REVIEW

Journal of Cachexia, Sarcopenia and Muscle 2023; **14**: 1596–1612
Published online 20 May 2023 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.13263

Association of muscle wasting with mortality risk among adults: A systematic review and meta-analysis of prospective studies

Huan-Huan Zhou[1,2], Yuxiao Liao[1,2], Zhao Peng[1,2], Fang Liu[3], Qi Wang[4] & Wei Yang[1,2]*

[1]*Department of Nutrition and Food Hygiene, Hubei Key Laboratory of Food Nutrition and Safety, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;* [2]*Department of Nutrition and Food Hygiene and MOE Key Lab of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;* [3]*School of Public Health, Wuhan University, Wuhan, China;* [4]*Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

Abstract

The relationship between muscle wasting and mortality risk in the general population remains unclear. Our study was conducted to examine and quantify the associations between muscle wasting and all-cause and cause-specific mortality risks. PubMed, Web of Science and Cochrane Library were searched until 22 March 2023 for main data sources and references of retrieved relevant articles. Prospective studies investigating the associations of muscle wasting with risks of all-cause and cause-specific mortality in the general population were eligible. A random-effect model was used to calculate the pooled relative risk (RR) and 95% confidence intervals (CIs) for the lowest versus normal categories of muscle mass. Subgroup analyses and meta-regression were performed to investigate the potential sources of heterogeneities among studies. Dose–response analyses were conducted to evaluate the relationship between muscle mass and mortality risk. Forty-nine prospective studies were included in the meta-analysis. A total of 61 055 deaths were ascertained among 878 349 participants during the 2.5- to 32-year follow-up. Muscle wasting was associated with higher mortality risks of all causes (RR = 1.36, 95% CI, 1.28 to 1.44, I^2 = 94.9%, 49 studies), cardiovascular disease (CVD) (RR = 1.29, 95% CI, 1.05 to 1.58, I^2 = 88.1%, 8 studies), cancer (RR = 1.14, 95% CI, 1.02 to 1.27, I^2 = 38.7%, 3 studies) and respiratory disease (RR = 1.36, 95% CI, 1.11 to 1.67, I^2 = 62.8%, 3 studies). Subgroup analyses revealed that muscle wasting, regardless of muscle strength, was significantly associated with a higher all-cause mortality risk. Meta-regression showed that risks of muscle wasting-related all-cause mortality (P = 0.06) and CVD mortality (P = 0.09) were lower in studies with longer follow-ups. An approximately inverse linear dose–response relationship was observed between mid-arm muscle circumference and all-cause mortality risk (P < 0.01 for non-linearity). Muscle wasting was associated with higher mortality risks of all causes, CVD, cancer and respiratory disease in the general population. Early detection and treatment for muscle wasting might be crucial for reducing mortality risk and promoting healthy longevity.

Keywords mortality; muscle loss; muscle mass; muscular atrophy; sarcopenia

Received: 25 August 2022; Revised: 29 March 2023; Accepted: 22 April 2023
**Correspondence to: Dr. Wei Yang, PhD, Associate Professor, Department of Nutrition and Food Hygiene and MOE Key Lab of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan, 430030, China. Email: yw8278@hotmail.com; yw8278@hust.edu.cn*

Introduction

Muscle wasting, characterized by progressive loss of skeletal muscle mass (SMM), occurs in aging and other clinical conditions, with an estimated prevalence varying from 24.2% to 40.4%.[1] Muscle wasting was regarded as the most common denominator and disease process of sarcopenia-associated disorders and cachexia, with no consensus definition or common classification system to date.[2–4] The loss of mass limits the basic ability of muscles to generate strength and also favours the onset or worsening of the joint degenerative process.[5] Skeletal muscle not only plays an important role in the regulation of systemic metabolism by regulating postprandial blood glucose but also acts as an endocrine organ by secreting myokines that regulate inflammation and other tissues,[6] which has evolved as the most basic, objective and promising parameter among components of sarcopenia-associated disorders.

Muscle wasting was associated with frailty,[7] falls and fracture,[8] hospitalizations,[9,10] metabolic syndromes[11] and multiorgan failure.[12] Notably, the early symptoms of muscle wasting are not obvious, which makes the diagnosis and early treatment difficult. It has been estimated that a 10% reduction in muscle wasting would result in annual savings of $1.1 billion in healthcare costs in the United States.[13] Recently, a meta-analysis showed that adults with sarcopenia were confronted with a two-fold higher risk of mortality.[14] Another pooled analysis suggested that muscle wasting was significantly associated with a 95% increased risk of all-cause mortality in patients with hepatocellular carcinoma.[15] Despite the accumulating evidence, the associations of muscle wasting with all-cause and cause-specific mortality in the general population are inconclusive now. Recently, some prospective studies found that muscle wasting was associated with increased mortality risk,[16,17] whereas others failed to find a such association.[18–20] The use of distinct indicators of muscle wasting, diverse duration of follow-up and participants' age may be key factors responsible for the differences among studies.

To the best of our knowledge, no available systematic review and meta-analysis was found on the relationship of muscle wasting with all-cause or cause-specific mortality in the general population. In this study, we aimed to perform a systematic review and meta-analysis of prospective cohort studies to investigate the association between muscle wasting and risks of all-cause and cause-specific mortality among residents.

Methods

This meta-analysis was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines[21] and registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022299232).

Search strategy

Relevant articles were searched up to 22 March 2023 from PubMed, Web of Science and Cochrane Library. The detailed search strategy was given in *Table S1*. We also conducted a manual search for reference lists of the included studies and relevant reviews.

Definition of muscle wasting

We defined muscle wasting as a loss of muscle mass due to aging or any underlying illness with or without decreases in muscle function or fat tissue wasting.[2–4] Based on previous studies,[22–24] we included studies that reported muscle mass loss of any severity under any definition criteria. The detailed information on cut-off points of muscle wasting for all included studies was presented in *Table S2*.

Study selection

Three authors (HHZ, YXL and ZP) independently screened titles and abstracts in the initial search, and then full text of all relevant articles was reviewed for eligibility. The senior investigator (WY) arbitrated any discrepancy to reach a consensus. We included prospective cohort studies that evaluated the relationship between muscle wasting and mortality in the general population. The inclusion criteria for this review were as follows: (1) The study design was a prospective cohort study; (2) the exposure of interest was decreased muscle mass; (3) the outcome was all-cause mortality or cause-specific mortality; and (4) the investigators reported relative risk (RR), hazard ratio (HR) or odds ratio (OR) of outcome risk and corresponding 95% confidence intervals (CIs). Meantime, the exclusion criteria included (1) participants who were not recruited from a generally healthy population and (2) reviews, randomized controlled trials (RCTs), case–control studies, retrospective cohort studies, non-human studies and letters without sufficient data. Only reports with the longest follow-up and the largest sample size were finally included if multiple ones from the same study reported.

Outcomes

The primary outcome was all-cause mortality. Secondary outcomes included mortality risks due to cardiovascular disease (CVD), cancer, stroke, respiratory disease, Alzheimer's disease and other forms of dementia, diabetes and kidney disease,

which were the top global causes of death in 2019 released by WHO.[25] In addition, we were also concerned about deaths from other diseases, if reported.

Data extraction

Data extraction was conducted by two trained researchers (HHZ and YXL) independently. The data from each eligible study were extracted to a standard form, including the first author's surname, publication year, study design, study location, sample size (total sample/number of deaths), mean age, follow-up years, sex (percentage of women), body mass index (BMI) of participants, handgrip strength (GS) of participants, the method used for assessment of muscle mass (e.g., dual-energy X-ray absorptiometry [DXA], bioimpedance analysis [BIA], anthropometry, computed tomography [CT] and magnetic resonance imaging [MRI]), predictors reported for muscle mass (e.g., appendicular skeletal muscle mass [ASM], appendicular lean mass [ALM], SMM, skeletal muscle index [SMI; equals to ASM/height^2, ALM/height^2 or SMM/height^2], fat-free mass [FFM], fat-free mass index [FFMI; equals to FFM/height^2], mid-arm muscle circumference [MAMC] and calf circumference [CC]) and corresponding effect size of comparison categories together with 95% CIs and covariates in the fully adjusted model. If several predictors of muscle mass were reported, the most frequently used and most recognized predictor would be analysed. If studies reported data separately by sex, they would be analysed as two separate reports.

Quality assessment

The quality of all included studies was assessed by two trained researchers (HHZ and YXL) independently using the Newcastle-Ottawa Scale (NOS) in consideration of selection (four stars), comparability (two stars) and outcomes (three stars).[26] Higher study scores indicate better study quality. We considered NOS scores of 0–3, 4–6 and 7–9 as low, medium and high quality, respectively. The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of evidence for outcomes.[27] According to the GRADE guideline, study design determines the baseline quality of the evidence; for example, observational studies were initially assigned a ranking of low, and other factors could downgrade or upgrade the quality of evidence. Discrepancies were resolved through discussion with the third reviewer (WY).

Statistical analysis

A random-effect model was used to pool risk estimates with 95% CIs of all-cause and cause-specific mortality risks for the lowest muscle mass (extreme category of muscle wasting) versus the normal muscle mass (reference), to incorporate the estimated between-study variation to allow for the anticipated clinical and methodological variability across studies. According to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, HR was approximately equal to RR.[28] Meanwhile, an OR was corrected into an RR using the following formula: RR = OR/[(1 − P_0) + (P_0 × OR)], where P_0 indicates the mortality rate in the reference group.[29] If an estimate was reported for the normal muscle mass versus the lowest muscle mass, we computed the estimate of the lowest versus normal according to the Orsini method.[30] We assessed the between-study heterogeneity using between-study variance (tau^2), the Q test and quantified by I^2-statistic.[31] The presence of significant heterogeneity was indicated by a P-value < 0.1 in the Q test or $I^2 > 50\%$.

As long as they were reported by at least five studies, subgroup analyses and meta-regression were performed to explore potential sources of between-study heterogeneities from age at baseline, gender (female% for meta-regression), BMI at baseline, location of study (specific country for meta-regression), duration of follow-up, number of participants, method and specific predictors used for assessment of muscle wasting, GS of participants (grouped according to the cut-off point proposed by Alley et al.[32]), study quality and adjustment for confounders (not performed for meta-regression). Additionally, the meta-regression model, which is a mix of interaction and trend tests, was also performed with continuous variables, except for the method of exposure assessment, specific predictors of muscle wasting and country of study. A P-value < 0.1 was considered statistically significant for meta-regression analysis.

