European Geriatric Medicine (2019) 10:853–862
https://doi.org/10.1007/s41999-019-00233-w

REVIEW

Sarcopenia and health-related outcomes: an umbrella review of observational studies

Nicola Veronese[1] · Jacopo Demurtas[2] · Pinar Soysal[3] · Lee Smith[4] · Gabriel Torbahn[5] · Daniel Schoene[6] · Lukas Schwingshackl[7] · Cornel Sieber[5,8] · Jurgen Bauer[9] · Matteo Cesari[10] · Oliviere Bruyere[11] · Jean-Yves Reginster[11] · Charlotte Beaudart[11] · Alfonso J. Cruz-Jentoft[12] · Cyrus Cooper[13,14] · Mirko Petrovic[15] · Stefania Maggi[1] on behalf of the Special Interest Groups in Systematic Reviews and Meta-analyses for healthy ageing Sarcopenia and Frailty and resilience in older persons of the European Geriatric Medicine Society (EuGMS)

Received: 21 May 2019 / Accepted: 23 August 2019 / Published online: 6 September 2019

Key summary points

Aim To investigate associations of sarcopenia with adverse health-related outcomes, through an umbrella review method.
Findings Sarcopenia appears to be significantly associated with several adverse outcomes in older people, with a strong evidence for increased risk of mortality, disability, and falls.
Message Sarcopenia is associated with several adverse health-related outcomes in older people, indicating the need of assessing this condition in daily practice.

Abstract

Background The clinical relevance of sarcopenia has increasingly been recognized. However, whether it is associated with the development of other medical conditions is still unclear. Therefore, we aimed to capture the scale of outcomes that have been associated with the presence of sarcopenia and systematically assess the quality, strength, and credibility of these associations using an umbrella review methodology.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s41999-019-00233-w) contains supplementary material, which is available to authorized users.

✉ Nicola Veronese
ilmannato@gmail.com

[1] National Research Council, Neuroscience Institute, Aging Branch Via Giustiniani, 2, Padua, Italy

[2] Primary Care Department Azienda, USL Toscana Sud Est, Grosseto, Italy

[3] Department of Geriatric Medicine, Bezmialem Vakif University, Istanbul, Turkey

[4] The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK

[5] Institute for Biomedicine of Aging, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nuremberg, Germany

[6] Institute of Medical Physics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

[7] Institute for Evidence in Medicine (for Cochrane Germany Foundation), Medical Center, University of Freiburg, Freiburg, Germany

[8] Kantonsspital Winterthur, Winterthur, Switzerland

[9] Center for Geriatric Medicine, University of Heidelberg, Agaplesion Bethanien Hospital, Heidelberg, Germany

[10] Geriatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

[11] WHO Collaborating Centre for Public Health Aspects of Musculoskeletal Health and Aging, Division of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

[12] Servicio de Geriatría, Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain

[13] MRC Life Course Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK

[14] NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK

[15] Department of Geriatrics, Ghent University Hospital, Ghent, Belgium

Methods A systematic review in several databases was carried out, until 20th February 2019. For each association, random-effects summary effect size, 95% confidence intervals (CIs), heterogeneity (I^2), evidence for small-study effect, evidence for excess significance bias, and 95%-prediction intervals were estimated. We used these metrics to categorize the evidence of significant outcomes ($p < 0.05$) from class I (convincing) to class IV (weak), according to pre-established criteria.
Results From 358 abstracts, 6 meta-analyses with 14 associations were included. Sarcopenia was associated with higher risk of other comorbidities and mortality in 11 of 14 outcomes explored. However, only 3 outcomes (i.e., association between sarcopenia and increased risk of death in community-dwelling older people [odds ratio, OR = 3.60; 95% CI 2.96–4.37; $n = 14{,}305$], disability [OR = 3.04; 95% CI 1.80–5.12; $n = 8569$], and falls [OR = 1.60; 95% CI 1.31–1.97; $n = 12{,}261$]) presented a highly suggestive evidence (class II). Other association was classified as having only a weak evidence.
Conclusion Sarcopenia is associated with several adverse health-related outcomes in older people, and its associations with mortality, disability, and falls are supported by a highly suggestive evidence. The effect of interventions on sarcopenia to improve these outcomes needs to be investigated.

Keywords Sarcopenia · Health · Umbrella review · Meta-analysis · Mortality · Fall · Disability · Risk factor

Introduction

Sarcopenia is defined as "age-related muscle loss, affecting a combination of appendicular muscle mass, muscle strength, and/or physical performance measures" traditionally associated with several adverse outcomes in older people [1]. A growing body of literature suggests that sarcopenia may increase the risk for falls [2], fractures [3], disability [4], and mortality [5–7], being consequently associated also with poor quality of life [8].

