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Review

# Thresholds of handgrip strength for all-cause, cancer, and cardiovascular mortality: A systematic review with dose-response meta-analysis

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ABSTRACT

*Background:* While handgrip strength is associated with all-cause and cause-specific mortality, whether such associations are dose-dependent is largely unknown. Therefore, we conducted a systematic review on the dose-response relationship of handgrip strength with all-cause mortality, cancer, and cardiovascular mortality.
*Methods:* The data source included three electronic databases (PubMed/MEDLINE, Web of Science and Scopus) from inception to 8 February 2022. Prospective cohort studies of healthy adults with objective measures of handgrip strength were included. Two researchers independently screened studies, extracted data, and assessed risk of bias. We used estimates regarding handgrip strength categories to conduct a random forest model, and a two-stage random-effects hierarchical meta-regression model pooling study-specific estimates for dose-response relationship. Outcomes included all-cause, cancer, and cardiovascular mortality.
*Reults:* Forty-eight studies comprising 3,135,473 participants (49.6% women, age range 35–85 years) were included. Random forest models showed a significant inverse association between handgrip strength and all-cause and cause-specific mortality. Dose-response meta-analyses showed that higher levels of handgrip strength significantly reduced the risk of all-cause mortality within 26–50 kg (Higginś $I^2$ =45.7%) in a close-to-linear inverse fashion. Cancer and cardiovascular mortality displayed a trend towards a U-shaped association with a significant risk reduction between 16 and 33 kg (Higginś $I^2$ =77.4%), and a close-to-linear inverse shaped and significant risk reduction ranging from 24 to 40 kg (Higginś $I^2$ =79.7%) respectively.
*Conclusion:* There is strong evidence for an association between lower handgrip strength with higher all-cause, cancer, and cardiovascular mortality risk. The dose-response relationship of handgrip strength substantially varies depending on the cause of mortality.

## 1. Introduction

Low muscle strength has been associated with an elevated risk of all-cause mortality in older adults, irrespective of total muscle mass (Li et al., 2019). Moreover, handgrip strength is a reliable proxy for overall muscle strength in adults (Vaidya and Nariya, 2021). Its measurement is simple and inexpensive, which makes it one of the most widely used markers of muscle strength (Bohannon, 2008; Cooper et al., 2013). Importantly, low handgrip strength is considered a reliable marker of morbidity and mortality outcomes in adults and older adults (Darryl P Leong et al., 2015; Sasaki et al., 2007). For example, an umbrella review by Soysal et al. (Soysal et al., 2021) identified lower handgrip strength as

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a risk factor for early all-cause and cardiovascular mortality. Similarly, a meta-analysis by García-Hermoso et al. (García-Hermoso et al., 2018) observed a consistent inverse association between higher levels of upper- and -lower muscular strength and all-cause mortality. Other studies have assessed the association between low handgrip strength and cancer mortality, but the evidence to date remains mixed (Celis-Morales et al., 2018; Karlsen et al., 2017; Kishimoto et al., 2014; Yates et al., 2017). Despite reference values of handgrip strength for different populations are available (Leong et al., 2016), scarce knowledge exists on the optimal levels of handgrip strength to prevent all-cause and cause-specific mortality in adults. Early attempts to identify relevant handgrip cut-off points to predict mortality exist for specific settings or conditions. However, most of the existing studies have assumed a linear relationship between handgrip strength and mortality outcomes (Cai et al., 2021; Wu et al., 2017), despite some evidence suggesting otherwise (López-Bueno et al., 2022a). Understanding the shape of this relationship is critical to determine the 'optimal dose' of handgrip strength, which remains unknown.

Considering the identified gaps in the literature, this study aimed to provide updated information on the association between handgrip strength and all-cause, cancer, and cardiovascular mortality among apparently healthy adults. To support the clinical interpretation of our study, we additionally conducted a dose-response meta-analysis and estimated the minimal and maximal handgrip strength values associated with a lower risk of all-cause, cancer, and cardiovascular mortality.

## 2. Methods

This pre-registered (PROSPERO; reference number CRD42022308810) systematic review and dose-response meta-analysis was reported following the MOOSE and PRISMA checklist (Page et al., 2021; Stroup et al., 2000).

### 2.1. Search strategy

We conducted a systematic search in PubMed/MEDLINE, Web of Science and Scopus databases from inception to 8 February 2022. The specific search strategies are displayed in the Supplement (Table S1). Title/abstract and full-text screening were conducted independently by RLB and RNC, with disagreements resolved by adjudication by BdPC. Additional studies from the reference lists of eligible articles and topic-related reviews were also screened. All records were analyzed in the free web version of Rayyan (http://rayyan.qcri.org) (Ouzzani et al., 2016).

### 2.2. Selection criteria

We selected (1) prospective cohort studies (2) written in English, and (3) using either a single or repetitive measures of objectively assessed handgrip strength. In addition, (4) studies had to report on at least one all-cause, cancer, or cardiovascular mortality outcome; and (5) include participants aged 18 years or over. Studies for which the effect of handgrip strength could not be isolated were excluded. In addition, studies with either hospitalized or institutionalized participants, as well as studies focusing specifically on clinical populations or health conditions were also excluded. Editorials, letters, reviews, meta-analyses, and in vivo and in vitro studies were not considered.

### 2.3. Data extraction

Data from the selected studies were independently retrieved by RLB and RNC, using a standardised protocol and reporting forms. Disagreements were resolved by consensus with the rest of authors. For all the included studies, we extracted the name of the first author, year of publication, nationality of the study population, number of participants, age, sex, follow-up time, type of dynamometer, outcome ascertainment, study/cohort, covariates, estimates and main results of the study. Full details of the included studies are shown in the Supplement (Table S2). For quantitative analyses, we selected the studies with the most adjusted models among those using the same cohort. Additional estimates on the association between handgrip strength and either all-cause or cause-specific mortality, which were necessary to examine dose-response patterns, could not be initially retrieved from the following published reports: Andrasfay et al., Fujita el al., Kishimoto et al., Laukkanen et al., Leong et al., Mc Grath et al., Mc Lean et al., Minneci et al., Newman et al., Sasaki et al., Stessman et al., Soares et al., Taniguchi et al., Turusheva et al., and Xue et al. (Andrasfay, 2020; Fujita et al., 1995; Kishimoto et al., 2014; Laukkanen et al., 1995; Leong et al., 2015; McGrath et al., 2018; McLean et al., 2014; Minneci et al., 2015; Newman et al., 2006; Sasaki et al., 2007; Soares et al., 2019; Stessman et al., 2017; Taniguchi et al., 2016; Turusheva et al., 2017; Xue et al., 2010) Therefore, we contacted the corresponding authors from such publications by e-mail and requested the necessary data. Of these, four authors provided the requested information (Kishimoto et al., 2014; Minneci et al., 2015; Soares et al., 2019; Strand et al., 2016). More information on the source of data used for the quantitative analyses is displayed in the Supplement (Table S3).

