Sarcopenia Is Associated with Mortality in Adults: A Systematic Review and Meta-Analysis

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Keywords
Sarcopenia · Muscular atrophy · Mortality · Population groups

Abstract

\textbf{Background:} Sarcopenia can predispose individuals to falls, fractures, hospitalization, and mortality. The prevalence of sarcopenia depends on the population studied and the definition used for the diagnosis. \textbf{Objective:} This systematic review and meta-analysis aimed to investigate the association between sarcopenia and mortality and if it is dependent on the population and sarcopenia definition. \textbf{Methods:} A systematic search was conducted in MEDLINE, EMBASE, and Cochrane from 1 January 2010 to 6 April 2020 for articles relating to sarcopenia and mortality. Articles were included if they met the following criteria – cohorts with a mean or median age ≥18 years and either of the following sarcopenia definitions: Asian Working Group for Sarcopenia (AWGS and AWGS2019), European Working Group on Sarcopenia in Older People (EWGSOP and EWGSOP2), Foundation for the National Institutes of Health (FNIH), International Working Group for Sarcopenia (IWGS), or Sarcopenia Definition and Outcomes Consortium (SDOC). Hazard ratios (HR) and odds ratios (OR) were pooled separately in meta-analyses using a random-effects model, stratified by population (community-dwelling adults, outpatients, inpatients, and nursing home residents). Subgroup analyses were performed for sarcopenia definition and follow-up period. \textbf{Results:} Out of 3,025 articles, 57 articles were included in the systematic review and 56 in the meta-analysis (42,108 participants, mean age of 49.4 ± 11.7 to 86.6 ± 1.0 years, 40.3% females). Overall, sarcopenia was associated with a significantly higher risk of mortality (HR: 2.00 [95% CI: 1.71, 2.34]; OR: 2.35 [95% CI: 1.64, 3.37]), which was independent of population, sarcopenia definition, and follow-up period in subgroup analyses. \textbf{Conclusions:} Sarcopenia is associated with a significantly higher risk of mortality, independent of population and sarcopenia definition, which highlights the need for screening and early diagnosis in all populations.

Jane Xu and Ching S. Wan contributed equally.
Introduction

Sarcopenia, age-related low muscle mass and function, is prevalent in 9.9–40.4% of community-dwelling adults [1, 2], 2–34% of outpatients [3], and 56% of hospitalized patients [4]. Sarcopenia is highly prevalent as comorbid disease, for example, in individuals with cardiovascular disease, dementia, diabetes mellitus, and respiratory disease [5]. Sarcopenia definitions have been proposed by various working groups and include muscle mass, muscle strength, and physical performance combinations and vary in cutoff points and diagnostic algorithms [6–11]. Independent of the definition used, sarcopenia is associated with adverse health outcomes such as falls and fractures [12], functional decline [13], and hospitalization [14].

Sarcopenia is associated with a 2 times higher risk of mortality in community-dwelling adults [15] and nursing home residents [16] and 3 times higher risk in cancer patients [17]. Previous systematic reviews evaluating the association of sarcopenia and mortality included articles published until 2017 [14–16, 18]. As new definitions of sarcopenia were proposed in 2018 [7], 2019 [6], and 2020 [19] and the prevalence of sarcopenia depends on the studied population and the definition used [20, 21], an updated systematic review on the association between sarcopenia and mortality is needed. The aim of this systematic review and meta-analysis was to assess the association between sarcopenia and mortality and if this association is dependent on population, sarcopenia definition, and follow-up period.

Methods

Data Sources and Searches

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) was followed for all steps in this systematic review (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517099) [22]. The protocol was registered on PROSPERO (international prospective register of systematic reviews): CRD42020179744. The electronic databases MEDLINE, EMBASE, and Cochrane Library (CENTRAL) were searched for from 1 January 2010 until 6 April 2020 for articles relating to sarcopenia and mortality. The start date of the search was chosen as 2010, the year the first working group definition was published [11]. The search was developed with the assistance of a senior academic librarian from a biomedical university library. The search strategy and search terms used for this search are detailed in online suppl. Table 2. The reference list of each included article was manually searched to identify additional articles. Authors were contacted if additional information was required to include the article in the meta-analysis.

Article Selection

Two reviewers independently screened the titles and abstracts and subsequently the included full text of articles (J.X. and K.K.). Any discrepancies were resolved by a third reviewer (C.S.W.). Articles were included if they met the following criteria – a longitudinal cohort with a mean or median age ≥18 years of age and reporting the association between sarcopenia and mortality using one of the following sarcopenia definitions: Asian Working Group for Sarcopenia (AWGS and AWGS2019) [6, 9], European Working Group on Sarcopenia in Older People (EWGSOP and EWGSOP2) [7, 11], Foundation for the National Institutes of Health (FNHI) [8], International Working Group for Sarcopenia (IWGS) [10], or Sarcopenia Definition and Outcomes Consortium (SDOC) [19]. Exclusion criteria included case reports (<20 individuals), reviews, conference abstracts, articles that were not published in the English language, or full text was not available. If articles reported data of the same cohort [23–26], the article with the largest sample size was included [24, 26].

Data Extraction and Risk of Bias Assessment

The following data were extracted independently by 2 reviewers (J.X. and K.K.): first author, publication year, country of included participants, sample size, sex, age, population, sarcopenia definition, sarcopenia prevalence, methodologies to measure muscle mass, muscle strength and physical performance and the respective cutoff values used, follow-up period, effect size and its 95% confidence intervals (CI) of the association between sarcopenia and mortality, and any adjustments made if multivariable models were reported. The weighted mean for age was calculated if age was stratified by groups.

