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Original Study

Association Between Muscular Strength and Mortality in Clinical Populations: A Systematic Review and Meta-Analysis

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A B S T R A C T

Objectives: To assess the relationship between muscular strength measures and mortality in outpatient populations with chronic diseases such as cancer, chronic obstructive pulmonary disease, renal disease, and metabolic and vascular diseases, and in critically ill hospitalized patients.
Design: A systematic review and random-effects meta-analysis of prospective cohort studies was performed.
Setting and participants: The databases Medline, Embase, Clinical Trial Register, and Cochrane Trial Register were searched from inception until September 30, 2018. The systematic literature review yielded 39 studies with a total of 39,852 participants.
Results: Lowest vs highest category of muscular strength revealed a statistically significant increased risk of all-cause mortality with a hazard ratio (HR) and 95% confidence intervals (CI) of 1.80 (95% CI 1.54–2.10). Lower muscular strength was associated with enhanced mortality in patients with cancer (HR 2.40; 95% CI 1.57–3.69), critical illness (HR 2.06; 95% CI 1.33–3.21), renal disease (HR 1.84; 95% CI 1.37–2.47), metabolic and vascular diseases (HR 1.64; 95% CI 1.26–2.14), and chronic obstructive pulmonary disease (HR 1.36; 95% CI 1.16–1.61). Conversely, a 5-kg higher level of muscular strength conferred a reduced risk of overall mortality (HR 0.72; 95% CI 0.59–0.89) and was accompanied by a reduction in mortality in patients with metabolic and vascular diseases (HR 0.52; 95% CI 0.29–0.91), critical illness (HR 0.78; 95% CI 0.61–0.99), and renal disease (HR 0.82; 95% CI 0.73–0.91).
Conclusions and implications: Muscular strength is inversely associated with mortality risk in various acute and chronic conditions. Future trials should focus on developing validated cut-points for diagnosing low muscular strength and their predictive value for hard end-points.

Muscular strength is a crucial component of physical fitness with an independent role in the prevention and treatment of almost all chronic diseases and becomes vital at older ages.[1] Skeletal muscle wasting is the single most common disease process across a large spectrum of cachexia and in sarcopenia-associated disorders.[2] In clinical settings, low muscle mass contributes significantly to several negative outcomes across the healthcare continuum such as greater postoperative complications, longer length of hospital stay, lower physical function, poorer quality of life, and shorter survival.[3] Furthermore, muscular strength and physical performance can substantially influence disability and comorbidities in older individuals and, as a consequence, health burden and costs.[4]

Recently, 2 meta-analyses of prospective cohort studies have shown that muscular strength was a predictor of all-cause mortality and cardiovascular diseases in community-dwelling populations.[5,6] Although grip strength as a component of frailty and marker of

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nutritional status has become a useful tool in clinical practice,[7] muscular strength has not been recommended on risk assessment of all-cause mortality in clinical guidelines. Indeed, muscular strength may represent a potential new marker for identifying patients with higher mortality risk but, even more importantly, permits the early identification of patients who may benefit from interventions for muscle anabolism.[8] Thus far, no previous meta-analysis has evaluated the relationship between different measurements of muscular strength and mortality risk among individuals with acute and chronic illness. Therefore, our goal was to systematically assess the quantitative associations between muscle strength measures and mortality in outpatient populations with chronic diseases such as cancer, chronic obstructive pulmonary disease (COPD), renal disease, and metabolic and vascular diseases (cardiovascular disease, peripheral artery disease, type 2 diabetes mellitus, and liver disease), and in critically ill hospitalized patients.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[9] (Supplementary Material).

Eligibility Criteria

Criteria for eligibility included (1) cohort and nested case-control studies; (2) studies investigating the association between muscular strength and mortality; and (3) studies reporting adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CIs) or providing sufficient data to calculate HRs. Editorials, letters, conference abstracts, and studies published in languages other than English were not included.

Systematic Literature Search

We searched Medline, Embase, Clinical Trial Register, and Cochrane Trial Register for studies published in English that assessed associations between muscular strength and mortality in clinical populations. The search was last updated on September 30, 2018. The following search terms were used: muscular strength, grip strength, mortality, sarcopenia, survival, critical illness, and chronic diseases (ie, cancer, chronic heart failure, chronic kidney disease, COPD, cardiovascular disease, hypertension, peripheral artery disease, and type 2 diabetes). In addition, a manual search was conducted based on the reference lists of the selected publications.

Data Extraction

Data were extracted by B.S. and double-checked by K.V. For each study, we extracted information regarding study characteristics, exposure and outcome assessment, covariates for adjustment, and the maximally adjusted HRs with their corresponding 95% CIs.

Statistical Analyses

Primary meta-analyses

Random-effects meta-analysis was used to calculate summary risk estimates for overall and disease-specific mortality to compare the lowest vs the highest level of muscular strength and for a 5-kg higher level of muscular strength. We calculated the reciprocals of the reported risk estimates and 95% CIs for studies that used the opposite reference categories. If studies provided risk estimates for both sexes combined and separated, we included risk estimates for both sexes combined. We prioritized risk estimates for knee extension strength to grip strength and for knee extension strength to knee flexion strength. If risk estimates were provided for muscular strength in both the left and the right hand or leg, we included risk estimates for muscular strength in the right hand or leg, respectively. We prioritized risk estimates for the lowest category of muscular strength if studies provided more than 1 category. Risk estimates that were provided in units other than per 5-kg increments (eg, per 1-kg difference, per 10-kg difference, or per unit decrease) were converted into 5-kg increments using logarithmic and exponential functions.

We tested for statistical heterogeneity between studies using the Q- and I^2-statistics[10] and evaluated potential publication bias by visual inspection of funnel plots and the Egger regression test[11] and Begg rank correlation test.[12]

Meta-regression Analyses

Random-effects meta-regression methods were used to investigate whether the association between muscular strength and all-cause mortality differed by geographic region (Europe, North America, South America, Asia), disease condition (ie, cancer, COPD, renal disease, critical illness, metabolic and vascular diseases), type of muscular strength assessment (grip strength, knee extension strength, other), and whether the HRs were adjusted for sex, body mass index (BMI), physical activity, or smoking. Random-effects meta-regression was performed for both low vs high levels of muscular strength and per 5-kg higher muscular strength.

Sensitivity Analyses

We performed outlier and influence diagnostics including leave-one-out diagnostics to evaluate whether a particular study may have strongly influenced the summary risk estimate.[13]

All statistical analyses were performed with R v 3.4.4 using the package "metaphor."[14] *P* values of $<.05$ were considered statistically significant.

Results

Study Selection

The literature search yielded 1211 records identified in the electronic databases. After exclusion of nonrelevant and duplicate articles, 64 articles were reviewed in full. We excluded studies with inappropriate outcome measurements (n = 17) because they did not assess muscular strength (n = 5), or because they did not provide HRs (n = 3). In total, 39 studies including 39,852 participants were eligible for inclusion in the meta-analysis.[15–53] Figure 1 shows the results of the literature search and study selection process.