### 2.4. Data synthesis

For quantitative analyses, we extracted the minimum required information to conduct both a random effect model and a dose-response meta-analysis, with the latter requiring the reporting of a minimum of three exposure categories (Geidl et al., 2020). We retrieved data on total number of participants and deaths per exposure category, hazard ratios (HRs) and 95% confidence intervals (CIs) per exposure from the most adjusted models. For the dose-response meta-analysis, in which homogeneity of measurement units is needed, we excluded 4 studies that measured handgrip strength in units other than kilogram and with no possibility of conversion to such unit (i.e., conversion from bars to kilograms required information on surface application area which we did not have). To homogenize reference categories of handgrip strength among studies, we used the method by Orsini (Orsini, 2010) to estimate HRs and 95% CIs. The random forest model required homogeneous estimates on categories of the examined associations, thus selected studies comprised three exposure categories, and studies with lower or higher number of categories were not considered in this analysis. Detailed information on extracted characteristics of studies included in the random forest model are shown in the Supplement (Tables S4, S5, S6).

For the dose-response meta-analyses, the reported mean or median of handgrip strength in each category was assigned to the corresponding HR (Geidl et al., 2020). When studies reported exposure categories as ranges, the midpoint between the lower and upper limit was calculated. We assumed that the width was the same as the adjacent category for open categories (Geidl et al., 2020). More information on the studies included in the dose-response meta-analyses are provided in the Supplement (Tables S7, S8, S9).

### 2.5. Risk of bias and quality of evidence

Three reviewers (RLB, RNC, and BdPC) assessed the risk of bias and quality of included studies using the Newcastle Ottawa Scale (Wells et al., 2013). Each included study was assessed using a star rating system in three domains of bias: selection (four stars); comparability (two stars); and exposure/outcome (three stars). The sum of stars indicates the methodological quality of each study, and the score ranged from 0 (poorest quality) to 9 (best quality) stars.

### 2.6. Statistical analyses

To assess the pooled association between handgrip strength and all-cause and specific mortality, we conducted a random forest model using Stata version 16.1 (StataCorp, Texas, USA). To estimate the pooled non-

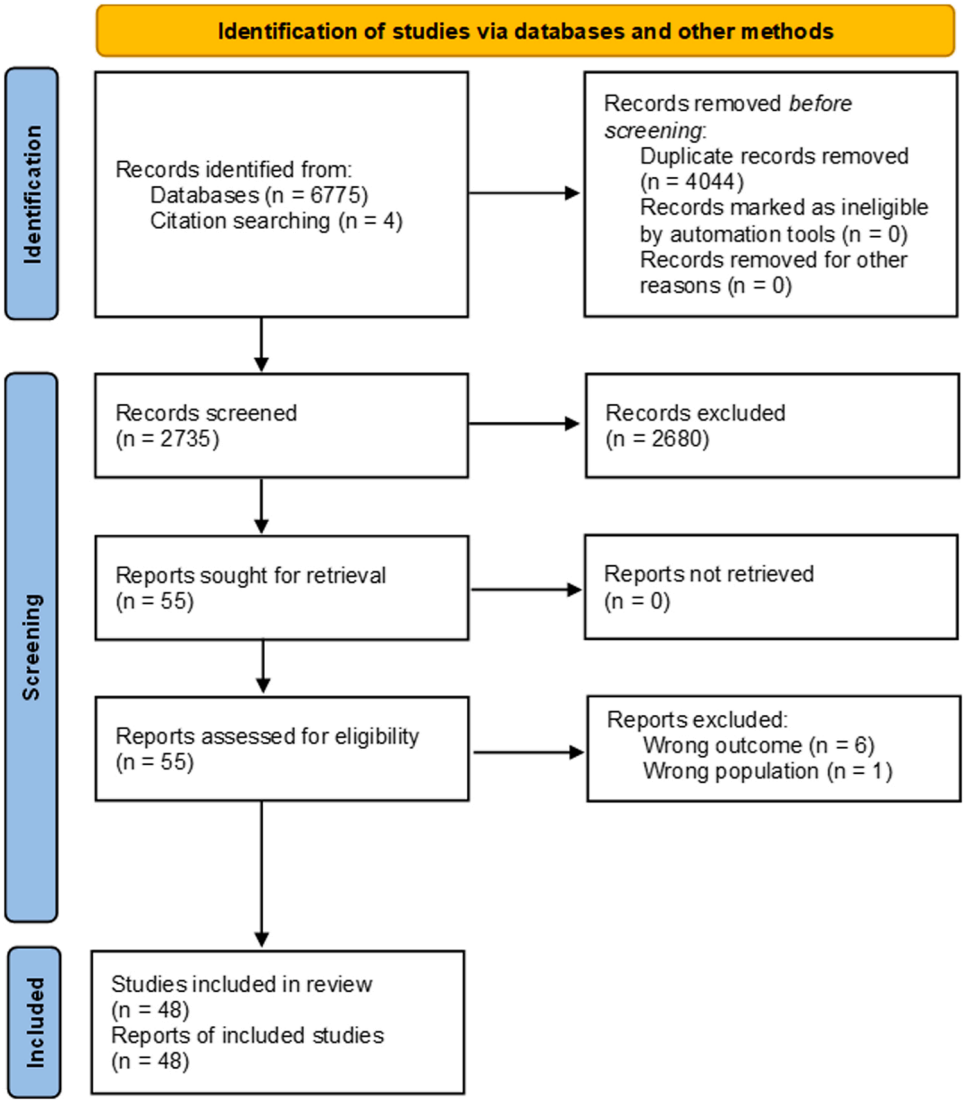



**Fig. 1.** Study selection flowchart.

linear dose-response relationship between handgrip strength and both all-cause and specific mortality, we used a two-stage random-effects hierarchical meta-regression model (Liu et al., 2009). For each individual study, we estimated the linear dose-response associations between the adjusted log-relative HRs and exposure level. To fit the dose-response curve, we pooled the study-specific estimates using the extension of the generalized least-squares method with restricted maximum likelihood estimation (Liu et al., 2009). Using three knots at the 10th, 50th and 90th percentile of handgrip strength, we assessed the potential non-linear association conducting a restricted cubic spline model (Harrell, 2001). We also checked deviations from linearity using a Wald test and used the Higginś $I^2$ statistics to assess heterogeneity (Higgins et al., 2019). Heterogeneity was classified as negligeable ($I^2$ =0%−40%), moderate ($I^2$ =30%−60%), substantial ($I^2$ =50%−90%) or considerable ($I^2$ =75%−100%) (Higgins et al., 2019). We also checked a linear model to test an alternative approach, which showed higher heterogeneity than the used model. Analyses for the dose-response analyses were conducted in R software (version 3.5.1) (R Core Team, 2021) with an accuracy of 1 kg. Stata and R codes developed to conduct the analyses of this study are shown in the Supplement along with a weblink to access the pooled data (Fig. S1). Results are reported as HRs with 95% CIs and levels of significance were set at $p < 0.05$.

