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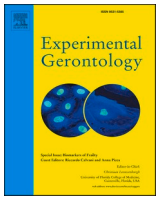

Longitudinal association of handgrip strength with all-cause and cardiovascular mortality in older adults using a causal framework

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ABSTRACT

To date, there is no study addressing the time-varying confounding bias in the association of handgrip strength (HGS) with all-cause or cardiovascular mortality. Therefore, we conducted marginal structural models (MSM) to provide causal estimations on the associations of HGS with all-cause and cardiovascular mortality in a representative sample of adults aged 50 years or older. Data from 29 countries including 121,116 participants (276,994 observations; mean age 63.7 years; 56.3 % women) free from prior heart attack or stroke were retrieved from consecutive waves of the Survey of Health, Ageing and Retirement in Europe (SHARE). During a median of 7.7 years follow-up (interquartile range 3.8–11.8) and 1,009,862 person-years, 6407 participants (5.3 %) died due to all causes, and 2263 (1.9 %) died due to cardiovascular diseases. Using repeated measures of handheld dynamometry, we determined absolute and relative to body mass index HGS of each participant. We applied adjusted MSM to estimate hazard ratios (HRs) associated with changes over time in HGS addressing the time-varying confounding bias. An increase of 5 kg in HGS was associated with a reduced risk of all-cause [HR 0.86, 95 % confidence interval (CI), 0.86–0.90], overall cardiovascular (HR 0.86, 95 % CI 0.82–0.86), heart attack (HR 0.90, 95 % CI 0.86–0.95), and stroke (HR 0.86, 95 % CI 0.82–0.90) mortality. The associations of relative HGS were of stronger magnitude in all cases. Our findings provide critical evidence on the importance of increasing general muscle strength in older adults to reduce mortality risk, particularly concerning cardiovascular causes.

1. Introduction

Active ageing is defined as the process of optimizing opportunities for health, participation and security to enhance quality of life as people age (World Health Organization (WHO), 2003). Active ageing is critical to extend healthy life expectancy and quality of life for all people, including those with non-communicable chronic conditions such as cardiovascular diseases or cancer (Mok et al., 2019). Particularly, the 2020 World Health Organization guidelines on physical activity and sedentary behaviour include specific advice targeted to older populations and emphasize the importance of both aerobic physical activity and muscular strength for healthy ageing (Paw et al., 2016). Specifically, handgrip strength (HGS) is considered a reliable biomarker of several relevant outcomes in older adults (Bohannon, 2019). For example, a previous study suggested that HGS moderates the established association between physical activity and all-cause mortality (Celis-Morales et al., 2017). Declining HGS trajectories has been associated with poor cognitive status, impaired mobility and suboptimal functional status among older adults (Bae et al., 2021; Rijk et al., 2016), as well as all-cause mortality of both older adults and the very old (i.e., people aged 85 years and over) (Ling et al., 2010). Other studies have reported inverse associations between increasing levels of HGS and

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cardiovascular mortality in middle-aged and older adults, although the associations between HGS and more specific causes of death such as stroke or heart attack have not yet been demonstrated (Celis-Morales et al., 2018; Kim et al., 2019; Leong et al., 2015; Yates et al., 2017). Nevertheless, the current literature investigating associations between HGS and mortality outcomes in older adults is limited by several methodological shortcomings. First, most of the existing evidence is based on single timepoint measurements of HGS (Ling et al., 2010), which could lead to biased estimates, and are likely subjected to reverse causality (Sattar and Preiss, 2017). Second, existing studies with available repeated measurements of HGS have failed to account for the effect of time-dependent confounders affected by prior exposure to HGS, which poses risks to unbiased estimates (Celis-Morales et al., 2018; Kim et al., 2019; Leong et al., 2015; Yates et al., 2017).

Marginal structural models (MSM) are a class of models for the estimation, from observational data, of the causal effect of a time-dependent exposure in the presence of time-dependent covariates that may be simultaneously confounders and intermediate variables; although scarce, existing research has already applied this modelling approach to investigate the causal effects of physical activity and sedentary behaviour on physical and cognitive functioning in older adults (Garciá-Esquinas et al., 2021). Unfortunately, there are no known studies using MSM to account for time-varying confounding effects when estimating the association between HGS and mortality outcomes. In view of these identified gaps, we aimed to use MSM to provide causal estimations on the associations of absolute and HGS values relative to BMI with all-cause and cardiovascular mortality in a representative sample of older adults 50 years and older. In addition, we also explored the associations of HGS with cardiovascular specific causes of death, including stroke and heart attack.

