety of different ways (ASM, ALM,

*Articles were considered potentially containing data of interest when this data was not reported in the published manuscript but otherwise expected to have been collected by the authors. In these situations, authors were contacted.

**Fig. 1.** Flowchart depicting the selection process of included studies in the meta-analysis.
FMM, SMM, circumference, etc.), which hamper the comparison between different methods (Cruz-Jentoft et al., 2010). Moreover, the cut-off for establishing LMM also varies widely and still lacks a definite consensus (Chen et al., 2014; Chumlea et al., 2011; Cruz-Jentoft et al., 2019). This methodologic heterogeneity affects how studies in the subject are designed and reported, which in turn interferes in an accurate assessment of the association between LMM and mortality. Thus, reported results so far have been inconclusive (Bunout et al., 2011; Graf et al., 2016; Spahillari et al., 2016).

Bunout et al. followed 1413 older healthy adults for a median time of 1594 days and found a positive association between low appendicular fat-free mass (a surrogate of appendicular skeletal muscle mass) assessed by DXA and increased mortality (Bunout et al., 2011). A similar positive result was reported by Graf et al., who followed 791 older adults for an average of 2 years, after assessing their muscle mass by BIA (Graf et al., 2016). On the other hand, a study reported by Spahillari et al. and assessing 1335 older adults in a 12-year follow-up found LMM estimated by DXA to be a protective factor for mortality (Spahillari et al., 2016).

### Table 2

Results of the meta-regression of ASMI SMD, including GS SMD, BMI, sex, study quality, method used to assess ASMI, site of study and age.

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SE</th>
<th>Lower CI 95%</th>
<th>Upper CI 95%</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.001</td>
<td>0.008</td>
<td>-0.012</td>
<td>0.020</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.044</td>
<td>0.020</td>
<td>-0.084</td>
<td>-0.004</td>
</tr>
<tr>
<td>Sex (percentage)</td>
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<td>0.203</td>
<td>-0.612</td>
<td>0.183</td>
</tr>
<tr>
<td>Study quality</td>
<td>-0.049</td>
<td>0.042</td>
<td>-0.131</td>
<td>0.033</td>
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<tr>
<td>Method used to assess ASMI</td>
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<td>0.068</td>
<td>-0.164</td>
<td>0.104</td>
</tr>
<tr>
<td>Grip strength SMD</td>
<td>-0.451</td>
<td>0.518</td>
<td>-1.470</td>
<td>0.564</td>
</tr>
<tr>
<td>Site of study</td>
<td>0.104</td>
<td>0.045</td>
<td>0.016</td>
<td>0.192</td>
</tr>
</tbody>
</table>

ASMI: appendicular skeletal muscle mass index; SMD: standardized mean difference; GS: grip strength; BMI: body mass index; SE: standard error.

### Fig. 2.
Meta-analysis of the ASMI SMD between dead and living individuals of eligible studies. Both FEM and REM show similar differences of ASMI and similar 95% confidence interval, but a statistically significant heterogeneity is present between included studies. ASMI: appendicular skeletal muscle mass index; SMD: standardized mean difference; FEM: fixed effect model; REM: random effect model.

### Fig. 3.
Effect size of ASMI SMD between dead and living individuals according to BMI in a meta-regression model. Higher BMI was associated with more profound differences in ASMI SMD between dead and living individuals. BMI: body mass index; ASMI: appendicular skeletal muscle mass index; SMD: standardized mean difference.

### Fig. 4.
Effect size of ASMI SMD between dead and alive individuals according to site of study. On the graphic, 2 stands for Latin America, 3 for Europe and 4 for Asia. Asian ethnicity was associated with more discrete differences in ASMI SMD between dead and living individuals. ASMI: appendicular skeletal muscle mass index; SMD: standardized mean difference.
Newman et al. also found no significant association between appendicular skeletal muscle mass and mortality in older adults (Newman et al., 2006). None of the above referenced studies were included in the present meta-analysis for none of them met the prespecified inclusion criteria, such as reporting skeletal muscle mass by ASMI. Although no single study comparing all methods has been reported, it is clear that the lack of standardization and a consensual definition on LMM lead to different outcome analysis. Currently, EWGSOP2 recommendation establishes both DXA and BIA as acceptable methods for estimating skeletal muscle mass and tries to summarize precise cut-offs for clinical practice (Cruz-Jentoft et al., 2019).