### 2.7. Publication bias

To assess the risk of publication bias, we used funnel plots and conducted Egger tests for each of the examined associations.

## 3. Results

### 3.1. Study selection

After removing duplicates, we identified a total of 2735 potential eligible studies in the initial electronic searches. After screening publications by title and abstract, we retrieved 55 potentially eligible studies for inclusion and obtained full-text articles. After applying the exclusion criteria, 48 studies remained in the final selection for the systematic review (Andrasfay, 2020; Arvandi et al., 2016; Bae et al., 2019; Cai et al., 2021; Celis-Morales et al., 2018; Chua et al., 2020; Eekhoff et al., 2019; Farmer et al., 2019; Fujita et al., 1995; Gao et al., 2022; Granic et al., 2017; Ho et al., 2019; Karlsen et al., 2017; Kim et al., 2019a, 2018, 2017; Kim, 2022; Kim and Ho, 2020; Kishimoto et al., 2014; Laukkanen et al., 2020, 1995; Leong et al., 2015; Ling et al., 2010; López-Bueno et al., 2022a, 2022b; McGrath et al., 2020; McLean et al., 2014; Minneci et al., 2015; Newman et al., 2006; Nofuji et al., 2016; Oksuzyan et al., 2017; Park et al., 2022; Petermann-Rocha et al., 2020; Peterson et al., 2016;

**Table 1**
Description and quality assessment of included studies (n = 48).

| Study, year (population) | Cohort/study | Participants (N) | Age (years) | Follow-up duration | Handheld dynamometer | Outcome assessment | Newcastle-Ottawa Quality Assessment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | a | b | c | d | e | f | g | h | Overall quality |
| Andrasfay (2020) (Taiwan) | KORA | 887 | Mean (SD) 70.1 (8.7) | 4.0 years. | North Coast. | Death certificate. | * | * | * | * | * | * | | * | Good |
| Arvandi, 2016 (Germany) | KORA | 1066 | Mean (SD) 76 (11) | 3.0 years. | Jamar. | Death-registry. | | * | * | * | * | | | * | Poor |
| Bae, 2019 (South Korea) | KLOSA | 9393 | Mean (SD) 61 (10.7) | 8.0 years. | Tanita, 6103. | Family interviews and death certificates. | * | * | * | * | * | * | * | * | Good |
| Cai, 2021 (Multi-country) | SHARE | 13,231 | 65 and over | 4.0 years. | Smedley. | Proxy respondent. | | * | * | * | * | | | * | Poor |
| Celis-Morales, 2018 (UK) | UK Biobank | 502,293 | Mean (SD) 56.5 (8.1) | 7.1 years. | Jamar, J00105. | Death certificates. | * | * | * | * | * | * | * | * | Good |
| Chua, 2020 (Singapur) | SCHS | 13,789 | Mean (SD) 74 (6.0) | 3.0 years. | Takei, TKK5401 Grip D. | Death registry. | * | * | * | * | * | * | | | Poor |
| Eekhoff, 2019 (Netherlands) | LASA | 1505 | Mean (SD) 76.0 (6.6) | 15.4 years. | Takei, TKK 5001. | Death municipal registries. | * | * | * | * | * | * | * | | Good |
| Farmer, 2019 (UK) | UK Biobank | 452,931 | Mean (SD) 55.9 (8.9) | 6.1 years. | Jamar. | Death registers. | | * | * | * | * | * | * | * | Good |
| Fujita, 1995 (Japan) | 7 Health-promotion centers | 6259 | Mean (SD) Men 53.6 (9.0) Women 54.5 (8.5) | 6.1 years. | Unknown. | Proxy respondent. | | * | | * | * | | * | * | Fair |
| Gao, 2021 (China) | CHARLS | 3686 | 65 and over | 7.0 years. | Yuejian, TM WL-1000. | Unknown. | * | * | * | * | * | * | * | | Good |
| Granic, 2017 (UK) | Newcastle 85 + Study | 845 | 85 and over | 9.6 years. | Takei, A5401. | Relative proxy. | | * | * | * | * | * | * | | Fair |
| Ho, 2019 (UK) | UK Biobank | 356,721 | Mean (SD) 55.7 (8.1) | 5.0 years. | Jamar, J00105. | Death certificates. | * | * | * | * | * | * | | * | Good |
| Karlsen, 2017 (Norway) | HUNT | 2529 | Mean (SD) 72.6 (4.8) | 15.6 years. | Martin Vigorimeter. | Death registry. | | * | * | * | * | * | * | * | Good |
| Kim, 2017 (UK) | UK Biobank | 403,199 | Range 40–69 | 7.0 years. | Jamar, J00105. | Death records. | * | * | * | * | * | * | * | * | Good |
| Kim, 2018 (UK) | UK Biobank | 70,913 | Mean (SD) 57.2 (8.2) | 5.7 years. | Jamar, J00105. | Linkage with death records. | * | * | * | * | * | * | * | * | Good |
| Kim, 2019 (South Korea) | KLOSA | 5859 | Mean (SD) 63.2 (8.8) | 7.9 years. | Tanita, 6103. | Proxy interview. | * | * | * | * | * | * | * | | Good |
| Kim, 2020 (South Korea) | KLOSA | 2927 | 67 and over | 10.0 years. | Unknown. | Unknown. | * | * | | * | * | * | * | | Good |
| Kim (2022) (South Korea) | KLOSA | 9229 | Mean (SD) 60.7 (0.1) | 9.4 years. | Tanita, 6103. | Proxy family. | * | * | * | * | * | * | * | * | Good |
| Kishimoto, 2014 (Japan) | Hisayama study | 2527 | 40 and over | 19.0 years. | Smedley. | Death certificates. | | * | * | * | * | * | * | * | Good |
| Laukkanen, 1995 (Finland) | Evergreen | 463 | Range 75–84 | 4.0–4.8 years. | Unknown. | Death register. | | * | | * | * | * | | | Poor |
| Laukkanen, 2020 (Finland) | KIHD | 861 | Mean (SD) 69.0 (3.0) | 12.6–18.4 years. | Martin-Balloon-Vigorimeter. | Death certificate registers. | | * | * | * | * | * | * | * | Good |
| Leong (2015) (Multi-country) | PURE | 139,691 | Median (IQR) 50 (42–58) | 4.0 years. | Jamar. | Proxy respondent. | * | * | * | * | * | * | | * | Good |
| Ling, 2010 (Netherlands) | Leiden 85-plus study | 555 | 85 and over | 9.5 years. | Jamar. | Unknown. | | * | * | * | * | * | * | * | Good |
| López-Bueno A, 2022 (Multi-country) | SHARE | 121,383 | Mean (SD) 63.9 (10.2) | 7.4 years. | Smedley, S Dynamometer, TTM. | Proxy-respondent | * | * | * | * | * | * | * | | Good |
| López-Bueno B, 2022 (Multi-country) | SHARE | 121,116 | Mean (SD) 63.7 (10.0) | 3.6 years. | Smedley, S Dynamometer, TTM. | Proxy-respondent | * | * | * | * | * | * | * | | Good |
| Mc Grath, 2020 (USA) | HRS | 19,729 | 50 and over | 12.0 years. | Smedley. | Linkage with national death register and proxy relative interviews. | | * | * | * | * | * | * | * | Good |
| Mc Lean, 2014 (Multi-country) | FNIH Sarcopenia project | 6280 | 68.5 and over | 10.0 years. | Jamar. | Death certificate (Framingham study). | | * | | * | * | * | * | | Fair |
| Minneci, 2015 (Italy) | ICARe Dicomano Study | 561 | Mean (SD) 72.9 (0.3) | 7.0 years. | Jamar. | Unknown. | | * | * | * | * | | * | * | Good |
| Newman, 2006 (USA) | Health, Aging and Body Composition Study | 2292 | 70 and over | 4.9 years. | Jamar. | Hospital records, death certificates, informant interviews, and autopsy data. | * | * | * | * | * | * | | * | Good |