2. Methods

2.1. Study design and population

The present longitudinal study used data from regular panel waves 1, 2, 4, 5, 6, and 7 of the Survey of Health, Ageing and Retirement in Europe (SHARE), a biannual survey recruiting individuals aged 50 or older from European countries and Israel (Bergmann et al., 2019; Börsch-Supan et al., 2013). Wave 3 lacked data on HGS and was dismissed for the present study. Representativeness of SHARE waves stems from a multi-stage stratified sampling design in which included countries are divided into different strata according to their geographical area. The number of countries included in SHARE has been progressively increasing with each SHARE wave, thus there are countries with longer follow-up periods than others, and 50 % of participants having 2 or more follow-ups. Municipalities or zip codes within these strata are considered the primary sampling units. Data used in SHARE were collected through home computer-assisted personal interviews from February 2004 to January 2019. Ex-ante harmonization was conducted to ease the comparability among countries and new respondents were added to compensate for the attrition bias due to losses from each wave. Participants aged 50 years or older and who were free from any prior heart attack or stroke diagnosis at study entry were considered in the current study (n = 122,676). Duplicated or overlapped observations as well as participants with missing values regarding time and death cause or unreliable values concerning covariates were excluded from the analyses (n = 1560). Missing values from included participants were estimated using multiple imputation (n = 30,691). We imputed data of 25 % of participants. Fig. 1 shows more descriptive information of the study sample. This study received the approval of the Ethics Committee of

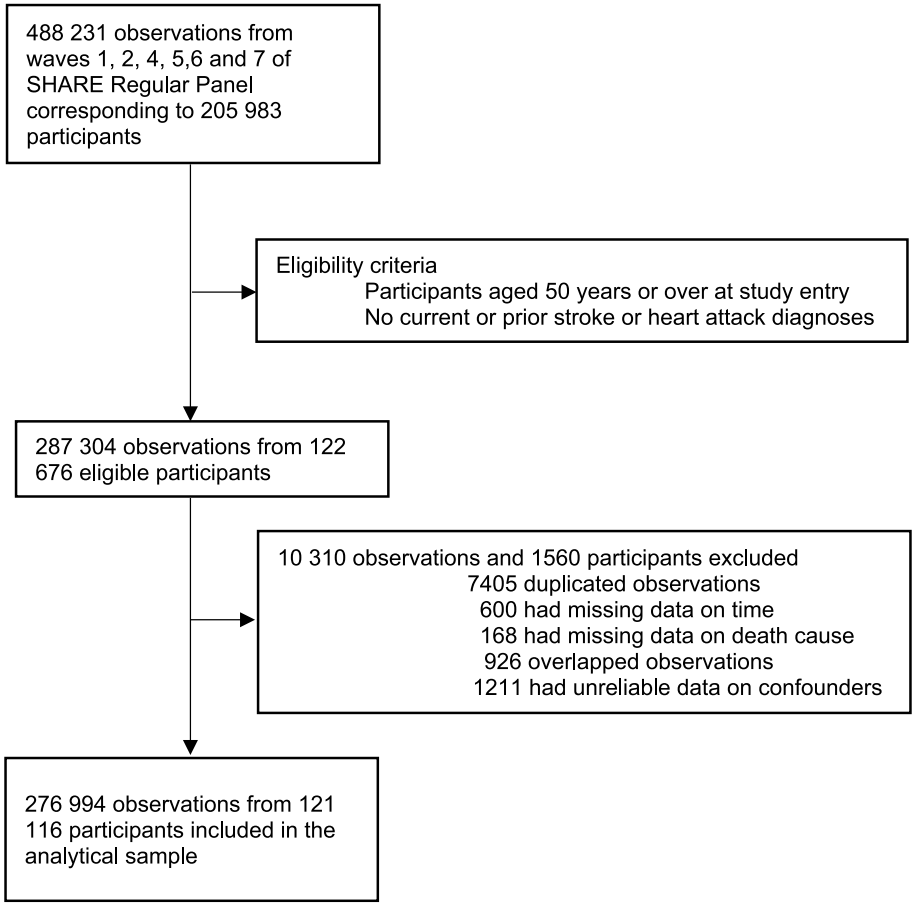

Fig. 1. Study profile.

