Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study

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Summary

Background Reduced muscular strength, as measured by grip strength, has been associated with an increased risk of all-cause and cardiovascular mortality. Grip strength is appealing as a simple, quick, and inexpensive means of stratifying an individual's risk of cardiovascular death. However, the prognostic value of grip strength with respect to the number and range of populations and confounders is unknown. The aim of this study was to assess the independent prognostic importance of grip strength measurement in socioculturally and economically diverse countries.

Methods The Prospective Urban-Rural Epidemiology (PURE) study is a large, longitudinal population study done in 17 countries of varying incomes and sociocultural settings. We enrolled an unbiased sample of households, which were eligible if at least one household member was aged 35–70 years and if household members intended to stay at that address for another 4 years. Participants were assessed for grip strength, measured using a Jamar dynamometer. During a median follow-up of 4·0 years (IQR 2·9–5·1), we assessed all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, myocardial infarction, stroke, diabetes, cancer, pneumonia, hospital admission for pneumonia or chronic obstructive pulmonary disease (COPD), hospital admission for any respiratory disease (including COPD, asthma, tuberculosis, and pneumonia), injury due to fall, and fracture. Study outcomes were adjudicated using source documents by a local investigator, and a subset were adjudicated centrally.

Findings Between January, 2003, and December, 2009, a total of 142 861 participants were enrolled in the PURE study, of whom 139 691 with known vital status were included in the analysis. During a median follow-up of 4·0 years (IQR 2·9–5·1), 3379 (2%) of 139 691 participants died. After adjustment, the association between grip strength and each outcome, with the exceptions of cancer and hospital admission due to respiratory illness, was similar across country-income strata. Grip strength was inversely associated with all-cause mortality (hazard ratio per 5 kg reduction in grip strength 1·16, 95% CI 1·13–1·20; p<0·0001), cardiovascular mortality (1·17, 1·11–1·24; p<0·0001), non-cardiovascular mortality (1·17, 1·12–1·21; p<0·0001), myocardial infarction (1·07, 1·02–1·11; p=0·002), and stroke (1·09, 1·05–1·15; p<0·0001). Grip strength was a stronger predictor of all-cause and cardiovascular mortality than systolic blood pressure. We found no significant association between grip strength and incident diabetes, risk of hospital admission for pneumonia or COPD, injury from fall, or fracture. In high-income countries, the risk of cancer and grip strength were positively associated (0·916, 0·880–0·953; p<0·0001), but this association was not found in middle-income and low-income countries.

Interpretation This study suggests that measurement of grip strength is a simple, inexpensive risk-stratifying method for all-cause death, cardiovascular death, and cardiovascular disease. Further research is needed to identify determinants of muscular strength and to test whether improvement in strength reduces mortality and cardiovascular disease.

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Introduction

Physical fitness is an important predictor of mortality and morbidity.[1,2] Physical fitness consists of cardiorespiratory fitness and muscular fitness. Both muscular endurance and muscle strength are indicators of muscular fitness. Reduced muscle strength, as measured by grip strength, has been associated with an increased risk of mortality in many studies.[2–11] However, the mechanism by which low muscle strength might predispose to death is uncertain. Grip strength measurement is appealing as a quick and inexpensive way to stratify an individual's risk of death. However, the information on the prognostic value of grip strength is largely derived from high-income countries, and data from low-income or middle-income countries are rare. The prognostic value of grip strength in these settings is uncertain but would be useful as an inexpensive and simple test.

The Prospective Urban-Rural Epidemiology (PURE) study is a prospective cohort study of more than 154 000 community-based individuals from 17 high-income, middle-income, and low-income countries. The aim of the PURE study was to examine the association

between societal factors, risk factors, and chronic non-communicable diseases across various sociocultural and economic environments.

Methods

Study design and participants

The design of the PURE study has been described previously.[12] In brief, we selected countries to achieve substantial socioeconomic heterogeneity. For reasons of feasibility, we did not undertake proportionate sampling of all countries worldwide, or of regions within countries. At the start of the study, we classified selected countries according to the World Bank scheme as high-income (Canada, Sweden, and United Arab Emirates), upper middle-income (Argentina, Brazil, Chile, Malaysia, Poland, South Africa, and Turkey), lower middle-income (China, Colombia, and Iran), and low-income (Bangladesh, India, Pakistan, and Zimbabwe). To achieve country-income strata with similar numbers of participants, we grouped participants from high-income and upper middle-income countries together as participants of high-income countries.

Within participating communities, our goal was to enrol an unbiased sample of households. Households were eligible if at least one member was aged 35–70 years and if household members intended to stay at that address for another 4 years. Of the 142 861 participants who were enrolled in the PURE study, the 139 691 participants with known vital status were included in the present analysis. Results of previous analyses[12,13] have shown that the population included can be used to make comparisons across countries because the risk factor levels and mortality rates were similar to those seen in independent studies including the same countries. The PURE study was approved by the relevant research ethics committees in the participating countries. All participants provided written informed consent.