Study Characteristics

Table 1 describes the main characteristics of the 39 studies included in the meta-analysis. All investigations were prospective cohort studies. Studies were conducted in North America (n = 15), Europe (n = 12), Asia (n = 8), and South America (n = 4). Of the 39 studies, 6 provided results for all-cause mortality in patients with cancer (501 deaths among 1370 participants; data not available for 1 study),[20] 4 provided results for all-cause mortality in patients with COPD (319 deaths among 1802 participants), 10 provided results for all-cause mortality in patients with renal disease (659 deaths among 3111 participants), 9 in patients with critical illness (453 deaths among 1878 participants), and 10 in patients with metabolic and vascular diseases (3362 deaths among 31,691 participants). The follow-up duration ranged from length of hospital stay (in days) to 18.3 years.

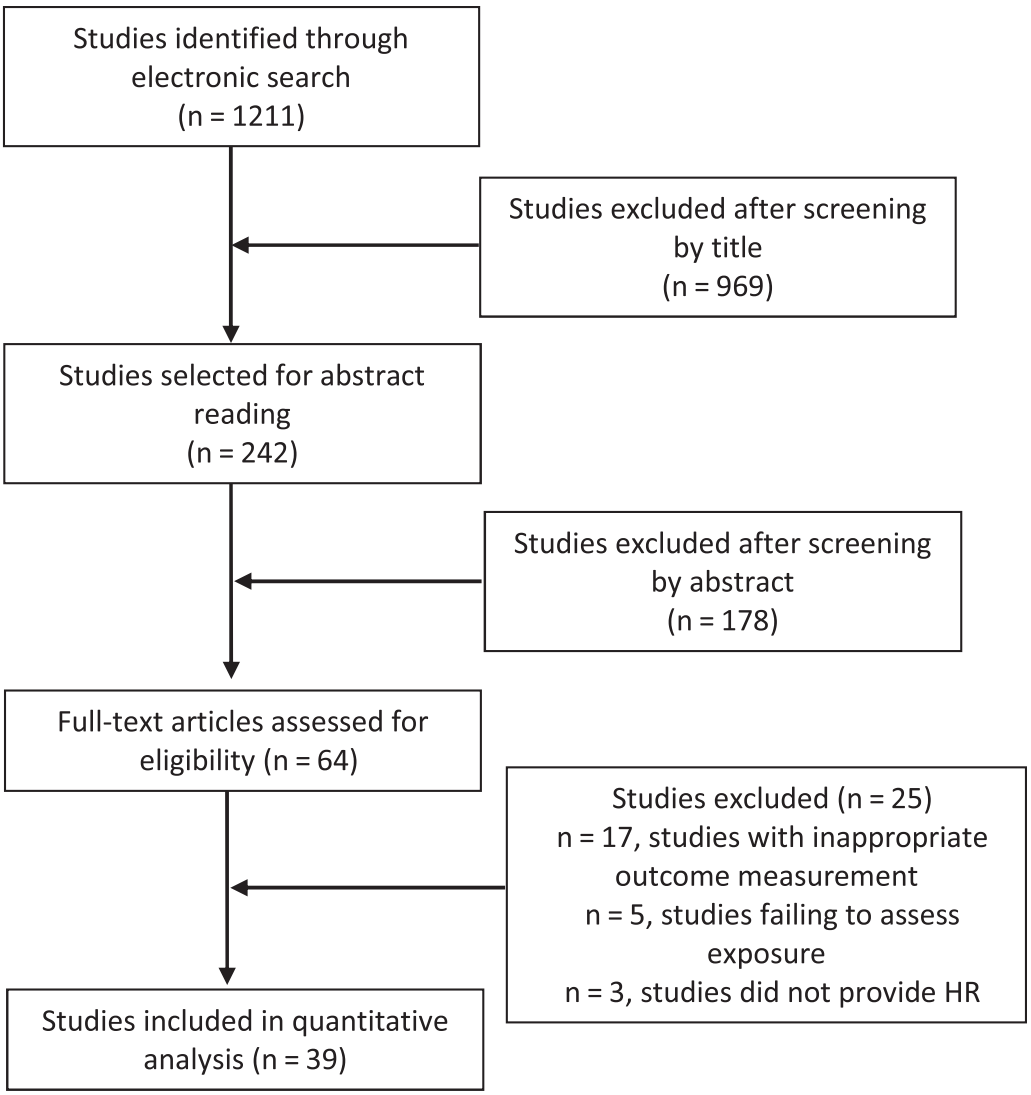

Fig. 1. Flow diagram depicting the process of study selection for meta-analysis.

Low vs High Muscular Strength in Relation to All-Cause Mortality in Patient Groups

Twenty-eight studies provided 29 risk estimates that were included in the meta-analysis comparing the lowest with the highest categories of muscular strength in relation to mortality. One study[49] provided separate risk estimates for men and women. Therefore, both risk estimates were included in our analysis. The majority (n = 20) of studies assessed muscular strength through grip strength. Nine studies used knee extension strength (n = 6) or other methods of muscular strength assessment (n = 3). Of 29 risk estimates, the vast majority were adjusted for sex (n = 22). Eleven risk estimates were adjusted for BMI, 7 were adjusted for smoking, and 6 were adjusted for physical activity.

Individuals who fell into the lowest vs the highest category of muscular strength showed a statistically significant increased risk of all-cause mortality (HR 1.80; 95% CI 1.54–2.10) (Figure 2). Overall, there was high heterogeneity ($I^2 = 89\%$, $P < .05$). The lowest compared with the highest categories of muscular strength were associated with enhanced mortality in patients with cancer (HR 2.40; 95% CI 1.57–3.69), critical illness (HR 2.06; 95% CI 1.33–3.21), renal disease (HR 1.84; 95% CI 1.37–2.47), metabolic and vascular diseases (HR 1.64; 95% CI 1.26–2.14), and COPD (HR 1.36; 95% CI 1.16–1.61). There was low to moderate heterogeneity in the HRs for COPD ($I^2 = 0\%$, $P = .62$), cancer ($I^2 = 42\%$, $P = .12$) and renal disease ($I^2 = 64\%$, $P < .05$). Heterogeneity was high in the HRs for metabolic and vascular diseases ($I^2 = 75\%$, $P < .05$) and critical illness ($I^2 = 88\%$, $P < .05$). The Egger regression test ($P \leq .05$) and funnel plot (Supplementary Figure 1) inspection suggested the presence of publication bias, whereas the Begg correlation test did not ($P = .54$).

Influence and outlier diagnostics did not yield any significant results. Omission of 1 study at a time from the overall analysis did not substantially alter the results.

Table 2 illustrates the results from random-effects meta-regression. Stratification by geographic region, disease condition, type of assessment of muscular strength, and adjustment for sex, BMI, physical activity, or smoking showed no significant differences in HRs.