Research in Humans of the institution, and was reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (von Elm et al., 2014). Participants gave their informed consent.

2.2. Handgrip strength (exposure)

HGS of both hands was measured twice using a handheld dynamometer (Smedley, S Dynamometer, TTM, Tokyo, 100 kg). According to the SHARE protocol (Bergmann et al., 2019), participants were instructed to maintain the elbow in a 90° angle flexion while either standing or sitting, with a neutral wrist position, and upper arm set vertical against the trunk. Interviewers verbally encouraged participants with standardized instructions to squeeze with maximum effort for a few seconds. HGS was defined as the maximum value reached in either hand. Because HGS in relation to BMI was identified as better predictor than absolute values of HGS alone for outcomes such as cancer (Yates et al., 2017), HGS was divided by BMI and thereafter standardized using sex-specific mean and standard deviation of the whole sample ([X − Mean] ÷ SD) (Parra-Soto et al., 2021a, 2021b). For the purpose of this study, exposure of both absolute HGS, and relative HGS over all-cause and cardiovascular mortality were examined.

2.3. All-cause, cardiovascular, heart attack, and stroke mortality (outcomes)

Participants were followed throughout the study period to determine mortality status. When deceased, information concerning both date and cause of death was obtained from a proxy interview (i.e., a relative, a household member, a neighbor, or any other person close to the deceased participant); in such case, mortality was determined through the following question: "*What was the main cause of respondent's death?*" The range of potential answers comprised cancer, heart attack, stroke, other cardiovascular disease related illnesses (heart failure and arrhythmia), respiratory, digestive, or severe infectious disease, and other causes. For all-cause mortality, participants were categorized into alive and deceased, whereas participants deceased due to heart attack, stroke, and other related-cardiovascular events were grouped as deceased due to cardiovascular mortality. Specific death due to either heart attack or stroke were also categorized as alive or deceased due to either of these causes.

2.4. Covariates

Based on a literature review, we explored potential causal and confounding pathways between HGS and all-cause and specific cardiovascular mortality using a directed acyclic graph (eFig. 1, eFig. 2 in the Supplement). Self-reported age and sex, country of residence at the time of interview, education, body mass index, alcohol consumption, smoking habit, physical inactivity, fruits and vegetable consumption and high blood pressure were identified as critical potential confounders in the main model. More information about covariates is provided in the Supplement.

2.5. Statistical analyses

We estimated the risk of the different types of mortality in relation to HGS. To address the time-varying confounding bias derived from the consecutive measurements of both exposure and covariates, we used an MSM (Fewell et al., 2004). This modelling approach was used because follow-up levels of time-varying covariates may simultaneously be confounders for later HGS and mediators for earlier HGS, and thus cannot be appropriately adjusted using standard methods. In the context of the current study, our model considered age at baseline, sex, and country as fixed (i.e., time-invariant) variables whereas the rest of covariates were assumed to possibly vary throughout the follow-up period. After assessing interactions between HGS and all the covariates, no significant interaction was detected. To account for time effects, natural cubic splines with knots placed at the 5th, 50th, and 95th percentiles of the time distribution and time-on-study in months variable were also included in the model. This model was fitted in a two-step process; first, we calculated each participant-specific inverse probability of treatment weights (IPTWs) based on the inverse of the predicted probability of a participant experiencing the exposure that they actually experienced. Secondly, the exposure–outcome association was estimated using a pooled logistic regression in which we modelled the probability that each individual was exposed in each wave using IPTWs stabilized weights. To account for informative censoring, we fitted logistic regression models to estimate inverse probability of censoring weights at each time interval. As with our IPTW, we derived the same models for the numerator and denominator of the stabilized inverse probability of censoring weights. The final stabilized weights were calculated by multiplying the exposure and censoring weights. Finally, we used the cluster option to derive robust standard errors allowing for clustering of effects within each participant. We conducted all statistical analyses in Stata version 16.1 (StataCorp, Texas, USA). The results were visualized as forest plots and estimations were provided as HRs and their 95 % confidence intervals (CIs).

