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The association of grip strength with health outcomes does not differ if grip strength is used in absolute or relative terms: a prospective cohort study

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Abstract

Background: higher grip strength is associated with better health outcomes. The optimal way to report grip strength (i.e. absolute vs. relative) for prediction, however, remains to be established.
Methods: in participants (aged 37–73 at baseline) from the UK Biobank, we examined the associations of grip strength, expressed in absolute terms (kilograms) and relative to anthropometric variables, with mortality and disease incidence, after exclusion of the first 2 years of follow-up, and compared risk predictions scores of handgrip strength when differentially expressed.
Results: of the 356 721 participants included in the analysis 6,234 died (1.7%) and 4,523 developed CVD (1.3%) over a mean follow-up of 5.0 years (ranging from 3.3 to 7.8) for mortality and 4.1 years (ranging from 2.4 to 7.0) for disease incidence data. As expected, baseline higher grip strength was associated with lower risk of all-cause and cause specific mortality and incidence. These associations did not meaningfully differ when grip-strength was expressed in absolute terms, vs. relative to height, weight, fat-free mass, BMI, fat-free mass index and fat-free mass, or as *z*-scores. Similarly the different ways of expressing grip strength had little effect on the ability of grip strength to improve risk prediction, based on C-index change, of an office-based risk score.
Conclusions: the ability of grip strength to predict mortality is not altered by changing how it is expressed.

Keywords

handgrip strength, mortality, CVD, cancer, prediction

Key points

- The association of grip strength with a variety of health outcomes does not differ when express as z-scores or relative to anthropometric variables.
- Similarly the predictive ability of grip strength does not differ when changing how it is expressed.
- For clinical utility grip strength can simply be expressed in absolute units (kg).

Introduction

On top of its functional role in allowing body movement, skeletal muscle is also the primary protein store within the body and the primary tissue for glucose disposal, and thus has an important role in health and disease [1, 2]. Several studies have shown that lower muscle function is associated with an increase in mortality and morbidity risk [3–9]. Indeed in our recent paper analysing data from 477 074 participants (aged 40–70 years) from the UK Biobank study we found that low grip strength was associated with an increased risk for all-cause, cardiovascular, cancer and respiratory disease mortality [10]. Furthermore, we found that the addition of handgrip strength to an office-based risk score, including age, sex, diabetes, body mass index, systolic blood pressure and smoking, improved all-cause and cardiovascular mortality risk prediction. Together these data indicate that the measurement of grip strength may have clinical utility in risk screening.

Currently, however, the measurement and reporting of grip strength data is not standardised [11], which not only presents issues with its use in research studies but also in clinical settings. For example, although the majority of reference ranges [12–14] and suggested clinical cut-off values for definition of sarcopenia and weakness [15] are given with handgrip strength measured in kilograms it is known that handgrip strength varies, not only by sex and age, but by anthropometric characteristics such as height, body mass, body mass index and fat free mass. Whether the expression of grip strength in relative, rather than absolute, terms strengthens the association of hand grip strength with mortality/morbidity remains to be established. Furthermore whether the expression of grip strength in relative terms improves the predictive ability of handgrip strength when added to a pre-existing risk score has yet to be investigated.

The aims of this study, therefore, were to investigate the associations of grip strength, expressed 1) in absolute terms (kilograms) and 2) relative to anthropometric variables, with mortality and disease incidence and to compare risk prediction scores of handgrip strength when differentially expressed.

Methods

Between April 2007 and December 2010, UK Biobank recruited >502 000 participants, aged 37–73 years from the general population [16]. Participants attended one of 22 assessment centres across England, Wales and Scotland [17, 18] where they completed a touch-screen questionnaire, had physical measurements taken and provided biological samples, as described in detail elsewhere [17, 18]. The outcomes in the current study were all cause mortality, and incidence and mortality of cancer, cardiovascular (CVD), and respiratory diseases, with the exposure variable being grip strength (both absolute and relative to anthropometric variables). Socio-demographic factors (age, sex, ethnicity and area-based socioeconomic status), month of recruitment, smoking status, height, body mass index, systolic blood pressure, medications for CVD, self-reported physical activity time and dietary intake were treated as potential confounders. Participants with the following prevalent morbidities at recruitment were excluded from analysis: alcohol related disorders, atrial fibrillation, cancer, coronary heart disease, bipolar disorder, chronic obstructive pulmonary disease, chronic liver disease, dementia, depression, diabetes, eating disorder, heart failure, inflammatory bowel disease, schizophrenia, substance related disorders, stroke.