Procedures

For baseline characteristics, trained study personnel gave a standardised questionnaire to at least one household member aged 35–70 years. These questions elicited self-reported demographics, cardiovascular risk factors, comorbid disorders, education levels, employment status, physical activity levels, tobacco and alcohol use, and dietary patterns. Study personnel also measured participant anthropometrics and blood pressure. Physical activity level was assessed with the International Physical Activity Questionnaire (IPAQ)[14] and was classified as low, moderate, or high (appendix). We assessed nutrient intake with food frequency questionnaires that were individualised and validated[15–17] for the countries participating in the PURE study. On the basis of responses to the food frequency questionnaire, we estimated daily calorie intake and the proportion of calorie intake from protein. We calculated body-mass index (BMI; kg/m²) from weight and height.

Grip strength was measured by study personnel at the baseline visit with a Jamar dynamometer, according to a standardised protocol. For the first study participants, three measurements were made from the participant's non-dominant hand. During the course of the study, the protocol was amended so that three measurements were made from both hands of each participant. We used only the maximum values obtained from each hand.[18] Where values were missing for one hand but were present for the other (38 974 missing dominant hand values and 929 missing non-dominant hand values), we estimated grip strength values for the missing hand using the coefficient and constant from the linear regression of non-dominant and dominant hand-grip strength. We calculated overall grip strength from the mean of the maximum values of non-dominant and dominant hand grip strength.

Information about participant vital status was obtained in person or by telephone calls at annual intervals.

Outcomes

We assessed time to all-cause mortality, cardiovascular mortality (defined as death due to myocardial infarction, stroke, heart failure, other cardiovascular cause, or sudden unexpected death), non-cardiovascular mortality, myocardial infarction, stroke, incident diabetes, pneumonia, hospital admission for pneumonia or COPD, hospital admission for any respiratory disease (including COPD, asthma, tuberculosis, or pneumonia), injury due to a fall, or fracture. We sought supporting documents for all outcomes. A local investigator, trained to apply standardised event-verification criteria, verified outcomes using the supporting documents. In a random subset of cases, a central adjudication committee assessed and confirmed or refuted outcomes using pre-specified definitions and criteria. If a participant was no longer living at their original address, their vital status was ascertained from other household members, when possible. If a participant had died and the cause of death was unknown, cause of death was determined by verbal autopsy.[19] The verbal autopsy is a series of standardised questions given to household members about symptoms and events surrounding a death. This method has been previously validated against administrative registry data.[19]

Statistical analysis

We calculated hazard ratios (HR) of time to all-cause mortality with Cox proportional hazards models. To account for the clustered nature of the data, we used shared frailty models. The clustering variable was the community to which each individual belonged. The proportional hazards assumption was checked by visual inspection of log-log plots. For all other outcomes, we adopted a competing risks framework, in which death occurring in the absence of the outcome of interest was treated as a competing risk

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See **Online** for appendix

For the **questionnaire** see http://www2.phri.ca/pure/baseline-docs/Adult_Oct2012.pdf

because the death precluded the occurrence of the event of interest. We present the results as cumulative incidence curves and we did the modelling with the approach of Fine and Gray,[20] with effect-sizes presented as subdistribution HRs.

To determine whether associations between grip strength and outcomes were uniform across countries of different income, we first modelled grip strength (divided by tertile) as part of an interaction term with country income (stratified as high income, middle income, or low