(*continued on next page*)

**Table 1** (*continued*)

| Study, year (population) | Cohort/study | Participants (N) | Age (years) | Follow-up duration | Handheld dynamometer | Outcome assessment | Newcastle-Ottawa Quality Assessment | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | a | b | c | d | e | f | g | h | Overall quality |
| Nofuji, 2016 (Japan) | TMIG-LISA | 1085 | Range 65–89 | 10.3 years. | Smedley. | Death registry. | | * | * | * | * | * | * | | Good |
| Oksuzyan, 2017 (Multi-country) | SAHR MADT LSADT ELSA | 15,130 | Range 55–89 | 6.2–7.5 years. | Smedley. | Death registry and proxy respondents. | | * | * | * | * | * | * | * | Good |
| Park, 2022 (UK) | UK Biobank | 324,486 | Range 40–69 | 4.0 years. | Jamar, J00105. | Death registry. | | * | * | * | * | * | | | Poor |
| Peterman-Rocha, 2020 (UK) | UK Biobank | 469,830 | Range 37–73 | 6.9 years. | Unknown. | Death registries. | * | * | | * | * | * | * | * | Good |
| Peterson, 2020 (Mexico-USA) | H-EPESE | 3050 | 65 and over | 16.0 years. | Jamar, 5030J1. | Death certificates. | * | * | * | * | * | * | * | * | Good |
| Prasitsiriphon, 2018 (Multi-country) | SHARE | 11,037 | 50 and over | 3.0 years. | Smedley. | Proxy interview. | | * | * | * | * | * | | * | Good |
| Rantanen, 2000 (USA) | Honolulu Study | 6040 | Range 45–68 | 30.0 years. | Smedley. | Death certificates and newspapers´obituaries. | | | * | * | * | * | * | * | Fair |
| Rantanen, 2012 (USA) | Honolulu Study | 2239 | Range 56–68 | 44.0 years. | Smedley. | Death certificates and newspapers obituaries. | | * | * | * | * | * | * | * | Good |
| Rolland, 2006 (France) | EPIDOS | 7250 | Mean (SD) 80.5 (3.8) | 3.8 years. | Martin Vigorimeter. | Proxy-respondents. | * | * | * | * | * | * | | | Poor |
| Sasaki, 2007 (Japan) | Hiroshima Study | 4912 | Range 35–74 | 27.0 years. | Unknown. | Death certificates. | * | * | * | * | * | * | * | * | Good |
| Smith, 2019 (UK) | ELSA | 5240 | Mean (SD) 65.9 (9.4) | 9.7 years. | Smedley. | Death registry. | | * | * | * | * | * | * | * | Good |
| Snih, 2002 (USA) | H-EPESE | 2488 | 65 and over | 5.0 years. | Jamar, 5030J1. | Death registers and proxy report. | | * | * | * | * | * | * | * | Good |
| Stessman, 2017 (Israel) | Jerusalem Longitudinal Study | 2241 | 70 and over | 25.0 years. | Takei. | Death notification. | | * | * | * | * | * | * | * | Good |
| Strand, 2016 (Norway) | Tromsø Study | 6850 | Range 50–80 | 17.0 years. | Martin vigorimeter (bars) | Death registry. | | * | * | * | * | * | * | * | Good |
| Soares, 2019 (Brazil) | FIBRA | 900 | 65 and over | 8.4 years. | Unknown. | Death register. | | * | * | * | * | * | * | | Good |
| Taniguchi, 2016 (Japan) | Kusatsu health examination | 1048 | Mean (SD) 71.6 (5.4) | 2188 days. | Unknown. | Unknown. | * | * | | * | * | * | * | * | Good |
| Turusheva, 2017 (Russia) | Northwest Russia | 611 | 65 and over | 5.0 years. | DK-50. | Death registry. | | * | * | * | * | * | * | | Good |
| Xue, 2010 (USA) | WHAS | 436 | Mean (SD) 73.6 (2.8) | 10.0 years. | Jamar, PC5030. | Proxy-interview, obituaries and death-registries. | | * | * | * | * | * | * | | Good |
| Yates, 2017 (UK) | UK Biobank | 420,727 | Median (IQR) 56.4 (38.9–73.7) | 6.3 years. | Jamar, J00105. | Death register. | * | * | * | * | * | * | * | * | Good |

