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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
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. ***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. ***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. ***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. ***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.

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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 (FNIH) [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)

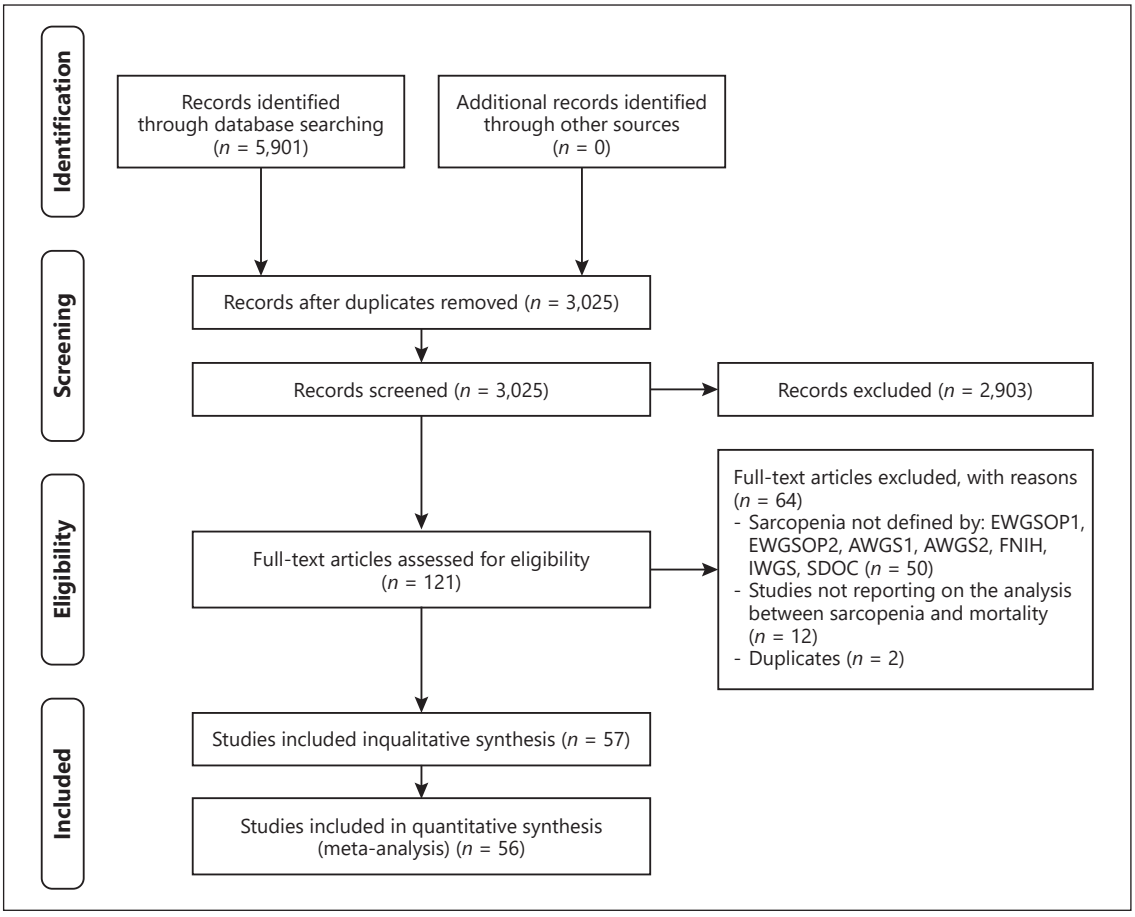

Fig. 1. PRISMA flow diagram of the article selection. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.

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 ≤25%, moderate as I^2 = 25–75%, and high as ≥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_b) 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

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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±0.6	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[e]
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 (80.0, 102.0)[c]	EWGSOP	Registry	120
Costanzo et al. [47]	ITA	Community	535	287 (53.6)	77.0±5.5	EWGSOP2	NR	37[d]
Cawthon et al. [33]	USA	Community	5,934	0	≥65	EWGSOP, FNIH, IWGS	Hospital	118±36
De Buyser 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
Bachettini 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[g]
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. [52]	CHN	Maintenance hemodialysis	131	51 (39.0)	49.4±11.7	EWGSOP	NR	12
Santos et al. [51]	NR	Liver cirrhosis	261	100 (38.3)	57.0 (51.8, 63.0)[c]	EWGSOP	NR	12
Aliberti et al. [55]	BRA	Acute day care hospital	665	421 (63.6)	78.7±8.3	FNIH	Phone	12
Kittiskulnam 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[a]	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
Sánchez-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[a]	EWGSOP	Hospital, phone	12
Vetrano et al. [59]	FRA	Geriatric and internal medicine acute care	770	431 (56.0)	81.0±7.0	EWGSOP	Phone	12
Zengarini et al. [70]	ITA	Geriatric and internal medicine acute care	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 care	610	313 (51.3)	80.7±6.6[a]	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								
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. [a]Weighted mean and SD. [b]Mean {standard error}. [c]Median (range). [d]Mean presented without SD. [e]Median. [f]Outpatients and inpatients. [g]Follow-up of 5 and 9.5 years.