	Entire cohort (n=139 691)	Women (n=81 039)			Men (n=58 652)		
		First third (n=27 035)	Second third (n=27 195)	Third third (n=26 809)	First third (n=19 631)	Second third (n=19 434)	Third third (n=19 587)
Grip strength, kg	30·6 (11·1)	17·2 (3·63)	24·6 (1·77)	32·4 (4·50)	27·5 (5·53)	38·7 (2·45)	49·9 (5·94)
Median age, years (IQR)	50 (42–58)	53 (44–60)	50 (42–58)	47 (40–54)	55 (46–63)	51 (43–59)	48 (41–55)
Ethnic origin							
South Asian	29 633 (21%)	8990 (33%)	4915 (18%)	2647 (10%)	7870 (40%)	4167 (22%)	1044 (5%)
Chinese	46 036 (33%)	6127 (23%)	10 234 (38%)	10 504 (39%)	4794 (24%)	7009 (36%)	7368 (38%)
Malaysian	9573 (7%)	3176 (12%)	1647 (6%)	661 (2%)	2251 (12%)	1276 (7%)	562 (3%)
Persian	6100 (5%)	834 (3%)	1389 (5%)	950 (4%)	542 (3%)	1011 (5%)	1374 (7%)
Arab	965 (1%)	231 (1%)	265 (1%)	162 (1%)	109 (<1%)	106 (<1%)	92 (<1%)
African	4354 (3%)	1284 (5%)	715 (3%)	986 (4%)	599 (3%)	409 (2%)	361 (2%)
European	15 524 (11%)	1645 (6%)	2781 (10%)	4351 (16%)	908 (5%)	1738 (9%)	4101 (21%)
Latin American	22 491 (16%)	4125 (15%)	4303 (16%)	5358 (20%)	2166 (11%)	3112 (16%)	3427 (18%)
Other	4605 (3%)	530 (2%)	873 (3%)	1118 (4%)	339 (2%)	540 (3%)	1205 (6%)
Country income							
High	50 791 (36%)	9510 (35%)	9033 (33%)	11 175 (42%)	5416 (28%)	6366 (33%)	9291 (48%)
Middle	59 029 (42%)	8567 (32%)	13 163 (49%)	12 757 (47%)	6350 (32%)	8906 (46%)	9286 (47%)
Low	29 871 (22%)	8958 (33%)	4999 (18%)	2877 (11%)	7865 (40%)	4162 (21%)	1010 (5%)
Education							
Pre-secondary school	59 745 (43)	15 256 (57%)	12 550 (46%)	10 369 (39%)	9503 (49%)	7064 (36%)	5003 (26%)
Secondary school	52 463 (38%)	8720 (32%)	9923 (37%)	10 461 (39%)	6840 (35%)	7882 (41%)	8637 (44%)
Post-secondary school	27 113 (19%)	2981 (11%)	4660 (17%)	5925 (22%)	3229 (16%)	4420 (23%)	5898 (30%)
Employed	68 082 (60%)	7822 (43%)	9436 (49%)	11 769 (58%)	11 561 (62%)	12 874 (68%)	14 620 (76%)
Physical activity level							
Low	19 241 (15%)	4091 (17%)	3106 (13%)	2606 (10%)	3564 (21%)	3010 (17%)	2784 (16%)
Moderate	49 209 (39%)	10 603 (44%)	10 489 (42%)	9710 (40%)	5904 (34%)	6318 (36%)	6185 (34%)
High	58 120 (46%)	9500 (39%)	11 187 (45%)	12 178 (50%)	7795 (45%)	8360 (47%)	9100 (50%)
Tobacco use							
Former	16 866 (12%)	1374 (5%)	1916 (7%)	2745 (10%)	3177 (16%)	3531 (18%)	4123 (21%)
Current	28 735 (21%)	2259 (8%)	2134 (8%)	2710 (10%)	7194 (37%)	7429 (38%)	7009 (36%)
Never	93 045 (67%)	23 255 (86%)	22 935 (85%)	21 147 (80%)	8932 (46%)	8384 (43%)	8392 (43%)
Alcohol use							
Former	6336 (5%)	600 (2)	675 (2)	683 (3%)	1629 (8%)	1469 (8%)	1280 (7%)
Current	36 626 (26%)	2494 (9)	3951 (15)	6529 (24%)	5335 (28%)	7718 (40%)	10 599 (54%)
Never	96 008 (69%)	23 864 (89)	22 454 (83)	19 465 (73%)	12 380 (64%)	10 183 (52%)	7662 (39%)
Median dietary energy intake, kcal/day (IQR)	2002 (1548–2590)	1805 (1400–2387)	1881 (1472–2420)	1935 (1525–2452)	2066 (1582–2705)	2204 (1724–2797)	2296 (1815–2850)
Dietary protein intake, % total energy intake	15·1% (3·47%)	14·5% (3·58%)	15·4% (3·44%)	15·8% (3·36%)	13·9% (3·47%)	14·8% (3·39%)	15·7% (3·15%)
Hypertension	29 008 (21%)	6846 (25%)	5884 (22%)	4993 (19%)	4185 (21%)	3711 (19%)	3389 (17%)
Diabetes	10 672 (8%)	2837 (11%)	1831 (7%)	1172 (4%)	2444 (12%)	1453 (7%)	935 (5%)
Coronary artery disease	5591 (4·0%)	1098 (4·0%)	1066 (3·9%)	688 (2·6%)	1212 (6·2%)	862 (4·4%)	665 (3·4%)
Heart failure	1252 (0·99%)	318 (1·4%)	227 (0·90%)	208 (0·81%)	227 (1·4%)	130 (0·75%)	142 (0·74%)
Stroke	2327 (1·7%)	487 (1·8%)	350 (1·3%)	246 (0·92%)	719 (3·7%)	329 (1·7%)	196 (1·0%)
Cancer	2293 (1·6%)	376 (1·4%)	444 (1·6%)	507 (1·9%)	414 (2·1%)	215 (1·1%)	337 (1·7%)
COPD	1451 (1·1%)	238 (1·0%)	215 (0·85%)	212 (0·82%)	459 (2·9%)	184 (1·1%)	143 (0·75%)

(Table 1 continues on next page)

	Entire cohort (n=139 691)	Women (n=81 039)			Men (n=58 652)		
		First third (n=27 035)	Second third (n=27 195)	Third third (n=26 809)	First third (n=19 631)	Second third (n=19 434)	Third third (n=19 587)
(Continued from previous page)							
Height, cm	161 (9·5)	153 (6·6)	156 (6·2)	159 (6·7)	164 (7·4)	168 (6·6)	172 (7·1)
Weight, kg	67 (16)	60 (16)	63 (14)	67 (15)	64 (15)	71 (15)	79 (16)
Body-mass index, kg/m²	25·7 (5·45)	25·7 (6·14)	26·0 (5·60)	26·6 (5·50)	23·9 (5·17)	25·2 (4·70)	26·7 (4·54)
Waist:hip ratio	0·872 (0·0849)	0·847 (0·0843)	0·842 (0·0792)	0·841 (0·0771)	0·905 (0·0799)	0·911 (0·0735)	0·918 (0·0696)
Right upper arm circumference, cm	28·8 (4·14)	27·8 (4·61)	28·5 (4·04)	29·4 (3·93)	27·4 (3·96)	29·0 (3·55)	30·8 (3·58)
Systolic blood pressure, mm Hg	131 (22)	131 (24)	130 (23)	129 (22)	133 (24)	133 (21)	133 (19)
Diastolic blood pressure, mm Hg	82 (15)	81 (15)	81 (15)	82 (17)	82 (14)	83 (14)	84 (17)

Numbers are mean (SD) or number (%), unless otherwise stated. COPD=chronic obstructive pulmonary disease.