Per 5-kg Higher Muscular Strength in Relation to All-Cause Mortality in Patient Groups

Fourteen studies provided 16 risk estimates that were included in the meta-analysis of a 5-kg difference in muscular strength in relation

Table 1
Characteristics of Clinical Studies Included in the Meta-Analysis Stratified by Disease Condition

Study, Year (Ref)	Study Design	Sample Size (Women, %)/Age, y (Mean, Median or Range)	Follow-up, mo	Number of Deaths	Muscle Strength Test	Low vs High Definition	Per Increment Definition	Adjustment for Covariates
Cancer								
Bosscher et al, 2016[15]	Prospective cohort study	207 (51% women)1 with oncologic emergencies/64.0	3	45	HGS	≤4.2 kg vs ≥1.2 kg deviation of the normative value		Age, sex
Cesari et al, 2013[16]	Prospective cohort study	200 women with gynecological cancer/73.5	12	23	HGS		per SD (7.6 kg) difference	Age, BMI, mini-mental state, quality of life, cancer stage
Kilgour et al, 2013[17]	Prospective cohort study	203 (43% women) with advanced cancer/64.3	28.8	152	HGS	$<10^{th}$ vs $\geq 50^{th}$ percentile		Age, sex, cancer type, treatment (radio/chemo), medications, time from diagnosis
Klepin et al, 2010[18]	Prospective cohort study	429 (36% women) with cancer/77.2	24	196	HGS		per 10 kg difference	Age, sex, race, education, COPD, CVD, T2D, mini-mental state, smoking, cancer type
Mauricio et al, 2016[19]	Prospective cohort study	228 (56% women) with GI cancer and breast cancer/62.1	34.2	85	HGS	low vs reference values (normal population)		Age, sex, cancer stage and type
Versteeg et al, 2018[20]	Prospective cohort study	103 (34% women) with advanced cancer/70.0	6	n/a	HGS	<30.3 kg (M)/<19.3 kg (F) vs higher values		Sex, cancer type, treatment line
COPD								
Burtin et al, 2016[21]	Prospective cohort study	998 (72% women) with COPD/67.0	46.8	162	HGS	5^{th} percentile of the normal population vs higher values		ADO index, BMI
Mehrotra et al, 2010[22]	Prospective cohort study	268 (43% women) with COPD/70–79	73.2	83	HGS, KES	lowest vs highest quartile		Age, sex, race, smoking, comorbidities
Puhan et al 2013[23]	Prospective cohort study	374 (43% women) with COPD/67.3	24	38	HGS		per 5 kg difference	Age, sex, dyspnea, FEV1, medication
Swallow et al, 2007[24]	Prospective cohort study	162 (33% women) with COPD/63.7	60	36	QMVC		per 10 % BMI difference (7.4 kg)	Age, BMI, FEV1, FFM, medication
Renal disease								
Isoyama et al, 2014[25]	Prospective cohort study	330 (38% women) on dialysis/53.0	60	95	HGS	<30 kg (M)/<20 kg (F) vs higher values		Age, sex, T2D, CVD, cholesterol, haemoglobin, GFR, CRP
Kim et al, 2017[26]	Prospective cohort study	142 (43% women) on dialysis/59.8	54	28	HGS	<30 kg (M)/<20 kg (F) vs higher values		Age, sex, BMI, albumin, dialysis adequacy, dialysis vintage, CRP, CVD, T2D
Kittiskulnam et al, 2017[27]	Prospective cohort study	645 (41% women) on dialysis/56.7	22.8	78	HGS	<26 kg (M)/<16 kg (F) vs higher values	per SD (10,6 kg) difference	Age, sex, race, CAD, CHF, T2D, albumin
Matos et al, 2014[28]	Prospective cohort study	443 (38% women) on dialysis/46.6	33.8	102	HGS	<28.3 kg (M)/<23.4 kg (F) vs higher values		Age, demographics, T2D, CHF, CVD, PAD, cancer history, dialysis adequacy/vintage, weekly erythropoietin dose, haemoglobin, creatinine, MIS
Matsuzawa et al, 2014[29]	Prospective cohort study	190 (53% women) on dialysis/64.0	84	30	KES	<40 % vs ≥ 40 % of median		Age, sex, BMI, dialysis vintage, comorbidities, albumin, CRP
Roshanravan et al, 2013[30]	Prospective cohort study	385 (16% women) with nondialysis -dependent CKD/61.0	36	50	HGS	lowest 20 % (adjusted for sex and BMI) vs higher values	per 5 kg difference	Age, sex, race, BMI, smoking, CAD, T2D, GFR
Stenvinkel et al, 2002[31]	Prospective cohort study	206 (39% women) with end-stage renal disease/52.0	37	55	HGS		per 1 kg difference	Age, CVD, T2D

Vogt et al, 2016[32]	Prospective cohort study	265 (46% women) on dialysis/58.0	13.4	53	HGS	low vs >22.5 kg (M)/>7 kg (F)		Age, dialysis vintage, T2D, albumin, creatinine, urea, CRP
Wang et al, 2005[33]	Prospective cohort study	233 (48% women) on dialysis/55.0	30	78	HGS		per 1 kg difference	Age, sex, CVD, T2D, GFR, hemoglobin, CRP, albumin
Yoda et al, 2012[34]	Prospective cohort study	272 (36% women) on dialysis/57.2	77	90	HGS	<12.4 kg/kg ALM vs ≥12.4 kg/kg ALM		Age, sex, T2D, dialysis vintage, albumin
Critical illness/ICU								
Ali et al, 2008[35]	Prospective cohort study	136 (52% women) in ICU/57.7	2	17	HGS MRC sum score	<11 kg (M)/<7 kg (F) vs higher values		Age, sex, ventilator days, organ failure, illness severity
Dinglas et al, 2017[36]	Prospective cohort study	156 (46% women) in ICU with ARDS syndrome/47.0	60	53	MRC sum score	MRC <48 vs higher values	per point difference (not included)	Age, comorbidities, SOFA score
Files et al, 2018[37]	Prospective cohort study	575 (39% women) in ICU/78.8	12	204	HGS		per 10 kg difference	Age, sex, race
Hermans et al, 2014[38]	Prospective cohort study	244 (41% women) in ICU/54–75	12	58	MRC sum score	MRC <36 vs higher values		Age, sex, APACHE II, BMI, NRS, COPD, T2D, malignancy, sepsis, preadmission dialysis, illness severity, risk factors during ICU (corticosteroids, neuromuscular blocking agents, BG, new infections)
Lee et al, 2012[39]	Prospective cohort study	107 (45% women) in ICU/61.2	In-hospital	10	HGS MRC sum score	<11 kg (M)/<7 kg (F) vs higher values	per point difference (not included)	Age, creatinine, INR, albumin, APACHE II, hemoglobin, BG
Wang et al, 2017[40]	Prospective cohort study	113 (35% women) in ICU with acute respiratory failure/69.8	In-hospital	29	QIS		per 1 kg/m2 difference in BMI	Age, sex, BMI, comorbidities, APACHE II, laboratory data
Martin-Ponce et al, 2014[41]	Prospective cohort study	310 (49% women) during hospitalization/61–99	In-hospital	41	HGS	<50th percentile vs higher values		Age, albumin, disease stress, subjective nutrition score, ABI, sepsis, cancer, comorbidities
Purser et al, 2006[42]	Prospective cohort study	155 (30% women) frail older adults with severe CAD/77.0	6	20	HGS	<25 kg vs higher values		Age, sex, race, treatment, activities of daily living, comorbidities, creatinine, cognition, depression, systolic BP, self-rated health, hematocrit
Xavier et al, 2017[43]	Prospective cohort study	82 (37% women) with acute kidney injury/62.3	6	21	HGS	<10 kg vs higher values		Age, sex, comorbidities, creatinine, illness severity
Metabolic and vascular diseases								
Artero et al, 2011[44]	Prospective cohort study	1506 men with hypertension/50.2	219.6	183	Bench press Leg press (1-RM)	lowest vs highest tertile of overall muscle strength		Age, physical activity, smoking, alcohol intake, BMI, BP, cholesterol, CVD, T2D, CRF
Izawa et al, 2009[45]	Prospective cohort study	148 men with CHF/62.8	44.4	13	HGS	<32.2 kg vs higher values		Age, left ventricular ejection fraction, CRF
Vidan et al, 2016[46]	Prospective cohort study	316 (56% women) frail and 100 (29% women) nonfrail older adults with CHF/80.0	12	93	HGS	lowest 20 % (adjusted for sex and BMI) vs higher values		Age, sex, comorbidities, NT-proBNP, NYHA class
Kamiya et al, 2015[47]	Prospective cohort study	1314 (20% women) with CAD/64.7	60	118 (+63 CV)	QIS	lowest vs highest quartile	per 10 % BW difference (6.8 kg)	Age, BMI, previous CHF, stroke and/or transient ischemic attack + for CV deaths: coronary artery bypass grafting, end-stage renal disease, coronary artery multivessel disease