Procedures

Date of death and date and cause of hospital admissions were identified as described previously [19]. Grip strength was measured as previously described [19] and the mean of the right and left values was calculated and expressed in absolute units (kg) and relative to height (cm), weight (kg), fat-free mass (kg), BMI (kg/m^2), fat-free mass index (kg/m^2) and fat-free mass (%) for subsequent analysis. Handgrip strength z-scores were also calculated and used in analysis (based on normative British data [20]). Physical activity was based on self-report, using the International Physical Activity Questionnaire short form [21], and total time spent in sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer and watching television.

The frequency of intake of food items was collected using a touchscreen questionnaire. Area-based socioeconomic status was derived from postcode of residence, using the Townsend score [22]. Age was calculated from dates of birth and baseline assessment. Smoking status was categorised into never, former and current smoking. Medical history and medications for CVD were collected from the self-completed, baseline assessment questionnaire. Height, body weight, and blood pressure were measured by trained nurses during the initial assessment centre visit. Body mass index (BMI) was calculated as ($weight/height^2$) and the WHO criteria used to classify BMI into: underweight <18.5, normal weight: 18.5 to <25, overweight: 25 to <30, obese: 30 to <35, obesity class 2: 35 to <40 and obesity class 3: $\geq 40\ kg.m^{-2}$. Body composition (body fat and fat free mass) were measured using bio-impedance by trained nurses. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical analyses

Non-linear associations between grip strength and health outcomes were visually explored using multivariable penalised cubic splines in Cox-proportional hazard models [23]. Penalised spline is a technique to balance between data fit and smoothness [24]. Spline curvature is penalised by the integrated second derivative. Knots were selected based on generalised cross validation (GCV) and were equally spaced across the range of the exposure variable. Spline values were restricted to be linear below the first and beyond the

final knots to ensure numerical stability [25]. The results were reported as hazard ratios together with 95% confidence intervals.

Eight representations of grip strength were analysed: (1) absolute grip strength in kg, (2) age- and sex-specific grip strength z-score based on a national reference [20], and (3) grip strength divided by height, weight, fat-free mass, BMI, fat-free mass index (fat-free mass ÷ squared height in metre) and fat-free mass proportion (fat-free mass ÷ weight). All these variables, except for the z-score, were standardised against their mean and standard deviation of the whole sample ($[X - Mean_X] \div SD_X$) for comparison.

Cox proportional hazard analyses were adjusted for socio-demographic recruitment covariates (age, sex, ethnicity, Townsend deprivation index and month of recruitment), smoking status, systolic blood pressure, medications for CVD, self-reported physical activity time and dietary intake. Participants with prevalent morbidity at baseline as above) were excluded from the analysis to minimise reverse causation. All the analyses were performed with the exclusion of events in the first two years (two-year landmark).

To compare the predictive ability of handgrip strength indicators, we calculated Harrell's C-index (which estimates the probability of concordance between observed and predicted responses) [26] for a model including office-based risk factors including age, sex, diabetes diagnosed, BMI (per 5 $kg.m^{-2}$), systolic blood pressure (per 10 mmHg) and smokers, and then compared the ability to predict all-cause mortality, as described elsewhere [10]. To validate the predictive ability of grip strength, a bootstrap validation (500 bootstrap samples of the analysed sample size [n = 356 721]) was conducted. C-indices of training (data used to estimate the model) and testing (data not used to estimate the model) data are reported. Bootstrapping is a non-parametric resampling technique to estimate the accuracy of prediction methods [27].

The proportional hazard assumption was checked by tests based on Schöenfeld residuals. All analyses were performed using R statistical software (version 3.5.1) with packages survival and rms.