Table 1: **Participant characteristics stratified by sex and by tertile of grip strength**

income). If this interaction was significant (at α=0·05), there might be heterogeneity of the association between grip strength and outcome across country-income strata. For all exposures, effect estimates are presented per 5 kg reduction in grip strength.

We made adjustment for the following potential confounders of the association between grip strength and outcomes: age; sex; education level; employment status; physical activity level; tobacco and alcohol use; daily dietary energy intake; proportion of calorie intake from protein; self-reported hypertension, diabetes, heart failure, coronary artery disease, COPD, prior stroke, or cancer; BMI; and waist-to-hip ratio. We did the following five sensitivity analyses: an analysis, from which participants dying within 6 months of enrolment were excluded to reduce the influence of reverse causation, whereby individuals with advanced disease have reduced grip strength as a consequence of the disease and are also more likely to die from the disease; an analysis restricted to grip strength in the dominant hand; an analysis restricted to grip strength in the non-dominant hand; an analysis restricted to maximum grip strength values from either hand, in keeping with published recommendations;[21] and an analysis excluding participants with cardiovascular disease or cancer at baseline.

To examine the prognostic importance of grip strength in participants with incident disease, we calculated the case-fatality rates stratified by grip-strength tertile in participants with incident myocardial infarction, stroke, cancer, pneumonia, hospital admission for pneumonia or COPD, injury from a fall, or fracture. We used STATA 13.1 software for the analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

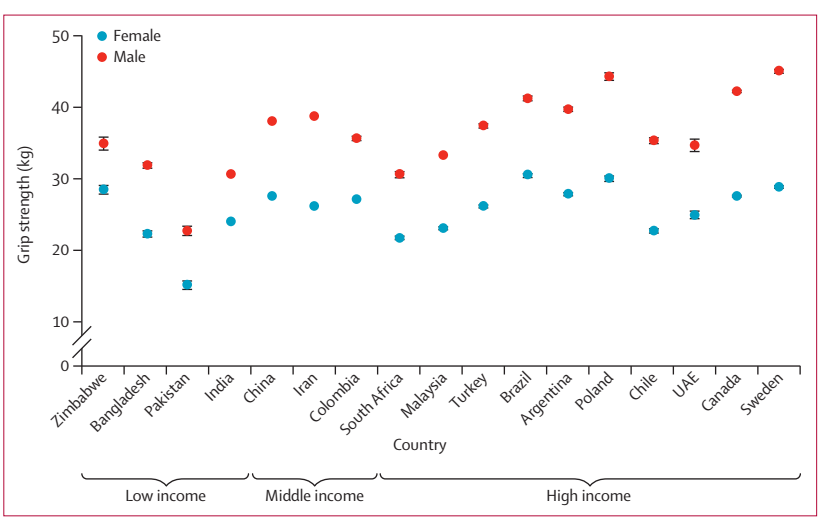

Figure 1: **Grip strength adjusted for age and height, stratified by sex and country**
Countries are grouped into low-income, middle-income, and high-income strata and are presented in order of increasing per capita GDP. Error bars represent 95% CI. UAE=United Arab Emirates.

Results

Participant characteristics were stratified by sex and grip-strength tertile (table 1). Baseline grip strength and vital status were recorded for 139 691 participants. Increased grip strength was associated with young age, male sex, high level of education, employment, high level of physical activity, high dietary calorie intake, of which a high proportion came from protein, and with increasing height, weight, and upper arm circumference. Previous use of alcohol or tobacco was associated with an increase in grip strength. Age and height-adjusted grip strength between countries (figure 1) and ethnic origin (figure 2) was heterogeneous.

For men, grip strength values adjusted for age and height were 30·2 kg (SD 8·20) in low-income countries, 37·3 kg (8·19) in middle-income countries, and 38·1 kg (8·98) in high-income countries. For women, grip strength values adjusted for age and height were 24·3 kg (8·67) in low-income countries, 27·9 kg (8·07) in middle-income countries, and 26·6 kg (8·19) in high-income countries (figure 1). Low grip strength was associated with the presence of the following baseline comorbid disorders: hypertension, coronary artery disease, heart failure, stroke, or COPD. No clear association was noted between a previous diagnosis of cancer and grip strength.

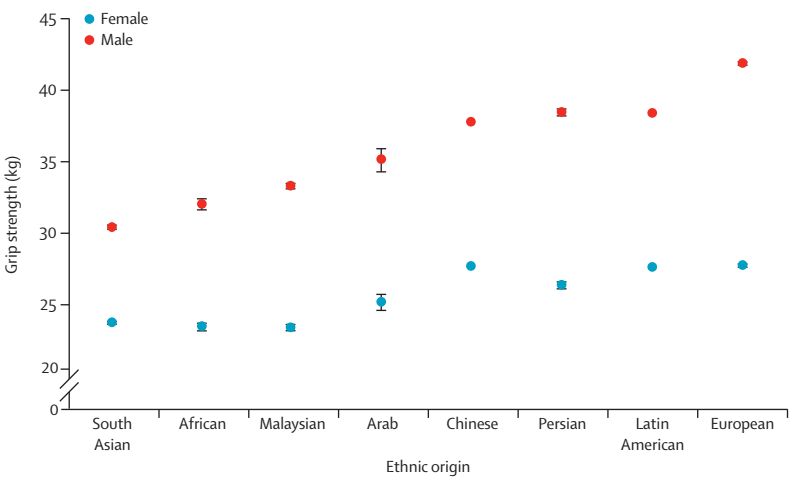

Figure 2: **Grip strength adjusted for age and height, stratified by ethnicity**
Error bars represent 95% CI.