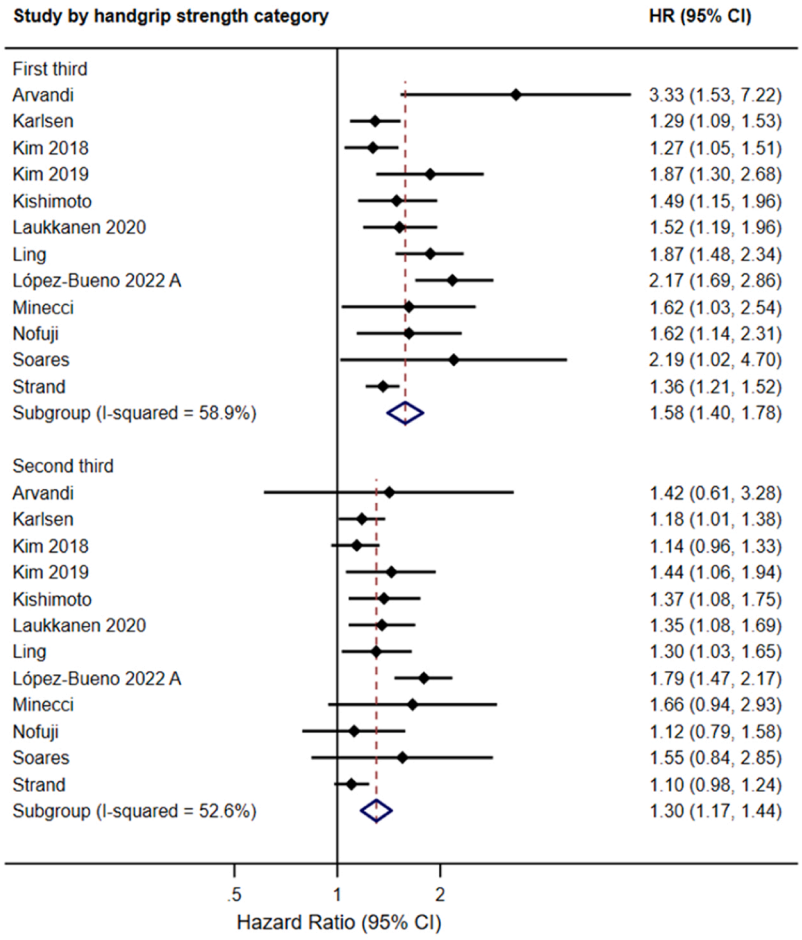
Notes: KORA (Cooperative Health Research in the Region of Augsburg); KLOSA (Korean Longitudinal Study of Aging); SHARE (Survey of Health, Ageing and Retirement in Europe); SCHS (Singapore Chinese Health Study); LASA (Longitudinal Aging Study Amsterdam); CHARLS (China Health and Retirement Longitudinal Study); HUNT (Norwegian Healthy survey of Northern Trøndelag); KIHD (Kuopio Ischemic Heart Disease); PURE (Prospective Urban-Rural Epidemiology); (HRS) Health and Retirement Study; FNIH (The Foundation for the National Institutes of Health); ICARe (Insufficienza Cardiaca negli Anziani Residenti); FIBRA (Brazilian Elderly Frailty); TMIG-LISA (Tokyo Metropolitan Institute of Gerontology Longitudinal Interdisciplinary Study on Aging); SARH (Stress Aging and Health in Russia); MADT (Study of Middle-Aged Danish Twins); LSADT (Longitudinal Study of Aging Danish Twins); ELSA (English Longitudinal Study of Ageing); H-EPESE (Hispanic Established Population for the Epidemiological Study of the Elderly); EPIDOS (Epidémiologie de l'ostéoporose); WHAS (Women's Health and Aging Study).
**Quality categories:** a, representativeness of the exposed cohort; b, selection of the non-exposed cohort; c, ascertainment of exposure; d, demonstration that the outcome of interest was not present at start of the study; e, comparability of cohorts on the basis of the design or analysis controlled for confounders; f, assessment of the outcome; g, follow-up was long enough for outcomes to occur (>5 years); h, adequacy of follow-up of cohort. **Quality thresholds**: i) Good quality (3 or 4 stars in *a-d* AND 1 or 2 stars in *e* and 2 OR 3 stars in *f-h*); ii) Fair quality (2 stars in *a-d* AND 1 or 2 stars in *e* AND 2 or 3 stars in *f-h*); iii) Poor quality (0 or 1 star in *a-d* OR 0 stars in *f-h*).

Prasitsiriphon and Pothisiri, 2018; Rantanen et al., 2012, 2000; Rolland et al., 2006; Sasaki et al., 2007; Smith et al., 2019; Snih et al., 2002; Soares et al., 2019; Stessman et al., 2017; Strand et al., 2016; Taniguchi et al., 2016; Turusheva et al., 2017; Xue et al., 2010; Yates et al., 2017), of which 16 were included in either quantitative analysis (Arvandi et al., 2016; Chua et al., 2020; Granic et al., 2017; Karlsen et al., 2017; Kim et al., 2019b, 2018; Kishimoto et al., 2014; Laukkanen et al., 2020; Ling et al., 2010; López-Bueno et al., 2022b, 2022a; Minneci et al., 2015; Nofuji et al., 2016; Soares et al., 2019; Strand et al., 2016; Yates et al., 2017). The flowchart of the study selection process is displayed in Fig. 1.

### 3.2. Study characteristics

The characteristics of included studies are displayed in Table 1. The present systematic review comprised 3135,473 participants (49.6% female) from more than 40 countries. The age of participants ranged from 35 to ≥ 85 years, whereas the year of publication of the studies ranged from 1995 to 2022. The duration of follow-up ranged from 2.3 to 44 years, while the sample size varied from 436 to 502,293 participants. The range of the examined handgrip strength values comprised those of the included studies, which ranged from 15 to 50 kg.

A. Handgrip strength and all-cause mortality




B. Handgrip strength and cancer mortality

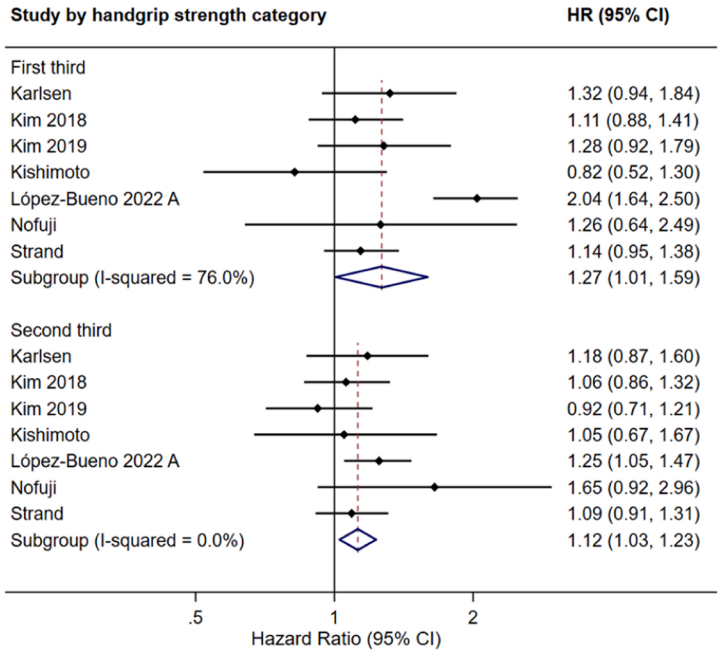



**Fig. 2.** Hazard ratios for the association between handgrip strength and all-cause and specific cause mortality comparing third tertile (reference) versus second and first tertiles. Diamonds represent the 95% CI for pooled estimates of effect.Handgrip strength and all-cause mortality Handgrip strength and cancer mortality Handgrip strength and cardiovascular mortality Notes: HR (Hazard Ratio); CI, (Confidence Interval).