The risk of bias assessment was performed independently by 2 reviewers (J.X. and K.K.) using a modified Newcastle-Ottawa Scale (NOS) [27] provided in online suppl. Table 3. Any discrepancies were resolved by a third reviewer (C.S.W.). The highest possible score for NOS, reflecting the lowest risk of bias, was 9 stars. A median score of 7 was used as the cutoff to classify an article as having either a low or high risk of bias [27].

Data Synthesis and Statistical Analysis

A random-effects model was used to pool hazard ratio (HR) and odds ratio (OR) separately for the association between sarcopenia and mortality. All analyses were stratified by population (community-dwelling adults, outpatients, inpatients, and nursing home residents). For the main meta-analysis, if multiple sarcopenia definitions were used, the following sarcopenia definition was included in the primary analysis for the association between sarcopenia and mortality: (1) the definition that was developed across the cohort’s country was selected (i.e., EWGSOP for European cohort) and (2) if the same definition was used more than once, the definition with the cutoff points closest to the original cutoff points was included.

If more than 1 statistical adjustment model for the association between sarcopenia and mortality was reported, the model included in the meta-analyses was based on the following hierarchy: (1) age and sex (when stratified by sex, the model that adjusted only for age was included; when stratified by age, the model that adjusted only for sex was included); (2) age, sex, cognitive impairment, and/or other comorbidities; (3) age, sex, cognitive impairment and/or other comorbidities, and other confounders; (4) age and other confounders; (5) age alone; and (6)
crude model. When articles reported more than 1 follow-up period, the model with the shortest follow-up time was included in the meta-analysis as confounding factors may have a greater effect at longer follow-up periods. Subgroup analyses for sarcopenia definition, follow-up period, and risk of bias were performed if 2 or more articles were included. For all populations, the median follow-up period was used as the cutoff for short (< median) and long term (≥ median).

Heterogeneity was assessed with $I^2$ statistics for each subgroup, with low defined as $I^2 \leq 25\%$, moderate as $I^2 = 25–75\%$, and high as $I^2 \geq 75\%$ [28]. The Cochran’s Q value was used to evaluate between-group heterogeneity and $p$ value of $<0.05$ of the Q value ($Q_p$) indicated a statistically significant difference between the groups [28]. Publication bias of the overall association of sarcopenia with mortality was assessed by funnel plots of log HR and log OR against its standard error. Egger’s regression test was used to evaluate the statistical significance of publication bias [29]. $p$ values $<0.05$ were considered statistically significant (2-tailed). Meta-analysis was performed using Comprehensive Meta-Analysis (CMA version 3.3; Biostat Inc., Englewood, NJ, USA).

**Results**

After retrieval of 5,901 articles from electronic databases and removal of duplicates, 3,025 articles were identified for title and abstract screening. In total, 121 articles were screened for full text, of which 57 articles were included in this systematic review. The authors of 1 article did not provide additional information for the meta-analysis; therefore, 56 articles were included in the meta-analysis (shown in Fig. 1).

Table 1 shows the study characteristics of the included articles. Nineteen articles included community-dwelling cohorts (31,008 individuals, age range of ≥60 years to 86.6 ± 1.0 years, 36.6% females) and the EWGSOP was most used (12/19 articles) [26, 30–40], followed by FNIH (10/19 articles) [33, 34, 37–39, 41–45], AWGS (4/19 articles) [34, 37, 44, 46], IWGS (3/19 articles) [33, 34, 37], and EWGSOP2 (3/19 articles) [39, 40, 47]. Nine articles
Table 1. Characteristics of included articles, stratified by population