Results

Of the 502 628 participants recruited to UK Biobank, 134 587 (26.8%) had prevalent morbidities at recruitment and were excluded. Among the remaining 368 041 participants, 11 320 (3.1%) had missing grip strength, implausible height (<1.4 m), BMI (<10 or >50), fat-free mass index, (<12.5 or >30) or fat-free mass proportion (<50% or >90%) and were therefore excluded, resulting in a final sample size of 356 721 participants for analysis. The mean follow-up period for all-cause and CVD mortality was 5.0 years (ranging from 3.3 to 7.8) and 4.1 years (ranging from 2.4 to 7.0) for disease incidence. Of those participants included in the respective analysis, over the follow up period 6,234 died (1.7%) and 4,523 developed CVD (1.3%).

The main characteristics of the participants by quartiles of grip strength are summarised in Table 1. In summary, a higher grip strength was found in males and non-smokers, and those with higher height, BMI, fat-free mass, fat-free mass index, fat-free mass proportion, physical activity levels, and energy intake.

Our data demonstrate that higher grip strength was associated with lower risk of all-cause, CVD, respiratory and cancer mortality (Figure 1 and Appendices 1, 2 and 4), and incident CVD, respiratory diseases and cancer (Figure 2 and Appendices 3 and 5). The association with all-cause mortality appeared to be an exponential decay pattern ($p_{nonlinear}$ = 0.002; Figure 1). Similar association patterns were also observed for CVD mortality (Appendix 1) and incidence (Figure 2) and respiratory disease mortality and incidence (Appendices 2 and 3). On the other hand, associations with cancer mortality ($p_{nonlinear}$ = 0.29) and incidence ($p_{nonlinear}$ = 0.15) appeared to be more linear (Appendices 4 and 5). Such association patterns were largely similar across different grip strength indicators, although a more linear relationship with incident CVD was seen when grip strength was expressed relative to weight and fat-free mass index (Figure 2). The association of grip strength relative to fat-free mass proportion appeared to have a suggestive U-shape even though there were wide confidence intervals at the upper end. These associations did not differ substantially between the minimally and comprehensively adjusted models (Data not shown) nor when comparing participants with and without co-morbidities (Data not shown). As detailed in appendix 6 when comparing Harrell's C-indices to predict all-cause and cause-specific mortality between the different ways to express grip strength there was very little difference and even where relative expressions were somewhat numerically higher, these were not statistically significant (P > 0.48).

Discussion

The main finding of the current study is that when comparing numerous different ways to express grip strength, ie absolute, relative to height, weight, fat-free mass, BMI, fat-free mass index and z-scores, there is no difference in the association of grip strength with all-cause, CVD or cancer mortality. These findings could have important public health implications as they suggest that the simplest method to report the measurement of grip strength i.e. in absolute units (kg) is perfectly suitable for the prediction of health outcomes within clinical practice.

The findings of an inverse association of grip strength with all-cause, CVD and cancer mortality is in line with the findings of previous studies [3–6, 10, 28]. Together these data provide strong evidence that the measurement of grip strength may have clinical utility in predicting an elevated risk of poorer subsequent health outcomes. Clearly, however, prior to potential implementation in clinical practice further work is needed to help guide how best to use grip strength to help with disease prediction. As grip strength is