A leave-one-out meta-analysis (LOOM) was conducted (when studies ≥ 5) as sensitivity analysis, that is, omitting one study at each time to assess the robustness of the primary results and the impact of each report on the effect or the heterogeneity.

Publication bias was assessed by Egger's regression test if five or more studies were available for inclusion. A P-value < 0.1 suggested the presence of publication bias.[33] The trim and fill method was utilized in case of publication bias.[34]

Studies that reported at least three categories of muscle mass with the same indicator of muscle mass assessed by the same method were included in the dose–response analysis, where the lowest category of muscle mass was designated as the reference. In the case of studies with a non-lowest category reference, the approach proposed by Hamling et al. was used for estimate conversion.[35] We assigned the median or mean muscle mass in each category to the corresponding RR for each study and assigned the midpoint of the upper and lower bound in each category for studies that did not report the median or mean per

category. When extreme categories were open-ended, we utilized the length of the adjacent interval to estimate the extreme values. A possible non-linear dose–response relationship between muscle mass and all-cause mortality was examined by random-effect dose–response meta-analysis through a restricted cubic splines model with three knots at fixed centiles of 10th, 50th and 90th of the distribution.[36] A likelihood ratio test was applied to assess the difference between the linear and non-linear models to test for non-linearity, with a *P*-value < 0.05 seemed as non-linearity. As the associations of predicted lean body mass were approximately log-linear below and above the median, we additionally used a linear model to calculate pooled RR per standard deviation (SD) increase in lean body mass. Separate dose–response analyses were conducted for studies reporting different indicators of muscle mass measured by different methods.

We performed data analyses by STATA Version 16.0 (Stata Corp, College Station, TX, USA) with double data input to avoid input errors. The *P*-value < 0.05 was deemed as statistically significant unless specified elsewhere.

Results

Literature search

The detailed process of literature searching and study selection was presented in the flow chart (*Figure 1*). A total of 7849 potential eligible articles were identified through the initial search. Then 7710 records were excluded because of duplication or not meeting the inclusion criteria. After the full-text screening, 86 articles were further eliminated because of the following reasons: 4 records lacked CIs of target outcomes, 4 records lacked risk estimates of target outcomes, 9 records had no usable data of target outcomes, 12 records were not involved in the exposure of interest, 27 records were conducted on diseased populations, 14 records were done on the same study populations, 13 records were review or meta-analysis and 3 records were retrospective cohort studies. The detailed information for excluded articles was presented in *Table S3*. Eventually, 49 eligible articles were included in the final meta-analysis.

Characteristics of included studies

Forty-nine articles with 66 reports reported muscle wasting-related effect sizes for mortality risks due to all causes,[16–20,37–79] eight articles with 11 reports due to CVD,[45,49,51,55,61,65,68,74] three articles with 4 reports due to cancer,[51,61,65] three articles with 4 reports due to respiratory disease[51,61,68] and one article with 2 reports due to diabetes.[55] No available information was found for mortality from other causes. The summary of the included 49 articles was shown in *Table 1* and details of those studies were shown in *Tables S4–S8*. The studies comprised 878 349 participants. The sample size ranged from 191 to 405 980. The total number of deaths was 61 055 (one trial not reported[46]), 7520 (two trials not reported[51,65]), 3726 (two trials not reported[51,65]), 3537 (one trial not reported[51]) and 107 from all causes, CVD, cancer, respiratory disease and diabetes, respectively. The mean age of participants ranged from 38.7 to 93.5 years. The mean duration of follow-up ranged from 2.5 to 32 years.

Study quality

The study quality was assessed by NOS and scores were shown in *Table S9*. As indicated by the NOS score, 46 studies had a high quality, 3 studies had a medium quality and none of them had a low quality. The mean study quality scores were 7.6 for all-cause mortality, 7.7 for CVD, 7.3 for cancer, 7.7 for respiratory mortality and 8 for diabetes.

Muscle wasting and mortality risk

In total, 49 studies with 66 reports were included in the analysis of muscle wasting and all-cause mortality risk. The pooled RR of all-cause mortality risk was 1.36 (95% CI, 1.28 to 1.44, $P < 0.001$) across the lowest to the normal muscle mass category, indicating a significant positive association between muscle wasting and all-cause mortality risk. High heterogeneity was observed among studies (I^2 = 94.9%, $P < 0.001$) (*Table 2* and *Figure 2*). Participants in the lowest muscle mass category had a higher CVD mortality risk (pooled RR = 1.29, 95% CI, 1.05 to 1.58, $P = 0.014$, 8 studies with 11 reports) than that in the normal category though of high heterogeneity (I^2 = 88.1%, $P < 0.001$) (*Table 2* and *Figure 3A*). For cancer mortality, which was examined in three articles with four reports, a positive association was found with muscle wasting. The pooled RR was 1.14 (95% CI, 1.02 to 1.27, $P = 0.020$) across the lowest to the normal muscle mass category, with low heterogeneity found between studies (I^2 = 38.7%, $P = 0.180$) (*Table 2* and *Figure 3B*). Similar findings were obtained for muscle wasting and respiratory disease mortality based on three publications with four reports. The pooled RR was 1.36 (95% CI, 1.11 to 1.67, $P = 0.003$), with moderate heterogeneity among the studies (I^2 = 62.8%, $P = 0.045$) (*Table 2* and *Figure 3C*). Otherwise, the summary effect size for diabetes mortality was 1.14 (95% CI, 0.67 to 1.92, $P = 0.630$), indicating no clear association. Evidence of low to moderate heterogeneity was found between studies (I^2 = 60.5%, $P = 0.112$) (*Table 2* and *Figure 3D*).

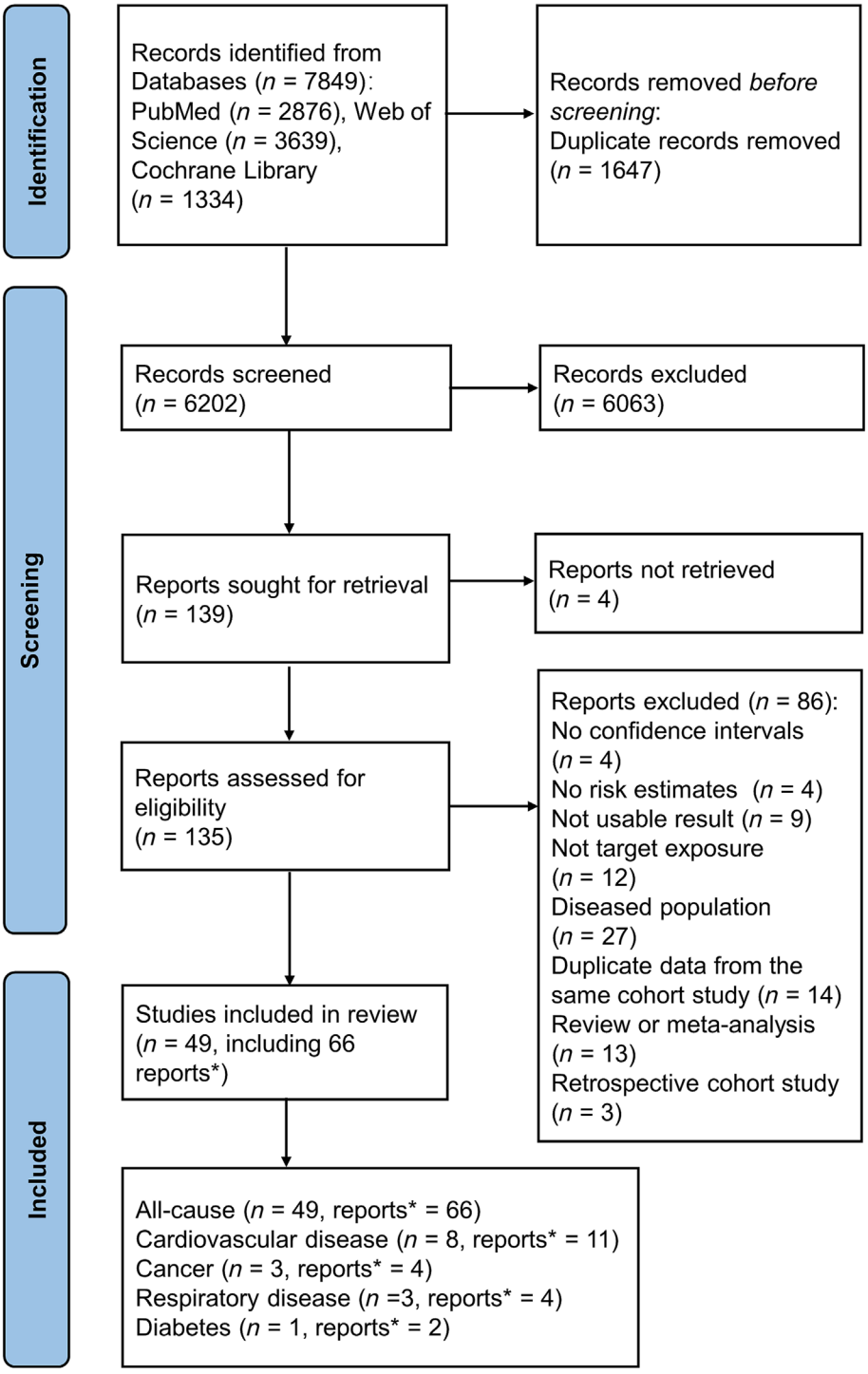

Figure 1 Flow chart of study selection. *If studies reported data separately by sex, they would be analysed as two separate reports.

Publication bias

The Egger test indicated no significant publication bias in the primary analysis for all-cause mortality (P = 0.400) and CVD mortality (P = 0.193).

Evidence level rated by the Grading of Recommendation, Assessment, Development and Evaluation approach

According to the GRADE protocol, as shown in *Table S10*, the evidence level of the result of all-cause mortality was at a moderate level. The results of cancer mortality and respiratory disease mortality were at a low level. The results of CVD mortality and diabetes mortality were at a very low level.