included outpatient cohorts (2,607 individuals, mean age 49.4 ± 11.7 to 78.7 ± 8.3 years, 45.0% females) and the EWGSOP was most used (5/9 articles) [48–52], followed by AWGS (3/9 articles) [49, 53, 54] and FNIH (2/9 articles) [55, 56]. Twenty-four articles included inpatient cohorts (7,227 individuals, median age of 55.0 [21.0, 68.0] to mean age of 85.2 ± 6.4 years, 49.2% females) and the EWGSOP was most used (16/24 articles) [24, 57–71], followed by AWGS (6/24 articles) [72–77], EWGSOP2 (2/24 articles) [78, 79], FNIH (2/24 articles) [57, 78], and IWGS (1/24 articles) [57]. Five articles included nursing home cohorts (1,385 individuals, mean age of 78.0.9 ± 7.9 to 85.6 ± 8.2 years, 63.2% females), and all used the EWGSOP definition [80–84]. The measurement methods and cutoffs for each sarcopenia definition used are given in online suppl. Table 4. The follow-up period ranged from 31 to 180 months for community-dwelling adults, 12–108 months for outpatients, 3–84 months for inpatients, and 6–24 months for nursing home residents. Short-term follow-up was defined as <72 months for community-dwelling adults, <36 months for outpatients, and <24 months for inpatients.

Risk of Bias

Table 2 shows the individual NOS scores for each criterion of the included articles. The risk of bias assessment resulted in 40 articles with low risk of bias (17 in community-dwelling adults, 6 in outpatients, 14 in inpatients, and 3 in nursing home residents) and 17 as high risk of bias (2 in community-dwelling adults, 3 in outpatients, 10 in inpatients, and 2 in nursing home residents).

Meta-Analysis

Table 3 shows the HRs and ORs of the association between sarcopenia and mortality that were included in the meta-analyses, stratified by population. All reported statistical models of the included articles can be found in online suppl. Table 5. Overall, sarcopenia was statistically significantly associated with a higher risk of mortality (HR = 2.00 [95% CI: 1.71, 2.34], I^2: 46.9%; OR = 2.35 [95% CI: 1.64, 3.37], I^2: 43.7%) (shown in Fig. 2, 3). The association was independent of population: community-dwelling adults (HR = 1.88 [95% CI: 1.59, 2.25], I^2: 32.4%; OR = 1.98 [95% CI: 1.03, 3.79], I^2: 0%), outpatients (HR = 1.81 [95% CI: 1.28, 2.55], I^2: 12.4%; OR = 4.33 [95% CI: 1.25, 14.9], I^2: 17.4%), inpatients (HR = 2.15 [95% CI: 1.76, 2.62], I^2: 62.1%; OR = 2.62 [95% CI: 1.72, 4.99], I^2: 60.3%), and nursing home residents (HR = 2.84 [95% CI: 1.40, 5.73], I^2: 0%; OR = 1.90 [95% CI: 1.01, 3.57], I^2: 0.68%) (shown in Fig. 2, 3). There was no statistically significant difference between the heterogeneity of populations (HR: $Q_bp = 0.528$; OR: $Q_bp = 0.594$).

Online suppl. Figures 1–4 show the subgroup analyses of the association stratified by sarcopenia definition. 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], I^2: 50.4%; EWGSOP2: HR = 1.73 [95% CI: 1.02, 2.93], I^2: 0%; FNIH: HR = 1.80 [95% CI: 1.41, 2.29], I^2: 5.4%), outpatients (EWGSOP: HR = 2.37 [95% CI: 1.43, 3.93], I^2: 29.8%; FNIH: HR = 1.69 [95% CI: 1.16, 2.47], I^2: 0%), and inpatients (EWGSOP: HR = 1.94 [95% CI: 1.39, 2.71], I^2: 45.3%; OR = 2.34 [95% CI: 1.37, 4.00], I^2: 60.4%; FNIH: HR = 2.16 [95% CI: 1.19, 3.93], I^2: 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], I^2: 56.7%) and inpatients (AWGS: HR = 2.31 [95% CI: 1.47, 3.63], I^2: 66.9%; OR = 6.41 [95% CI: 1.76, 23.28], I^2: 17.6) but not significant in outpatients (HR: 1.40 [95% CI: 0.91, 2.16], I^2: 0%). There was no significant difference between the heterogeneity of effect estimates (community-dwelling adults [HR: $Q_bp = 0.972$], outpatients [HR: $Q_bp = 0.300$], and inpatients [HR: $Q_bp = 0.883$; OR: $Q_bp = 0.158$]).