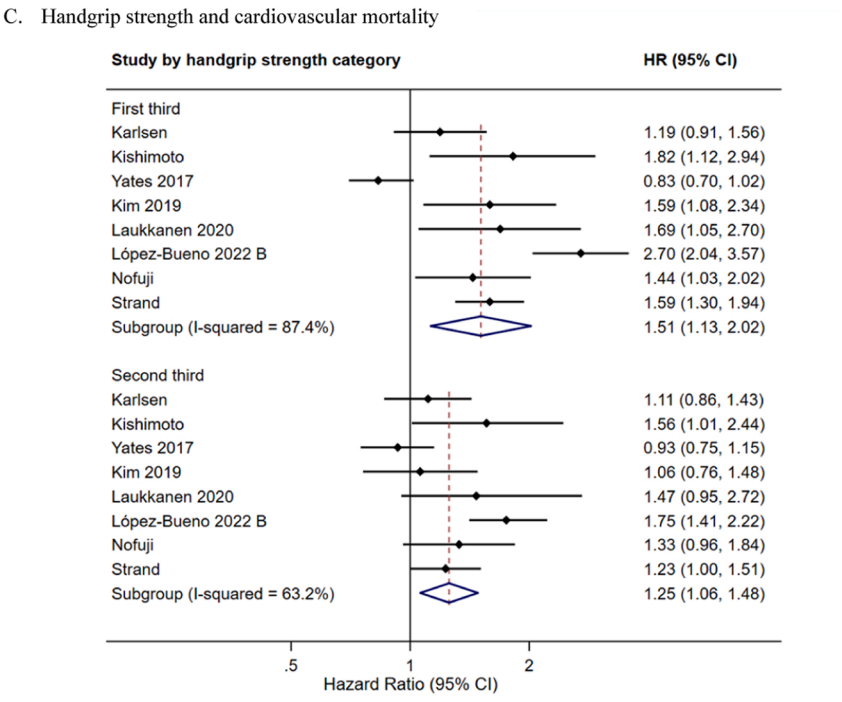



**Fig. 2.** (*continued*).

### 3.3. Random forest model

Pooled HRs estimates from 12 studies with three handgrip strength categories were included in the analyses for all-cause mortality (Fig. 2). Compared with the last third, the second (HR=1.30 [95% CI 1.17–1.44], $I^2$ =52.6%) and first third of handgrip strength (HR=1.58 [95% CI 1.40–1.78], $I^2$ =58.9%; reference: last third) showed a significantly higher risk of all-cause mortality.

More attenuated estimates were observed for the association of handgrip strength and risk of cancer mortality (Fig. 2). Second (HR=1.12 [95% CI 1.03–1.23]; $I^2$ =0.0%) and first (HR=1.27 [95% CI 1.01–1.59]; $I^2$ =76.0%) categories of handgrip strength showed a higher risk of cancer mortality compared with their stronger counterparts (i.e., third category). Finally, second HR= 1.25 [95% CI 1.06–1.48]; $I^2$ = 63.2%) and first HR= 1.51 [95% CI 1.13–2.02]; $I^2$ = 87.4%) categories of handgrip strength exhibited a significantly higher risk of cardiovascular mortality compared to the third category (Fig. 2).

### 3.4. Dose-response relationship

Fig. 3 shows the dose-response association between handgrip strength and all-cause, cancer, and cardiovascular mortality. Higher levels of handgrip strength significantly reduced the risk of all-cause mortality within 26–50 kg ($I^2$ =45.7%) in a close-to-linear inverse dose-response fashion. Cancer mortality exhibited a flattened U-shaped association with a significant risk reduction between 16 and 33 kg ($I^2$ =77.4%). A similar pattern of association was found for cardiovascular mortality, for which a significant risk reduction ranging from 24 to 40 kg ($I^2$ =79.7%) was found.

### 3.5. Risk of bias assessment

Of the included studies, 38 out of 48 studies (79.2%) were considered good quality according to the Newcastle Ottawa Scale. The overall mean score was 7.5 out of a maximum of 9 stars. All the studies included in the quantitative analyses had good quality. More detailed data on bias assessment is displayed in Table 1. Regarding the assessment of publication bias, we did not detect substantial asymmetry in the funnel plots for all-cause and specific mortality causes (Figs. S1-S3). No significant risk for publication bias was also confirmed in Egger tests (Table S10).

## 4. Discussion

This is the first dose-response meta-analysis on the associations between handgrip strength and all-cause, cancer, and cardiovascular mortality in adults. Our results provide critical information with important clinical and public health implications. First, we observed a consistent inverse association between low levels of handgrip strength and an increased risk of all-cause mortality, which was exacerbated amongst participants with the lowest level of handgrip strength. Similar associations were confirmed for cancer and cardiovascular mortality. Second, our dose-response meta-analyses allowed the estimation of minimal and maximum handgrip strength values associated with significant lower risks of all-cause, cancer, and cardiovascular mortality. This finding is particularly relevant since it provides a range of reference values for preventing all-cause and cause-specific mortality, which may be particularly useful in clinical settings as well as to inform future guidelines and public health recommendations.

Our results from the random forest model endorse those estimated in prior research, which observed a consistent association between lower handgrip strength and both all-cause and cardiovascular mortality risk (García-Hermoso et al., 2018; Soysal et al., 2021). Although the different study designs used in the included studies for all-cause and cardiovascular mortality outcomes may hamper comparability, the robustness of the evidence is overall firm and well spread around different countries and settings (Leong et al., 2015; López-Bueno et al., 2022a).