The prevalence of sarcopenia is particularly high in older adults. A recent systematic review and meta-analysis suggested that its prevalence is approximately 10% in this population [9]. However, variations in estimates exist due to different criteria used to diagnose sarcopenia [9]. At the same time, sarcopenia is a relatively new concept in geriatric medicine. For example, only in September 2016, it was introduced in the ICD-10-CM as a medical condition [10, 11]. Finally, the interest in sarcopenia is also increasing beyond the perimeter of geriatric medicine [12], such as in oncology [13], cardiology [14]. and respiratory medicine [15].

However, to estimate the magnitude of sarcopenia with various outcomes could be of importance to understand which specific medical conditions sarcopenia may be considered a risk factor for. Therefore, we aimed to capture the scale of outcomes, in magnitude of associations, which have been longitudinally associated with the presence of sarcopenia. Moreover, we systematically assessed the quality, strength, and credibility of these associations. To achieve this aim, we used the umbrella review method to combine evidence from a wide range of outcomes and populations, included in observational studies.

Materials and methods

This umbrella review followed a structured protocol (available upon request from the corresponding author) that was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=122509) and is reported according to the reporting guideline by Shenkin et al. [16].

Data sources and searches

We conducted an umbrella review [17] searching several databases (Epistemonikos, MEDLINE through Ovid, CINHAL, EMBASE, Cochrane library, and JBI Database of Systematic Reviews and Implementation Reports) from inception until 20th February 2019. The search strategy used in MEDLINE is reported, as example in Supplementary Table 1. The search strategy was adapted to the other databases. Furthermore, we hand-searched the reference lists of included articles. No language restrictions were applied.

Study selection

In this umbrella review, we included: (1) peer-reviewed systematic reviews with meta-analyses that compared people with sarcopenia (defined as a combination of an estimate of low muscle mass and a test of physical performance and/or muscle strength) according to validated criteria (e.g., European Working Group on Sarcopenia in Older People (EWGSOP) [18] or Asian Working Group on Sarcopenia (AWGS) [19]) vs. those without sarcopenia; (2) meta-analyses including observational studies (prospective cohort studies and case–control studies) that investigated the association of sarcopenia with any health-related outcome (for example, cardiovascular disease, cancer, fractures, and mortality). Studies reporting sarcopenia only as low muscle mass or low performance in tests of physical function and/or muscle

Õ Health outcomes and evidence class reported in included meta-analyses of observational studies

Outcome	Setting	Diagnostic criteria for sarcopenia	Study design	No of studies	Cases	Sample size	Type of metric	Mean ES (95% CI)	*p*	I^2	Small-study effects	Excess significance bias	E/O significant studies	Largest study significant	Prediction intervals	Level of evidence
Mortality [39]	Community	EWGSOP	Cohort	12	3436	14,035	OR	3.60 (2.96–4.37)	1.28E−37	31.5	No	Yes	10.64/2	Yes	2.28–5.56	II
Falls [37]	Community\ nursing home	FNIH\ AWGS\ EWGSOP	Cohort	12	2701	12,261	OR	1.60 (1.31–1.97)	6.54E−06	35.2	No	Yes	8.89/0	Yes	0.96–2.67	II
Disability [39]	Community	EWGSOP	Cohort	6	2354	8569	OR	3.04 (1.80–5.12)	0.00003	82.4	No	Yes	4.97/1	Yes	0.17–16.52	II
Post-operative complications of gastric cancer [41]	Hospital (patients with gastric cancer)	EWGSOP	Cohort/ case control	6	357	1515	OR	2.60 (2.00–3.40)	1.14E−12	0	Yes	Yes	5.21/0	Yes	1.79–3.78	IV
Post-operative pneumonia [41]	Hospital (patients with gastric cancer)	EWGSOP	Cohort/ case control	5	48	1357	OR	5.96 (3.17–11.23)	3.13E−08	0	Yes	Yes	4.12/0	Yes	2.14–16.66	IV
Mortality [42]	Nursing home	EWGSOP	Cohort	5	239	1329	HR	1.91 (1.43–2.60)	0.00001	2	No	Yes	2.99/0	Yes	1.16–3.34	IV
Post-operative ileus [41]	Hospital (patients with gastric cancer)	EWGSOP	Cohort/ case control	4	25	1258	OR	5.16 (2.31–13.08)	0.001	0	No	Yes	2.14/0	Yes	0.67–39.76	IV
Fragility fractures [38]	Community	EWGSOP\ AWGS	Cohort	8	2420	21,487	RR	1.35 (1.11–1.63)	0.002	1	No	Yes	4.39/0	No	1.05–1.73	IV
Severe postoperative complications [41]	Hospital (patients with gastric cancer)	EWGSOP	Cohort/ case control	5	74	1270	OR	2.03 (1.22–3.38)	0.007	0	Yes	Yes	2.04/0	No	0.88–4.65	IV