2.6. Sensitivity analyses

To further test the robustness of our estimates, we conducted three different sensitivity analyses. First, we adjusted the main model for disease-related confounders (i.e., medication and diabetes diagnosis) instead of lifestyle-related factors (i.e., physical inactivity and fruits and vegetables consumption) in the alternative model (Model 2) (eFig. 3 in the Supplement). Second, as body mass index might be considered a potential mediator of the association between HGS and mortality, we carried out sensitivity analyses excluding it (eFig. 4 in the Supplement). Finally, we repeated the main model with no imputation of missing values (i.e., with observed values only), (eFig. 5 in the Supplement).

3. Results

3.1. Demographics

The final sample included 52,863 men (43.7 %; 118,138 observations) and 68,253 women (56.3 %; 158,856 observations) with a mean age of 63.7 years (SD 10.0) at study entry. During a median of 7.7 years follow-up (interquartile range 3.8–11.8) and 1,009,862 person-years, 6407 participants (5.3 %) died due to all-causes, whereas 2263 (1.9 %) died due to any cardiovascular related-cause. Mean values of HGS were 34.2 kg (SD 12.0) (Table 1).

3.2. All-cause mortality

Results from the main model showed that each kilogram increment in HGS was associated with a reduced risk of all-cause mortality (HR 0.97, 95 % CI 0.97–0.98). A five-kilogram increase in absolute HGS showed a significant risk reduction (Fig. 3), whereas the risk reduction for HGS relative to BMI was also significant (HR 0.82, 95 % CI 0.79–0.85) (Fig. 2).

3.3. Cardiovascular mortality

Overall, one kilogram increment of HGS significantly reduced the risk of overall cardiovascular mortality (HR 0.97, 95 % CI 0.96–0.97), as well as both specific heart attack (HR 0.98, 95 % CI 0.97–0.99) and stroke mortality (HR 0.97, 95 % CI 0.96–0.98). A five-kilogram increase in absolute HGS showed a significant risk reduction for overall and specific cardiovascular mortality (Fig. 3). Finally, HGS relative to BMI was associated with a significant risk reduction of overall cardiovascular

Table 1
Characteristics of participants at study entry.

N = 121,116	n (%)	Mean (SD)
Age (y)		63.7 (10.0)
Sex		
Men	52,863 (43.7)	
Women	68,253 (56.3)	
Body Mass Index (kg/m^2)		26.8 (4.5)
Education[a]		
None	5263 (4.4)	
Primary	22,097 (18.2)	
Lower secondary	21,182 (17.5)	
Upper secondary	41,850 (34.6)	
Post-secondary non-tertiary	5395 (4.4)	
First stage of tertiary	24,468 (20.2)	
Second stage of tertiary	861 (0.7)	
Alcohol consumption		
Almost every day	18,230 (15.1)	
Five or six days a week	2910 (2.4)	
Three or four days a week	9192 (7.6)	
Once or twice a week	20,258 (16.7)	
Once or twice a month	17,761 (14.7)	
Less than once a month	12,900 (10.6)	
Not at all in the last 6 months	39,865 (32.9)	
High blood pressure ever diagnosed		
No	78,517 (64.8)	
Yes	42,599 (35.2)	
Current smoking habit		
No	86,516 (71.4)	
Yes	34,600 (28.6)	
Fruits and vegetables consumption		
Less than once a week	876 (0.7)	
Once a week	1301 (1.1)	
Twice a week	3628 (3.0)	
3–6 times a week	40,144 (33.1)	
Every day	75,167 (62.1)	
Physical inactivity		
No	10,060 (8.3)	
Yes	111,056 (91.7)	
Country		
Austria	5722 (4.7)	
Belgium	8786 (7.3)	
Bulgaria	1590 (1.3)	
Croatia	2481 (2.0)	
Cyprus	974 (0.8)	
Czech Republic	7439 (6.1)	
Denmark	5246 (4.3)	
Estonia	6757 (5.6)	
Finland	1666 (1.4)	
France	7226 (6.0)	
Germany	7729 (6.4)	
Greece	5694 (4.7)	
Hungary	2424 (2.0)	
Ireland	903 (0.7)	
Israel	3391 (2.8)	
Italy	7784 (6.4)	
Latvia	1336 (1.1)	
Lithuania	1536 (1.3)	
Luxembourg	1945 (1.6)	
Malta	1124 (0.9)	
Netherlands	5629 (4.7)	
Poland	5104 (4.2)	
Portugal	1901 (1.6)	
Romania	1803 (1.5)	
Slovakia	1894 (1.6)	
Slovenia	4888 (4.0)	
Spain	8057 (6.7)	
Switzerland	4263 (3.5)	
Sweden	5824 (4.8)	
Handgrip strength (kg)		34.2 (12.0)
All-cause mortality		
No	114,709 (94.7)	
Yes	6407 (5.3)	
Cardiovascular mortality		
No	118,853 (98.1)	
Yes	2263 (1.9)	
Heart-attack mortality		
No	120,300 (99.3)	
Yes	816 (0.7)	
Stroke mortality		
No	120,467 (99.5)	
Yes	649 (0.5)	