	Incidence	Adjusted model	Country-income interaction p value*
All-cause mortality	3379 (2·4%)	1·16 (1·13–1·20); p<0·0001	0·7607
Cardiovascular mortality	1184 (0·9%)	1·17 (1·11–1·24); p<0·0001	0·9731
Non-cardiovascular mortality	2195 (1·6%)	1·17 (1·12–1·21); p<0·0001	0·7674
Myocardial infarction	1539 (1·1%)	1·07 (1·02–1·11); p=0·0024	0·9345
Stroke	1212 (0·9%)	1·09 (1·05–1·15); p<0·0001	0·9255
Diabetes	2939 (2·1%)	1·03 (0·996–1·06); p=0·0836	0·7710
Cancer	2042 (1·5%)	0·950 (0·919–0·982); p=0·0024†	0·0264
Pneumonia	1047 (0·7%)	0·991 (0·947–1·04); p=0·715	0·7465
Hospital admission for pneumonia or COPD	505 (0·4%)	1·04 (0·974–1·12); p=0·2278	0·3407
Hospital admission with respiratory illness	1111 (0·8%)	1·03 (0·981–1·08); p=0·241‡	0·0146
Injury from fall	2894 (2·0%)	0·968 (0·939–0·998); p=0·0348	0·1873
Fracture	1981 (1·4%)	0·966 (0·931–1·00); p=0·0689	0·3094

Numbers are HR (95% CI) or number (%). COPD=chronic obstructive pulmonary disease. HR=hazard ratio. HR are adjusted for age; sex; education level; employment status; physical activity level; tobacco and alcohol use; daily dietary energy intake; proportion of caloric intake from protein; self-reported hypertension, diabetes, heart failure, coronary artery disease, and chronic obstructive pulmonary disease; and self-reported prior stroke or cancer; body-mass index and waist-to-hip ratio. *p values refer to the interaction between grip strength by tertile and country income. Other p values refer to main effects estimates. †For cancer, subdistribution HRs stratified by country income were 0·916 (0·880–0·953; p<0·0001) for high-income countries, 1·01 (0·950–1·08; p=0·7) for middle-income countries, and 1·12 (0·934–1·34; p=0·2) for low-income countries. ‡For hospital admission for any respiratory illness, subdistribution HRs stratified by country income were 1·00 (0·946–1·06; p=0·9) for high-income countries, 1·08 (0·968–1·20; p=0·2) for middle-income countries, and 1·16 (1·00–1·34; p=0·045) for low-income countries.

Table 2: **Incidence and HR for all-cause mortality and subdistribution HR for outcomes per 5 kg reduction in grip strength**

During a median follow-up of 4·0 years (2·9–5·1), 3379 (2·4%) of 139 691 participants died. The cause was known for 2677 (79%) of 3379 deaths, whereas the cause of death was ascribed by verbal autopsy in 702 (21%) cases. Table 2 shows the number of deaths from cardiovascular and non-cardiovascular comorbidity and the number of cases of myocardial infarctions, strokes, diabetes, incident cancers, injuries related to a fall, hospital admissions for COPD or pneumonia, and hospital admission for any respiratory illness, as well as the associations between grip strength and these outcomes. After adjustment, the association between grip strength and each outcome, with the exceptions of cancer and hospital admission due to respiratory illness, was similar across country-income strata. Grip strength was inversely associated with all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, myocardial infarction, and stroke, and no significant association between grip strength and incident diabetes was found. After adjustment, we found no strong association between grip strength and the risk of hospital admission for pneumonia or COPD, injury from fall, or fracture. In high-income countries, the risk of cancer and grip strength were positively associated, but this association was not found in middle-income and low-income countries (table 2).

The sensitivity analyses yielded similar findings to the principal analysis (appendix). In all sensitivity analyses, the inverse association between grip strength and incident diabetes was significant, although the effect-size remained similar. Additionally, the grip-strength and country-income interaction terms were significant for hospital admission related to respiratory illness, and in some of the sensitivity analyses, grip strength and country income were significantly associated with cancer. The patterns of effect sizes, both overall and stratified by country income, were similar in the sensitivity analyses to the main analysis.