Table 1. Participant characteristics

	Overall	Grip strength quintile				
	(*n* = 356,721)	≤21.5 (*n* = 72,108)	>21.5 to 27 (*n* = 77,641)	>27 to 33 (*n* = 67,602)	>33 to 41.5 (*n* = 69,177)	>41.5 (*n* = 70,161)
Females, n (%)	194,540 (54.5)	69,419 (96.3)	70,180 (90.4)	44,213 (65.4)	10,166 (14.7)	535 (0.8)
Mean (SD) age, years	55.73 (8.12)	58.49 (7.41)	56.14 (7.85)	54.67 (8.21)	55.67 (8.31)	53.51 (7.98)
Mean (SD) deprivation index	−1.46 (3.00)	−1.30 (3.04)	−1.48 (2.96)	−1.41 (3.03)	−1.46 (3.02)	−1.67 (2.93)
Ethnicity, n (%)						
White	335,946 (94.6)	66,835 (93.2)	73,291 (94.8)	63,553 (94.5)	65,335 (94.9)	66,905 (95.8)
South Asians	6,578 (1.9)	2,200 (3.1)	1,312 (1.7)	1,153 (1.7)	1,221 (1.8)	688 (1.0)
Black	5,844 (1.6)	996 (1.4)	1,227 (1.6)	1,222 (1.8)	1,126 (1.6)	1,273 (1.8)
Chinese	1,293 (0.4)	395 (0.6)	327 (0.4)	236 (0.4)	208 (0.3)	127 (0.2)
Mixed background	5,380 (1.5)	1,263 (1.8)	1,173 (1.5)	1,118 (1.7)	955 (1.4)	870 (1.2)
Smoking status, n (%)						
Never	204,004 (57.5)	44,572 (62.3)	46,748 (60.5)	38,920 (57.8)	36,486 (53.0)	37,259 (53.3)
Previous	116,330 (32.8)	21,616 (30.2)	24,180 (31.3)	21,637 (32.2)	24,610 (35.7)	24,277 (34.7)
Current	34,705 (9.8)	5,411 (7.6)	6,379 (8.3)	6,733 (10.0)	7,790 (11.3)	8,391 (12.0)
Mean (SD) SBP, mmHG	139.59 (19.66)	138.50 (20.48)	137.40 (20.38)	137.91 (19.85)	141.76 (18.98)	142.64 (17.73)
Mean height (SD), m	1.69 (0.09)	1.61 (0.06)	1.64 (0.07)	1.68 (0.07)	1.74 (0.07)	1.78 (0.06)
BMI categories, n (%)						
Underweight	1,548 (0.4)	590 (0.8)	494 (0.6)	332 (0.5)	107 (0.2)	25 (0.0)
Normal weight	124,211 (34.8)	28,036 (38.9)	32,448 (41.8)	26,457 (39.1)	21,065 (30.5)	16,198 (23.1)
Overweight	155,974 (43.7)	28,013 (38.8)	29,961 (38.6)	27,402 (40.5)	33,635 (48.6)	36,948 (52.7)
Obese	74,988 (21.0)	15,469 (21.5)	14,738 (19.0)	13,411 (19.8)	14,370 (20.8)	16,990 (24.2)
Mean (SD) BMI, kg/m^2	26.96 (4.27)	26.74 (4.54)	26.44 (4.41)	26.67 (4.39)	27.22 (4.01)	27.80 (3.79)
Mean (SD) fat-free mass, kg	53.08 (11.47)	43.60 (5.68)	45.63 (6.72)	50.88 (9.16)	60.32 (8.54)	66.04 (7.37)
Mean (SD) Fat-free mass index, kg/m^2	18.47 (2.55)	16.81 (1.74)	17.00 (1.87)	17.99 (2.31)	19.88 (2.13)	20.85 (1.82)
Mean (SD) Fat-free proportion	0.69 (0.08)	0.64 (0.07)	0.65 (0.07)	0.68 (0.08)	0.74 (0.07)	0.76 (0.05)
Mean (SD) physical activity, MET-min/week	2,730 (3,812)	2,316 (3,174)	2,482 (3,284)	2,661 (3,663)	2,991 (4,194)	3,240 (4,555)
Mean (SD) grip strength, kg	31.32 (10.98)	17.59 (3.39)	24.49 (1.64)	30.18 (1.69)	37.47 (2.36)	48.04 (5.12)

Data presented as mean and standard deviation (SD) for continuous variables and as number and % for categorical variables. SBP: systolic blood pressure; BMI: body mass index; MET: metabolic equivalent task; kcal: kilocalories.

known to vary dependent on many factors which are routinely collected, such as height, body mass, body mass index and fat free mass, establishing the optimal way to express grip is a key step in this process. The current study found that the shape and magnitude of the associations of grip strength with health outcomes was not changed by expressing grip strength relative to these factors, nor by using z-scores.