(*continued on next page*)

Table 1 (*continued*)

Study, Year (Ref)	Study Design	Sample Size (Women, %)/Age, y (Mean, Median or Range)	Follow-up, mo	Number of Deaths	Muscle Strength Test	Low vs High Definition	Per Increment Definition	Adjustment for Covariates
McDermott et al, 2012[48]	Prospective cohort study	434 (46% women) with PAD/75.0	47.6	103	HGS, KES	lowest vs highest tertile		Age, sex, race, BMI, ABI, smoking, physical activity, comorbidities
Singh et al, 2010[49]	Prospective cohort study	410 (40% women) with PAD/>55	60	126	Isometric KES, KFS	lowest vs highest quartile		Age, race, comorbidities, smoking, physical activity, BMI, ABI
Celis-Morales et al, 2017[50]	Prospective cohort study	13,373 (39% women) with T2D (UK Biobank)/59.1	58.8	569	HGS	lowest vs highest tertile		Age, sex, race, deprivation index, education, income, month of recruitment, duration of T2D, systolic BP, hypertension, medication, lifestyle (BMI, smoking, TV, PC screen time, sleep duration, physical activity, dietary intake)
Hamasaki et al, 2017[51]	Prospective cohort study	1282 (45% women) with T2D/63.8	28.8	20	HGS		per 1 kg difference	Age, sex, BMI, smoking, alcohol intake, physical activity, GFR, HbA1c, duration of T2D, medication
Lopez-Jaramillo et al, 2014[52]	Prospective cohort study	12,516 (35% women) with IGT and T2D/63.6	74.4	1,913	HGS		per 1 kg difference	Age, BMI, waist circumference hip circumference
Wang et al, 2016[53]	Prospective cohort study	292 (34% women) with liver disease/61.0	15	61	HGS		per 5 kg difference	Age, sex, race, BMI, liver disease etiology, model for end-stage liver disease-Na, hepatocellular carcinoma

1-RM, 1-repetition maximum; ABI, ankle brachial index; ADO, multidimensional disease index based on age, dyspnea symptoms and FEV_1; ALM, arm lean mass; APACHE II, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BG, blood glucose; BP, blood pressure; BW, body weight; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; CRF, cardiorespiratory fitness; CRP, C-reactive protein; CVD, cardiovascular disease; F, female; FEV1, forced expiratory volume in 1 second; FFM, fat-free mass; GFR, glomerular filtration rate; GI, gastrointestinal; HbA1c, glycated hemoglobin A1c; HGS, hand grip strength; ICU, intensive care unit; IGT, impaired glucose tolerance; INR, International Normalized Ratio; KES, knee extension strength; KFS, knee flexion strength; M, male; MIS, malnutrition-inflammation score; MRC, Medical Research Council scale for muscle strength; NRS, nutritional risk score; NT-proBNP, N terminal pro brain natriuretic peptide; PAD, peripheral artery disease; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; T2D, type 2 diabetes mellitus; QIS, quadriceps isometric strength; QMVC, quadriceps maximal voluntary contraction force.