Õ (continued)

Outcome	Setting	Diagnostic criteria for sarcopenia	Study design	No of studies	Cases	Sample size	Type of metric	Mean ES (95% CI)	*p*	I^2	Small-study effects	Excess significance bias	E/O significant studies	Largest study significant	Prediction intervals	Level of evidence
Long length of stay (LOS) [40]	Community	EWGSOP	Cohort	2	874	4000	OR	1.58 (1.13–2.20)	0.007	40.4	Np	Yes	1.71/0	Yes	NP	IV
Hospitalization [40]	Unselected\community\hospital	EWGSOP	Cohort	8	1059	4174	RR	1.40 (1.31–1.89)	0.03	67.4	Yes	Yes	2.63/0	No	0.55–3.55	IV
Post-operative intra-abdominal infection [41]	Hospital (patients with gastric cancer)	EWGSOP	Cohort/case control	5	35	1357	OR	1.22 (0.58–2.56)	0.601	0	Yes	No	0.92/0	No	0.37–4.05	NS
Post-operative delayed gastric emptying [41]	Hospital (patients with gastric cancer)	EWGSOP	Cohort/case control	3	16	788	OR	1.59 (0.24–10.51)	0.628	54.8	No	No	1.13/0	No	0–63.86	NS
Post-operative anastomotic leakage [41]	Hospital (patients with gastric cancer)	EWGSOP	Cohort/case control	5	30	1357	OR	1.19 (0.52–2.69)	0.681	0	No	No	0.46/0	No	0.31–4.47	NS

AWGS Asian Working Group on Sarcopenia, *E* expected, *ES* effect size, *EWGSOP* European Working Group on Sarcopenia in Older People, *FNIH* Foundation for the National Institutes of Health, *HR* hazard ratio, *O* observed, *OR* odds ratio, *RR* relative risk

strength and meta-analyses including only cross-sectional investigations were excluded.

Two reviewers (PS and JD) performed the primary and secondary screening (i.e., title/abstract and full-text screening, respectively) and disagreements were resolved through consensus with another independent reviewer (LS).

Data extraction

Two independent investigators (PS and JD) extracted the following information for each meta-analysis included: (1) first author name; (2) year of publication; (3) the number of included studies and the total number of people included in the review; (4) the definition used for sarcopenia; (5) the effect size; (6) study design (prospective cohort studies and case–control studies); (7) number of cases (i.e., people having the event of interest, e.g., deaths) and controls (i.e., people without events) for each study; (8) setting; (9) mean age (more or less than 65 years). We planned to extract functional status (e.g., disabled or not) for each study, but this information was not extensively reported. Disagreements were resolved through discussion/consensus with another independent author (LS).

We extracted the study-specific estimated relative risk for health outcomes [relative risk (RR), odds ratio (OR), and hazard ratio (HR)], along with the 95% confidence interval (95% CI), adjusted for the highest number of covariates possible in each study. If two meta-analyses were available for the same association, we included the largest in terms of studies.

Outcomes

We included all health-related outcomes, defined as medical conditions (such as mortality, disability, falls, length of stay, and cardiovascular disease) and mortality.

Methodological quality of systematic reviews

One reviewer (PS) assessed the methodological quality of the included meta-analyses using AMSTAR [20]. Another author checked this task (JD). We then categorized the overall AMSTAR score as high (8–11 items achieved), moderate (4–7 items), or low (0–3 items) [20].

Statistical analysis

For each meta-analysis, we re-calculated the summary effect size and its 95%-CI under the assumption of the random-effects models [21].

We planned to stratify the findings for: (1) diagnostic criteria used for sarcopenia (EWGSOP in 2010 [18], AWGS [19], FNIH [22]), or others; (2) mean age (≥ 65 vs. < 65 years); (3) functional status (disabled or not); (4) setting (community, nursing home, hospital, and others). The stratification for mean age was not possible, since all the studies included older people.

We estimated the prediction interval and its 95%-CI, which further accounts for between-study effects and estimates the certainty of the association if a new study addresses that same association [23]. For the largest data set of each meta-analysis, we calculated the standard error (SE) of the effect size to investigate if the largest study was more conservative than the real effect size. Heterogeneity was estimated using the I^2 metric, with values $\geq 50\%$ indicative of high heterogeneity, and values $\geq 75\%$ suggesting very high heterogeneity. [24, 25]. In addition, we calculated the evidence of small-study effects (i.e., whether small studies would have inflated effect sizes compared to larger ones). To this end, we used the regression asymmetry test developed by Egger et al. [26], using a p value < 0.10 [27]. Finally, we applied the Ioannidis' excess of significance test [28] that evaluates whether the number of studies with nominally significant results (i.e., with $p < 0.05$) among those included in a meta-analysis is too large based on the power that these data sets have to detect effects at $\alpha = 0.05$. The number of expected 'positive' (E; i.e., statistically significant studies) was compared with the observed (O) number of statistically significant studies through a χ^2-based test [28]. A p value < 0.10 was considered indicating of excess statistical significance.