| Author                  | Country | Population/ward     | N     | Female, n (%) | Age, years | Sarcopenia definition | Mortality source | FU, months |
|-------------------------|---------|---------------------|-------|---------------|------------|-----------------------|------------------|------------|
| **Community-dwelling adults** |         |                     |       |               |            |                       |                  |            |
| Yuki et al. [46]        | JPN     | Community           | 720   | 355 (49.0)    | 71.4±0.5\a | AWGS                  | Registry         | 132\d      |
| Alexandre et al. [31]   | BRA     | Community           | 1,149 | 712 (59.5)    | 69.6±2.0   | EWGSOP                | Registry         | 60         |
| Arango-Lopera et al. [30]| MEX   | Community           | 345   | 184 (53.3)    | 78.5±7.0   | EWGSOP                | Registry         | 36         |
| Bianchi et al. [35]     | ITA     | Community           | 538   | 288 (53.5)    | 77.1±5.5   | EWGSOP                | Registry         | 108        |
| Brown et al. [36]       | USA     | Community           | 4,425 | 2,500 (56.5)  | 70.1 (0.1)\b | EWGSOP                | Registry         | 173\c      |
| Kim et al. [32]         | KOR     | Community           | 556   | 272 (49.0)    | ≥65        | EWGSOP                | Registry         | 72         |
| Landi et al. [26]       | ITA     | Community           | 354   | 236 (67.0)    | 84.2±10.2  | EWGSOP2               | Registry         | 120        |
| Costanzo et al. [47]    | ITA     | Community           | 535   | 287 (53.6)    | 77.0±5.5   | EWGSOP2               | NR               | 37\d       |
| Costanzo et al. [47]    | BRA     | Community           | 1,291 | 808 (62.6)    | ≥65        | EWGSOP, FNIH, IWGS    | Hospital         | 118±36     |
| De Buysere et al. [43]  | BEL     | Community           | 191   | 0             | 78.4±3.5   | FNIH                  | Survey           | 180        |
| Hirani et al. [42]      | AUS     | Community           | 1,678 | 0             | 76.8±2.3\a | FNIH                  | Registry         | 113        |
| McLean et al. [41]      | USA, ITA| Community           | 6,280 | 1,869 (30.0)  | 74.7±2.3\a | FNIH                  | Registry         | 120        |
| Tang et al. [45]        | CHN     | Community           | 728   | 343 (47.1)    | 73.4±5.4   | FNIH                  | Phone            | 32.9±8.8   |
| Moon et al. [44]        | KOR     | Community           | 560   | 275 (49.0)    | 73.8±7.4   | AWGS, FNIH            | Registry         | 72         |
| Bachetti et al. [40]    | BRA     | Community           | 1,291 | 808 (62.6)    | ≥60        | EWGSOP, EWGSOP2       | Registry         | 31         |
| Sim et al. [38]         | AUS     | Community           | 903   | 903 (100)     | 79.9±2.6   | EWGSOP, FNIH          | Registry         | 60 and 114\d|
| Sobestiansky et al. [39]| SWE     | Community           | 287   | 0             | 86.6±1.0   | EWGSOP, EWGSOP2, FNIH | Registry         | 36         |
| Locquet et al. [37]     | BEL     | Community           | 534   | 323 (60.5)    | 73.5±6.2   | AWGS, EWGSOP, FNIH, IWGS| Phone           | 36         |
| Woo et al. [34]         | HKG     | Community           | 4,000 | 2,000 (50.0)  | >65        | AWGS, EWGSOP, FNIH, IWGS| NR              | 120        |
| **Outpatients**         |         |                     |       |               |            |                       |                  |            |
| Kamijo et al. [53]      | JPN     | Peritoneal dialysis | 119   | 35 (29.4)     | 66.8±13.2  | AWGS                  | NR               | 19\d       |
| Mori et al. [54]        | JPN     | Hemodialysis        | 308   | 123 (39.9)    | 58.1±3.3\a | AWGS                  | NR               | 108        |
| Giglio et al. [48]      | BRA     | Hemodialysis        | 170   | 60 (35.0)     | 70.6±7.2   | EWGSOP                | Hospital, phone  | 36         |
| Olesen et al. [50]      | DNK     | Chronic pancreatitis| 182   | 56 (31.0)     | 57.4±12.9  | EWGSOP                | Hospital         | 12         |
| Ren et al. [51]         | CHN     | Maintenance hemodialysis | 131 | 51 (39.0) | 49.4±11.7 | EWGSOP, FNIH          | NR               | 12         |
| Santos et al. [51]      | NR      | Liver cirrhosis     | 261   | 100 (38.3)    | 57.0 (51.8, 63.0)\c | EWGSOP           | NR               | 12         |
| Alberti et al. [55]     | BRA     | Acute day care hospital | 665 | 421 (63.6)  | 78.7±8.3   | FNIH                  | Phone            | 12         |
| Kätkusiknam et al. [56] | USA     | Hemodialysis        | 645   | 267 (41.4)    | 56.7±14.5  | FNIH                  | Hospital         | 38         |
| Lin et al. [49]         | CHN     | Hemodialysis        | 126   | 61 (48.4)     | 63.2±13.0  | AWGS, EWGSOP          | Hospital         | 36         |
| **Inpatients**          |         |                     |       |               |            |                       |                  |            |
| Harimoto et al. [72]    | JPN     | Living donor liver transplant | 102 | 56 (51.6) | 55.8 (54.0, 57.7)\c | AWGS           | NR               | 6          |
| Hu et al. [73]          | CHN     | Acute geriatric     | 453   | 135 (29.8)    | 79.0±7.8   | AWGS                  | Registry         | 36         |
| Kaido et al. [74]       | JPN     | Living donor liver transplant | 72 | 34 (47.0) | 55.0 (21.0, 68.0)\c | AWGS           | NR               | 12         |
| Yang et al. [75]        | CHN     | Acute geriatric     | 288   | 63 (21.9)     | 81.1±6.6   | AWGS                  | Registry, phone  | 36         |
| Yoo et al. [76]         | KOR     | Hip fracture        | 324   | 246 (75.9)    | 77.8±9.7   | AWGS                  | Hospital, phone  | 12         |
| Zhang et al. [77]       | CHN     | Coronary heart disease | 345 | 137 (39.7)  | 74.0 (69.0, 79.0)\c | AWGS           | Phone            | 12         |
| Atmis et al. [66]       | TUR     | Unspecified         | 350   | 196 (56.0)    | 77.2±7.7   | EWGSOP                | Registry         | 24         |
| Bayraktar et al. [60]   | TUR     | Geriatric and internal medicine acute care | 200 | 104 (52.0) | 74.5±6.3  | EWGSOP                | Hospital         | 8          |
| Beretta et al. [58]     | BRA     | Unspecified         | 610   | 313 (51.0)    | 71.4±6.5   | EWGSOP                | Registry         | 24         |
| Bernabeu-Wittel et al. [67]\f | SPN   | Unspecified         | 444   | 200 (45.0)    | 77.3±8.4   | EWGSOP                | NR               | 12         |
Table 1 (continued)