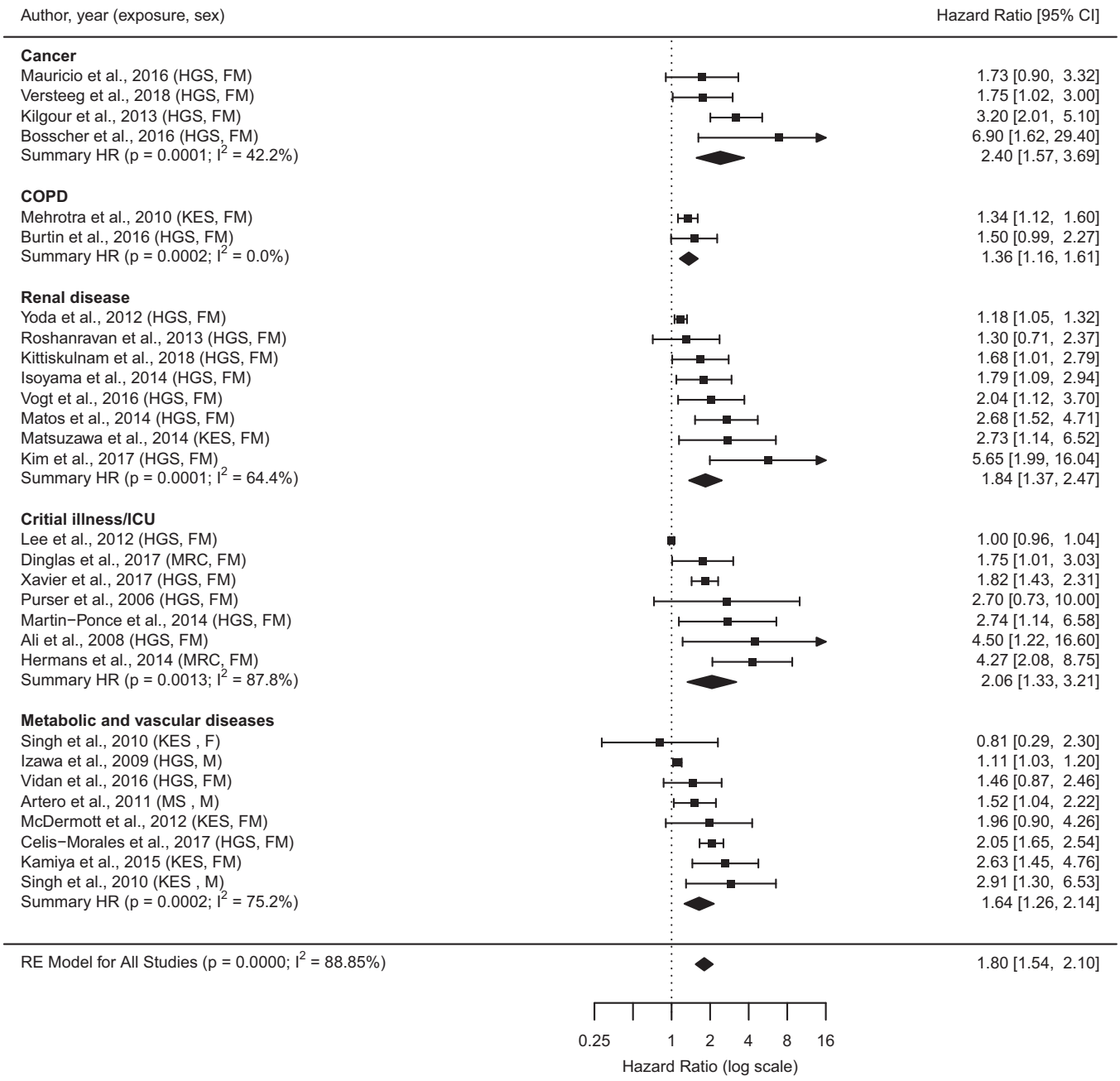

Fig. 2. Random-effects (RE) meta-analysis of adjusted HRs of low vs high muscular strength in relation to mortality. The black square and the respective line represent the HRs and the corresponding 95% CI for each study. The diamonds represent the summary risk estimates for low vs high muscular strength and all-cause mortality in different patient groups. I^2, heterogeneity among studies. F = females; FM = females and males; HGS = hand grip strength; ICU = intensive care unit; KES = knee extension strength; M = males; MRC = Medical Research Council scale for muscle strength; MS = muscle strength.

to all-cause mortality. Stenvinkel et al[31] and Lopez-Jaramillo et al[52] provided separate risk estimates for men and women. Therefore, we included both risk estimates in our meta-analysis. The majority of studies (n = 11) assessed muscular strength through grip strength. Whereas most risk estimates were not adjusted for physical activity (n = 15 out of 16 risk estimates) or smoking (n = 13 out of 16 risk estimates), 9 out of 16 risk estimates were adjusted for BMI, and almost all (n = 14) were sex adjusted.

A 5-kg higher level of muscular strength was associated with a statistically significant difference in total mortality (HR 0.72; 95% CI 0.59–0.89) (Figure 3). Overall, there was very high heterogeneity ($I^2 = 97\%$, $P < .05$). The association was most pronounced in patients with metabolic and vascular diseases (HR 0.52; 95% CI 0.29–0.91), followed by critically ill patients (HR 0.78; 95% CI 0.61–0.99) and patients with renal disease (HR 0.82; 95% CI 0.73–0.91). In patients with cancer and COPD, all-cause mortality was not statistically significantly associated with muscular strength. There was low to moderate heterogeneity in the HRs for cancer ($I^2 = 0\%$, $P = .60$), renal disease ($I^2 = 32\%$, $P = .23$), COPD ($I^2 = 32\%$, $P = .23$), and critical illness ($I^2 = 63\%$, $P = .09$). Heterogeneity was high in the HR for metabolic and vascular diseases ($I^2 = 99\%$, $P < .05$). Whereas the Egger regression test ($P = .89$) and Begg rank correlation test ($P = .08$) did not point toward publication bias, visual inspection of the funnel plot (Supplementary Figure 2) indicated some publication bias.

Table 2
Pooled Risks of Low vs High Muscular Strength and per 5-kg Higher Levels of Muscular Strength in Relation to Mortality Stratified by Potential Effect Modifying Factors

Effect Modifying Factors	Low vs High Muscular Strength				Per 5-kg Higher Muscular Strength			
	N	HR (95% CI)	I^2 (%)	P^*	N	HR (95% CI)	I^2 (%)	P^*
Overall	29	1.80 (1.54–2.10)	89		16	0.72 (0.59–0.89)	97	
Region				.6117				.4558
Europe	8	1.97 (1.69–2.29)	0		5	0.86 (0.76–0.98)	57	
North America	12	1.65 (1.28–2.12)	81		7	0.63 (0.40–0.98)	99	
South America	4	1.92 (1.58–2.34)	0		0	–	–	
Asia	5	1.92 (1.10–3.34)	97		4	0.78 (0.70–0.87)	17	
Disease condition				.5864				.2435
Cancer	4	2.40 (1.57–3.69)	42		2	0.93 (0.78–1.12)	0	
COPD	2	1.36 (1.16–1.61)	0		2	0.92 (0.84–1.00)	32	
Renal disease	8	1.84 (1.37–2.47)	64		5	0.82 (0.73–0.91)	32	
Critical illness/ICU	7	2.06 (1.33–3.21)	88		2	0.78 (0.61–0.99)	63	
Metabolic and vascular diseases	8	1.64 (1.26–2.14)	75		5	0.52 (0.29–0.91)	99	
Assessment of muscular strength				.6183				.5976
HGS	20	1.76 (1.46–2.12)	92		13	0.70 (0.54–0.90)	97	
KES	6	1.84 (1.28–2.64)	51		3	0.84 (0.71–0.99)	84	
Other (muscle strength, MRC)	3	2.12 (1.18–3.78)	72		0	–	–	
Adjustment for sex				.9262				.4583
Yes	22	1.77 (1.50–2.09)	79		14	0.70 (0.55–0.88)	96	
No	7	1.91 (1.31–2.78)	80		2	0.89 (0.79–1.01)	78	
Adjustment for BMI				.2122				.2779
Yes	11	2.02 (1.60–2.56)	46		9	0.65 (0.45–0.94)	99	
No	18	1.68 (1.39–2.03)	92		7	0.82 (0.77–0.88)	0	
Adjustment for physical activity				.3671				.9485
Yes	6	1.57 (1.15–2.15)	80		1	0.70 (0.49–1.00)	NA	
No	23	1.88 (1.57–2.26)	86		15	0.72 (0.58–0.90)	98	
Adjustment for smoking				.4108				.4781
Yes	7	1.61 (1.30–2.01)	49		3	0.89 (0.79–1.01)	0	
No	22	1.91 (1.57–2.33)	92		13	0.70 (0.54–0.89)	98	

HGS, hand grip strength; ICU, intensive care unit; KES, knee extension strength; MRC, Medical Research Council scale for muscle strength; n, number of risk estimates.
*P value for difference (from meta-regression).

Influence and outlier diagnostics did not yield any significant results. Omission of 1 study at a time from the overall analysis did not substantially alter the results.

The results of our meta-regression analyses showed no detectable differences in pooled HRs by study region, disease condition, type of assessment of muscular strength, and adjustments for sex, BMI, physical activity, or smoking (Table 2).

Discussion

This meta-analysis was designed to investigate the role of different measures of muscular strength on mortality risk in different patient groups. We found evidence of associations between all measures of muscular strength investigated and all-cause mortality. Our meta-analysis indicates that patients with lower levels of muscular strength had a 1.8-fold increased risk of death compared with patients with higher muscular strength. Conversely, a 5-kg higher level of muscular strength was associated with a 28% difference in all-cause mortality risk. The observed associations did not differ by study region, type of assessment of muscular strength, or disease condition, and remained evident after controlling for sex, BMI, physical activity, or smoking.

The importance of muscular strength in predicting survival has been systematically assessed in community-dwelling healthy populations.[5,6,54] Our population was unique in that it afforded us the opportunity to assess persons with existing acute and chronic diseases. Our data demonstrate that muscular strength is a similar or even more important marker of mortality risk in a clinical population. Therefore, physicians should consider using muscular strength in clinical settings to improve risk prediction, patient management and, most importantly, patient health.