The association between handgrip strength and cancer mortality risk remains unclear in the literature (Celis-Morales et al., 2018; Karlsen et al., 2017; Kim et al., 2019b; Kishimoto et al., 2014; López-Bueno et al., 2022a). The differential effects that muscular strength may have over different types of cancer and/or the different cancer compositions of the studied populations may account for the discrepancies found in the literature (Celis-Morales et al., 2018; Sung et al., 2021). Other plausible explanations, including sex-differences have been previously reported (López-Bueno et al., 2022a). Albeit weaker than for all-cause and cardiovascular mortality, our results indicate the existence of an association

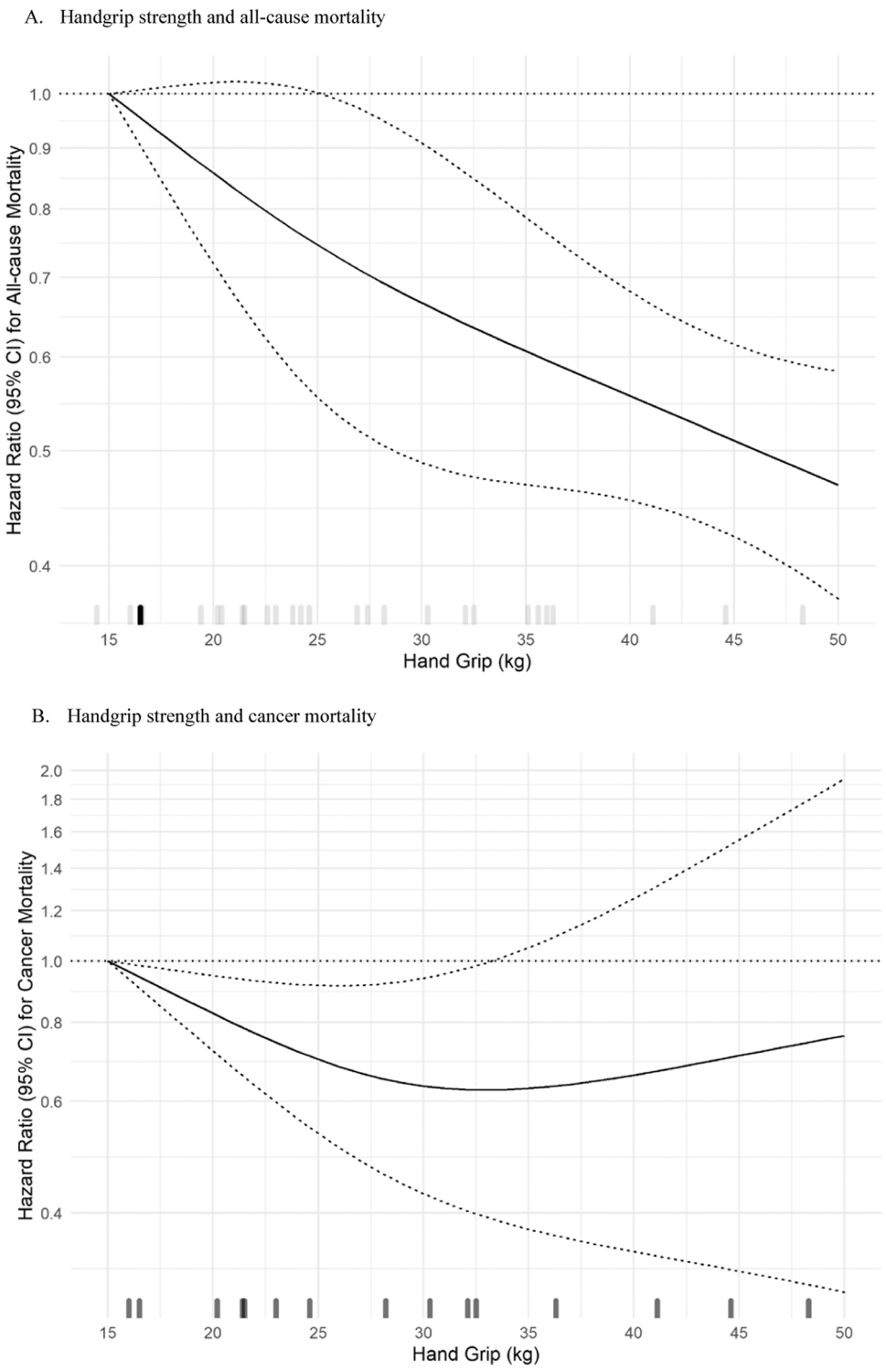



**Fig. 3.** Dose-response association between handgrip strength and all-cause and specific cause mortality. Handgrip strength and all-cause mortality Handgrip strength and cancer mortality Handgrip strength and cardiovascular mortality.

between low handgrip strength and increased risk of cancer mortality.

The major novelty of this study was the estimation of minimal and maximum handgrip strength values associated with lower risks of all-cause and cancer and cardiovascular mortality. Notably, we found that these values differed by cause of mortality. While the dose response association of handgrip strength with all-cause and cardiovascular mortality showed a robust close-to linear inverse response within a specific range of handgrip values, the association of handgrip strength with cancer and cardiovascular mortality exhibited a U-shaped dose-response association. These differences of handgrip strength values and dose-response patterns in relation to different causes of mortality may be due to a variety of reasons. It has been observed that the risk of other relevant causes of death such as respiratory diseases increase with lower handgrip strength (Celis-Morales et al., 2018; Petermann-Rocha