| Author                        | Country | Population/ward                        | N   | Female, n (%) | Age, years | Sarcopenia definition | Mortality source | FU, months |
|-------------------------------|---------|----------------------------------------|-----|---------------|------------|-----------------------|------------------|------------|
| Cerri et al. [63]             | ITA     | Acute geriatric                        | 80  | 48 (60.0)     | 84.3±2.7   | EWGSOP                | Phone            | 3          |
| Gariballa et al. [61]         | NR      | Unspecified                            | 432 | 205 (47.5)    | 77.2±2.5   | EWGSOP                | NR               | 6          |
| Isoyama et al. [62]           | SWE     | Incident dialysis                      | 330 | 127 (38.0)    | 53.0±13.0  | EWGSOP                | NR               | 60         |
| Perez-Zepeda et al. [64]      | AUS     | GEMU                                   | 172 | NR            | 85.2±6.4   | EWGSOP                | Registry         | 12         |
| Pourhassan et al. [65]        | DEU     | Acute geriatric                        | 198 | 139 (70.2)    | 82.8±5.9   | EWGSOP                | Phone            | 12         |
| Rustani et al. [68]           | ITA     | Internal medicine                      | 119 | 60 (50.4)     | 82.8±7.0   | EWGSOP                | Hospital         | 12         |
| Sanchez-Rodriguez et al. [69] | SPN     | Subacute geriatric                     | 95  | 60 (63.2)     | 84.5±6.5   | EWGSOP                | Hospital, phone  | 3          |
| Sanchez-Rodriguez et al. [24] | SPN     | Subacute geriatric                     | 99  | 61 (61.6)     | 84.6±6.6   | EWGSOP                | Hospital, phone  | 3          |
| Teng et al. [71]              | CHN     | Cardiac surgery                        | 242 | 80 (33.0)     | 61.0±3.4   | EWGSOP                | Hospital, phone  | 12         |
| Vetrano et al. [59]           | FRA     | Geriatric and internal medicine acute  | 770 | 431 (56.0)    | 81.0±7.0   | EWGSOP                | Phone            | 12         |
| Zengarini et al. [70]         | ITA     | Geriatric and internal medicine acute  | 624 | 350 (56.1)    | 80.1±7.0   | EWGSOP                | Phone            | 12         |
| Malafarina et al. [79]        | SPN     | Hip fracture                           | 187 | 138 (73.8)    | 85.2±6.3   | EWGSOP2               | NR               | 84         |
| Bianchi et al. [78]           | ITA     | Geriatric and internal medicine acute  | 610 | 313 (51.3)    | 80.7±6.6   | EWGSOP2, FNIH         | Registry         | 36         |
| Sipers et al. [57]            | NLD     | Acute geriatric                        | 81  | 59 (73.0)     | 84.0±5.0   | EWGSOP, FNIH, IWGS    | Hospital, caregiver | 24         |

Nursing home residents

| Author                        | Country | Population/ward                        | N   | Female, n (%) | Age, years | Sarcopenia definition | Mortality source | FU, months |
|-------------------------------|---------|----------------------------------------|-----|---------------|------------|-----------------------|------------------|------------|
| Buckinx et al. [84]           | BEL     | Nursing home                           | 662 | 480 (72.5)    | 83.2±9.0   | EWGSOP                | Hospital         | 12         |
| Henwood et al. [82]           | AUS     | Nursing home                           | 58  | 41 (70.7)     | 85.6±8.2   | EWGSOP                | NR               | 18         |
| Landi et al. [80]             | ITA     | Nursing home                           | 122 | 91 (75.0)     | 84.1±4.8   | EWGSOP                | NR               | 6          |
| Saka et al. [81]              | NR      | Nursing home                           | 402 | 199 (49.0)    | 78.0±7.9   | EWGSOP                | Hospital         | 12         |
| Yalcin et al. [83]            | TUR     | Nursing home                           | 141 | 64 (45.7)     | 79.2±8.0   | EWGSOP                | Hospital         | 24         |

AUS, Australia; AWGS, Asian Working Group for Sarcopenia; BEL, Belgium; BRA, Brazil; CHN, China; DEU, Germany; DNK, Denmark; EWGSOP, European Working Group on Sarcopenia in Older People 2010; EWGSOP2, European Working Group on Sarcopenia in Older People 2018; FNIH, Foundation for the National Institutes of Health; FRA, France; FU, follow-up; GEMU, geriatric evaluation and management unit; HKG, Hong Kong; ITA, Italian; IWGS, International Working Group for Sarcopenia; JPN, Japan; KOR, Korea; MEX, Mexico; NLD, the Netherlands; NR, not reported; SPN, Spain; SWE, Sweden; TUR, Turkey. aWeighted mean and SD. bMean [standard error]. cMedian (range). dMean presented without SD. eMedian. fOutpatients and inpatients. gFollow-up of 5 and 9.5 years.
Sarcopenia diagnosed by the EWGSOP, EWGSOP2, and FNIH was associated with significantly higher risk of mortality in all populations: community-dwelling adults (EWGSOP: HR = 1.90 [95% CI: 1.52, 2.37], I²: 50.4%; EWGSOP2: HR = 1.73 [95% CI: 1.02, 2.93], I²: 0%; FNIH: HR = 1.80 [95% CI: 1.41, 2.29], I²: 5.4%), outpatients (EWGSOP: HR = 2.37 [95% CI: 1.43, 3.93], I²: 29.8%; FNIH: HR = 1.69 [95% CI: 1.16, 2.47], I²: 0%), and inpatients (EWGSOP: HR = 1.94 [95% CI: 1.39, 2.71], I²: 45.3%; OR = 2.34 [95% CI: 1.37, 4.00], I²: 60.4%; FNIH: HR = 2.16 [95% CI: 1.19, 3.93], I²: 81.3%). Sarcopenia diagnosed by the AWGS was associated with significantly higher risk of mortality in community-dwelling adults (AWGS: HR = 1.96 [95% CI: 1.29, 2.96], I²: 56.7%) and inpatients (AWGS: HR = 2.31 [95% CI: 1.47, 3.63], I²: 66.9%; OR = 6.41 [95% CI: 1.76, 23.28], I²: 17.6) but not significant in outpatients (HR: 1.40 [95% CI: 0.91, 2.16], I²: 0%). There was no significant difference between the heterogeneity of effect estimates (community-dwelling adults [HR: Qdp = 0.972], outpatients [HR: Qdp = 0.300], and inpatients [HR: Qdp = 0.883; OR: Qdp = 0.158]).