We planned to perform sensitivity analysis by restricting analyses to prospective observational studies with convincing (class I) or highly suggestive (class II) evidence only (for methods of evidence grading, see paragraph below). However, the three outcomes in class II included only cohort studies. In addition, for associations supported by either class I or class II evidence, we used credibility ceilings, a sensitivity analysis tool that accounts for potential methodological limitations of observational studies, which might lead to spurious precision of combined effect estimates. This method assumes that every observational study has a probability c (credibility ceiling) that the true effect size could be in a different direction from the one suggested by its point estimate. The pooled effect size was re-estimated using a wide range of credibility ceilings. Finally, for class I and II evidence, we specifically evaluated the risk of bias using the AMSTAR risk of bias tool.

Grading the evidence

Using the criteria mentioned in the statistical analysis section, associations that presented nominally statistically significant random-effects summary estimates (i.e. $p < 0.05$) were categorized into convincing, highly suggestive, suggestive, or weak evidence (class I–IV), following a grading

scheme that has already been applied in various fields of medicine [29–36]. These criteria are fully reported in Supplementary Table 2.

Results

Literature search

We initially identified 358 non-duplicated papers. Of these, 50 full texts were screened (see the full texts excluded in Supplementary Table 3), and finally, 6 meta-analyses [37–42], including 14 different outcomes, were included (Fig. 1).

Meta-analyses of observational studies

Table 1 reports the main analyses of our work. The median number of studies for each outcome was 5, the median number of participants was 1436, and the median number of cases (i.e., people having the event of interest) was 298.