Subgroup analysis and meta-regression

The results of subgroup analysis and meta-regression for all-cause and CVD mortality risks were summarized in *Tables S11* and *S12*. For all-cause mortality, between-study heterogeneity was found among studies stratified by country of study ($P < 0.001$), follow-up duration (P = 0.062), indicators of muscle mass (P = 0.062), hypertension adjustment (P = 0.080) and CVD adjustment (P = 0.001). Moreover, the muscle wasting-related all-cause mortality risk was lower in studies with longer follow-up duration (*Figure 4A*). We also found that muscle wasting, regardless of muscle strength, was significantly associated with elevated all-cause mortality risk. The pooled RRs for mortality risk were 1.54 (95% CI, 1.11 to 2.08, P = 0.007), 1.17 (95% CI, 1.00 to 1.38, P = 0.045) and 1.19 (95% CI, 1.10 to 1.28, $P < 0.001$) for participants with weak, intermediate and strong muscle strength, respectively. Additionally, there was a higher risk of all-cause mortality in studies with participants aged 65 years or older (1.47, 95% CI, 1.32 to 1.63, $P < 0.001$) than that of studies with participants aged between 45 and 65 years (1.11, 95% CI, 1.03 to 1.19, P = 0.006). Similarly, there was a higher risk of all-cause mortality in studies assessed muscle wasting by DXA (1.52, 95% CI, 1.27 to 1.80, $P < 0.001$) than that in studies assessed by BIA (1.16, 95% CI, 1.08 to 1.25, $P < 0.001$).

For CVD mortality, between-study heterogeneity was found when stratified studies by duration of follow-up (P = 0.091), hypertension adjustment (P = 0.086) and diabetes adjustment (P = 0.086). The pooled RRs of muscle wasting-associated CVD mortality risks were 7.62 (95% CI, 4.57 to 12.7, $P < 0.001$), 1.46 (95% CI, 1.19 to 1.79, $P < 0.001$) and 1.02 (95% CI, 0.88 to 1.16) for participants with a follow-up of <5, 5–10 and ≥10 years, respectively (*Figure 4B*). A significant increased risk of CVD mortality was only observed in males (1.52, 95% CI, 1.04 to 2.23) but not in females (1.01, 95% CI, 0.62 to 1.66).

Table 1 Summary characteristics of included studies

Characteristics	No. of studies (no. of participants)
Total no. of studies	49 (all-cause mortality: 49, cardiovascular disease mortality: 8, cancer mortality: 3, respiratory disease mortality: 3, diabetes mortality: 1)
Total no. of participants (total no. of deaths)	878 349 (61 055)
Median (range), no. of participants	1358 (191–405 980)
Median (range), follow-up (years)	9.2 (2.5–32)
Median (range), female%	53.4 (0–100)
Median (range), age (years)	73.5 (38.7–93.5)
Nationality	
European	16
Asian	11
American	15
Others	7

Sensitivity analysis

Regarding the robustness of overall effect sizes, we performed LOOM for sensitivity analysis. Sensitivity analysis showed that the exclusion of any single study at a time did not significantly alter the values of estimates (*Figure S1*). The results also suggested that 25[16,19,37,38,42,45,49,51,53,55–59,61,63,66,67,70–72,74,76,77,80] (out of all 49) and 2[49,55] (out of

Table 2 Associations of muscle wasting with all-cause and cause-specific mortality

Mortality	Reports	RR (95% CI)	$P_{(association)}$	Heterogeneity		
				I^2 (%)	$P_{(heterogeneity)}$	tau^2
All-cause	66	1.36 (1.28 to 1.44)	**<0.001**	94.9	**<0.001**	0.036
CVD	11	1.29 (1.05 to 1.58)	**0.014**	88.1	**<0.001**	0.091
Cancer	4	1.14 (1.02 to 1.27)	**0.020**	38.7	0.180	0.005
Respiratory disease	4	1.36 (1.11 to 1.67)	**0.003**	62.8	**0.045**	0.027
Diabetes	2	1.14 (0.67 to 1.92)	0.630	60.5	0.112	0.096

Note: P^1 value for RR; P^2 value for heterogeneity between studies; significant P-values are highlighted in bold prints.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.

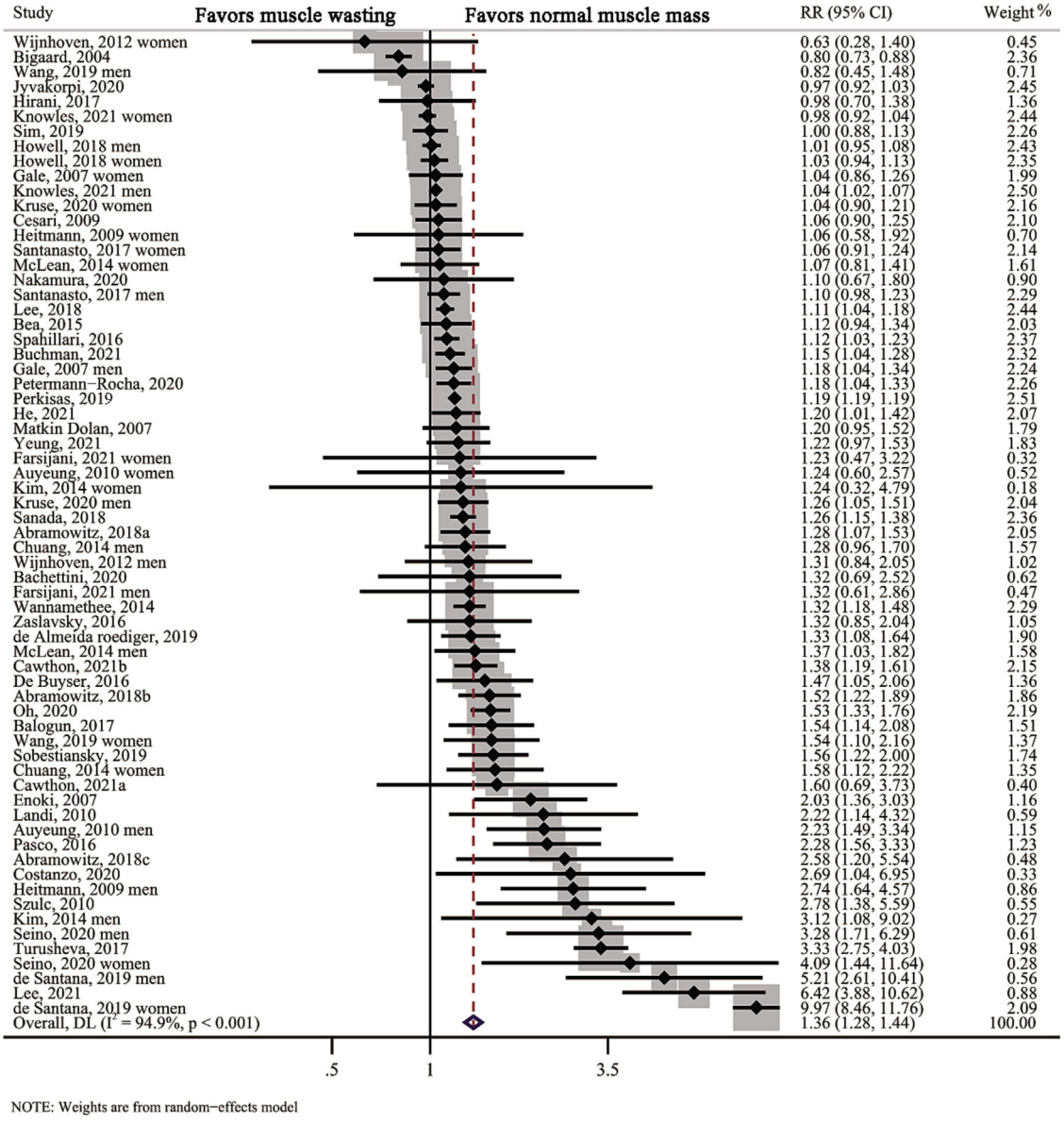

Figure 2 The forest plot of muscle wasting (lowest vs. normal category of muscle mass) and the risk of all-cause mortality by pooling data from 49 studies. CI, confidence interval; RR, relative risk.

all 8) studies contributed more to the between-study heterogeneities in the primary meta-analysis of all-cause mortality and CVD mortality, respectively (*Table S13*). The heterogeneities significantly disappeared when we excluded 28 studies and 2 studies in the results of all-cause mortality (I^2 = 32.3%, P = 0.079) and CVD mortality (I^2 = 37.5%, P = 0.130), respectively (*Table S13*). Nevertheless, after excluding those studies, the associations were not substantially altered for the results of both all-cause mortality (1.31, 95% CI, 1.23 to 1.39, $P < 0.001$) and CVD mortality (1.18, 95% CI, 1.07 to 1.30, P = 0.007) (*Table S13*).