In view of the significant association between grip strength and all-cause mortality, cardiovascular mortality, and incident cardiovascular disease in the PURE study population, we did a post-hoc comparison of the prognostic importance of grip strength with systolic blood pressure (a robust causal factor for death) and with physical activity levels (expressed as the natural logarithm of metabolic equivalent of task [MET]-min per week of activity). After adjustment, grip strength is a stronger predictor of death (HR per SD reduction in grip strength 1·37, 95% CI 1·28–1·47; p<0·0001) than is systolic blood pressure (1·15, 1·10–1·21; p<0·0001) and has similar predictive value for cardiovascular-related death (1·45, 1·30–1·63; p<0·0001), whereas systolic blood pressure exhibited a larger

association with incident cardiovascular-related disease (HR 1·39, 95% CI 1·32–1·47; p<0·0001) than did grip strength (1·21, 1·13–1·29; p<0·0001) (table 3). Physical activity levels were worse predictors of death (1·07, 1·02–1·11; p=0·002), cardiovascular-related death (1·09, 1·02–1·16; p=0·01), and incident cardiovascular-related disease (1·04, 0·991–1·09; p=0·1) than either grip strength or systolic blood pressure.

The inverse association between grip strength and death was consistent between the sexes (interaction p=1·0) and across age by tertile (interaction p=0·1). The inverse association between grip strength and cardiovascular-related death was also consistent between the sexes (interaction p=0·9) and across age (interaction p=0·4).

High grip strength was associated with low case-fatality rate in individuals with incident myocardial infarction, stroke, cancer, pneumonia, hospital admission for pneumonia or COPD, injury from a fall, or fracture (figure 3).

Discussion

In people of diverse economic and sociocultural backgrounds, grip strength is a strong predictor of cardiovascular mortality and a moderately strong predictor of incident cardiovascular disease. Grip strength is also predictive for non-cardiovascular mortality, but is not predictive of incident non-cardiovascular disease. Low grip strength is associated with higher case-fatality rates in people who develop cardiovascular or non-cardiovascular disease. These findings suggest that muscle strength is a risk factor for incident cardiovascular disease and can predict the risk of death in people who develop either cardiovascular or non-cardiovascular disease.

Importantly, grip strength has a stronger association with cardiovascular mortality than with incident cardiovascular disease, with an effect-size that was twice as large for cardiovascular death as for cardiovascular disease. This finding implies that the increased risk of incident cardiovascular disease associated with lower grip strength is insufficient to account for its more profound increased risk for cardiovascular death and suggests that low grip strength is associated with increased susceptibility to cardiovascular death in people who do develop cardiovascular disease. The high case-fatality rates in people who developed cardiovascular disease is consistent with this postulate.

Our findings with respect to cardiovascular disease and cardiovascular mortality are consistent with two studies from the Swedish military conscription register,[2,22] the results of which showed a 35% reduction in the risk of cardiovascular mortality in high grip-strength groups relative to the group with the lowest decile grip strength and a more modest (5%) reduction in the risk of cardiovascular disease per SD increase in grip strength. These Swedish studies were, however, limited to men, aged 16–19 years, and only a few confounding factors were assessed. The results of our study show that these findings are generalisable for people of both sexes, of a wide age range and living in countries of all income strata.

The association between grip strength and incident cardiovascular disease persisted after adjustment for confounding factors, thus prompting speculation as to whether loss of muscular strength might be part of the causal cascade leading to cardiovascular events. We were unable to discern the mechanism responsible for the inverse association between muscle strength and

	Adjusted model
All-cause mortality	
Grip strength	1·37 (1·28–1·47); p<0·0001
Systolic blood pressure	1·15 (1·10–1·21); p<0·0001
MET-min per week	1·09 (1·04–1·15); p=0·002
Cardiovascular mortality	
Grip strength	1·45 (1·30–1·63); p<0·0001
Systolic blood pressure	1·43 (1·32–1·57); p<0·0001
MET-min per week	1·12 (1·03–1·22); p=0·01
Cardiovascular disease	
Grip strength	1·21 (1·13–1·29); p<0·0001
Systolic blood pressure	1·39 (1·32–1·47); p<0·0001
MET-min per week	1·04 (0·991–1·09); p=0·1

HRs are per SD reduction in grip strength, per SD reduction in log(MET-min per week), and per SD increase in systolic blood pressure. Model adjusted for age; sex; country income level; education level; employment status; tobacco and alcohol use; daily dietary energy intake; proportion of caloric intake from protein; diabetes, heart failure, coronary artery disease, and chronic obstructive pulmonary disease; self-reported prior stroke; self-reported prior cancer; body-mass index; and waist-to-hip ratio. Physical activity levels and a past history of hypertension were omitted as covariates because of collinearity with log (MET-min per week) and systolic blood pressure, respectively. HR=hazard ratio. MET=metabolic equivalent of task.

Table 3: **HR for all-cause mortality and subdistribution HR for cardiovascular mortality and cardiovascular disease**

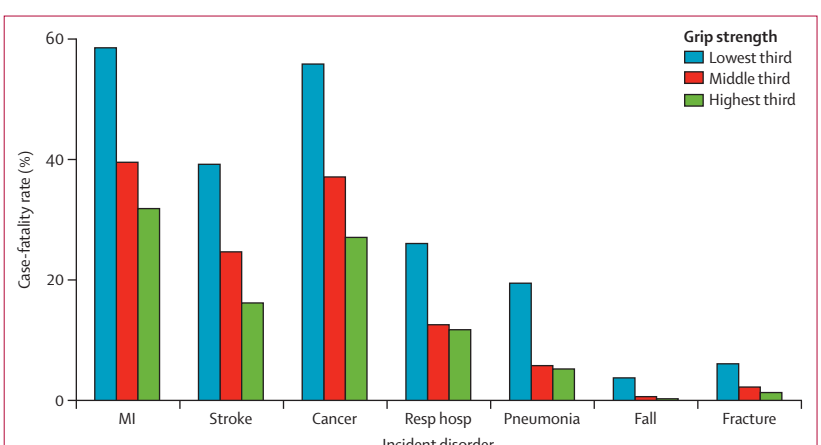

Figure 3: **Case-fatality rates for incident cases of myocardial infarction, stroke, cancer, hospital admission for pneumonia or COPD, pneumonia, injury from a fall, and fracture, stratified by grip strength tertile**
COPD=chronic obstructive pulmonary disease. MI=myocardial infarction. Resp hosp=hospital admission for pneumonia or COPD.