The biologic mechanisms underlying the benefits of muscular strength for mortality risk are still unclear but appear to be multifactorial. First, muscular strength is strongly associated with skeletal muscle mass, a major tissue responsible for blood glucose disposal and an extensive reservoir of amino acids stored as protein. A loss of protein stores resulting from aging or illness is linked to metabolic dysregulation,[55] increased systemic low-grade inflammation,[56] immunosuppression,[57] reduced tolerance to treatments,[58] and, ultimately, reduced survival.[3] Second, skeletal muscle is directly related to the integrated function of numerous processes that contribute to whole-body metabolism and crucial body functions.[59] Thus, a low level of muscular strength may simply reflect poor nutrition and health state. Indeed, loss of muscle mass is a critical consequence of malnutrition, resulting in increased risk of mortality in hospitalized patients.[60] Third, decreasing muscular strength represents a hallmark of the aging process and is likely related to muscle mitochondrial dysfunction.[61] According to the concept of "coordinated de-adaptation," the functional capacities of the cardiovascular and respiratory systems will also decline when mitochondrial volume decreases, for example, as a result of aging or disease.[62] However, it has been shown that chronological age per se does not influence quality control in skeletal muscle, but rather that BMI and cardiorespiratory fitness play a dominant role in mitochondrial dysfunction in aging muscle.[63] Although our meta-analysis was adjusted for BMI and physical activity, we were unable to adjust for cardiorespiratory fitness, which has been shown to be an independent predictor of mortality in healthy and diseased populations.[64]

For the assessment of muscular strength, we used the grip strength, knee extension strength, and Medical Research Council sum score in critically ill patients. Although the type of muscular strength test did not influence observed associations in our meta-analysis, recent findings suggest that grip strength alone should not be considered a proxy for overall muscular strength at both the population and the individual level, rather, grip strength weakness may be increasingly linked to knee extension strength weakness in lower health status.[65] Multiple muscular strength measures

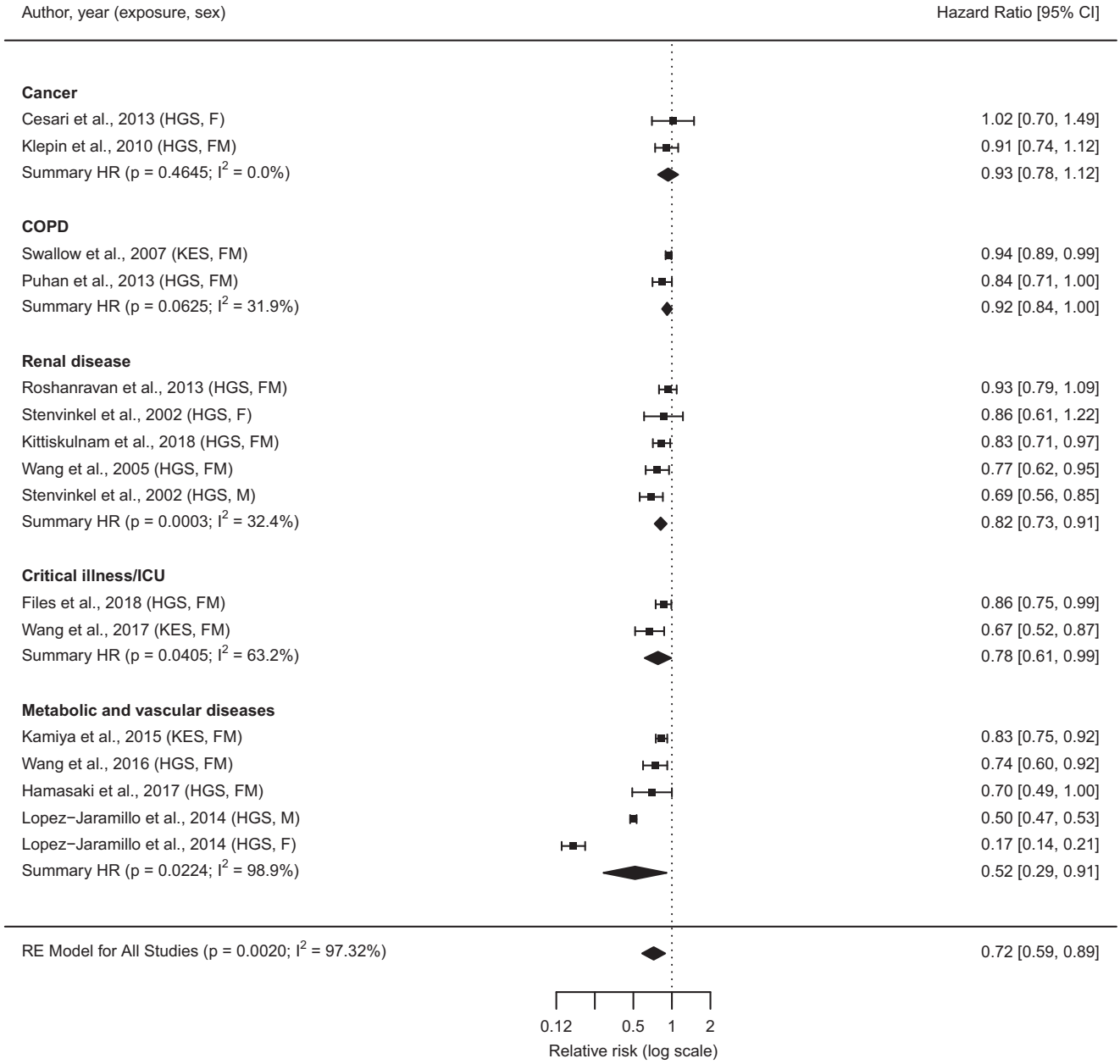

Fig. 3. Random-effects (RE) meta-analysis of adjusted hazard ratios (HR) of per 5-kg higher muscular strength in relation to mortality. The black square and the respective line represent the HRs and the corresponding 95% CI for each study. The diamonds represent the summary risk estimates for a per 5-kg increase in muscular strength and all-cause mortality in different patient groups. I^2, heterogeneity among studies. F = females; FM = females and males; HGS = hand grip strength; ICU = intensive care unit; KES = knee extension strength; M = males.

including lower and upper body limb muscles may be better predictors as the association between muscular strength and mortality can change depending on sex and muscular group (eg, upper and lower limb muscles) analyzed.[66] However, considering that only very few of the included studies tested knee extension strength, which is also more difficult to measure in a standardized and reliable way than grip strength, it remains questionable whether it is worthwhile to measure both grip strength and knee extension strength. Moreover, the new definition of sarcopenia focuses on low grip strength (<27 kg for men and <16 kg for women) as the first defining characteristic,[67] whereas cut-points for knee extension strength are not available at present. Indeed, the diagnosis of knee extension strength weakness is rather arbitrary, and there is a strong need for sex-specific threshold values for low muscular strength based on normative data across the life course, as has been reported recently for grip strength.[68]

Based on the results of our meta-analysis, not including muscular strength in clinical assessments fails to provide an optimal approach to stratifying patients according to mortality risk. Muscular strength has concurrent and prognostic value.[69] For example, grip strength is not only related to health status but also provides useful information regarding nutritional status, muscle mass, and physical function, and is used for sarcopenia case-finding.[67] Acute sarcopenia is usually related to an acute illness and refers to acute loss of muscle mass and function associated with hospitalization, whereas chronic sarcopenia is associated with chronic and progressive conditions, and it increases the risk of mortality. The implementation of simple physical tests that may reliably evaluate the muscular strength state of the patient has

value in any phase of illness, but particularly in advanced illness that may invoke inflammatory processes (eg, cancer or chronic renal disease). Measures of muscular strength could eventually be combined with measures of muscle quality such as phase angle to create a score that would better predict clinical outcomes and mortality risk. For example, phase angle was more accurate in predicting survival compared with grip strength in one of our included studies in cancer patients.[19] This enables a more personalized approach for treatment, which may help in enhancing the effectiveness and acceptability of currently available therapies.