Dose–response analysis

Out of all 49 studies, 8[38,52,53,60–62,78,79] studies were eligible for the muscle mass and all-cause mortality risk dose–response relationship analysis. The result of the likelihood

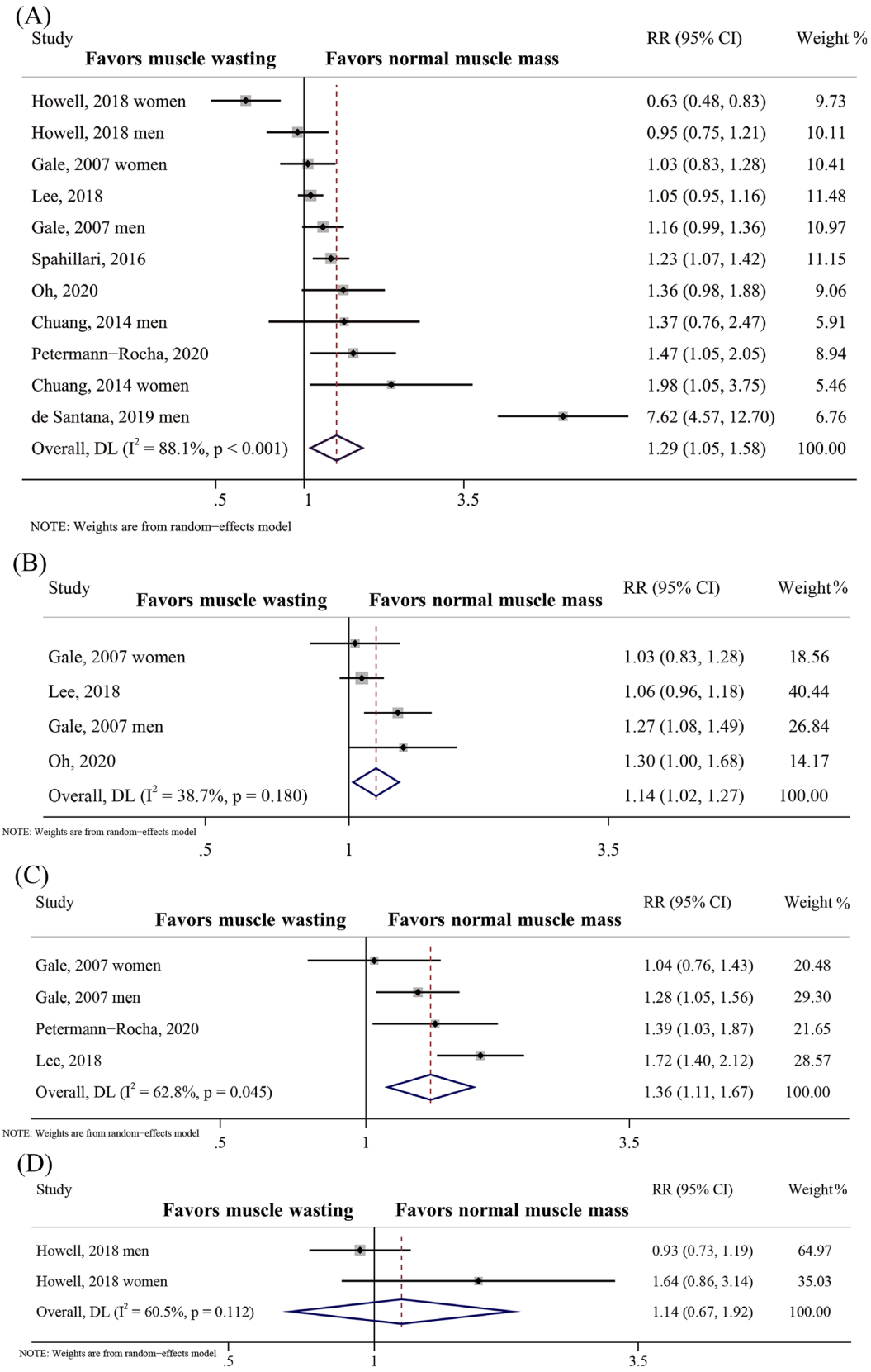

Figure 3 The forest plot of muscle wasting (lowest vs. normal category of muscle mass) and the risk of cardiovascular disease (A), cancer (B), respiratory disease (C) and diabetes (D) mortality. CI, confidence interval; RR, relative risk.

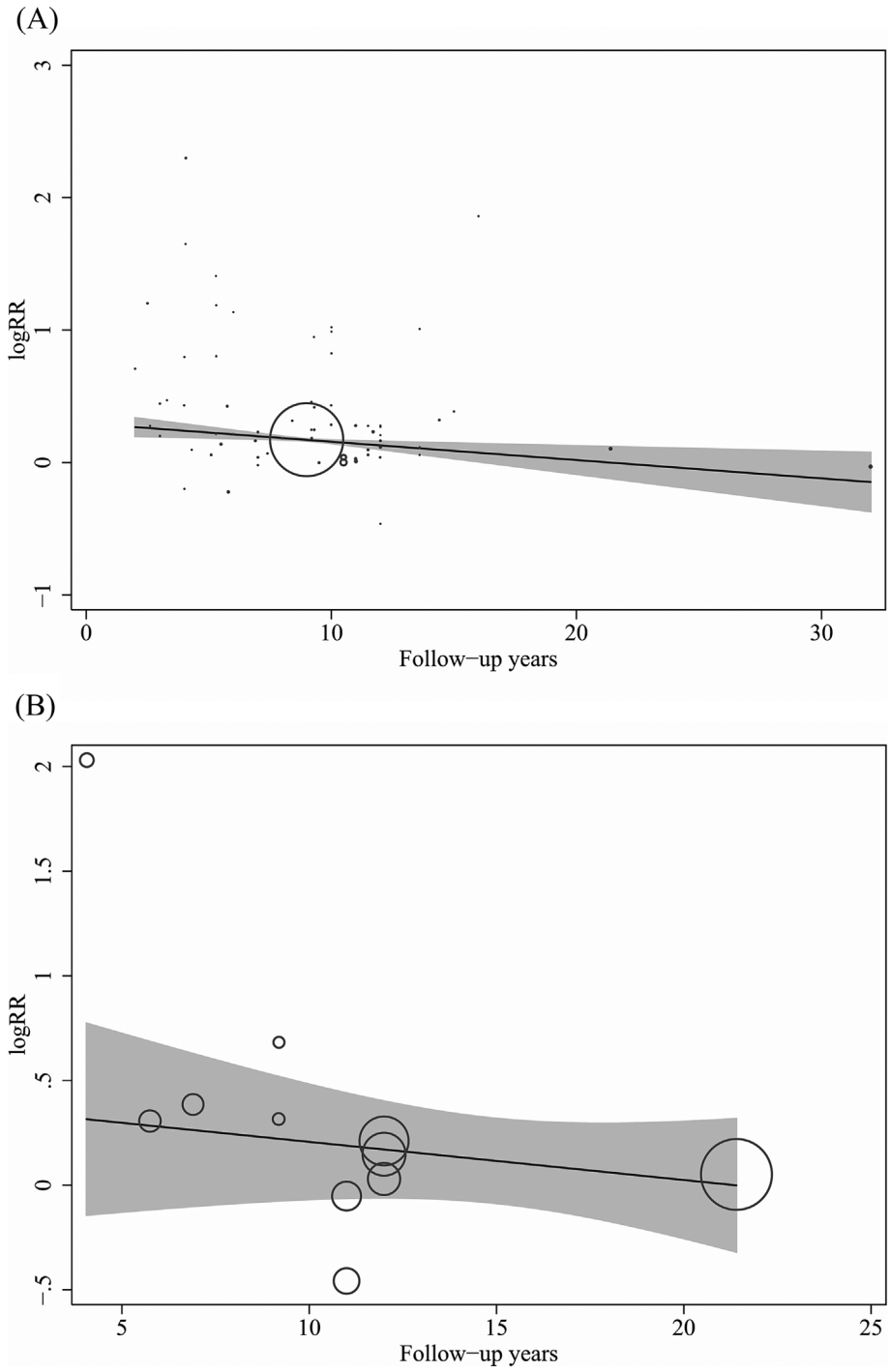

Figure 4 Meta-regression model for the effect of muscle wasting on the risk of all-cause (A) and cardiovascular disease (B) mortality adjusted for follow-up years of study. RR, relative risk.

ratio test to select the model of dose–response analysis was shown in *Table S14*. A significant inverse association between MAMC and all-cause mortality risk was found in the non-linear dose–response analysis ($P_{\text{non-linearity}} < 0.01$, 4 studies; *Figure 5A*). A nearly U-shaped association was found between lean body mass and all-cause mortality risk, with the lowest risk of all-cause mortality at a lean body mass around 36 kg ($P_{\text{non-linearity}} < 0.01$, 2 studies; *Figure 5B*). No significant association was found between FFMI-predicted muscle mass and all-cause mortality ($P_{\text{non-linearity}} = 0.77$, 4 studies; *Figure 5C*).

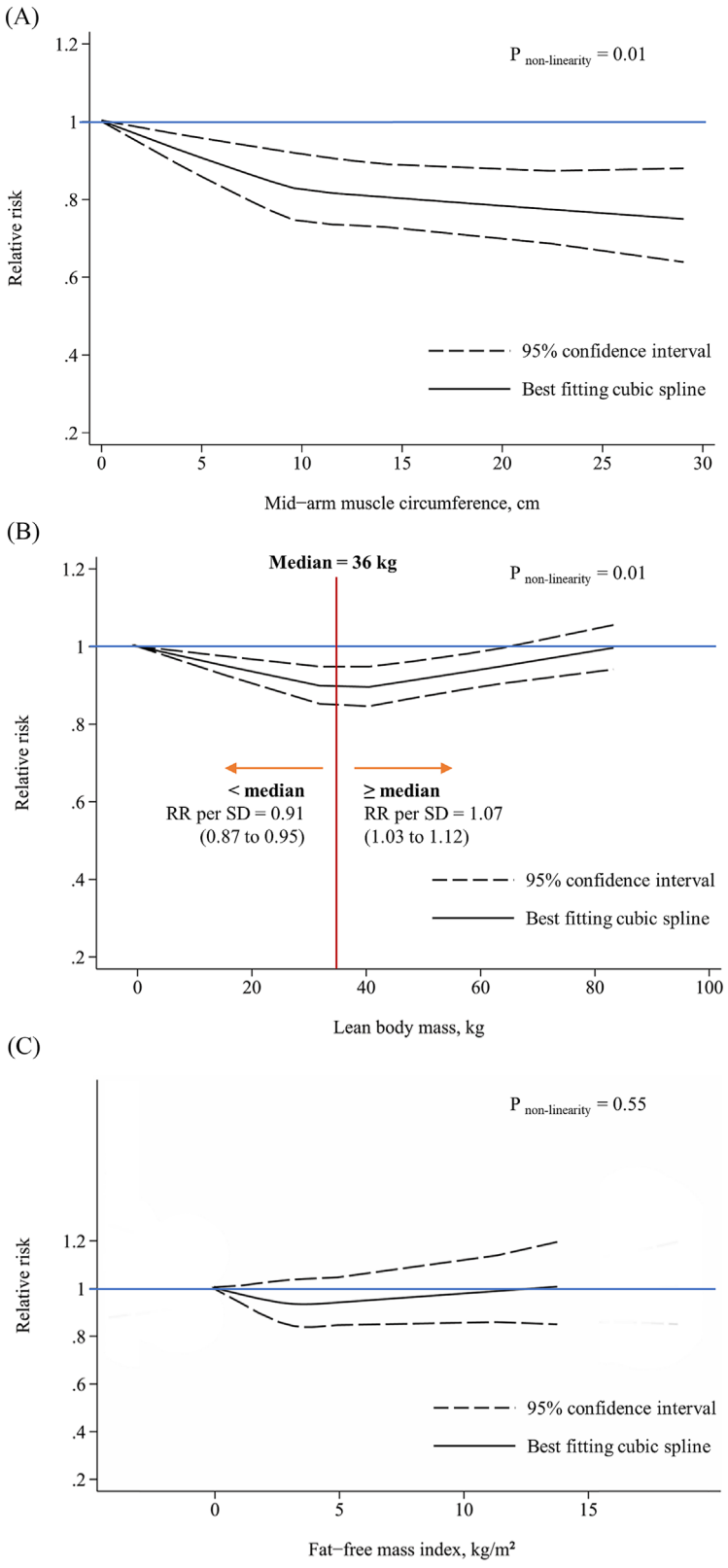

Figure 5 Associations of mid-arm muscle circumference (A), lean body mass (B) and fat-free mass index (C) with all-cause mortality. Reference point is the lowest value for each of mid-arm muscle circumference, lean body mass and fat-free mass index, with knots placed at 10th, 50th and 90th centiles of each mid-arm muscle circumference, lean body mass and fat-free mass index distribution. Standard deviation (SD) for lean body mass is 28.8 kg. Solid black line indicates the best fitting cubic spline; dashed lines represent 95% confidence intervals. RR, relative risk.