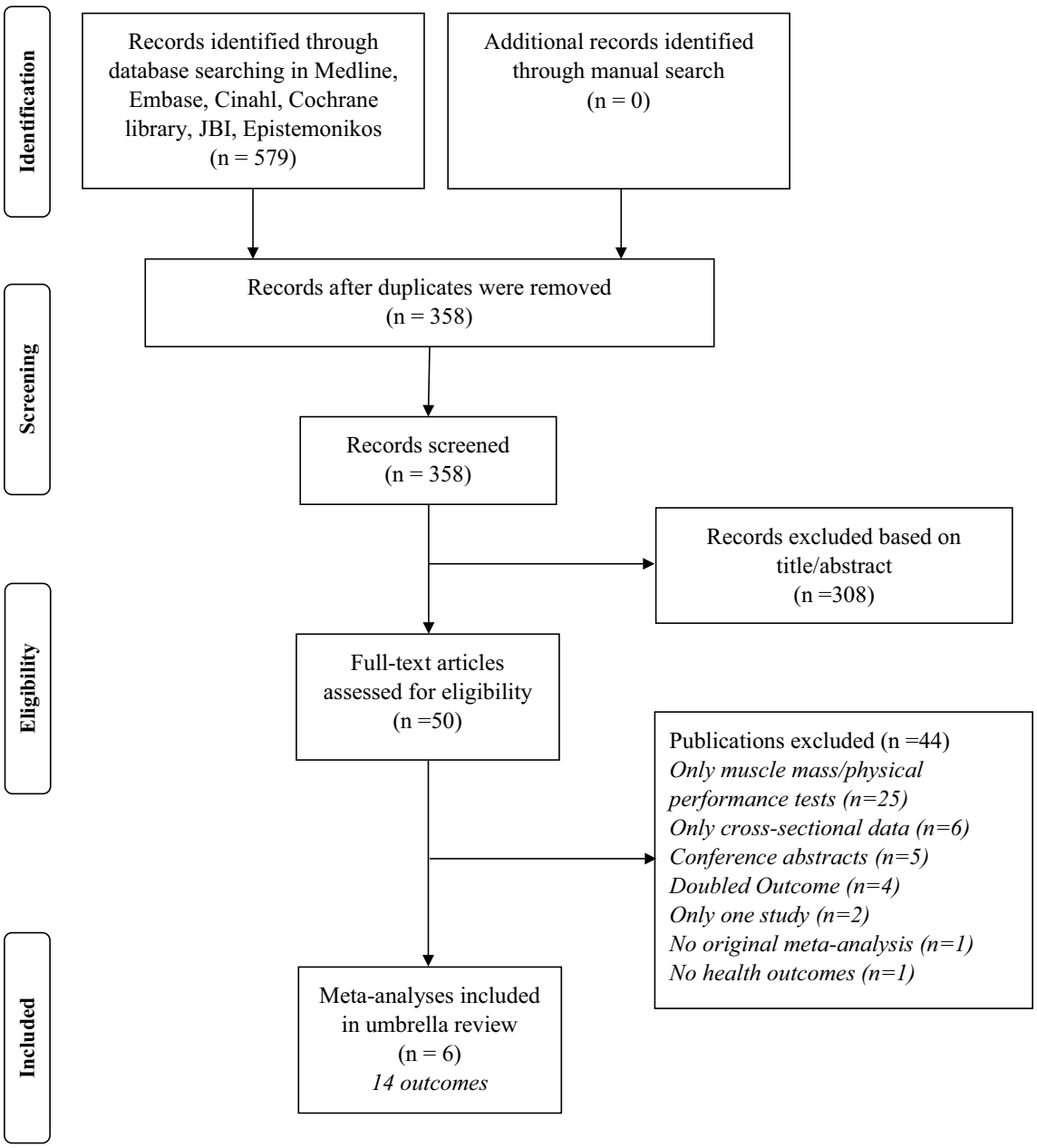

Fig. 1 PRISMA flow-chart

Seven of the 14 outcomes included post-operative complications associated with sarcopenia in hospitalized older people with gastric cancer, and 2 outcomes were related to death (one meta-analysis explored the association between sarcopenia and mortality in nursing home residents and another one in community-dwelling people). All the outcomes included studies using the criteria suggested by EWGSOP, except 2 outcomes using the criteria suggested by the AWGS and Foundation for the National Institutes of Health (FNIH). Half of the outcomes included only cohort studies, and the other half in a mix of cohort and case–control studies.

Supplementary Table 4 reports the assessment of the quality of the meta-analyses included, showing that these works had moderate/high quality.

Overall, 11/14 (79%) reported nominally significant summary results ($p < 0.05$), but only 4 associations survived when a more stringent p value ($p < 10^{-6}$) was introduced, as shown in Table 1.

The largest studies were statistically significant in 8/14 of the outcomes included. Heterogeneity among studies was generally low, having only three outcomes with an $I^2 > 50\%$, and, of them, only one with very high heterogeneity ($I^2 \geq 75\%$). Five associations presented 95%-prediction intervals excluding the null value. Evidence for excess statistical significance was present in 11/14 outcomes and small-study effects were also reported in 5/14 of the outcomes.

Based on the above-mentioned criteria, none of the outcomes presented a convincing evidence (class I), whilst three outcomes (i.e., association between sarcopenia and increased risk of death in community-dwelling older people [OR = 3.60; 95% CI 2.96–4.37, $n = 14{,}305$ participants], disability [OR = 3.04; 95% CI 1.80–5.12, $n = 8569$], and falls [OR = 1.60; 95% CI 1.31–1.97, $n = 12{,}261$]) presented a highly suggestive evidence (class II), mainly due to the presence of excess statistical significance. The other associations between sarcopenia and medical conditions/death presented a weak strength of evidence.

For the three outcomes in class II, we ran some sensitivity analyses, as mentioned in the statistical analysis section. First, the application of the 10% credibility ceiling did not affect any class II associations. According to the risk of bias assessment using AMSTAR, one meta-analysis [39] including two class II outcomes reported a moderate-study quality (mainly because grey literature was not explored and the conflict of interest of the single studies not reported) and the other one had a high quality [37].

In one meta-analysis exploring the association between sarcopenia and falls [37], we were able to further stratify our analysis by setting and by criteria of sarcopenia used. After excluding two studies conducted in nursing home residents, the re-calculated credibility evidence remained of class II, since we identified the presence of excess statistical significance and small-study effect.

Finally, for the association between sarcopenia and falls, there were no significant differences between the studies using the FNIH ($n = 6$ studies) [22] and the EWGSOP criteria ($n = 5$ studies), having both a class II evidence. Only one study used the AWGS criteria and, consequently, no analysis was done.

Discussion

The present umbrella review, including 6 systematic reviews with meta-analyses and focusing on 14 different outcomes, summarized the current evidence regarding sarcopenia as a risk factor for negative health-related outcomes and mortality in older people. Overall, several conditions were found to be associated with sarcopenia, but a highly suggestive evidence was only found for mortality, disability and falls. For the other outcomes included, the strength of associations was weak, mainly owing to the low number of incident cases reported.