Additionally, when comparing the C-indices the predictive ability of grip strength did differed negligibly by the different methods to express grip strength. Indeed as we have shown previously [10] the addition of absolute grip strength to an office based risk score (age, sex, diabetes diagnosed, BMI, systolic blood pressure and smoking status) improved the C-index by 0.013. This magnitude of improvement is similar to that seen when adding high density lipoprotein cholesterol (C-index change 0.007) and N-terminal pro b-type natriuretic peptide (C-index change 0.020), for a composite outcome of coronary heart disease plus stroke and heart failure, to conventional risk factor scores (age, sex, smoking, systolic blood pressure, history of diabetes, and concentration of total cholesterol) [29]. There was little difference in the improvement in C-indices when grip strength was expressed relatively or as a Z-score, and although the C-index was numerically higher when grip strength was expressed relative to height, weight and fat-free mass this was not significantly different nor likely to be of clinical significance (C-index increases of 0.0003 to 0.0017, above C-index for absolute grip strength). This would suggest, therefore, that when grip strength is implemented in clinical practice any of these ways to express grip strength would be valid, but that the use of absolute units (kg) may be the simplest way forward.

Study limitations

The UK Biobank is not representative of the UK general population in several ways. The UK Biobank is relatively representative of the general UK population in terms of age, sex, ethnicity and socioeconomic status but is only partially representative in terms of lifestyle. Therefore, caution should be heeded in generalising the results to the general population [30]. Participants were more likely to be older, women, live in less socioeconomically deprived areas and were less likely to be obese, smoke, drink alcohol on a daily basis and had fewer self-reported health outcomes. Rates of all-cause mortality and cancer incidence were also lower [16, 30]. Reverse causality is possible in any observational study; and whilst our design excluded many comorbidities at baseline and results were similar after a landmark analysis of events occurring from 2 years after recruitment, we cannot fully exclude the potential of reverse causality. Similarly