[a] Based on ISCED 1997 classification.

(HR 0.77, 95 % CI 0.72–0.81), heart attack (HR 0.84, 95 % CI 0.78–0.91), and stroke mortality (HR 0.80, 95 % CI 0.74–0.86) (Fig. 2).

3.4. Sensitivity analyses

Compared with the main model, the sensitivity model adjusting for disease-related confounders yielded stronger associations for all outcomes examined for both absolute and relative HGS (eFig. 3 in the Supplement). The main model without adjustment for BMI showed minor differences with the main analyses (eFig. 4 in the Supplement). The main model with observed values yielded similar results except for specific outcomes (i.e., heart attack and stroke mortality) (eFig. 5 in the Supplement).

4. Discussion

Our results show an inverse prospective association of incremental levels of HGS with all-cause and cardiovascular mortality in adults aged 50 years or older. The observed associations were stronger using relative HGS as exposure. Because of the robustness of the modelling approach used and the consistency of the estimations, the findings of the current study are highly reliable. Additionally, we provide first evidence on the associations of HGS with heart attack and stroke mortality among middle-aged to older adults. Taken together, our findings could inform clinical guidelines to detect middle-aged to older individuals at risk of premature mortality due to the examined causes, and stablish preventive strategies.

4.1. All-cause mortality

Our findings support existing evidence from studies on different populations of adults (Celis-Morales et al., 2018; Kim et al., 2019; Kim, 2022; Laukkanen et al., 2020; Leong et al., 2015; Yates et al., 2017) and confirm, using a causal inference framework, the existance of an association between HGS and all-cause mortality in middle-aged to older adults. Nevertheless, direct comparisons of effect estimations with previous studies are not possible since several of this existing evidence use categories of HGS as the main exposure (Kim et al., 2019; Kim, 2022; Laukkanen et al., 2020; Yates et al., 2017). A study with HGS used as a continuous exposure variable suggested a modest risk reduction per five kilogram increase in HGS among middle-aged adults from the UK biobank (Celis-Morales et al., 2018). A similar increase was also estimated in a meta-analysis with 42 studies and 3,002,203 community-dwelling older adults (Wu et al., 2017). Similar estimates have also been reported in the Prospective Urban-Rural Epidemiology (PURE) study, a longitudinal analysis comprising 139,691 adults from 17 countries (Leong et al., 2015). One-year changes in HGS have also been associated with estimates of similar magnitude than those found in our study (Malhotra et al., 2020). Interestingly, the use of HGS relative to BMI was more strongly associated with mortality in our study. This observation has been previously reported for the association of HGS with cancer and cardiovascular outcomes, although the evidence remains inconclusive (Ho et al., 2019; Jang et al., 2020; Parra-Soto et al., 2021a, 2021b). Nevertheless, our results, and those from previous studies, warrant the promotion of muscle strengthening activities in adults and older adults, including those with existing chronic conditions (Ling et al., 2010;