Sarcopenia stirs an increasing interest among geriatricians and also among experts in other medical specialties, for instance oncology and nephrology [43]. To avoid results that would have to be attributed specifically to muscle strength/function or to low muscle mass only and not to the modern concept of sarcopenia, the present review included only studies that applied the criteria and definitions suggested by international societies that nowadays include both dimensions, muscle mass estimation, and muscle strength/function [44]. This newer concept allows to better understand that the two dimensions of sarcopenia (function and anatomy) co-exist in the clinical presentation of this syndrome [45].

In the light of the present findings, one can speculate that sarcopenia would be associated with a higher risk of mortality, which is mediated by an increased risk of falls and disability, since these outcomes are supported by a highly suggestive evidence, even if the mediation effects have not been investigated so far. Nevertheless, risk of falls and disability are not supported by convincing evidence (class I) due to excess statistical significance, a common issue in meta-analyses. Biases that increase the proportion of 'positive' (significant) results may also inflate the observed summary effect size leading to an overestimation in the expected significant studies, as found in the present umbrella review [28]. Sarcopenia is associated with multiple factors typical for the ageing process [46], unhealthy lifestyle [47], and inflammation [48, 49], and all these factors are associated per se with higher risk of disability, falls, and mortality [50]. Even if we choose the most adjusted estimates among those available in each meta-analysis, it is likely that these factors can

explain the association between sarcopenia and the negative outcomes mentioned.

In the present umbrella review, sarcopenia was also significantly associated with post-operative complications in older participants undergoing surgical procedures, but this is only supported by weak evidence, mainly due to the few numbers of incident cases reported in the included meta-analyses [41]. Even if these findings are exploratory, they suggest that sarcopenia may be a useful tool to stratify prognosis in the context of (major) surgical interventions with the intention to better stratify the prognosis of these patients. In this context, it has to be acknowledged that an increasing number of studies have reported a possible prognostic role for sarcopenia in other medical disciplines, such as surgery [51], cardiology [52], and oncology [53]. Unfortunately, we did not find any meta-analysis in these fields of great interest.

Even being novel, the findings of this work should be interpreted within limitations. First, only 6 meta-analyses with a limited number of studies and participants were included. Altogether, these findings suggest that we need future studies using validated criteria for sarcopenia for understanding the role of sarcopenia as a risk factor for other diseases, such as cancer, cardiovascular disease, or mood disorders. Second, meta-analyses included studies with significant differences in design, population, and other basic characteristics. Therefore, it is possible that heterogeneity may be a relevant issue. We, consequently, used an $I^2 < 50\%$ as one of the criteria for class I evidence (convincing) to assign the best-evidence grade only to robust associations. However, clinical heterogeneity might be of importance, even in the absence of statistical heterogeneity [54]. Finally, it was not possible to precisely carry out all aspects of the pre-registered protocol, in particular pre-planned sensitivity analyses. Although we conducted a comprehensive systematic literature search in major medical databases without language restrictions, language bias cannot be excluded, since these databases mostly include journals from the US and Europe.

In conclusion, sarcopenia seems to be significantly associated with several negative health-related outcomes in older people, although only the association with mortality, disability, and falls is supported by a highly suggestive evidence. Considering the relevance of these factors for the independence and quality of life of older people, the present findings provide evidence for the potential implementation of a brief screening for sarcopenia in clinical practice and subsequent treatment if appropriate. However, before a robust recommendation can be provided stronger, epidemiological evidence is needed to support the importance of sarcopenia in daily practice as an independent risk factor for different medical conditions and mortality in older people. Next, experimental studies are required that investigate whether screening and successive interventions in clinical practice improve the outcomes identified in this umbrella review.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval It was not requested being a revision of already published literature.

Informed consent No patients were included in this review.

Sponsor's role None.