Our study has important strengths. This is the first meta-analysis to assess the relationship between muscular strength and mortality risk in outpatient and hospitalized patients. We included a considerable number of studies in our meta-analysis and were able to perform important subgroup analyses according to disease conditions and other potential effect-modifying factors. Limitations of the present meta-analysis include the large heterogeneity across studies that cannot be explained by subgroup analysis and meta-regression of potential effect-modifying factors. However, stratification by disease condition revealed that heterogeneity was highest among patients with metabolic and vascular diseases ($I^2 = 98.9\%$) and critical illness ($I^2 = 63.2\%$), but was much lower in the subgroups of individuals with cancer, COPD, or renal disease ($I^2 = 0$ to 32.4%). Heterogeneity may be explained in part by differences in clinical status at baseline and changes in treatment regimens during follow-up. Furthermore, the included studies used different definitions of low vs high levels of muscular strength, which further complicates interpretation. In addition, variation in the distribution of confounders by disease entity and potential residual confounding by unknown or unmeasured factors are also of concern. The associations observed could indeed be proxies for undetected measures of disease severity or progression or of other comorbid illnesses such as rheumatologic disease of inflammaging.

Conclusions and Implications

In conclusion, muscular strength is inversely associated with mortality risk in various acute and chronic conditions and should be used in clinical settings to improve risk prediction and patient management. Even small differences in muscular strength levels may affect mortality in several patient groups. To guide clinical practice, future research should focus on developing validated cut-points for diagnosing low muscular strength and their predictive value for hard end-points, such as survival. Ultimately, clinical trials need to establish whether routine implementation of muscular strength development measures improves clinical outcomes in the secondary care setting. It is of critical importance to empower healthcare professionals to understand and communicate the positive impact of muscular fitness on disease processes.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2019.05.015.

References

1. Strasser B, Volaklis K, Fuchs D, Burtscher M. Role of dietary protein and muscular fitness on longevity and aging. Aging Dis 2018;9:119–132.
2. Anker SD, Coats AJ, Morley JE, et al. Muscle wasting disease: A proposal for a new disease classification. J Cachexia Sarcopenia Muscle 2014;5:1–3.
3. Prado CM, Purcell SA, Alish C, et al. Implications of low muscle mass across the continuum of care: A narrative review. Ann Med 2018;50:675–693.
4. Mijnarends DM, Luiking YC, Halfens RJG, et al. Muscle, health and costs: A glance at their relationship. J Nutr Health Aging 2018;22:766–773.
5. García-Hermoso A, Cavero-Redondo I, Ramírez-Vélez R, et al. Muscular strength as a predictor of all-cause mortality in an apparently healthy population: A systematic review and meta-analysis of data from approximately 2 million men and women. Arch Phys Med Rehabil 2018;99:2100–2113.e5.
6. Wu Y, Wang W, Liu T, Zhang D. Association of grip strength with risk of all-cause mortality, cardiovascular diseases, and cancer in community-dwelling populations: A meta-analysis of prospective cohort studies. J Am Med Dir Assoc 2017;18:551.e17–551.e35.
7. McGrath RP, Kraemer WJ, Snih SA, Peterson MD. Handgrip strength and health in aging adults. Sports Med 2018;48:1993–2000.
8. Wischmeyer PE, Puthucheary Z, San Millán I, et al. Muscle mass and physical recovery in ICU: Innovations for targeting of nutrition and exercise. Curr Opin Crit Care 2017;23:269–278.
9. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
10. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558.
11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.
12. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1101.
13. Viechtbauer W, Cheung MW. Outlier and influence diagnostics for meta-analysis. Res Synth Methods 2010;1:112–125.
14. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Software 2010;36:1–48.
15. Bosscher MR, Bastiaannet E, van Leeuwen BL, Hoekstra HJ. Factors associated with short-term mortality after surgical oncologic emergencies. Ann Surg Oncol 2016;23:1803–1814.
16. Cesari M, Cerullo F, Zamboni V, et al. Functional status and mortality in older women with gynecological cancer. J Gerontol A Biol Sci Med Sci 2013;68:1129–1133.
17. Kilgour RD, Vigano A, Trutschnigg B, et al. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. Support Care Cancer 2013;21:3261–3270.
18. Klepin HD, Geiger AM, Tooze JA, et al. Health, Aging and Body Composition Study. Physical performance and subsequent disability and survival in older adults with malignancy: Results from the health, aging and body composition study. J Am Geriatr Soc 2010;58:76–82.
19. Mauricio SF, Ribeiro HS, Correia MI. Nutritional status parameters as risk factors for mortality in cancer patients. Nutr Cancer 2016;68:949–957.
20. Versteeg KS, Blauwhoff-Buskermolen S, Buffart LM, et al. Higher muscle strength is associated with prolonged survival in older patients with advanced cancer. Oncologist 2018;23:580–585.
21. Burtin C, Ter Riet G, Puhan MA, et al. Handgrip weakness and mortality risk in COPD: A multicentre analysis. Thorax 2016;71:86–87.
22. Mehrotra N, Freire AX, Bauer DC, et al. Health ABC Study. Predictors of mortality in elderly subjects with obstructive airway disease: The PILE score. Ann Epidemiol 2010;20:223–232.
23. Puhan MA, Siebeling L, Zoller M, et al. Simple functional performance tests and mortality in COPD. Eur Respir J 2013;42:956–963.
24. Swallow EB, Reyes D, Hopkinson NS, et al. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. Thorax 2007;62:115–120.
25. Isoyama N, Qureshi AR, Avesani CM, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. Clin J Am Soc Nephrol 2014;9:1720–1728.
26. Kim JK, Kim SG, Oh JE, et al. Impact of sarcopenia on long-term mortality and cardiovascular events in patients undergoing hemodialysis. Korean J Intern Med 2019;34:599–607.
27. Kittiskulnam P, Chertow GM, Carrero JJ, et al. Sarcopenia and its individual criteria are associated, in part, with mortality among patients on hemodialysis. Kidney Int 2017;92:238–247.
28. Matos CM, Silva LF, Santana LD, et al. Handgrip strength at baseline and mortality risk in a cohort of women and men on hemodialysis: A 4-year study. J Ren Nutr 2014;24:157–162.
29. Matsuzawa R, Matsunaga A, Wang G, et al. Relationship between lower extremity muscle strength and all-cause mortality in Japanese patients undergoing dialysis. Phys Ther 2014;94:947–956.
30. Roshanravan B, Robinson-Cohen C, Patel KV, et al. Association between physical performance and all-cause mortality in CKD. J Am Soc Nephrol 2013;24:822–830.
31. Stenvinkel P, Barany P, Chung SH, et al. A comparative analysis of nutritional parameters as predictors of outcome in male and female ESRD patients. Nephrol Dial Transplant 2002;17:1266–1274.
32. Vogt BP, Borges MCC, Goés CR, Caramori JCT. Handgrip strength is an independent predictor of all-cause mortality in maintenance dialysis patients. Clin Nutr 2016;35:1429–1433.
33. Wang AY, Sea MM, Ho ZS, et al. Evaluation of handgrip strength as a nutritional marker and prognostic indicator in peritoneal dialysis patients. Am J Clin Nutr 2005;81:79–86.
34. Yoda M, Inaba M, Okuno S, et al. Poor muscle quality as a predictor of high mortality independent of diabetes in hemodialysis patients. Biomed Pharmacother 2012;66:266–270.