The significant association between sarcopenia and mortality was independent of the follow-up period in all populations: community-dwelling adults (long-term HR = 1.78 [95% CI: 1.48, 2.14], I²: 36.7%; short-term HR = 2.01 [95% CI: 1.55, 2.60], I²: 0%); outpatients (long-term HR = 1.64 [95% CI: 1.12, 2.38], I²: 0%; short-term HR = 2.12 [95% CI: 1.22, 3.70], I²: 73.0%); and inpatients (long-term HR = 2.68 [95% CI: 2.02, 3.55], I²: 58.3%; short-term HR = 1.51 [95% CI: 1.06, 2.17], I²: 32.5%). There was no statistically significant difference between the heterogeneity of effect estimates for the follow-up period for community-dwelling adults (HR: Qdp = 0.461) and outpatients (HR: Qdp = 0.448), but for inpatients (HR: Qdp = 0.015) (online suppl. Fig. 5–7).

The association of sarcopenia with mortality was independent of risk of bias (high risk of bias: HR = 2.58 [95% CI: 1.90, 3.52], I²: 63.7%; OR = 3.19 [95% CI: 2.23, 4.56], I²: 20.1%; low risk of bias: HR = 1.89 [95% CI: 1.66, 2.15], I²: 36.9%; OR = 1.74 [95% CI: 1.29, 2.34], I²: 32.2%). The heterogeneity of effect estimates for risk of bias was not statistically significant for HRs (Qdp = 0.069), but for ORs (Qdp = 0.010) (online suppl. Fig. 8, 9). Overall, heterogeneity was low to moderate across all pooled HRs and ORs apart from the pooled FNIH HR stratifying for sarcope-
Table 2. Quality assessment of included articles using the NOS, stratified by population

| Author                                | Selection | Comparability | Outcome | Total score |
|----------------------------------------|-----------|---------------|---------|-------------|
|                                        | Q1 | Q2 | Q3 | Q4 | Q1 | Q1 | Q2 | Q3 |               |
| **Community-dwelling adults**          |   |   |   |   |   |   |   |   |               |
| Yuki et al. [46]                       | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8            |
| Alexandre et al. [31]                  | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| Arango-Lopera et al. [30]              | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 5            |
| Bianchi et al. [35]                    | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| Brown et al. [36]                      | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 7            |
| Kim et al. [32]                        | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 6            |
| Landi et al. [26]                      | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| Costanzo et al. [47]                   | 0 | 1 | 1 | 1 | 2 | 0 | 1 | 1 | 7            |
| Cawthon et al. [33]                    | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8            |
| De Buys et al. [43]                    | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7            |
| Hirani et al. [42]                     | 1 | 1 | 1 | 1 | 2 | 0 | 1 | 1 | 8            |
| McLean et al. [41]                     | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 7            |
| Tang et al. [45]                       | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9            |
| Moon et al. [44]                       | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7            |
| Bachettini et al. [40]                 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 7            |
| Sim et al. [38]                        | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8            |
| Sobestiansky et al. [39]               | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8            |
| Locquet et al. [37]                    | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| Woo et al. [34]                        | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7            |
| **Outpatients**                        |   |   |   |   |   |   |   |   |               |
| Kamijo et al. [53]                     | 1 | 1 | 1 | 1 | 2 | 0 | 1 | 1 | 8            |
| Mori et al. [54]                       | 1 | 1 | 1 | 1 | 2 | 0 | 1 | 0 | 7            |
| Giglio et al. [48]                     | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9            |
| Olesen et al. [50]                     | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 5            |
| Ren et al. [52]                        | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 5            |
| Santos et al. [51]                     | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 6            |
| Aliberti et al. [55]                   | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| Kittiskulnam et al. [56]               | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| Lin et al. [49]                        | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| **Inpatients**                         |   |   |   |   |   |   |   |   |               |
| Harimoto et al. [72]                   | 0 | 1 | 1 | 1 | 2 | 0 | 1 | 1 | 7            |
| Hu et al. [73]                         | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 6            |
| Kaido et al. [74]                      | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 6            |
| Yang et al. [75]                       | 0 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 8            |
| Yoo et al. [76]                        | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9            |
| Zhang et al. [77]                      | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9            |
| Atmis et al. [66]                      | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 7            |
| Bayraktar et al. [60]                  | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 5            |
| Beretta et al. [58]                    | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 7            |
| Bernabeu-Wittel et al. [67]a           | 0 | 1 | 1 | 1 | 2 | 0 | 1 | 0 | 6            |
| Cerri et al. [63]                      | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 6            |
| Gariballa et al. [61]                  | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 4            |
| Isoyama et al. [62]                    | 0 | 1 | 1 | 1 | 2 | 0 | 0 | 1 | 6            |
| Perez-Zepeda et al. [64]               | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| Pourhassan et al. [65]                 | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 7            |
| Rustani et al. [68]                    | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 6            |
| Sanchez-Rodriguez et al. [69]          | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| Sanchez-Rodriguez et al. [24]          | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 6            |
| Teng et al. [71]                       | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 6            |
| Vetrano et al. [59]                    | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
| Zengarini et al. [70]                  | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8            |
nia definitions in inpatients, where heterogeneity was high.

**Publication Bias**

Asymmetry was observed by visual inspection of funnel plots for articles that reported HR and OR (online suppl. Fig. 10). Egger’s regression test revealed significant publication bias among the included articles in the meta-analysis for articles that reported HRs ($p = 0.006$), but not for articles that reported ORs ($p = 0.053$).

**Discussion**

Sarcopenia is significantly associated with mortality in adults, independent of the population studied, sarcopenia definition, follow-up period, and risk of bias. This review adds significantly to the literature, as it includes the updated definition of sarcopenia, which are being implemented into clinical practice [7]. The findings that sarcopenia is significantly associated with mortality are consistent with the reviews published previously [14–16, 18]. The results from the subgroup analyses showing the independence of the association of population [14], follow-up [14, 15], and risk of bias [14] are also consistent with the reviews that examined these relations.