Discussion

Principal findings

Our study demonstrated that muscle wasting was associated with 36%, 29%, 14% and 29% increased risk of all-cause (moderate certainty), CVD (very low certainty), cancer (low certainty) and respiratory disease mortality (very low certainty), respectively, in the general population. We also found that the association remained significant regardless of muscle strength, which indicated that muscle wasting, probably independent of muscle strength, contributed to elevated all-cause mortality risk. Moreover, the risk of all-cause mortality related to muscle wasting was higher in the elderly than that in the younger populations. Muscle wasting assessed by DXA might be a more sensitive predictor of mortality. Dose–response analysis showed a significant inverse non-linear association between MAMC and all-cause mortality risk. Additionally, subgroup analysis and meta-regression revealed that the muscle wasting-associated all-cause and CVD mortality risks were lower in studies with longer follow-ups than those with shorter follow-ups.

Comparison with other studies

This is the first meta-analysis to comprehensively evaluate the relationship between muscle wasting and mortality risk in the general population, highlighting muscle wasting as a critical public health issue. Previous meta-analyses were targeted at patients awaiting or undergoing liver transplantation,[81] and patients with tumours[15] or post-operative patients.[82] However, the majority of them did not focus on the general population. A recent meta-analysis by Lee et al.[83] has involved nine studies and evaluated the relationship between lower lean mass and mortality in elderly populations with different health conditions. They found a 21% higher risk of all-cause mortality in response to reduced lean mass, which is lower than the counterpart values in our study. Another pooled analysis of nine observational studies conducted by de Santana et al.[84] reported that SMI was associated with higher mortality risk in older adults (standardized mean difference [SMD] for SMI −0.18, 95% CI, −0.23 to −0.12), which is consistent with our findings.

There is an ongoing debate about the contribution of a single muscle quality measurement to mortality risk. Our finding was in line with the results of de Santana et al.,[84] which found that the association between low muscle mass and mortality could not be fully explained by differences in muscle strength. Some studies have found that low muscle strength, rather than low muscle mass, contributed to high risks of mortality in patients with critical illnesses.[85,86] Nevertheless, some others found that both low muscle strength and low muscle mass were associated with higher mortality risk in patients with less serious diseases[87,88] and healthy populations.[89–91] It should be noted that muscle wasting is different from cachexia. Cachexia, characterized by loss of muscle with or without loss of fat mass and inflammation, is commonly observed in patients with cancer or end-stage diseases.[92] Consequently, we postulated that age-related muscle wasting but not disease-related muscle wasting, independent of muscle strength, was associated with all-cause mortality in the general population. Further studies are required to clarify the relationship between muscle mass, muscle strength and mortality under different physical conditions to confirm this postulation.

Muscle mass is usually evaluated by several measurements, including SMI, FFMI and ALM, measured with a wide range of techniques (DXA, BIA and others).[93] Of them, which measurement can predict mortality best has always been a topic of concern. Our findings suggested that muscle wasting assessed by DXA might be a more sensitive predictor of mortality. However, no dose–response relationship was found between FFMI and all-cause mortality risk. It needs to be noted that the FFMI was assessed by BIA in three[53,78,79] of four[38,53,78,79] studies included in the dose–response analysis. The BIA equipment is used to derive the estimated value of muscle mass by correcting the reference lean body weight predicted by DXA according to the whole-body conductivity. Moreover, the estimated value of muscle mass varies with different instrument brands and reference populations. Hence, more studies using DXA or more reliable methods to assess FFMI are required. Furthermore, a significant inverse dose–response relationship was found between MAMC and all-cause mortality risk in our study, which is consistent with previous studies.[94,95] The MAMC is often used to determine subcutaneous muscle mass of the mid-arm. We suggest that the MAMC could be a simple measure of muscle mass to predict mortality risk. Our results also showed a nearly U-shaped dose–response relationship between lean body mass and all-cause mortality risk, with either lower or higher levels of lean body mass contributing to an increased risk of all-cause mortality. This observation was largely consistent with a recent study of 356 590 UK Biobank participants, which demonstrated a J-shaped association between ASM and all-cause mortality risk.[58] Lean body mass is an absolute muscle mass without height or weight adjustment. Higher lean body mass might be associated with higher body mass and fat mass.[96] Notably, higher fat mass is positively related to larger mortality risk. Thus, the increased risk of mortality in the lower lean body mass range (<36 kg) could be attributed to the high mortality risk of muscle wasting, whereas the increase in mortality risk in the higher lean body mass range (≥36 kg) could be due to the high mortality risk associated with fat mass.

Additionally, we found that the risks of all-cause and CVD mortality were remarkably lower reported by studies

with longer follow-ups. A meta-analysis of sarcopenia and all-cause mortality risk association also found a lower all-cause mortality risk in studies with a duration of 5 years or more.[97] One possible reason might be that studies with a shorter duration of follow-up were more likely to include the elderly population. As our meta-analysis has found, the risk of all-cause mortality was higher in the elderly than that in the younger populations. In our present study, participants were older than 75 years in 7[18,20,50,60,73,76,77] of 11[18,20,38,39,49,50,60,64,73,76,77] studies followed for <5 years, whereas participants were older than 75 years only in 5[46,48,69,70,74] of 22[16,19,40,41,43,46–48,51,53,55,56,58,61,66,69,70,74,75,78–80] studies followed for 10 years or longer. Therefore, our study could suggest that the length of follow-up, which might be influenced by the age of participants, was a potential confounder in the muscle wasting and all-cause mortality risk association. Besides, previous studies often focused on the elderly or diseased populations, thereby our results also provided insights into the relationship between muscle wasting and mortality among the younger populations. Taking the lower risk of mortality among younger people into account, we proposed that early diagnosis and intervention of muscle wasting at an early age might have broader and more substantial public health benefits.

Mechanisms

Muscle wasting is triggered by an imbalance of skeletal muscle protein synthesis and degradation, mainly due to decreased mitochondrial function, increased oxidative stress and/or inflammation.[98,99] With the aging process, the levels of testosterone, insulin-like growth factor-1 (IGF-1), and growth hormone decrease, accompanied by inactivity and malnutrition, which may accelerate the decrease in muscle mass.[100–102] Besides, poor oral conditions during aging, such as dysphagia and masticatory dysfunction, might be directly linked to malnutrition and ultimately lead to muscle wasting.[103] It was found that protein synthesis during muscle wasting was reduced by inhibiting the activity of the phosphoinositide 3-kinase (PI_3K)–AKT–mammalian target of rapamycin (mTOR) signalling pathway.[104] At the same time, protein degradation could be activated by the ubiquitin-proteasome system (UPS)[105] and autophagy.[106] Exercise training has been proven to be the most feasible therapy for muscle wasting.[107] Exercise can increase muscle mass by increasing protein synthesis, inhibiting degradation, increasing insulin sensitivity and reducing the response to inflammation and oxidative stress.[108] Resistance training may be more effective for increasing SMM, and muscle mass can be equally beneficial from both low- and high-load resistance training.[109,110] This is noteworthy because individuals with muscle wasting may have physical limitations to engage in high-load resistance training because of aging or diseases. Besides, older populations have lower muscle protein synthesis rates and are more likely to lack exercise as compared with younger populations, which may also play a role in age-related muscle wasting.[111] In addition, nutritional therapy has also been identified as a protective factor against muscle wasting, including excess protein intake,[112,113] vitamin and mineral supplements and omega-3 polyunsaturated fatty acids supplements.[114,115] The combination of exercise and nutritional supplements might be a promising strategy to prevent and treat muscle wasting.

Many lines of evidence suggested that muscle wasting could cause a variety of comorbidities. Such medical conditions, in turn, can lead to rapid muscle wasting.[116,117] Then, a vicious circle may develop, leading to more severe muscle wasting, worse health and ultimately an increased risk of mortality. Moreover, many myokines, such as irisin, myostatin and interleukin-6 (IL-6), which are released by skeletal muscle, have been described as protecting muscle mass, coordinating inflammatory response, regulating the metabolism of almost all organs in the body and regulating vascular function.[118,119] Therefore, when suffering from muscle wasting, these endocrine functions of myokines will also be affected, eventually resulting in disease occurrence and/or death.

The presence of many chronic diseases can promote the development of muscle wasting. Below may be the main explanations for muscle wasting-associated disease-specific mortality risk. In CVD, malnutrition, physical inactivity, decreased skeletal muscle growth factor and increased oxidative damage caused by decreased cardiac output and systemic congestion further exacerbate muscle wasting.[120] Cancer could activate the production of tumour necrosis factor-alpha (TNF-α), IL-6 and other cytokines, resulting in increased protein catabolism and decreased protein anabolism, which accelerates muscle wasting.[121] In respiratory diseases, chronic or intermittent hypoxaemia may affect mitochondrial function, resulting in oxidative stress, reduced energy utilization and protein synthesis, thereby leading to excessive muscle loss.[122] These factors work together to aggravate adverse outcomes of muscle wasting and the above diseases, which could lead to increased mortality from those diseases. Observational studies have demonstrated that accelerated loss of muscle mass was found in diabetes patients.[123,124] It was suggested that dysglycaemia and insulin resistance are important risk factors for advanced muscle wasting in diabetes.[125] However, our review found no relation between muscle wasting and diabetes mortality with only one study was analysed, so the relationship between muscle wasting and diabetes mortality needs to be further investigated by future research.