The association between decreased muscle strength and adverse outcomes is well documented in the literature (Cawthon et al., 2020; Schaap et al., 2013; Wu et al., 2017). The handgrip measurement is an excellent predictor of poor prognosis, being associated with mortality and other negative outcomes in older subjects (Cawthon et al., 2020; Schaap et al., 2013; Wu et al., 2017). Schaap et al. evaluated the isolated components’ ability (muscle strength and muscle mass) to predict functional decline in the elderly. They found that muscle strength and not muscle mass were associated with this decline (Schaap et al., 2013). These results generated concern about the capacity of the muscle mass used as a single measure to predict mortality. However, since the publication of the systematic review by Schaap et al. in 2012, new studies evaluated muscle mass in different populations. Analysis of the Sarcopenia Definitions and Outcomes Consortium (SDOC), which included eight cohort studies carried out on different continents, confirmed the handgrip’s ability to predict falls, hip fractures, decreased mobility, and mortality (Cawthon et al., 2020). On the other hand, although muscle mass, assessed as ALMI, was not associated with other outcomes, it was consistently associated with mortality (Cawthon et al., 2020). These results agree with those found by our meta-analysis in which the individuals who died had a lower ASMI than the survivors. It’s noteworthy that muscle mass is essentially a continuous variable; however, it’s frequently categorized using cut-off points. The use of different low-sensitivity cut-off points in specific populations may be one factor

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Total</th>
<th>Total by category</th>
</tr>
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<tr>
<td>Moon et al. (2016)</td>
<td>****</td>
<td>**</td>
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<td>9</td>
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<tr>
<td>De Buyser et al. (2016)</td>
<td>****</td>
<td>*</td>
<td>**</td>
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<td>****</td>
<td>**</td>
<td>***</td>
<td>9</td>
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<tr>
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<td>***</td>
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<td>*</td>
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<td>de Santana et al. (2019)</td>
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<td>*</td>
<td>6</td>
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<td>Nakamura et al. (2020)</td>
<td>****</td>
<td>**</td>
<td>***</td>
<td>9</td>
<td>4, 2, 3</td>
</tr>
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</table>

Table 3: Quality of studies included in the meta-analysis assessed by the Newcastle-Ottawa Scale.

*a Each study is given up to 9 stars in the Newcastle-Ottawa Scale. Studies classified with ≥7 stars are considered of high quality.

Fig. 5. Leave-one-out meta-analysis (LOOM). Effect size of ASMI SMD and its heterogeneity on excluding each study at a time. Nakamura 2020 is found to be the greatest responsible for the heterogeneity in the ASMI SMD REM meta-analysis. ASMI: appendicular skeletal muscle mass index; SMD: standardized mean difference; REM: random effect model.
In our systematic review, we found an association between LMM measured by ASMI and mortality; however, in the meta-regression analysis, the magnitude of this association was not explained by differences in muscle strength. On the other hand, in our study, differences found between individuals who died and survived seems to be influenced by BMI and ethnicity. We found that patients with higher BMI are influenced to a higher degree to similar changes in muscle mass when compared to individuals with lower BMI. These findings are in agreement with the current concept of sarcopenic obesity, where sarcopenia and obesity synergistically increase mortality (Atkins et al., 2014). One possible explanation for these findings is that obese individuals might be more dependent on the positive metabolic effect of muscle mass (Park and Yoon, 2013). Muscle tissue is responsible for glucose uptake and has an essential effect on insulin sensitivity (Walowski et al., 2020). Also, it secretes several myokines with metabolic action in adipose, liver, brain, and muscle tissue (Walowski et al., 2020). Finally, in our study, Asian subjects have a smaller magnitude of difference in muscle mass between the elderly who die and survive, suggesting that muscle mass has less impact on mortality in this population. These differences might be due to cultural or genetic components, which is consistent with previous studies reporting an estimated heritability of muscle mass of up to 60% (Trajanoska et al., 2019).

The present meta-analysis has several strengths. As far as we are concerned, it’s the first one to assess the association between skeletal muscle mass (in contrast to sarcopenia) and mortality in older adults. Furthermore, its pooled sample is large (n = 10,028 individuals). Data collection consisted of both passive and active approaches, and we managed to include into the meta-analysis data not otherwise published in some of the original articles. Finally, metrics assessing appendicular muscle mass among studies were similar (ASM). Although some slight differences in how these metrics might have occurred, we attenuated this fact using standardized mean differences (SMD) within each study.

We must acknowledge that results from our meta-analysis might have been negatively impacted by some limitations. First, not all included studies assessed all potential confounding factors. Hence, meta-regression analysis was limited by not including all studies for all covariates. Heterogeneity was deemed to be moderate between studies ($I^2 = 61\%$, $p < 0.01$ for Cochran’s Q test) and was only partially explained by included covariates in sensitivity analysis and meta-regression. Hence, confounding factors otherwise not assessed in the present meta-analysis might have influenced the results. Finally, influences from methodologic differences between studies cannot be ruled out.

5. Conclusions

In summary, we found that appendicular skeletal muscle mass adjusted for height, as assessed by ASMI, is inversely associated with mortality in older adults. This association cannot be completely explained by differences in muscle strength, as assessed by handgrip strength, or other known clinical and demographic factors. It appears, however, that the intensity of the association between ASMI and mortality does modify according to such factors. For instance, in overweight and obese individuals (higher BMI), the influence of ASMI on mortality is more prominent. These results emerge as important findings in the field of sarcopenia since current research on muscle mass as a prognostic tool in older adults has consistently been overshadowed by research on muscle performance and strength. Whether other metrics for skeletal muscle mass estimation can also consistently predict mortality in older adults, however, still remains to be elucidated.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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