35. Ali NA, O'Brien JM Jr, Hoffmann SP, et al. Midwest Critical Care Consortium. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med 2008;178:261–268.
36. Dinglas VD, Aronson Friedman L, Colantuoni E, et al. Muscle weakness and 5-year survival in acute respiratory distress syndrome survivors. Crit Care Med 2017;45:446–453.
37. Files DC, Neiberg R, Rushing J, et al. Influence of prehospital function and strength on outcomes of critically ill older adults. J Am Geriatr Soc 2018;66:525–531.
38. Hermans G, Van Mechelen H, Clerckx B, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2014;190:410–420.
39. Lee JJ, Waak K, Grosse-Sundrup M, et al. Global muscle strength but not grip strength predicts mortality and length of stay in a general population in a surgical intensive care unit. Phys Ther 2012;92:1546–1555.
40. Wang CH, Lin HC, Chang YC, et al. Predictive factors of in-hospital mortality in ventilated intensive care unit: A prospective cohort study. Medicine (Baltimore) 2017;96:e9165.
41. Martín-Ponce E, Hernández-Betancor I, González-Reimers E, et al. Prognostic value of physical function tests: Hand grip strength and six-minute walking test in elderly hospitalized patients. Sci Rep 2014;4:7530.
42. Purser JL, Kuchibhatla MN, Fillenbaum GG, et al. Identifying frailty in hospitalized older adults with significant coronary artery disease. J Am Geriatr Soc 2006;54:1674–1681.
43. Xavier SP, Goes CR, Bufarah MN, et al. Handgrip strength and weight predict long-term mortality in acute kidney injury patients. Clin Nutr ESPEN 2017;17:86–91.
44. Artero EG, Lee DC, Ruiz JR, et al. A prospective study of muscular strength and all-cause mortality in men with hypertension. J Am Coll Cardiol 2011;57:1831–1837.
45. Izawa KP, Watanabe S, Osada N, et al. Handgrip strength as a predictor of prognosis in Japanese patients with congestive heart failure. Eur J Cardiovasc Prev Rehabil 2009;16:21–27.
46. Vidán M, Blaya-Novakova V, Sánchez E, et al. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. Eur J Heart Fail 2016;18:869–875.
47. Kamiya K, Masuda T, Tanaka S, et al. Quadriceps strength as a predictor of mortality in coronary artery disease. Am J Med 2015;128:1212–1219.
48. McDermott MM, Liu K, Tian L, et al. Calf muscle characteristics, strength measures, and mortality in peripheral arterial disease: A longitudinal study. J Am Coll Cardiol 2012;59:1159–1167.
49. Singh N, Liu K, Tian L, et al. Leg strength predicts mortality in men but not in women with peripheral arterial disease. J Vasc Surg 2010;52:624–631.
50. Celis-Morales CA, Petermann F, Hui L, et al. Associations between diabetes and both cardiovascular disease and all-cause mortality are modified by grip strength: Evidence from UK Biobank, a prospective population-based cohort study. Diabetes Care 2017;40:1710–1718.
51. Hamasaki H, Kawashima Y, Katsuyama H, et al. Association of handgrip strength with hospitalization, cardiovascular events, and mortality in Japanese patients with type 2 diabetes. Sci Rep 2017;7:7041.
52. Lopez-Jaramillo P, Cohen DD, Gómez-Arbeláez D, et al. ORIGIN Trial Investigators. Association of handgrip strength to cardiovascular mortality in pre-diabetic and diabetic patients: A subanalysis of the ORIGIN trial. Int J Cardiol 2014;174:458–461.
53. Wang CW, Feng S, Covinsky KE, et al. A comparison of muscle function, mass, and quality in liver transplant candidates: Results from the Functional Assessment in Liver Transplantation Study. Transplantation 2016;100:1692–1698.
54. Cooper R, Kuh D, Hardy R. Mortality Review Group; FALCon and HALCyon Study Teams. Objectively measured physical capability levels and mortality: Systematic review and meta-analysis. BMJ 2010;341:c4467.
55. Puthucheary ZA, Astin R, Mcphail MJW, et al. Metabolic phenotype of skeletal muscle in early critical illness. Thorax 2018;73:926–935.
56. Volaklis KA, Halle M, Koenig W, et al. Association between muscular strength and inflammatory markers among elderly persons with cardiac disease: Results from the KORA-Age study. Clin Res Cardiol 2015;104:982–989.
57. Hawkins RB, Raymond SL, Stortz JA, et al. Chronic critical illness and the persistent inflammation, immunosuppression, and catabolism syndrome. Front Immunol 2018;9:1511.
58. Mazzuca F, Onesti CE, Roberto M, et al. Lean body mass wasting and toxicity in early breast cancer patients receiving anthracyclines. Oncotarget 2018;9:25714–25722.
59. Argilés JM, Campos N, Lopez-Pedrosa JM, et al. Skeletal muscle regulates metabolism via interorgan crosstalk: Roles in health and disease. J Am Med Dir Assoc 2016;17:789–796.
60. Deutz NEP, Ashurst I, Ballesteros MD, et al. The underappreciated role of low muscle mass in the management of malnutrition. J Am Med Dir Assoc 2019;20:22–27.
61. Short KR, Bigelow ML, Kahl J, et al. Decline in skeletal muscle mitochondrial function with aging in humans. Proc Natl Acad Sci USA 2005;102:5618–5623.
62. Burtscher M. Exercise limitations by the oxygen delivery and utilization systems in aging and disease: Coordinated adaptation and deadaptation of the lung-heart muscle axis – a mini-review. Gerontology 2013;59:289–296.
63. Distefano G, Standley RA, Dubé JJ, et al. Chronological age does not influence ex-vivo mitochondrial respiration and quality control in skeletal muscle. J Gerontol A Biol Sci Med Sci 2017;72:535–542.
64. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
65. Yeung SSY, Reijnierse EM, Trappenburg MC, et al. Handgrip strength cannot be assumed a proxy for overall muscle strength. J Am Med Dir Assoc 2018;19:703–709.
66. Guadalupe-Grau A, Carnicero JA, Gómez-Cabello A, et al. Association of regional muscle strength with mortality and hospitalisation in older people. Age Ageing 2015;44:790–795.
67. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing 2019;48:16–31.
68. Dodds RM, Syddall HE, Cooper R, et al. Grip strength across the life course: Normative data from twelve British studies. PLoS One 2014;9:e113637.
69. Bohannon RW. Muscle strength: Clinical and prognostic value of hand-grip dynamometry. Curr Opin Clin Nutr Metab Care 2015;18:465–470.