Strengths and limitations of this study

This study has several strengths. First, we included studies conducted in different countries and populations and included various muscle mass indicators. Thus, we could obtain a more powerful and comprehensive conclusion than any single study. Second, all included studies were of a prospective design, which could minimize the possibility of selection bias and recall bias. Finally, our results provided new insight into the association between muscle wasting and mortality in the general population, especially the younger populations.

However, a few limitations must be noted. First, evident between-study heterogeneities were found. According to the results of subgroup analysis and meta-regression, the heterogeneities might be attributed to the differences in study location, duration of follow-up and indicators of muscle mass. Second, in most of the included studies, muscle strength was not adjusted as a confounder in the fully adjusted model. Thus, we could not rule out the possibility of residual confounding introduced by muscle strength. Third, different methods of muscle mass assessment were recruited in this present meta-analysis; thus, measurement errors in different assessments are inevitable. Finally, we could not clarify the association of muscle loss with mortality under certain circumstances, such as caloric restriction.

Conclusions, policy implications and future research

Muscle wasting was significantly associated with higher mortality risks of all causes, CVD, cancer and respiratory disease in the general population. There was a significant inverse association between MAMC and all-cause mortality risk and a nearly U-shaped association between lean body mass and all-cause mortality risk.

Our findings highlighted muscle wasting as an important public health issue, as the huge death burden caused by muscle wasting in the general population. Paying attention to the early detection and intervention of muscle wasting might contribute to the improvement of life expectancy and quality of life, and substantial savings in healthcare costs. Therefore, more research should be carried out to explore the most effective strategy to prevent and treat muscle wasting at different ages and clinical conditions.

Acknowledgements

We are grateful to Associate Prof. Dr. Xing-Jie Hao (Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology) for his assistance in the data analysis. The authors certify that they comply with the ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[126]

Conflict of interest statement

All the authors declare that they have no conflict of interest.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

References

1. Mayhew AJ, Amog K, Phillips S, Parise G, McNicholas PD, de Souza RJ, et al. The prevalence of sarcopenia in community-dwelling older adults, an exploration of differences between studies and within definitions: a systematic review and meta-analyses. *Age Ageing* 2019;**48**: 48–56.
2. Anker SD, Coats AJS, Morley JE, Rosano G, Bernabei R, von Haehling S, et al. Muscle wasting disease: a proposal for a new disease classification. *J Cachexia Sarcopenia Muscle* 2014;**5**:1–3.
3. Palus S, von Haehling S, Springer J. Muscle wasting: an overview of recent developments in basic research. *J Cachexia Sarcopenia Muscle* 2014;**5**: 193–198.
4. Duan KP, Gao X, Zhu DM. The clinical relevance and mechanism of skeletal muscle wasting. *Clin Nutr* 2021;**40**:27–37.
5. Bernetti A, Agostini F, Alviti F, Giordan N, Martella F, Santilli V, et al. New viscoelastic hydrogel Hymovis MO.RE. single intra-articular injection for the treatment of knee osteoarthritis in sportsmen: safety and efficacy study results. *Front Pharmacol* 2021;**12**:673988.
6. Gomarasca M, Banfi G, Lombardi G. Myokines: the endocrine coupling of skeletal muscle and bone. *Adv Clin Chem* 2020;**94**:155–218.
7. Xu L, Zhang J, Shen S, Hong X, Zeng X, Yang Y, et al. Association between body composition and frailty in elder inpatients. *Clin Interv Aging* 2020;**15**:313–320.
8. Yeung SSY, Reijnierse EM, Pham VK, Trappenburg MC, Lim WK, Meskers CGM, et al. Sarcopenia and its association with falls and fractures in older adults: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* 2019;**10**: 485–500.
9. Alley DE, Koster A, Mackey D, Cawthon P, Ferrucci L, Simonsick EM, et al. Hospitalization and change in body composition and strength in a population-based cohort of older persons. *J Am Geriatr Soc* 2010;**58**:2085–2091.
10. Prado CM, Purcell SA, Alish C, Pereira SL, Deutz NE, Heyland DK, et al. Implications of low muscle mass across the continuum of care: a narrative review. *Ann Med* 2018;**50**:675–693.

11. Kim G, Lee SE, Jun JE, Lee YB, Ahn J, Bae JC, et al. Increase in relative skeletal muscle mass over time and its inverse association with metabolic syndrome development: a 7-year retrospective cohort study. *Cardiovasc Diabetol* 2018; **17**:23.
12. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. *JAMA* 2013;**310**:1591–1600.
13. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc* 2004;**52**:80–85.
14. Xu J, Wan CS, Ktoris K, Reijnierse EM, Maier AB. Sarcopenia is associated with mortality in adults: a systematic review and meta-analysis. *Gerontology* 2021;**68**: 1–16.
15. Chang KV, Chen JD, Wu WT, Huang KC, Hsu CT, Han DS. Association between loss of skeletal muscle mass and mortality and tumor recurrence in hepatocellular carcinoma: a systematic review and meta-analysis. *Liver Cancer* 2018;**7**: 90–103.
16. Lee C, Kim HJ, Chang TI, Kang EW, Joo YS, Kim HW, et al. Synergic association of diabetes mellitus and chronic kidney disease with muscle loss and cachexia: results of a 16-year longitudinal follow-up of a community-based prospective cohort study. *Aging* 2021;**13**:21941–21961.
17. Buchman AS, Leurgans SE, Wang T, Schnaider-Beeri M, Agarwal P, Dawe RJ, et al. Motor function is the primary driver of the associations of sarcopenia and physical frailty with adverse health outcomes in community-dwelling older adults. *PLoS ONE* 2021;**16**:e0245680.
18. Yeung SSY, Chan JHY, Chan RSM, Sham A, Ho SC, Woo J. Predictive value of the GLIM criteria in Chinese community-dwelling and institutionalized older adults aged 70 years and over. *J Nutr Health Aging* 2021;**25**:645–652.
19. Farsijani S, Xue L, Boudreau RM, Santanasto AJ, Kritchevsky SB, Newman AB. Body composition by computed tomography vs dual-energy X-ray absorptiometry: long-term prediction of all-cause mortality in the Health ABC cohort. *J Gerontol A Biol Sci Med Sci* 2021;**76**: 2256–2264.
20. Cawthon PM, Blackwell T, Cummings SR, Orwoll ES, Duchowny KA, Kado DM, et al. Muscle mass assessed by the D3-creatine dilution method and incident self-reported disability and mortality in a prospective observational study of community-dwelling older men. *J Gerontol A Biol Sci Med Sci* 2021;**76**: 123–130.
21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *J Clin Epidemiol* 2021;**134**: 178–189.
22. Fazzini B, Markl T, Costas C, Blobner M, Schaller SJ, Prowle J, et al. The rate and assessment of muscle wasting during critical illness: a systematic review and meta-analysis. *Crit Care* 2023;**27**:2.
23. Ni HJ, Hsu TF, Chen LK, Chou HL, Tung HH, Chow LH, et al. Effects of exercise programs in older adults with muscle wasting: a systematic review and meta-analysis effects of exercise programs in muscle wasting. *Arch Gerontol Geriatr* 2022;**99**:104605.
24. Wang PY, Wang SD, Li X, Lin GH, Ma Y, Xiao RX, et al. Skeletal muscle wasting during neoadjuvant therapy as a prognosticator in patients with esophageal and esophagogastric junction cancer: a systematic review and meta-analysis. *Int J Surg* 2022;**97**:106206.
25. Galli A, Colombo M, Carrara G, Lira Luce F, Paesano PL, Giordano L, et al. Low skeletal muscle mass as predictor of postoperative complications and decreased overall survival in locally advanced head and neck squamous cell carcinoma: the role of ultrasound of rectus femoris muscle. *Eur Arch Otorhinolaryngol* 2020;**277**: 3489–3502.
26. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol* 2014;**14**:45.
27. Goldet G, Howick J. Understanding GRADE: an introduction. *J Evid Based Med* 2013;**6**:50–54.
28. Higgins JPT. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Available from: https://www.cochrane-handbook.org/
29. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;**280**:1690–1691.
30. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata J* 2006;**6**:40–57.
31. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003;**327**:557–560.
32. Alley DE, Shardell MD, Peters KW, McLean RR, Dam TT, Kenny AM, et al. Grip strength cutpoints for the identification of clinically relevant weakness. *J Gerontol A Biol Sci Med Sci* 2014;**69**:559–566.
33. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997;**315**:629–634.
34. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;**56**:455–463.
35. Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008;**27**: 954–970.
36. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol* 2012;**175**:66–73.
37. Abramowitz MK, Hall CB, Amodu A, Sharma D, Androga L, Hawkins M. Muscle mass, BMI, and mortality among adults in the United States: a population-based cohort study. *PLoS ONE* 2018;**13**:e0194697.
38. Auyeung TW, Lee JSW, Leung J, Kwok T, Leung PC, Woo J. Survival in older men may benefit from being slightly overweight and centrally obese—a 5-year follow-up study in 4,000 older adults using DXA. *J Gerontol A Biol Sci Med* 2010;**65**: 99–104.
39. Bachettini NP, Bielemann RM, Barbosa-Silva TG, Menezes AMB, Tomasi E, Gonzalez MC. Sarcopenia as a mortality predictor in community-dwelling older adults: a comparison of the diagnostic criteria of the European Working Group on Sarcopenia in Older People. *Eur J Clin Nutr* 2020;**74**:573–580.
40. Balogun S, Winzenberg T, Wills K, Scott D, Jones G, Aitken D, et al. Prospective associations of low muscle mass and function with 10-year falls risk, incident fracture and mortality in community-dwelling older adults. *Australas J Ageing* 2017;**36**: 23–848.
41. Bea JW, Thomson CA, Wertheim BC, Nicholas JS, Ernst KC, Hu C, et al. Risk of mortality according to body mass index and body composition among postmenopausal women. *Am J Epidemiol* 2015; **182**:585–596.
42. Bigaard J, Frederiksen K, Tjonneland A, Thomsen BL, Overvad K, Heitmann BL, et al. Body fat and fat-free mass and all-cause mortality. *Obes Res* 2004;**12**: 1042–1049.
43. Cawthon PM, Harrison SL, Rogers-Soeder T, Webber K, Jonnalagadda S, Pereira SL, et al. Body weight, BMI, percent fat and associations with mortality and incident mobility limitation in older men. *Geriatrics* 2021;**6**:53.
44. Cesari M, Pahor M, Lauretani F, Zamboni V, Bandinelli S, Bernabei R, et al. Skeletal muscle and mortality results from the InCHIANTI Study. *J Gerontol A Biol Sci Med Sci* 2009;**64**:377–384.
45. Chuang SY, Chang HY, Lee MS, Chen RC-Y, Pan WH. Skeletal muscle mass and risk of death in an elderly population. *Nutr Metab Cardiovasc Dis* 2014;**24**:784–791.
46. Costanzo L, De Vincentis A, Di Iorio A, Bandinelli S, Ferrucci L, Antonelli Incalzi R, et al. Impact of low muscle mass and low muscle strength according to EWGSOP2 and EWGSOP1 in community-dwelling older people. *J Gerontol A Biol Sci Med Sci* 2020;**75**: 1324–1330.
47. de Almeida Roediger M, de Fatima Nunes Marucci M, Quintiliano Scarpelli Dourado DA, de Oliveira C, Licio Ferreira Santos J, de Oliveira Duarte YA. Body composition changes and 10-year mortality risk in older Brazilian adults: analysis of prospective data from the SABE study. *J Nutr Health Aging* 2019;**23**:51–59.