References

1. Sarcopenia Woo J (2017) Clin Geriatr Med 33(3):305–314
2. Landi F, Liperoti R, Russo A, Giovannini S, Tosato M, Capoluongo E et al (2012) Sarcopenia as a risk factor for falls in elderly individuals: results from the ilSIRENTE study. Clin Nutr 31(5):652–658. https://doi.org/10.1016/j.clnu.2012.02.007
3. Cederholm T, Cruz-Jentoft AJ, Maggi S (2013) Sarcopenia and fragility fractures. Eur J Phys Rehabil Med 49(1):111–117
4. Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB (2010) Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporos Int J Establ Result Coop Between Eur Found Osteoporos Natl Osteoporos Found USA 21(4):543–559. https://doi.org/10.1007/s00198-009-1059-y
5. Cesari M, Pahor M, Lauretani F, Zamboni V, Bandinelli S, Bernabei R et al (2009) Skeletal muscle and mortality results from the InCHIANTI Study. J Gerontol Ser A Biol Sci Med Sci 64(3):377–384. https://doi.org/10.1093/gerona/gln031
6. Gariballa S, Alessa A (2013) Sarcopenia: prevalence and prognostic significance in hospitalized patients. Clin Nutr (Edinb Scotl) 32(5):772–776. https://doi.org/10.1016/j.clnu.2013.01.010
7. Perkisas S, De Cock A-M, Vandewoude M, Verhoeven V (2018) Prevalence of sarcopenia and 9-year mortality in nursing home residents. Aging Clin Exp Res 31(7):951–959
8. Rizzoli R, Reginster JY, Arnal JF, Bautmans I, Beaudart C, Bischoff-Ferrari H et al (2013) Quality of life in sarcopenia and frailty. Calcif Tissue Int 93(2):101–120. https://doi.org/10.1007/s00223-013-9758-y
9. Mayhew A, Amog K, Phillips S, Parise G, McNicholas P, de Souza R et al (2018) 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 48(1):48–56
10. Anker SD, Morley JE, von Haehling S (2016) Welcome to the ICD-10 code for sarcopenia. J Cachexia Sarcopenia Muscle 7(5):512–514
11. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A et al (2017) Sarcopenia: an overview. Aging Clin Exp Res 29(1):11–17
12. Dent E, Morley J, Cruz-Jentoft A, Arai H, Kritchevsky S, Guralnik J et al (2018) International clinical practice guidelines for sarcopenia (ICFSR): screening, diagnosis and management. J Nutr Health Aging 22(10):1148–1161
13. Chindapasirt J (2015) Sarcopenia in cancer patients. Asian Pac J Cancer Prev APJCP 16(18):8075–8077

14. von Haehling S (2018) Muscle wasting and sarcopenia in heart failure: a brief overview of the current literature. ESC Heart Fail 5(6):1074–1082. https://doi.org/10.1002/ehf2.12388
15. Jones SE, Maddocks M, Kon SS, Canavan JL, Nolan CM, Clark AL et al (2015) Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. Thorax 70(3):213–218. https://doi.org/10.1136/thoraxjnl-2014-206440
16. Shenkin SD, Harrison JK, Wilkinson T, Dodds RM, Ioannidis JP (2017) Systematic reviews: guidance relevant for studies of older people. Age Ageing 46(5):722–728
17. Ioannidis JP (2009) Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. CMAJ 181(8):488–493. https://doi.org/10.1503/cmaj.081086
18. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F et al (2010) Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing 39(4):412–423. https://doi.org/10.1093/ageing/afq034
19. Chen L-K, Liu L-K, Woo J, Assantachai P, Auyeung T-W, Bahyah KS et al (2014) Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 15(2):95–101
20. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C et al (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 7(1):10. https://doi.org/10.1186/1471-2288-7-10
21. Lau J, Ioannidis JP, Schmid CH (1997) Quantitative synthesis in systematic reviews. Ann Intern Med 127(9):820–826
22. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB et al (2014) The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol Ser A Biomed Sci Med Sci 69(5):547–558
23. Higgins JP, Thompson SG, Spiegelhalter DJ (2009) A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc. 172(1):137–159. https://doi.org/10.1111/j.1467-985X.2008.00552.x
24. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539–1558. https://doi.org/10.1002/sim.1186
25. Ioannidis JP, Patsopoulos NA, Evangelou E (2007) Uncertainty in heterogeneity estimates in meta-analyses. BMJ 335(7626):914–916. https://doi.org/10.1136/bmj.39343.408449.80
26. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634
27. Carvalho AF, Kohler CA, Brunoni AR, Miskowiak KW, Herrmann N, Lanctot KL et al (2016) Bias in peripheral depression biomarkers. Psychother Psychosom 85(2):81–90. https://doi.org/10.1159/000441457
28. Ioannidis JP, Trikalinos TA (2007) An exploratory test for an excess of significant findings. Clin Trials 4(3):245–253. https://doi.org/10.1177/1740774507079441
29. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P (2015) Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Healthc 13(3):132–140. https://doi.org/10.1097/xeb.0000000000000055
30. Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I (2016) Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. BMC Med 14(1):147. https://doi.org/10.1186/s12916-016-0692-5
31. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP (2016) Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. Parkinsonism Related Disord 23:1–9. https://doi.org/10.1016/j.parkreldis.2015.12.008
32. Dinu M, Pagliai G, Casini A, Sofi F (2017) Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomized trials. Nutr Metabol Cardiovasc Dis 27(1):e21. https://doi.org/10.1016/j.numecd.2016.11.055
33. Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H et al (2017) Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 356(28):j477. https://doi.org/10.1136/bmj.j477
34. Li X, Meng X, Timofeeva M, Tzoulaki I, Tsilidis KK, Ioannidis PA et al (2017) Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. BMJ 357:j2376
35. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JPA (2014) Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ Br Med J 348:g2035
36. Veronese N, Solmi M, Caruso MG, Giannelli G, Osella AR, Evangelou E et al (2018) Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. Am J Clin Nutr 107(3):436–444. https://doi.org/10.1093/ajcn/nqx082
37. Zhang X, Huang P, Dou Q, Wang C, Zhang W, Yang Y et al (2019) Falls among older adults with sarcopenia dwelling in nursing home or community: a meta-analysis. Clin Nutr (Edinb Scotl) 25:25. https://doi.org/10.1016/j.clnu.2019.01.002
38. Zhang Y, Hao Q, Ge M, Dong B (2018) Association of sarcopenia and fractures in community-dwelling older adults: a systematic review and meta-analysis of cohort studies. Osteoporos Int J Establ Result Coop Between Eur Found Osteoporos Natl Osteoporos Found USA 29(6):1253–1262. https://doi.org/10.1007/s00198-018-4429-5
39. Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyere O (2017) Health outcomes of sarcopenia: a systematic review and meta-analysis. PLoS One 12(1):e0169548. https://doi.org/10.1371/journal.pone.0169548
40. Zhao Y, Zhang Y, Hao Q, Ge M, Dong B (2019) Sarcopenia and hospital-related outcomes in the old people: a systematic review and meta-analysis. Aging Clin Exp Res 31(1):5–14. https://doi.org/10.1007/s40520-018-0931-z
41. Yang Z, Zhou X, Ma B, Xing Y, Jiang X, Wang Z (2018) Predictive value of preoperative sarcopenia in patients with gastric cancer: a meta-analysis and systematic review. J Gastrointest Surg Off J Soc Surg Aliment Tract 22(11):1890–1902. https://doi.org/10.1007/s11605-018-3856-0
42. Zhang X, Wang C, Dou Q, Zhang W, Yang Y, Xie X (2018) Sarcopenia as a predictor of all-cause mortality among older nursing home residents: a systematic review and meta-analysis. BMJ Open 8(11):e021252. https://doi.org/10.1136/bmjopen-2017-021252
43. Sayer AA (2014) Sarcopenia the new geriatric giant: time to translate research findings into clinical practice. Br Geriatr Soc 43(6):736–737
44. Beaudart C, Rolland Y, Cruz-Jentoft A, Bauer J, Sieber C, Cooper C et al (2019) Assessment of Muscle Function and Physical Performance in Daily Clinical Practice: a position paper endorsed by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Calcif Tissue Int. https://doi.org/10.1007/s00223-019-00545-w
45. Cruz-Jentoft AJ, Sayer AA (2019) Sarcopenia. Lancet 393(10191):2636–2646. https://doi.org/10.1016/S0140-6736(19)31138-9
46. Calvani R, Marini F, Cesari M, Tosato M, Anker SD, Von Haehling S et al (2015) Biomarkers for physical frailty and sarcopenia: state of the science and future developments. J Cachexia Sarcopenia Muscle 6(4):278–286. https://doi.org/10.1002/jcsm.12051