Original studies and systematic reviews have extensively demonstrated that individuals with sarcopenia are at risk of functional decline [13], frailty [85], decreased mobility [86], falls, fractures [12], and hospitalization [87], which can all contribute to a higher mortality risk. One of the main mechanisms relating sarcopenia to mortality is falls. Low muscle mass and strength contribute to the impairment of balance [88], which is associated with falls [89]. As osteoporosis and malnutrition are highly prevalent in older adults [90–92], this increases the susceptibility of fractures accompanying falls that can lead to hospitalization. Prolonged inactivity and bed rest during hospitalization could contribute to a decrease in muscle mass and strength [93], leading to functional decline and a greater risk of future falls following hospital discharge and higher incidence of readmissions [75]. Sarcopenia is also associated with a higher length of hospital stay [94] and as hospitalization contributes to loss of muscle mass and strength [93], this perpetuating cycle of functional decline and rehospitalization may contribute to mortality. Early screening and diagnosis of sarcopenia in primary care and hospitals are crucial for the implementation of prevention or intervention programs to alleviate the associated risks of sarcopenia and reduce the healthcare burden and costs.

Irrespective of the definition used for the diagnosis, sarcopenia was associated with a higher risk of mortality. This is remarkable, as the use of different definitions leads to a different prevalence of sarcopenia [21, 95] and therewith to comparisons of different proportions of populations determined to be affected. The association between sarcopenia and other clinically relevant outcomes such as falls and fractures [12] remains significant, while using different definitions highlights the strong clinical association of sarcopenia with adverse health outcomes irrespective of the definition used for diagnosis. Therewith, iden-
## Table 3. The association between sarcopenia and mortality, stratified by population

| Author                  | Sarcopenia definition | EM     | Effect size (95% CI) | Adjustments                                                                                                                                                                                                 |
|-------------------------|-----------------------|--------|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Community-dwelling adults** |                       |        |                      |                                                                                                                                                                                                          |
| Yuki et al. [46]        | AWGS                  | HR     | M: 1.86 (1.03, 3.37) F: 1.03 (0.41, 2.60) | Age                                                                                                                                                                                                       |
| Alexandre et al. [31]   | EWGSOP                | HR     | 1.72 (1.20, 2.47)    | Age, sex, income, marital status, education, smoking, weekly alcohol intake, sedentary lifestyle, PAH, DM, lung disease, CVD stroke, cancer, number of diseases, falls, hospitalization, MMSE, GDS, ADL, and IADL |                                                                                                                                                                                                          |
| Arango-Lopera et al. [30]| EWGSOP               | HR     | 2.39 (1.05, 5.43)    | Age, IHD, health self-perception, and ADL                                                                                                                                                                 |
| Bianchi et al. [35]     | EWGSOP                | HR     | 2.12 (1.05, 4.30)    | Age and sex                                                                                                                                                                                                |
| Brown et al. [36]       | EWGSOP                | HR     | 1.40 (1.25, 1.57)    | Age and sex                                                                                                                                                                                                |
| Kim et al. [32]         | EWGSOP                | HR     | M: 4.63 (1.62, 13.3) F: 0.86 (0.18, 4.01) | Age and BMI                                                                                                                                                                                                 |
| Landi et al. [26]       | EWGSOP                | HR     | 2.91 (1.50, 5.67)    | Age and sex                                                                                                                                                                                                |
| Costanzo et al. [47]    | EWGSOP2               | HR     | 2.30 (0.85, 6.18)    | Age and sex                                                                                                                                                                                                |
| Cawthon et al. [33]     | FNIH                  | HR     | 3.49 (2.01, 6.05)    | Age                                                                                                                                                                                                         |
| De Buyser et al. [43]   | FNIH                  | HR     | 2.50 (1.30, 4.79)    | Age                                                                                                                                                                                                         |
| Hirani et al. [42]      | FNIH                  | HR     | 1.69 (1.17, 2.44)    | Age, income, living status, BMI, comorbidities, dementia, ADL disability, low Hb, polypharmacy, and low albumin                                                                                             |
| McLean et al. [41]      | FNIH                  | HR     | M: 1.27 (0.65, 2.46) F: 1.51 (0.61, 3.71) | Age                                                                                                                                                                                                       |
|                        |                       |        | F: 1.15 (0.28, 4.70) F: 1.65 (0.52, 5.25) |                                                                                                                                                                                                          |
|                        |                       |        | F: 3.62 (0.49, 26.6) F: 0.60 (0.08, 4.36) |                                                                                                                                                                                                          |
| Tang et al. [45]        | FNIH                  | HR     | 3.44 (1.17, 10.1)    | Age and sex                                                                                                                                                                                                |
| Moon et al. [44]        | AWGS                  | HR     | M: 1.83 (0.89, 3.79) F: 0.98 (0.27, 3.50) | Age, BMI, SBF, fasting glucose, total cholesterol, Cr, ALT, free T4, and CIRS                                                                                                                                 |
|                        | FNIH                  | HR     | M: 4.45 (2.12, 9.34) F: 1.0 (0.31, 3.25) | Age, BMI, SBF, fasting glucose, total cholesterol, Cr, ALT, free T4, and CIRS                                                                                                                                 |
| Bachettini et al. [40]  | EWGSOP                | HR     | 1.18 (0.53, 2.65)    | Age, sex, marital status, working, smoking, physical activity at leisure, BMI, comorbidities, and depressive symptoms                                                                                  |
|                        | EWGSOP2               | HR     | 1.36 (0.52, 3.57)    | Age, sex, marital status, working, smoking, physical activity at leisure, BMI, comorbidities, and depressive symptoms                                                                                  |
| Sim et al. [38]         | EWGSOP                | HR     | 1.88 (1.24, 2.85)    | Age                                                                                                                                                                                                         |
|                        | FNIH                  | HR     | 1.08 (0.56, 2.08)    | Age                                                                                                                                                                                                         |
| Sobestiansky et al. [39]| EWGSOP                | HR     | 1.95 (1.12, 3.40)    | Age, CCI, education, smoking, and MMSE                                                                                                                                                                     |
|                        | EWGSOP2               | HR     | 1.70 (0.94, 3.05)    | Age, CCI, education, smoking, and MMSE                                                                                                                                                                     |
|                        | FNIH                  | HR     | 1.65 (0.73, 3.72)    | Age, CCI, education, smoking, and MMSE                                                                                                                                                                     |
| Locquet et al. [37]     | AWGS                  | HR     | 5.85 (2.47, 13.8)    | Age and sex                                                                                                                                                                                                |
|                        | EWGSOP                | HR     | 4.20 (1.74, 10.1)    | Age and sex                                                                                                                                                                                                |
|                        | FNIH                  | HR     | 2.47 (0.68, 8.93)    | Age and sex                                                                                                                                                                                                |
**Table 3** (continued)