48. De Buyser SL, Petrovic M, Taes YE, Toye KRC, Kaufman J-M, Lapauw B, et al. Validation of the FNIH sarcopenia criteria and SOF frailty index as predictors of long-term mortality in ambulatory older men. *Age Ageing* 2016;**45**:603–609.
49. de Santana FM, Domiciano DS, Gonçalves MA, Machado LG, Figueiredo CP, Lopes JB, et al. Association of appendicular lean mass, and subcutaneous and visceral adipose tissue with mortality in older Brazilians: the São Paulo Ageing & Health Study. *J Bone Miner Res* 2019;**34**: 1264–1274.
50. Enoki H, Kuzuya M, Masuda Y, Hirakawa Y, Iwata M, Hasegawa J, et al. Anthropometric measurements of mid-upper arm as a mortality predictor for community-dwelling Japanese elderly: the Nagoya Longitudinal Study of Frail Elderly (NLS-FE). *Clin Nutr* 2007;**26**: 597–604.
51. Gale CR, Martyn CN, Cooper C, Sayer AA. Grip strength, body composition, and mortality. *Int J Epidemiol* 2007;**36**: 228–235.
52. He L, Yang N, Wang J, Huang J, Li W, Xu L, et al. Mid-arm muscle and subcutaneous fat associated with all-cause mortality independent of BMI: a prospective cohort study. *Obesity (Silver Spring)* 2021;**29**: 1203–1214.
53. Heitmann BL, Hills AP, Frederiksen P, Ward LC. Obesity, leanness, and mortality: effect modification by physical activity in men and women. *Obesity* 2009;**17**: 136–142.
54. Hirani V, Naganathan V, Blyth F, Le Couteur DG, Seibel MJ, Waite LM, et al. Longitudinal associations between body composition, sarcopenic obesity and outcomes of frailty, disability, institutionalisation and mortality in community-dwelling older men: the Concord Health and Ageing in Men Project. *Age Ageing* 2017;**46**:413–420.
55. Howell CR, Mehta T, Ejima K, Ness KK, Cherrington A, Fontaine KR. Body composition and mortality in Mexican American adults: results from the National Health and Nutrition Examination Survey. *Obesity* 2018;**26**:1372–1380.
56. Jyvakorpi SK, Urtamo A, Kivimaki M, Salomaa V, Strandberg TE. Association of midlife body composition with old-age health-related quality of life, mortality, and reaching 90 years of age: a 32-year follow-up of a male cohort. *Am J Clin Nutr* 2020;**112**:1287–1294.
57. Kim JH, Lim S, Choi SH, Kim KM, Yoon JW, Kim KW, et al. Sarcopenia: an independent predictor of mortality in community-dwelling older Korean men. *J Gerontol A Biol Sci Med Sci* 2014;**69**: 1244–1252.
58. Knowles R, Carter J, Jebb SA, Bennett D, Lewington S, Piernas C. Associations of skeletal muscle mass and fat mass with incident cardiovascular disease and all-cause mortality: a prospective cohort study of UK Biobank participants. *J Am Heart Assoc* 2021;**10**:e019337.
59. Kruse NT, Buzkova P, Barzilay JI, Valderrabano RJ, Robbins JA, Fink HA, et al. Association of skeletal muscle mass, kidney disease and mortality in older men and women: the Cardiovascular Health Study. *Aging* 2020;**12**:21023–21036.
60. Landi F, Russo A, Liperoti R, Pahor M, Tosato M, Capoluongo E, et al. Midarm muscle circumference, physical performance and mortality: results from the aging and longevity study in the Sirente geographic area (ilSIRENTE study). *Clin Nutr* 2010;**29**:441–447.
61. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. *BMJ-Brit Med J* 2018;362.
62. Matkin Dolan C, Kraemer H, Browner W, Ensrud K, Kelsey JL. Associations between body composition, anthropometry, and mortality in women aged 65 years and older. *Am J Public Health* 2007;**97**: 913–918.
63. McLean RR, Shardell MD, Alley DE, Cawthon PM, Fragala MS, Harris TB, et al. Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the Foundation for the National Institutes of Health (FNIH) sarcopenia project. *J Gerontol A Biol Sci Med Sci* 2014;**69**:576–583.
64. Nakamura K, Yoshida D, Honda T, Hata J, Shibata M, Hirakawa Y, et al. Prevalence and mortality of sarcopenia in a community-dwelling older Japanese population: the Hisayama Study. *J Epidemiol* 2021;**31**:320–327.
65. Oh H, Kwak S-Y, Jo G, Lee J, Park D, Lee DH, et al. Adiposity and mortality in Korean adults: a population-based prospective cohort study. *Am J Clin Nutr* 2021;**113**:142–153.
66. Pasco JA, Mohebbi M, Holloway KL, Brennan-Olsen SL, Hyde NK, Kotowicz MA. Musculoskeletal decline and mortality: prospective data from the Geelong Osteoporosis Study. *J Cachexia Sarcopenia Muscle* 2017;**8**:482–489.
67. Perkisas S, De Cock AM, Vandewoude M, Verhoeven V. Prevalence of sarcopenia and 9-year mortality in nursing home residents. *Aging Clin Exp Res* 2019;**31**: 951–959.
68. Petermann-Rocha F, Ho FK, Welsh P, Mackay D, Brown R, Gill JMR, et al. Physical capability markers used to define sarcopenia and their association with cardiovascular and respiratory outcomes and all-cause mortality: a prospective study from UK Biobank. *Maturitas* 2020;**138**: 69–75.
69. Sanada K, Chen R, Willcox B, Ohara T, Wen A, Takenaka C, et al. Association of sarcopenic obesity predicted by anthropometric measurements and 24-y all-cause mortality in elderly men: the Kuakini Honolulu Heart Program. *Nutrition (Burbank, Los Angeles County, Calif)* 2018;**46**:97–102.
70. Santanasto AJ, Goodpaster BH, Kritchevsky SB, Miljkovic I, Satterfield S, Schwartz AV, et al. Body composition remodeling and mortality: the Health Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci* 2017;**72**:513–519.
71. Seino S, Kitamura A, Abe T, Taniguchi Y, Yokoyama Y, Amano H, et al. Dose-response relationships between body composition indices and all-cause mortality in older Japanese adults. *J Am Med Dir Assoc* 2020;**21**:726, 33.e4.
72. Sim M, Prince RL, Scott D, Daly RM, Duque G, Inderjeeth CA, et al. Sarcopenia definitions and their associations with mortality in older Australian women. *J Am Med Dir Assoc* 2019;**20**:76–82.e2.
73. Sobestiansky S, Michaelsson K, Cederholm T. Sarcopenia prevalence and associations with mortality and hospitalisation by various sarcopenia definitions in 85–89 year old community-dwelling men: a report from the ULSAM study. *BMC Geriatr* 2019;**19**:318.
74. Spahillari A, Mukamal KJ, DeFilippi C, Kizer JR, Gottdiener JS, Djousse L, et al. The association of lean and fat mass with all-cause mortality in older adults: the Cardiovascular Health Study. *Nutr Metab Cardiovasc Dis* 2016;**26**:1039–1047.
75. Szulc P, Munoz F, Marchand F, Chapurlat R, Delmas PD. Rapid loss of appendicular skeletal muscle mass is associated with higher all-cause mortality in older men: the prospective MINOS study. *Am J Clin Nutr* 2010;**91**:1227–1236.
76. Turusheva A, Frolova E, Hegendoerfer E, Degryse JM. Predictors of short-term mortality, cognitive and physical decline in older adults in northwest Russia: a population-based prospective cohort study. *Aging Clin Exp Res* 2017;**29**: 665–673.
77. Wang H, Hai S, Liu Y, Liu Y, Dong B. Skeletal muscle mass as a mortality predictor among Nonagenarians and Centenarians: a prospective cohort study. *Sci Rep* 2019; **9**:2420.
78. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr* 2007;**86**:1339–1346.
79. Zaslavsky O, Rillamas-Sun E, Li W, Going S, Datta M, Snetselaar L, et al. Association of dynamics in lean and fat mass measures with mortality in frail older women. *J Nutr Health Aging* 2017;**21**:112–119.
80. Wijnhoven HA, Snijder MB, van Bokhorst-de van der Schueren MA, Deeg DJ, Visser M. Region-specific fat mass and muscle mass and mortality in community-dwelling older men and women. *Gerontology* 2012;**58**:32–40.
81. Chang KV, Chen JD, Wu WT, Huang KC, Han DS. Association of loss of muscle mass with mortality in liver cirrhosis without or before liver transplantation: a systematic review and meta-analysis. *Medicine* 2019;**98**:e14373.
82. Antoniou GA, Rojoa D, Antoniou SA, Alfahad A, Torella F, Juszczak MT. Effect