47. Cruz-Jentoft AJ, Kiesswetter E, Drey M, Sieber CC (2017) Nutrition, frailty, and sarcopenia. Aging Clin Exp Res 29(1):43–48
48. Bano G, Trevisan C, Carraro S, Solmi M, Luchini C, Stubbs B et al (2017) Inflammation and sarcopenia: a systematic review and meta-analysis. Maturitas 96:10–15. https://doi.org/10.1016/j.maturitas.2016.11.006
49. Can B, Kara O, Kizilarslanoglu MC, Arik G, Aycicek GS, Sumer F et al (2017) Serum markers of inflammation and oxidative stress in sarcopenia. Aging Clin Exp Res 29(4):745–752
50. Dunn JE, Rudberg MA, Furner SE, Cassel CK (1992) Mortality, disability, and falls in older persons: the role of underlying disease and disability. Am J Public Health 82(3):395–400
51. Du Y, Karvellas CJ, Baracos V, Williams DC, Khadaroo RG, Group ESA (2014) Sarcopenia is a predictor of outcomes in very elderly patients undergoing emergency surgery. Surgery 156(3):521–527
52. Anker MS, Von Haehling S, Springer J, Banach M, Anker SD (2013) Highlights of the mechanistic and therapeutic cachexia and sarcopenia research 2010 to 2012 and their relevance for cardiology. Int J Cardiol 162(2):73–76
53. Joglekar S, Nau PN, Mezhir JJ (2015) The impact of sarcopenia on survival and complications in surgical oncology: a review of the current literature. J Surg Oncol 112(5):503–509
54. Ioannidis JP, Patsopoulos NA, Rothstein HR (2008) Reasons or excuses for avoiding meta-analysis in forest plots. BMJ 336(7658):1413–1415. https://doi.org/10.1136/bmj.a117