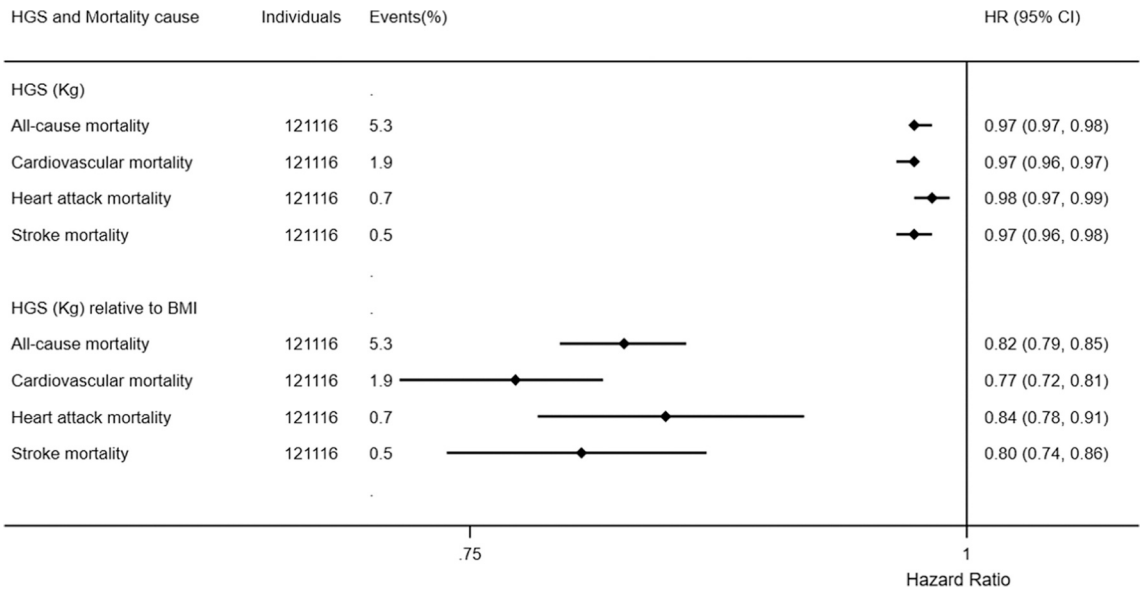

Fig. 2. Prospective causal associations between handgrip strength and handgrip strength relative to body mass index with all-cause and cardiovascular mortality*.
HGS: Handgrip Strength (kg).
BMI: Body Mass Index (kg/m^2).
*Absolute HGS model is adjusted for age, sex, country, and baseline, current and lagged education, body mass index, alcohol consumption, smoking habit, physical inactivity, fruits and vegetable consumption and high blood pressure. Relative BMI model is adjusted for the same variables than Absolute HGS model with the exception of body mass index.

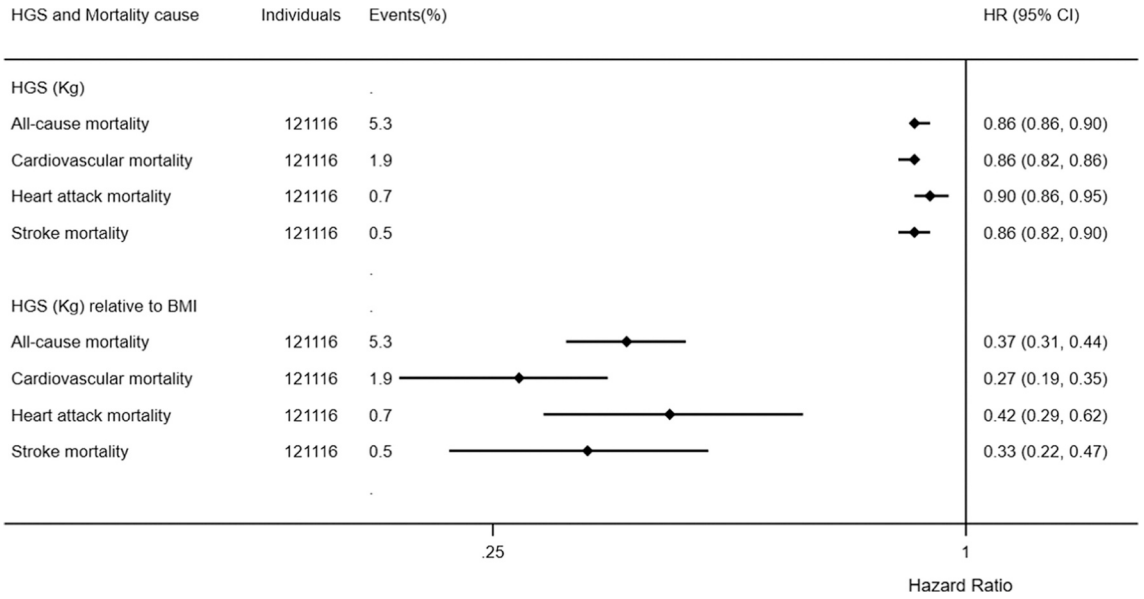

Fig. 3. Prospective associations between 5-kilogram increase of handgrip strength with all cause and cardiovascular mortality*.
HGS: Handgrip Strength (kg).
BMI: Body Mass Index (kg/m^2).
*Absolute HGS model is adjusted for age, sex, country, and baseline, current and lagged education, body mass index, alcohol consumption, smoking habit, physical inactivity, fruits and vegetable consumption and high blood pressure. Relative BMI model is adjusted for the same variables than Absolute HGS model with the exception of body mass index.