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], I^2: 36.7%; short-term HR = 2.01 [95% CI: 1.55, 2.60], I^2: 0%), outpatients (long-term HR = 1.64 [95% CI: 1.12, 2.38], I^2: 0%; short-term HR = 2.12 [95% CI: 1.22, 3.70], I^2: 73.0%), and inpatients (long-term HR = 2.68 [95% CI: 2.02, 3.55], I^2: 58.3%; short-term HR = 1.51 [95% CI: 1.06, 2.17], I^2: 32.5%). There was no statistically significant difference between the heterogeneity of effect estimates for the follow-up period for community-dwelling adults (HR: $Q_bp = 0.461$) and outpatients (HR: $Q_bp = 0.448$), but for inpatients (HR: $Q_bp = 0.015$) (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], I^2: 63.7%; OR = 3.19 [95% CI: 2.23, 4.56], I^2: 20.1%; low risk of bias: HR = 1.89 [95% CI: 1.66, 2.15], I^2: 36.9%; OR = 1.74 [95% CI: 1.29, 2.34], I^2: 32.2%). The heterogeneity of effect estimates for risk of bias was not statistically significant for HRs ($Q_bp = 0.069$), but for ORs ($Q_bp = 0.010$) (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 Buyser 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	2	0	1	1	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	0	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	0	0	1	1	5
Ren et al. [52]	0	1	1	1	0	0	1	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	2	1	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	1	0	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
Sánchez-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

Table 2 (continued)

Author	Selection				Comparability	Outcome			Total score
	Q1	Q2	Q3	Q4	Q1	Q1	Q2	Q3	
Malafarina et al. [79]	0	1	1	1	2	0	1	1	7
Bianchi et al. [78]	1	1	1	1	2	1	1	1	9
Sipers et al. [57]	1	1	1	1	0	1	1	1	7
Nursing home residents									
Buckinx et al. [84]	0	1	1	1	2	1	1	1	8
Henwood et al. [82]	0	0	1	1	2	0	1	0	5
Landi et al. [80]	0	1	1	1	2	1	1	1	8
Saka et al. [81]	0	1	1	1	0	0	1	1	5
Yalcin et al. [83]	0	1	1	1	2	1	1	1	8

NOS, Newcastle-Ottawa Scale. [a]Outpatients and inpatients.

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)[a] M: 1.51 (0.61, 3.71)[b] F: 1.15 (0.28, 4.70)[b] F: 1.65 (0.52, 5.25)[c] F: 3.62 (0.49, 26.6)[d] F: 0.60 (0.08, 4.56)[e]	Age
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, SBP, 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, SBP, 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) F: 1.55 (1.03, 2.32)	Age, education, COPD, DM, hypertension, CVD, current smoker, MMSE, and depression
	FNIH	OR	M: 2.32 (1.23, 4.37) F: 2.67 (1.16, 6.15)	Age, education, COPD, DM, hypertension, CVD, current smoker, MMSE, and depression
	IWGS	OR	M: 1.26 (0.97, 1.63) F: 1.11 (0.81, 1.54)	Age, education, COPD, DM, hypertension, CVD, current smoker, MMSE, and depression
Outpatients				
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				
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)[g] 1.66 (0.48, 5.72)[h] 4.78 (2.09, 11.0)[i]	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][j]	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

Table 3 (continued)

Author	Sarcopenia definition	EM	Effect size (95% CI)	Adjustments
Sánchez-Rodriguez et al. [24]	EWGSOP	OR	2.20[f]	Crude
Teng et al. [71]	EWGSOP	OR	0.87[f]	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
	FNIH	HR	1.54 (1.11, 2.15)	Age and sex
Sipers et al. [57]	EWGSOP	HR	4.31 (2.09, 8.85)	Crude
	FNIH	HR	3.57 (1.90, 6.71)	Crude
Nursing home residents				
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[f]	Crude
Landi et al. [80]	EWGSOP	HR	3.19 (1.17, 8.66)	Age and sex
Saka et al. [81]	EWGSOP	OR	2.97[f]	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.

tifying individuals who are at risk of sarcopenia using screening tools and diagnosing sarcopenia timely is essential to delay adverse health outcomes.