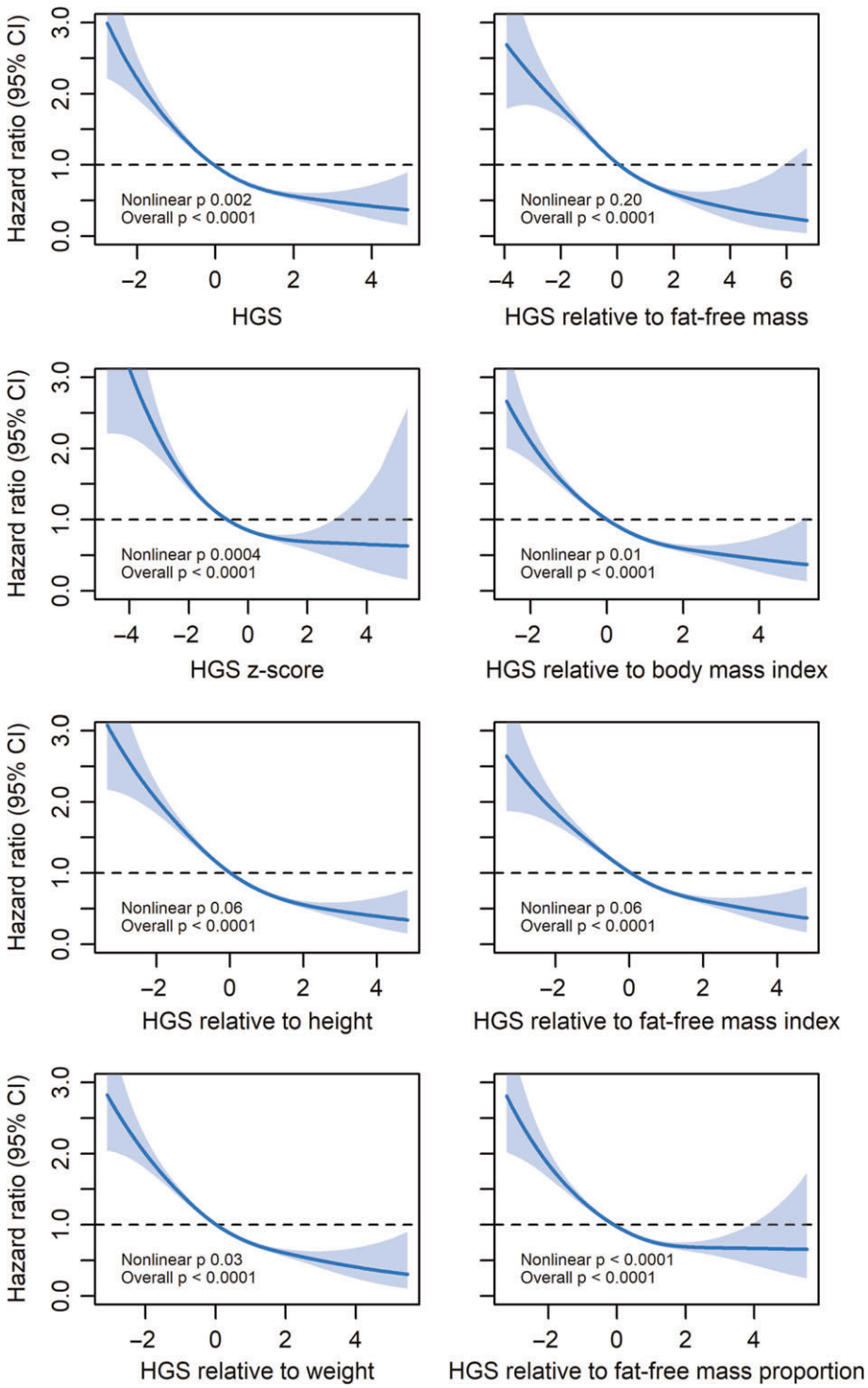

Figure 1. Association between all-cause mortality and handgrip strength expressed in absolute and relative terms in fully adjusted models. Data is presented as hazard ratio and its 95%CI. Absolute and relative markers of handgrip strength were standarised against their mean and SD to allow comparison across diferent markers of handgrip strength. Analyses were conducted using a 2-year landmark analyses and participants with major comorbidities were excluded from the analyses (n = 129,100). All analyses were adjusted for age, sex, ethnicity, Townsend deprivation index and month of recruitment); smoking status, systolic blood pressure, medications for CVD, self-reported physical activity time and dietary intake of red meat, processed meat, fruit and vegetables, and oily fish. HGS: handgrip strength.