Panel: Research in context

Systematic review

We searched PubMed for relevant research published between Jan 1, 2005, and Jan 1, 2015, using the term "muscle strength" AND "mortality" OR "prognosis" OR "cardiovascular" OR "stroke" OR "cancer" OR "injury" OR "fall" OR "pneumonia" OR "chronic obstructive pulmonary disease". We screened papers by title and abstract to identify full-text reports that were relevant to the study aims. We also screened citation lists from these full-text reports to identify other relevant research. We considered papers if they contained an evaluation of the relation between muscle strength and at least one of the outcomes of interest. The papers cited in this report were selected to be representative of the existing evidence base, are not an exhaustive list of relevant research.

Interpretation

Existing evidence on the prognostic value of muscle-strength measurement was limited to high-income countries and focused on all-cause and cause-specific mortality. The results of our study show that there is heterogeneity in muscle strength in people living in different countries and country-income settings; not only is there a significant inverse association between muscle strength and the risk of mortality, but also the risk of incident cardiovascular disease; and low muscle strength is a biomarker of susceptibility in individuals with incident disease, and might identify a high-risk group in people who develop either cardiovascular or non-cardiovascular disease.

incident cardiovascular disease. Unmeasured factors, such as endothelial dysfunction and autonomic imbalance, both of which can be improved by exercise,[23–25] as well as arterial stiffness, might mediate the association between muscle strength and cardiovascular events.[26] Further research is needed to understand whether improved muscle strength directly reduces the risk of incident cardiovascular disease.

That grip strength is strongly inversely associated with the risk of non-cardiovascular mortality, but not with incident non-cardiovascular diseases, is novel. Furthermore, case-fatality rates from non-cardiovascular diseases were high in individuals with low grip strength. These results suggest that low muscle strength might not play a major causal part in the occurrence of cancer, falls, fractures, or the need for hospital admission for respiratory illnesses, but that, as with incident cardiovascular disease, low muscle strength predisposes to a fatal outcome if these non-cardiovascular diseases develop.

The absence of a strong association between grip strength and the risk of injury from a fall was unexpected. A systematic review[27] of resistance training suggested that muscle strengthening alone might not improve balance. Thus, the mechanisms underlying falls are complex and probably involve sensorineural factors. This complexity might explain, in part, the absence of a strong association between grip strength and injury from a fall. Furthermore, evidence suggests that upper limb strength might not be a suitable surrogate for lower limb strength,[28] which could be a more relevant marker of risk of falls.

We found no strong association between grip strength and incident diabetes. There is a paucity of previous evidence to establish an association between muscle strength and the risk of diabetes. Associations between reduced muscle strength and insulin resistance have been identified in adults at risk of diabetes[29] and in adolescents.[30] However, to our knowledge, we are the first to examine the association between muscle strength and the incidence of clinical diabetes. The inverse association before adjustment, which was not recorded after adjustment, suggests that confounders might account for previous suggestions of an association between muscle strength and diabetes.

Our analysis revealed an unexpected association between grip strength and the risk of cancer. Low muscle strength was associated with a low cancer risk in high-income countries. This finding requires confirmation in further research and examination of different cancer subtypes.

The strength of our study is that it was done in a large cohort of participants from various countries, ethnic origins, and socioeconomic backgrounds and who were sampled in a representative manner. This permits our findings to be widely generalisable. Our study also incorporated a wide range of outcomes, many of which had never been assessed with muscle strength as an exposure, and accounted for a large number of potential covariates. The associations between grip strength and outcomes remained after excluding participants who died within 6 months of grip-strength measurement or participants with pre-existing cardiovascular disease or cancer, which partly allays concerns over reverse causation.

The observational nature of this study does not allow us to make strong conclusions on the causal role of muscular strength in death or cardiovascular disease. Although we adjusted for many potential confounders, we cannot exclude the possibility that residual confounding underlies the associations between grip strength and these outcomes. To enhance follow-up, we only sampled households with residents who intended to remain at the same address for at least 4 years, but there is no reason to expect that this could have affected the validity of our results, although it might exclude people with no fixed address.

Our study suggests that measurement of grip strength is a simple, inexpensive risk-stratifying method to assess risk of death, particularly in individuals who develop a major illness, and that muscle strength is a risk marker for incident cardiovascular disease in a number of countries and populations. Further research is needed to determine how people with low muscle strength might be helped to improve their outlook.