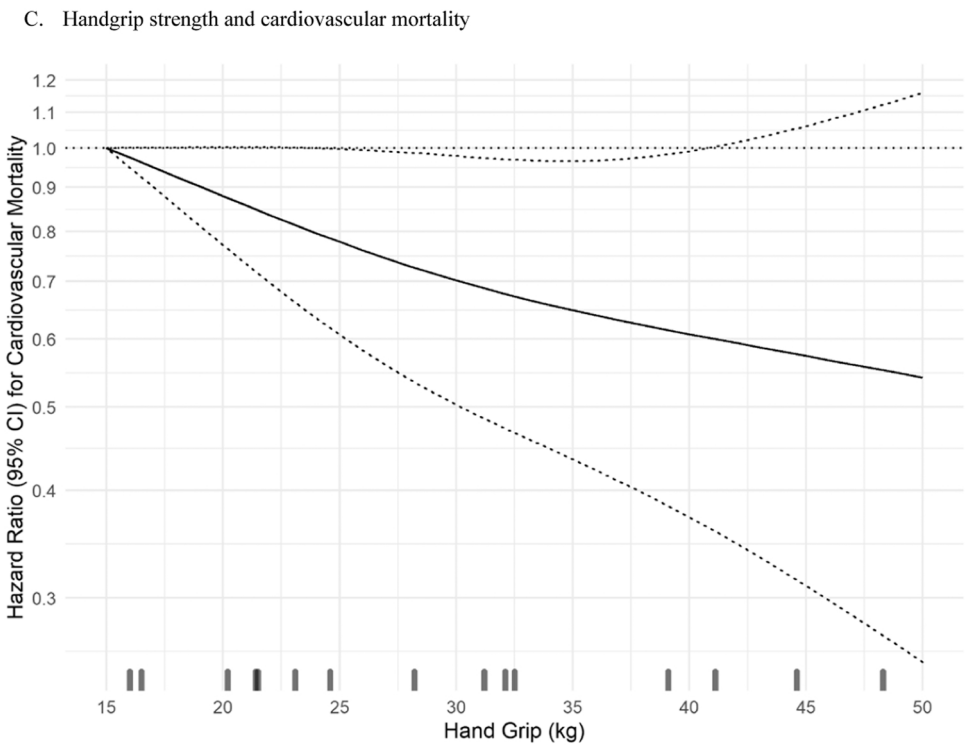



**Fig. 3.** (*continued*).

et al., 2020), which may contribute to strengthen the association between lower handgrip strength and all-cause mortality, and probably widening the handgrip strength range for such associations. Interestingly, prior research has observed lower thresholds for handgrip strength and the association with all-cause mortality (i.e., a maximum threshold of 42 kg for men and 25 kg for women) (López-Bueno et al., 2022a). This prior research, however, was conducted in older adults which may explain this observation (Metter et al., 2002).

In line with our findings, previous research has shown consistent associations of lower handgrip strength with overall and specific cardiovascular mortality causes such as stroke and heart attack (López-Bueno et al., 2022b). Because sarcopenia is closely related to some of the most relevant cardiovascular diseases (i.e., hypertension, heart failure, atherosclerosis and coronary heart disease), which, in turn, have been associated with a decline in muscle function (He et al., 2021), it is reasonable to expect that a reduction in handgrip strength will eventually lead to a higher risk of cardiovascular mortality.

In contrast to our findings for cardiovascular or all-cause mortality (for which significant risks reductions were evident after some level of handgrip strength), we found no minimal threshold for the beneficial associations between handgrip strength and cancer mortality. This is in agreement with recent findings that suggest that low levels of handgrip strength (i.e., a cut-off point of 16 kg for women and 22 kg for men) confer beneficial effects for reducing cancer mortality risk in cancer patients (Zhuang et al., 2020). Furthermore, because cancer accelerates the process of muscle strength losses even small gains or maintenance of muscular strength in acceptable levels might be enough to reduce the risk of cancer mortality (Christensen et al., 2014; Kilgour et al., 2010). Nevertheless, the association of lower handgrip strength with cancer mortality differs depending on the type of cancer. While significant inverse associations were observed for lung, colorectal and breast cancers, no association has been reported for prostate cancer (Celis-Morales et al., 2018; Zhuang et al., 2020). Thus, a wide range of tumour, therapy- and lifestyle-related factors of different cancer types and how it affects muscle strength may partly explain the different results across studies (Christensen et al., 2014). Future research is needed to elucidate the optimal levels of handgrip strength to reduce the risk of mortality associated with different types of cancer and/or stages of development.

### 4.1. Strengths and limitations

This systematic review retrieved data from 48 studies comprising approximately 3.1 million adults from more than 40 countries. Our novel dose-response meta-analyses has yielded several insights with major clinical implications. First, we provide estimations that could be used to inform the handgrip strength levels that are recommendable to reduce risk for all-cause, cancer, and cardiovascular risk mortality in adults. Second, our findings show that different dose-response handgrip strength associations exist depending on the cause of mortality. Third, our results also show that there is still a margin for improving muscular strength in order to reduce the risk of all-cause mortality, and to a lesser extent, cardiovascular mortality. Additionally, long-term hospitalized patients and other specific target populations with particularly low levels of muscular strength might also reduce their risk of cancer mortality by either maintaining or increasing muscular strength.

The present study should be considered in the light of the following limitations: the maximum threshold identified for all-cause and specific mortality causes is limited by the estimates obtained from the included studies, and individuals with higher handgrip levels than those observed in this study might also benefit from an even lower risk of both all-cause and specific mortality. A related limitation is that the uptick of the dose-response curves at the higher end of the exposure may simply represent lack of data rather than a genuine lack of association. The inversion of the right part of the dose-response curves in this study likely reflect the sparsity of data/events rather than a genuine lack of beneficial association at higher levels of handgrip strength. Importantly, high levels of heterogeneity were observed when pooling data from the included studies in several quantitative analyses; thus, despite exhaustive analyses, precise answers to broad meta-analytic questions about subjective issues might be difficult to achieve. Also, generalization of the results is constrained to the studies that comprise the present systematic review, and in which high-income countries were overrepresented. Thus,

different results might be found for populations from low- to middle-income countries (Leong et al., 2015). Similarly, since the age range of the present study comprises middle-aged to older adults, generalizations to younger populations is not possible. Although we used estimations from the most adjusted models of each cohort, this does not necessarily imply that selection of covariates was appropriately conducted. Several studies included in the analyses did not appropriately address or inform about the proportional hazards assumption, (Kishimoto et al., 2014; Minneci et al., 2015), which might affect the reliability of the estimates. Moreover, because there is substantial heterogeneity concerning follow-up periods among studies, certain degree of measurement bias may still be present. Finally, because we could not obtain further data on estimates from eleven studies, there is still a chance for some degree of selection bias. However, since studies with both larger number of participants and higher quality were included in our analyses, it is unlikely that not included studies could substantially modify the present results.

## 5. Conclusion

This systematic review with meta-analysis identified robust associations of lower levels of handgrip strength with higher risk for all-cause and cardiovascular mortality risk, and weaker associations for higher risk of cancer mortality. The dose-response relationship of handgrip strength substantially varies depending on the cause of mortality, and specific handgrip strength ranges are more appropriate to reduce one type of mortality than others. Our results may inform about adequate levels of handgrip strength among adults as well provide clinical guidance for exercise prescription.

## CRediT authorship contribution statement

**Rubén López-Bueno:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Lars Louis Andersen:** Investigation, Writing – review & editing. **Ai Koyanagi:** Investigation, Writing – review & editing. **Rodrigo Núñez-Cortés:** Investigation, Data curation, Writing – review & editing. **Joaquín Calatayud:** Investigation, Writing – review & editing. **José Casaña:** Investigation, Writing – review & editing. **Borja del Pozo Cruz:** Methodology, Investigation, Data curation, Writing – review & editing, Supervision.

## Data Availability

Data will be made available on request.

## Acknowledgements

We thank the authors of original manuscripts for providing the data that was requested.

*Disclosures*

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101778.

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