Malhotra et al., 2020).

4.2. Cardiovascular mortality (overall, stroke, and heart-attack)

We observed a significant inverse association between HGS and overall cardiovascular mortality. Other longitudinal studies have consistently reported similar associations among populations from different countries and age-ranges, including older adults (Kim et al., 2019; Yates et al., 2017). The PURE study by Leong et al. (Leong et al., 2015) reported values per 5 kg of HGS and exhibited estimates of similar magnitude. These observations have also been indicated in a meta-analysis (Lee, 2020) and confirm the role of HGS for cardiovascular mortality in older adults. Our study also provides first time evidence of an inverse association of HGS with heart attack and stroke. The observed associations were stronger for HGS relative to BMI. Previous studies have identified low HGS as a risk factor for coronary heart disease,

myocardial infarction and stroke onsets (Laukkanen et al., 2020; Leong et al., 2015; Wu et al., 2017). Furthermore, prior research has suggested an association between arterial abdominal aortic calcification and declines in HGS, which may partly explain the detrimental effects of low HGS on cardiovascular mortality (Ramírez-Vélez et al., 2021). Interestingly, a recent study suggested an association between low HGS and arterial stiffness hence providing a closer pathway by which HGS may be associated with cardiovascular mortality (König et al., 2021).

4.3. Strenghts and limitations

Key strengths of the present study include the use of robust longitudinal analyses addressing a broad range of time-varying potential confounders in a large and representative sample from 29 countries. Moreover, the use of objective measures of HGS reduces the chance of measurement bias. However, the findings from the present study must be interpreted in light of its limitations. First, we imputed a substantial proportion of missing values in several confounder variables (e.g., smoking habits or hypertension diagnosis). Nevertheless, analyses with complete-case observations yielded consistent results, with a more pronounced slight variation concerning HGS relative to BMI all-cause mortality that can be observed when comparing Fig. 2 and eFig. 5 in the Supplement. . However, the low number of available cases for these two narrower outcomes after removing missings may have resulted in unstable estimations. Second, all variables of interest in the study but the main exposure (i.e., HGS) were self-reported, which may have lead to a certain degree of recall and social desirability bias. Third, although biologically plausible, there is currently a lack of studies describing the confounding and mediating role of several covariates used in our study (e.g., physical inactivity or fruit and vegetables consumption). This may hamper some of the assumptions in our modelling approach (i.e., the role of any of the time-varying confounders in the model might not truly imply both concurrent confounding and mediation). However, we tested the robustness of our estimates using an alternative model with different potential time-varying confounders, finding very similar estimates than those for the main model. Fourth, owing to the panel methodology conducted in SHARE, the follow-up period for a substantial number of participants, particularly those from countries that have been incorporated later to SHARE, might not be long enough to encompass a significant time frame to attribute causality to the exposure variable. Also, the use of a proxy for assessing the outcome variable might lead to a certain degree of misclassification. Nevertheless, a death proxy is a reliable substitute to identify death in adult populations when fact of death is not available (Mealing et al., 2012), which along with the high SHARE retention rate (81 %) and the use of refresher samples limit the chance of both selection and misclassification bias. Lastly, despite the broad range of confounders in this study, we cannot rule out the existance of residual confounding. Nevertheless, our results support previous findings with alternative sets of confounders in adult populations (Celis-Morales et al., 2018; Yates et al., 2017).

5. Conclusions

Higher levels of absolute and relative HGS were associated with a reduced risk of all-cause and cardiovascular mortality. Further investigations delving into the causes behind these observations are warranted. Nonetheless, our results point out to the importance of increasing general muscle strength in middle-aged to older adults to achieve healthy ageing.

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Appendix A. Supplementary data

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