Contributors
DPL designed the present study, performed its statistical analysis, and had primary responsibility for writing the manuscript. SY conceived and initiated the Prospective Urban Rural Epidemiology (PURE) study, supervised its conduct and data analysis, and provided critical comments on all drafts of the manuscript. SR coordinated the worldwide study and reviewed and commented on drafts. KKT was the coprincipal investigator of the study and reviewed and commented on drafts. All other authors coordinated the study and collected the data in their respective countries and provided comments on drafts of the manuscript.

Declaration of interests
We declare no competing interests.

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References

1 Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009; **301:** 2024–35.
2 Ortega FB, Silventoinen K, Tynelius P, Rasmussen F. Muscular strength in male adolescents and premature death: cohort study of one million participants. *BMJ* 2012; **345:** e7279.
3 Rantanen T, Harris T, Leveille SG, et al. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. *J Gerontol A Biol Sci Med Sci* 2000; **55:** M168–73.
4 Lopez-Jaramillo P, Cohen DD, Gomez-Arbelaez D, et al. Association of handgrip strength to cardiovascular mortality in pre-diabetic and diabetic patients: a subanalysis of the ORIGIN trial. *Int J Cardiol* 2014; **174:** 458–61.
5 Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *BMJ* 2008; **337:** a439.
6 Gale CR, Martyn CN, Cooper C, Sayer AA. Grip strength, body composition, and mortality. *Int J Epidemiol* 2007; **36:** 228–35.
7 Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. *Am J Med* 2007; **120:** 337–42.
8 Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci* 2006; **61:** 72–77.
9 Fujita Y, Nakamura Y, Hiraoka J, et al. Physical-strength tests and mortality among visitors to health-promotion centers in Japan. *J Clin Epidemiol* 1995; **48:** 1349–59.
10 Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol A Biol Sci Med Sci* 2002; **57:** B359–65.
11 Al Snih S, Markides KS, Ray L, Ostir GV, Goodwin JS. Handgrip strength and mortality in older Mexican Americans. *J Am Geriatr Soc* 2002; **50:** 1250–56.
12 Corsi DJ, Subramanian SV, Chow CK, et al. Prospective Urban Rural Epidemiology (PURE) study: baseline characteristics of the household sample and comparative analyses with national data in 17 countries. *Am Heart J* 2013; **166:** 636–46.
13 Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med* 2014; **371:** 818–27.
14 Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; **35:** 1381–95.
15 Dehghan M, del Cerro S, Zhang X, et al. Validation of a semi-quantitative Food Frequency Questionnaire for Argentinean adults. *PLoS One* 2012; **7:** e37958.
16 Dehghan M, Ilow R, Zatonska K, et al. Development, reproducibility and validity of the food frequency questionnaire in the Poland arm of the Prospective Urban and Rural Epidemiological (PURE) study. *J Hum Nutr Diet* 2012; **25:** 225–32.
17 Iqbal R, Ajayan K, Bharathi AV, et al. Refinement and validation of an FFQ developed to estimate macro- and micronutrient intakes in a south Indian population. *Public Health Nutr* 2009; **12:** 12–18.
18 Vaz M, Thangam S, Prabhu A, Shetty PS. Maximal voluntary contraction as a functional indicator of adult chronic undernutrition. *Br J Nutr* 1996; **76:** 9–15.
19 Gajalakshmi V, Peto R, Kanaka S, Balasubramanian S. Verbal autopsy of 48 000 adult deaths attributable to medical causes in Chennai (formerly Madras), India. *BMC Public Health* 2002; **2:** 7.
20 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94:** 496–509.
21 Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* 2011; **40:** 423–29.
22 Silventoinen K, Magnusson PK, Tynelius P, Batty GD, Rasmussen F. Association of body size and muscle strength with incidence of coronary heart disease and cerebrovascular diseases: a population-based cohort study of one million Swedish men. *Int J Epidemiol* 2009; **38:** 110–18.
23 Taylor AC, McCartney N, Kamath MV, Wiley RL. Isometric training lowers resting blood pressure and modulates autonomic control. *Med Sci Sports Exerc* 2003; **35:** 251–56.
24 Charakida M, Masi S, Luscher TF, Kastelein JJ, Deanfield JE. Assessment of atherosclerosis: the role of flow-mediated dilatation. *Eur Heart J* 2010; **31:** 2854–61.
25 Clarkson P, Montgomery HE, Mullen MJ, et al. Exercise training enhances endothelial function in young men. *J Am Coll Cardiol* 1999; **33:** 1379–85.
26 Yamamoto K, Kawano H, Gando Y, et al. Poor trunk flexibility is associated with arterial stiffening. *Am J Physiol Heart Circ Physiol* 2009; **297:** H1314–18.
27 Orr R, Raymond J, Fiatarone Singh M. Efficacy of progressive resistance training on balance performance in older adults: a systematic review of randomized controlled trials. *Sports Med* 2008; **38:** 317–43.
28 Jenkins ND, Buckner SL, Bergstrom HC, et al. Reliability and relationships among handgrip strength, leg extensor strength and power, and balance in older men. *Exp Gerontol* 2014; **58:** 47–50.
29 Chen CN, Chuang LM, Wu YT. Clinical measures of physical fitness predict insulin resistance in people at risk for diabetes. *Phys Ther* 2008; **88:** 1355–64.
30 Benson AC, Torode ME, Singh MA. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. *Int J Pediatr Obes* 2006; **1:** 222–31.