Furthermore, the association between sarcopenia and mortality was independent of the follow-up period. Our finding that the mortality risk is higher in the long term (follow-up period >24 months) for inpatients is different from a previous study conducted in acute settings where short-term (in-hospital) mortality risk was higher than long-term (12 months) mortality [59]; however; this could be explained by the differences in cutoffs utilized to define short and long term. The comparison of short- and long-term mortality within populations is limited. Given 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

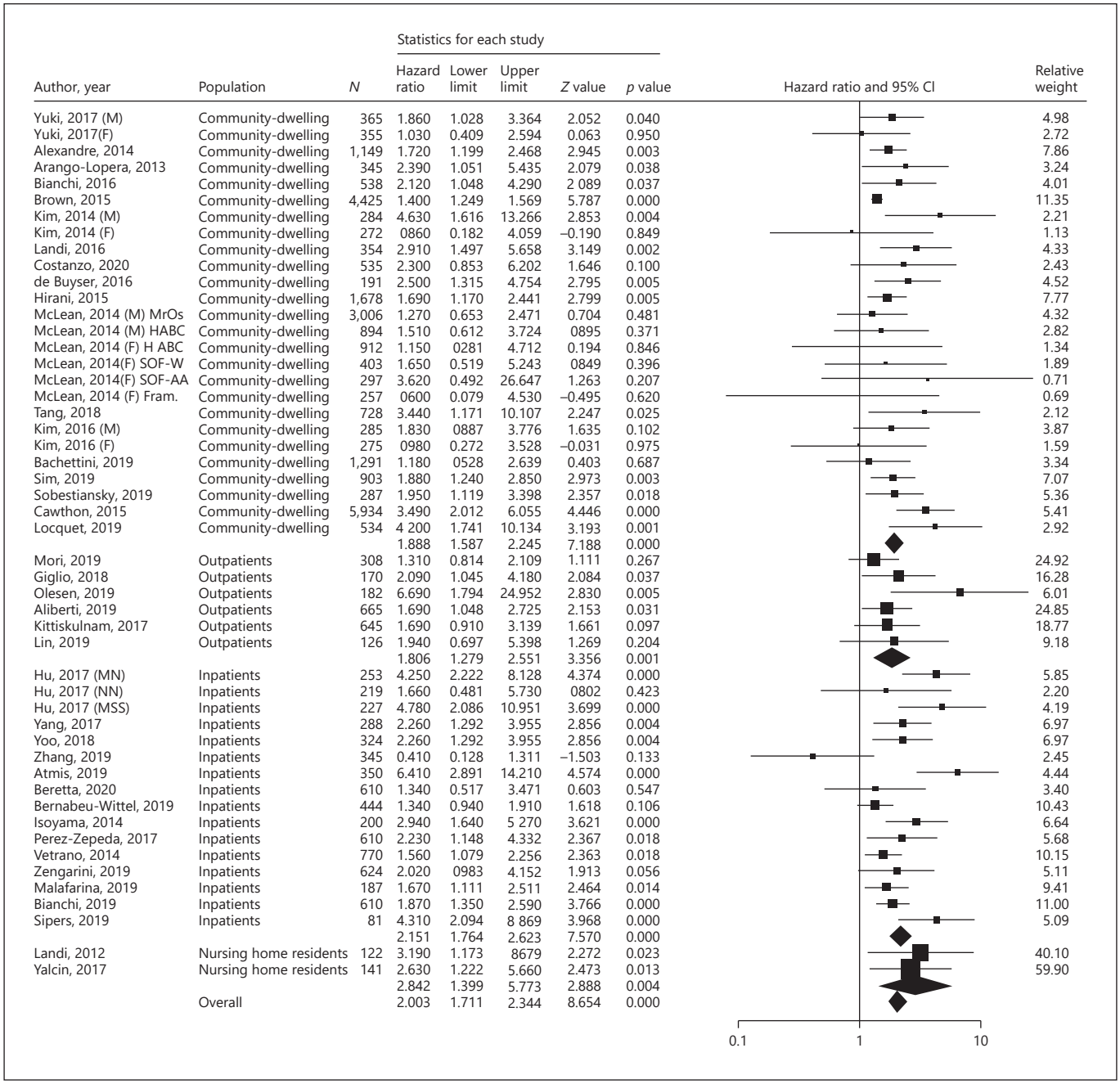

Fig. 2. Meta-analysis of the association between sarcopenia and mortality presented in HRs, stratified by population. Heterogeneity (I^2): community-dwelling adults (32.4%), outpatients (12.4%), inpatients (62.1%), and nursing home residents (0%). HR, hazard ratio, M, males; F, females; MrOs, Men Study Sleep Study Ancillary Study; HABC, Health Aging and Body Composition Study; SOF-W, Study of Osteoporotic Fractures – Original; 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.