| Author | Sarcopenia definition | EM | Effect size (95% CI) | Adjustments |
|--------|-----------------------|----|----------------------|-------------|
| Woo et al. [34] | EWGSOP | OR | M: 2.74 (1.95, 3.85) | Age, education, COPD, DM, hypertension, CVD, current smoker, MMSE, and depression |
| FNIH | OR | M: 2.32 (1.23, 4.37) | Age, education, COPD, DM, hypertension, CVD, current smoker, MMSE, and depression |
| IWGS | OR | M: 1.26 (0.97, 1.63) | Age, education, COPD, DM, hypertension, CVD, current smoker, MMSE, and depression |

**Outpatients**

| Author | Sarcopenia definition | EM | Effect size (95% CI) | Adjustments |
|--------|-----------------------|----|----------------------|-------------|
| Mori et al. [54] | AWGS | HR | 1.31 (0.81, 2.10) | Age, sex, duration of hemodialysis (years), BMI, DM, serum albumin, Kt/V, and nPCR |
| Giglio et al. [48] | EWGSOP | HR | 2.09 (1.05, 4.20) | Age, sex, dialysis vintage, and DM |
| Olesen et al. [50] | EWGSOP | HR | 6.69 (1.79, 24.9) | Crude |
| Ren et al. [52] | EWGSOP | OR | 14.0^f | Crude |
| Santos et al. [51] | EWGSOP | OR | 3.06^f | Crude |
| Aliberti et al. [55] | FNIH | HR | 1.69 (1.05, 2.73) | Age, sex, race, income, CCI, depressive symptoms, cognitive impairment, and unintentional weight loss |
| Kittiskulnam et al. [56] | FNIH | HR | 1.69 (0.91, 3.14) | Age, sex, and race |
| Lin et al. [49] | AWGS | HR | 1.94 (0.70, 5.42) | Age, sex |

**Inpatients**

| Author | Sarcopenia definition | EM | Effect size (95% CI) | Adjustments |
|--------|-----------------------|----|----------------------|-------------|
| Harimoto et al. [72] | AWGS | OR | 4.02 (1.19, 13.5) | Recipient age, donor age, recipient sex, recipient status (hospitalized/home), BMI, DM, MELD score, HCC/non-HCC, major vessel shunt, GV/SLV, portal vein pressure at laparotomy, and low skeletal muscle area |
| Hu et al. [73] | AWGS | HR | 4.25 (2.22, 8.12)^f | Crude |
| Kaido et al. [74] | AWGS | OR | 13.11^f | Crude |
| Yang et al. [75] | AWGS | HR | 2.26 (1.29, 3.95) | Age and sex |
| Yoo et al. [76] | AWGS | HR | 1.84 (0.69, 4.92) | Age, sex, BMI, and Koval (≥4) |
| Zhang et al. [77] | AWGS | HR | 0.41 (0.13, 1.33) | Age, sex, and CCI |
| Atmis et al. [66] | EWGSOP | HR | 6.41 (2.93, 14.4) | Age, sex, BMI, and ADL |
| Bayraktar et al. [60] | EWGSOP | OR | 3.22^f | Crude |
| Beretta et al. [58] | EWGSOP | HR | 1.34 (0.52, 3.49) | Age and sex |
| Bernabeu-Wittel et al. [67] | EWGSOP | HR | 1.34 (0.94, 1.91) | Age and sex |
| Cerri et al. [63] | EWGSOP | OR | 8.56^f | Crude |
| Gariballa et al. [61] | EWGSOP | OR | 3.46^f | Crude |
| Isoyama et al. [62] | EWGSOP | HR | 2.94 (1.64, 5.27) | Age and sex |
| Perez-Zepeda et al. [64] | EWGSOP | HR | 2.23 (1.15, 4.34) | Age, sex, and CCI |
| Pourhassan et al. [65] | EWGSOP | OR | 1.67^f | Crude |
| Rustani et al. [68] | EWGSOP | OR | 4.58^f | Crude |
| Sanchez-Rodriguez et al. [69] | EWGSOP | OR | 0.85 (0.44, 1.63) | Age, sex, CCI ≥2, unintentional weight loss, malnutrition, overweight-obesity, nutritional deficiency, and cachexia |
the heterogeneous nature of inpatient characteristics, further research is warranted to explore the appropriate cutoff for short-term and long-term mortality of patients admitted due to different reasons.