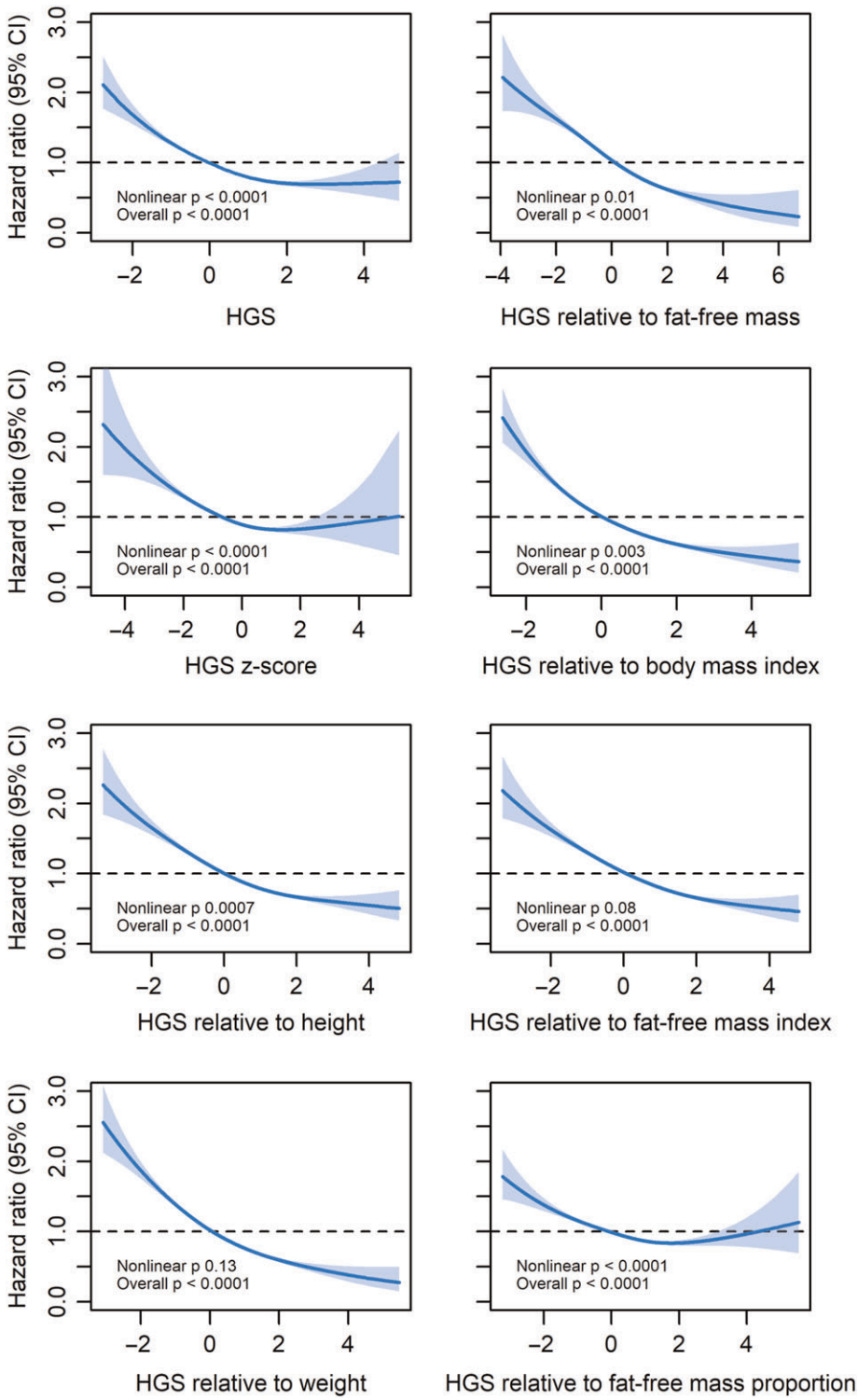

Figure 2. Association between incident CVD and handgrip strength expressed in absolute and relative terms in fully adjusted models. Data is presented as hazard ratio and its 95%CI. Absolute and relative markers of handgrip strength were standarised against their mean and SD to allow comparison across diferent markers of handgrip strength. Analyses were conducted using a 2-year landmark analyses and participants with major comorbidities were excluded from the analyses (n = 129,100). All analyses were adjusted for age, sex, ethnicity, Townsend deprivation index and month of recruitment); smoking status, systolic blood pressure, medications for CVD, self-reported physical activity time and dietary intake of red meat, processed meat, fruit and vegetables, and oily fish. HGS: handgrip strength.

residual confounding is always possible and the associations observed may not imply causality. However, given that we are largely interested in prediction and identification of individuals at increased risk, and not seeking to make causal inferences, reverse causality is not a major limitation in this type of work.

Conclusions

The ability of grip strength to predict all-cause mortality and other important disease outcomes appears not to be altered by changing how it is expressed. This means that as grip strength in absolute values can predict health outcomes as well as the more complex ratios this may simplify the use of grip strength in both research and clinical practice for risk prediction. It is worth pointing out, however, that in practice the clinical interpretation of a grip strength score may be easiest using population derived z-scores, accounting for sex and age.

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Ethical approval: UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment in the study, which was conducted in accord with the principles of the Declaration of Helsinki.

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Increased levels of soluble Receptor for Advanced Glycation End-products (RAGE) are associated with a higher risk of mortality in frail older adults

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Abstract

Objective: to evaluate the relationship between serum levels of the soluble Receptor for Advanced Glycation End-products (sRAGE) and mortality in frail and non-frail older adults.
Methods: we studied 691 subjects (141 frail and 550 non-frail) with a median age of 75 years from two population-based cohorts, the Toledo Study of Healthy Aging and the AMI study, who were enrolled to the FRAILOMIC initiative. Multivariate Cox proportional hazards regression and Kaplan–Meier survival analysis were used to assess the relationship between baseline sRAGE and mortality.
Results: during 6 years of follow-up 101 participants died (50 frail and 51 non-frail). Frail individuals who died had significantly higher sRAGE levels than those who survived (median [IQR]: 1563 [1015-2248] vs 1184 [870-1657] pg/ml, $P = 0.006$), whilst no differences were observed in the non-frail group (1262 [1056-1554] vs 1186 [919-1551] pg/ml, $P = 0.19$).