of low skeletal muscle mass on post-operative survival of patients with abdominal aortic aneurysm: a prognostic factor review and meta-analysis of time-to-event data. *Eur J Vasc Endovasc Surg* 2019;**58**:190–198.
83. Lee GKY, Chun-Ming AP, Hoi-Yee Li G, Chan M, Li HL, Man-Yung Cheung B, et al. Sarcopenia and mortality in different clinical conditions: a meta-analysis. *Osteoporos Sarcopenia* 2021;**7**:S19–s27.
84. de Santana FM, Premaor MO, Tanigava NY, Pereira RMR. Low muscle mass in older adults and mortality: a systematic review and meta-analysis. *Exp Gerontol* 2021;**152**:111461.
85. Isoyama N, Qureshi AR, Avesani CM, Lindholm B, Bàràny P, Heimbürger O, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. *Clin J Am Soc Nephrol* 2014;**9**:1720–1728.
86. Sidhu SS, Saggar K, Goyal O, Varshney T, Kishore H, Bansal N, et al. Muscle strength and physical performance, rather than muscle mass, correlate with mortality in end-stage liver disease. *Eur J Gastroenterol Hepatol* 2021;**33**:555–564.
87. Scheerman K, Meskers CGM, Verlaan S, Maier AB. Sarcopenia, low handgrip strength, and low absolute muscle mass predict long-term mortality in older hospitalized patients: an observational inception cohort study. *J Am Med Dir Assoc* 2021;**22**:816, 20.e2.
88. McDermott MM, Liu K, Tian L, Guralnik JM, Criqui MH, Liao Y, et al. Calf muscle characteristics, strength measures, and mortality in peripheral arterial disease: a longitudinal study. *J Am Coll Cardiol* 2012;**59**:1159–1167.
89. Reinders I, Murphy RA, Brouwer IA, Visser M, Launer L, Siggeirsdottir K, et al. Muscle quality and myosteatosis: novel associations with mortality risk: the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study. *Am J Epidemiol* 2016;**183**:53–60.
90. Balogun S, Winzenberg T, Wills K, Scott D, Jones G, Aitken D, et al. Prospective associations of low muscle mass and function with 10-year falls risk, incident fracture and mortality in community-dwelling older adults. *J Nutr Health Aging* 2017;**21**:843–848.
91. Han P, Chen X, Yu X, Zhang Y, Song P, Cai M, et al. The predictive value of sarcopenia and its individual criteria for cardiovascular and all-cause mortality in suburb-dwelling older Chinese. *J Nutr Health Aging* 2020;**24**:765–771.
92. Meza-Valderrama D, Marco E, Dávalos-Yerovi V, Muns MD, Tejero-Sánchez M, Duarte E, et al. Sarcopenia, malnutrition, and cachexia: adapting definitions and terminology of nutritional disorders in older people with cancer. *Nutrients* 2021;**13**:761.
93. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;**48**:601.
94. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. *J Am Geriatr Soc* 2014;**62**:253–260.
95. Wu LW, Lin YY, Kao TW, Lin CM, Liaw FY, Wang CC, et al. Mid-arm muscle circumference as a significant predictor of all-cause mortality in male individuals. *PLoS ONE* 2017;**12**:e0171707.
96. Schautz B, Later W, Heller M, Müller MJ, Bosy-Westphal A. Total and regional relationship between lean and fat mass with increasing adiposity—impact for the diagnosis of sarcopenic obesity. *Eur J Clin Nutr* 2012;**66**:1356–1361.
97. Liu P, Hao Q, Hai S, Wang H, Cao L, Dong B. Sarcopenia as a predictor of all-cause mortality among community-dwelling older people: a systematic review and meta-analysis. *Maturitas* 2017;**103**:16–22.
98. Shen Y, Zhang Q, Huang Z, Zhu J, Qiu J, Ma W, et al. Isoquercitrin delays denervated soleus muscle atrophy by inhibiting oxidative stress and inflammation. *Front Physiol* 2020;**11**:988.
99. Johnson ML, Robinson MM, Nair KS. Skeletal muscle aging and the mitochondrion. *Trends Endocrinol Metab* 2013;**24**:247–256.
100. Nguyen CP, Hirsch MS, Moeny D, Kaul S, Mohamoud M, Joffe HV. Testosterone and "age-related hypogonadism"—FDA concerns. *N Engl J Med* 2015;**373**:689–691.
101. Hermann M, Berger P. Hormonal changes in aging men: a therapeutic indication? *Exp Gerontol* 2001;**36**:1075–1082.
102. Curcio F, Ferro G, Basile C, Liguori I, Parrella P, Pirozzi F, et al. Biomarkers in sarcopenia: a multifactorial approach. *Exp Gerontol* 2016;**85**:1–8.
103. Nakamura M, Hamada T, Tanaka A, Nishi K, Kume K, Goto Y, et al. Association of oral hypofunction with frailty, sarcopenia, and mild cognitive impairment: a cross-sectional study of community-dwelling Japanese older adults. *J Clin Med* 2021;**10**:1626.
104. Latres E, Amini AR, Amini AA, Griffiths J, Martin FJ, Wei Y, et al. Insulin-like growth factor-1 (IGF-1) inversely regulates atrophy-induced genes via the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway. *J Biol Chem* 2005;**280**:2737–2744.
105. Sacheck JM, Hyatt JP, Raffaello A, Jagoe RT, Roy RR, Edgerton VR, et al. Rapid disuse and denervation atrophy involve transcriptional changes similar to those of muscle wasting during systemic diseases. *FASEB J* 2007;**21**:140–155.
106. Zhao J, Brault JJ, Schild A, Cao P, Sandri M, Schiaffino S, et al. FoxO3 coordinately activates protein degradation by the autophagic/lysosomal and proteasomal pathways in atrophying muscle cells. *Cell Metab* 2007;**6**:472–483.
107. Psilander N, Eftestøl E, Cumming KT, Juvkam I, Ekblom MM, Sunding K, et al. Effects of training, detraining, and retraining on strength, hypertrophy, and myonuclear number in human skeletal muscle. *J Appl Physiol (Bethesda, Md: 1985)* 2019;**126**:1636–1645.
108. Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, Ramírez-Vélez R, García-Hermoso A, Cadore EL, et al. Changes in muscle power after usual care or early structured exercise intervention in acutely hospitalized older adults. *J Cachexia Sarcopenia Muscle* 2020;**11**:997–1006.
109. Schoenfeld BJ, Grgic J, Ogborn D, Krieger JW. Strength and hypertrophy adaptations between low- vs. high-load resistance training: a systematic review and meta-analysis. *J Strength Cond Res* 2017;**31**:3508–3523.
110. Lixandrão ME, Ugrinowitsch C, Berton R, Vechin FC, Conceição MS, Damas F, et al. Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance training associated with blood-flow restriction: a systematic review and meta-analysis. *Sports Med (Auckland, NZ)* 2018;**48**:361–378.
111. Distefano G, Goodpaster BH. Effects of exercise and aging on skeletal muscle. *Cold Spring Harb Perspect Med* 2018;**8**:a029785.
112. Malafarina V, Uriz-Otano F, Iniesta R, Gil-Guerrero L. Effectiveness of nutritional supplementation on muscle mass in treatment of sarcopenia in old age: a systematic review. *J Am Med Dir Assoc* 2013;**14**:10–17.
113. Prado CM, Purcell SA, Laviano A. Nutrition interventions to treat low muscle mass in cancer. *J Cachexia Sarcopenia Muscle* 2020;**11**:366–380.
114. von Haehling S, Ebner N, Dos Santos MR, Springer J, Anker SD. Muscle wasting and cachexia in heart failure: mechanisms and therapies. *Nat Rev Cardiol* 2017;**14**:323–341.
115. Dupont J, Dedeyne L, Dalle S, Koppo K, Gielen E. The role of omega-3 in the prevention and treatment of sarcopenia. *Aging Clin Exp Res* 2019;**31**:825–836.
116. Dirks ML, Wall BT, van de Valk B, Holloway TM, Holloway GP, Chabowski A, et al. One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. *Diabetes* 2016;**65**:2862–2875.
117. Wall BT, Dirks ML, Snijders T, Senden JM, Dolmans J, van Loon LJ. Substantial skeletal muscle loss occurs during only 5 days of disuse. *Acta Physiol (Oxf)* 2014;**210**:600–611.
118. Febbraio MA, Pedersen BK. Contraction-induced myokine production and release: is skeletal muscle an endocrine organ? *Exerc Sport Sci Rev* 2005;**33**:114–119.

119. Karstoft K, Pedersen BK. Skeletal muscle as a gene regulatory endocrine organ. *Curr Opin Clin Nutr Metab Care* 2016;**19**: 270–275.
120. Yin J, Lu X, Qian Z, Xu W, Zhou X. New insights into the pathogenesis and treatment of sarcopenia in chronic heart failure. *Theranostics* 2019;**9**:4019–4029.
121. Dodson S, Baracos VE, Jatoi A, Evans WJ, Cella D, Dalton JT, et al. Muscle wasting in cancer cachexia: clinical implications, diagnosis, and emerging treatment strategies. *Annu Rev Med* 2011;**62**: 265–279.
122. Buford TW, Anton SD, Judge AR, Marzetti E, Wohlgemuth SE, Carter CS, et al. Models of accelerated sarcopenia: critical pieces for solving the puzzle of age-related muscle atrophy. *Ageing Res Rev* 2010;**9**:369–383.
123. Park SW, Goodpaster BH, Lee JS, Kuller LH, Boudreau R, de Rekeneire N, et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. *Diabetes Care* 2009;**32**:1993–1997.
124. Park SW, Goodpaster BH, Strotmeyer ES, Kuller LH, Broudeau R, Kammerer C, et al. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the Health, Aging, and Body Composition Study. *Diabetes Care* 2007;**30**: 1507–1512.
125. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. *Lancet Diab Endocrinol* 2014;**2**: 819–829.
126. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2021. *J Cachexia Sarcopenia Muscle* 2021;**12**:2259–2261.