A significant association with mortality was found in both high and low risk of bias articles. High risk of bias articles lack adjustments for confounding effects, which may result in an overestimation of the association between sarcopenia and mortality. As the prevalence of sarcopenia is higher in males and with chronological age [96, 97], analyses not adjusted for confounders such as age and sex are therefore likely to have overestimated the association compared to adjusted analyses. A higher pooled HR and OR in

| Author                       | Sarcopenia definition | EM  | Effect size (95% CI) | Adjustments               |
|------------------------------|-----------------------|-----|----------------------|---------------------------|
| Sánchez-Rodriguez et al. [24]| EWGSOP OR             | 2.20 |                      | Crude                     |
| Teng et al. [71]             | EWGSOP OR             | 0.87 |                      | Crude                     |
| Vetrano et al. [59]          | EWGSOP HR             | 1.56 | (1.10, 2.30)         | Age and sex               |
| Zengarini et al. [70]        | EWGSOP HR             | 2.02 | (0.98, 4.14)         | Age and sex               |
| Malafarina et al. [79]       | EWGSOP2 HR            | 1.67 | (1.11, 2.51)         | Age, sex, and dialysis center |
| Bianchi et al. [78]          | EWGSOP2 HR            | 1.87 | (1.35, 2.59)         | Age and sex               |
| Zengarini et al. [70]        | FNIH HR               | 1.54 | (1.11, 2.15)         | Age and sex               |
| Sipers et al. [57]           | EWGSOP HR             | 4.31 | (2.09, 8.85)         | Crude                     |
| Sipers et al. [57]           | FNIH HR               | 3.57 | (1.90, 6.71)         | Crude                     |

**Nursing home residents**

| Author                       | Sarcopenia definition | EM  | Effect size (95% CI) | Adjustments                                           |
|------------------------------|-----------------------|-----|----------------------|-------------------------------------------------------|
| Buckinx et al. [84]          | EWGSOP OR             | 1.70 | (1.10, 2.92)         | Age, sex, arm circumference, general health perception, emotional role function, TFI, SHARE-FI, living in nursing homes, TT, and SPPB |
| Henwood et al. [82]          | EWGSOP OR             | 1.32 |                      | Crude                                                 |
| Landi et al. [80]            | EWGSOP HR             | 3.19 | (1.17, 8.66)         | Age and sex                                           |
| Saka et al. [81]             | EWGSOP OR             | 2.97 |                      | Crude                                                 |
| Yalcin et al. [83]           | EWGSOP HR             | 2.63 | (1.22, 5.65)         | Age and sex                                           |

ADL, activities of daily living; ALT, alanine transaminase; AWGS, Asian Working Group for Sarcopenia; CCI, Charlson Comorbidity Index; CIRS, chronic inflammatory response syndrome; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CVD, cardiovascular disease; DM, diabetes mellitus; EM, effect measure; EWGSOP, European Working Group on Sarcopenia in Older People 2010; EWGSOP2, European Working Group on Sarcopenia in Older people 2018; F, Female; FNIH, Foundation for the National Institutes of Health; GDS, Geriatric Depression Scale; GV/SLV, graft volume/standard liver volume; Hb, hemoglobin; HCC, hepatocellular carcinoma; HR, hazard ratio; IADL, instrumental activities of daily living; IHD, ischemic heart disease; IWGS, International Working Group for Sarcopenia; Kt/V, fractional urea clearance; M, Male; MELD, model for end-stage liver disease; MMSE, Mini-Mental State Examination; nPCR, normalized protein catabolic rate; OR, odds ratio; PAH, pulmonary arterial hypertension; SBP, systolic blood pressure; SHARE-FI, share frailty instrument; SPPB, short physical performance battery; T4, thyroxine; TFI, Tilburg Frailty Index; TT, Tinetti Test. a Men Study Sleep Study Ancillary Study. b Health Aging and Body Composition Study. c Study of Osteoporotic Fractures – Original. d Study of Osteoporotic Fractures – African American cohorts. e Framingham Study Offspring cohort. f Calculated by 2 × 2 table. g Sarcopenia with risk of malnutrition. h Sarcopenia and normal nutrition. i Malnutrition-sarcopenia syndrome. j Outpatients and inpatients.
Fig. 2. Meta-analysis of the association between sarcopenia and mortality presented in HRs, stratified by population. Heterogeneity ($I^2$): community-dwelling adults (32.4%), outpatients (12.4%), inpatients (62.1%), and nursing home residents (0%). HR, hazard ratio; M, males; F, females; MrOs, Men Study Sleep Study Ancillary Study; HABC, Health Aging and Body Composition Study; SOF-AA, Study of Osteoporotic Fractures – African American cohorts; Fram., Framingham Study Offspring cohort; MN, sarcopenia with a risk of malnutrition; NN, sarcopenia with normal nutrition; MSS, malnutrition-sarcopenia syndrome.
high risk of bias articles is hence observed compared to low risk of bias articles, although the heterogeneity of effect estimates was only significantly different for the pooled OR.

Low to moderate heterogeneity was found across all populations, definitions, follow-up periods, and risk of bias groups apart from the pooled FNIH HR in inpatients, where the heterogeneity was high. The high heterogeneity observed in the FNIH subgroup can be explained by the inclusion of both a crude and an adjusted HR in subgroups [57, 78].

**Strengths and Limitations**

This is the first systematic review and meta-analysis analyzing the association between sarcopenia and mortality within various populations, stratified by the latest working group definitions of sarcopenia: EWGSOP, EWGSOP2, AWGS, and FNIH. Due to the variation in the number of articles included within each population, subgroup analyses were not performed for nursing home residents and individuals with specific diseases such as cancer or renal failure, limiting the generalizability of our results. Furthermore, muscle mass was frequently measured by bioelectrical impedance analysis, which might lead to over-/underestimation of lean mass.

**Conclusion**

Sarcopenia is associated with a significantly higher risk of mortality, independent of population, sarcopenia definition, follow-up period, and risk of bias. This stresses the need for early detection and diagnosis of sarcopenia in all populations to implement interventions preventing and treating sarcopenia in a timely manner.

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**Statement of Ethics**

Ethical approval was not required.

**Conflicts of Interest Statement**

J.X., C.S.W., K.K., E.M.R., and A.B.M. declare they have no conflicts of interest.
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