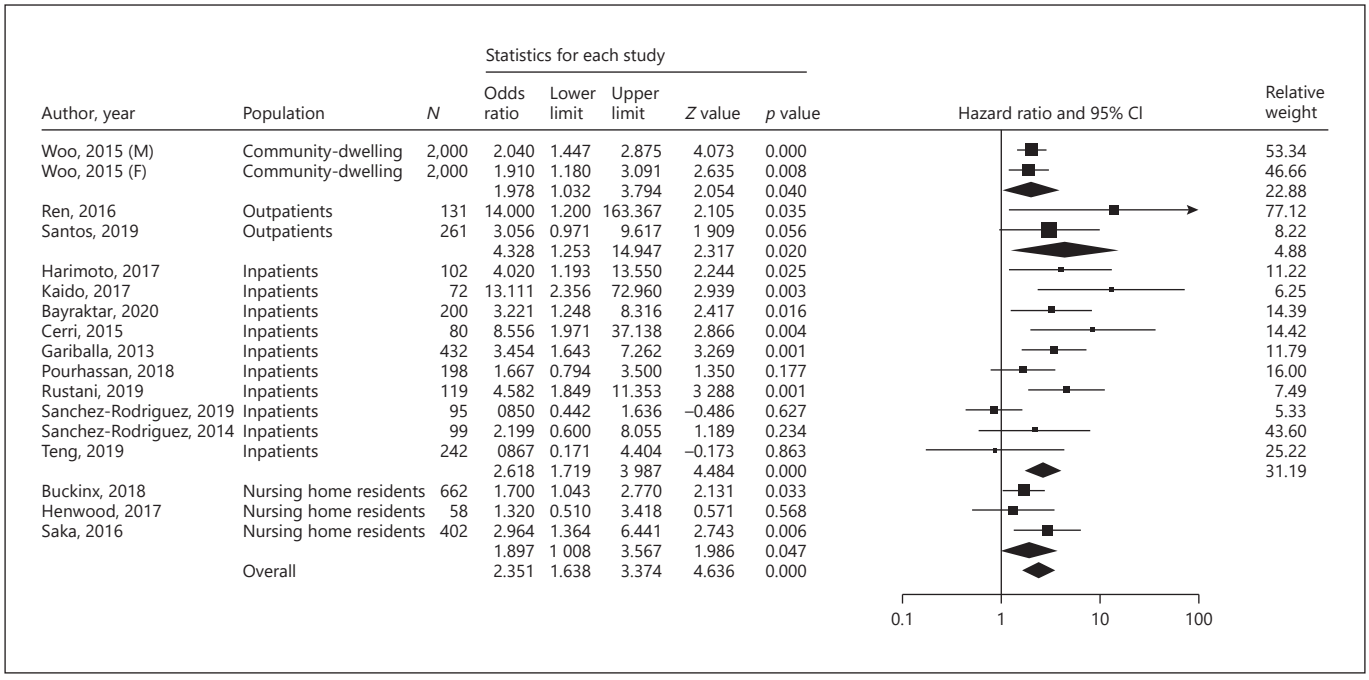

Fig. 3. Meta-analysis of the association between sarcopenia and mortality presented in ORs, stratified by population. Heterogeneity (I^2): community-dwelling adults (0%), outpatients (17.4%), inpatients (60.3%), and nursing home residents (0.7%). OR, odds ratios; M, males; F, females.

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.

Conflict 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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Author Contributions

J.X.: conceptualization, methodology, investigation, data curation, formal analysis, and writing – original draft. C.S.W.: conceptualization, methodology, investigation, data curation, supervision, and writing – review and editing. K.K.: conceptualization, methodology, investigation, data curation, and writing – review and editing. E.M.R.: conceptualization, methodology, investigation, supervision, and writing – review and editing. A.B.M.: conceptualization, methodology, investigation, supervision, and writing – review and editing.

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