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ORIGINAL ARTICLE

Cumulative Muscle Strength and Risk of Cardiovascular Disease and All-cause mortality: A Prospective Cohort Study

Shanhu Qiu,[a,b] Qianqian Wang,[c] Wenji Chen,[a,b] Bo Xie,[a,b] Duolao Wang,[d] Xue Cai,[e,*] Zilin Sun,[c,*] and Tongzhi Wu[f]

[a] *Department of General Practice, Zhongda Hospital; Institute of Diabetes, School of Medicine, Southeast University, Nanjing, China*
[b] *Research and Education Centre of General Practice, Zhongda Hospital, Southeast University, Nanjing, China*
[c] *Department of Endocrinology, Zhongda Hospital; Institute of Diabetes, School of Medicine, Southeast University, Nanjing, China*
[d] *Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom*
[e] *Department of Nursing Management, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China*
[f] *Adelaide Medical School and Centre of Research Excellence (CRE) in Translating Nutritional Science to Good Health, The University of Adelaide, Adelaide, Australia*

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Background. The existing literature regarding the association between muscle strength and cardiovascular disease (CVD) and all-cause mortality relies mostly on a single measurement of muscle strength but has seldomly focused on the accumulated exposure.

Objective. This study explored the association between cumulative muscle strength and risks of CVD and all-cause mortality in middle-aged and older adults.

Methods. A total of 6,972 patients from the China Health and Retirement Longitudinal Study, who underwent 3 repeated measurements of muscle strength over 4 years and were followed-up for another 3 years for CVD and all-cause mortality outcomes participated in this study. Muscle strength was evaluated by grip strength and chair-rising time. Cumulative muscle strength was calculated as the area under the curve. Odds ratio (OR) and 95% confidence intervals (CIs) were analyzed.

Results. The odds of CVD and all-cause mortality decreased as cumulative grip strength increased or cumulative chair-rising time decreased. For each 1 standard deviation (SD) increment in cumulative grip strength, the multivariable-adjusted OR for CVD and all-cause mortality were 0.81 (95% CI 0.73-0.91) and 0.85 (95% CI 0.73–0.99), respectively. For each 1 SD decrease in cumulative chair-rising time, the corresponding OR were 0.81 (95% CI 0.75–0.88) and 0.87 (95% CI 0.77–0.98), respectively. However, neither the change-slope of grip strength nor that of chair-rising time was related to decreased OR of CVD or of all-cause mortality.

Conclusions. Cumulative muscle strength was associated with a reduced risk of CVD and all-cause mortality in middle-aged and older Chinese adults.

Key Words: Cumulative muscle strength, Cardiovascular, All-cause mortality, Longevity, Cohort.

Introduction

The prevalence of cardiovascular disease (CVD) has been rising steadily worldwide (1,2), and has nearly doubled from 271 million in 1990 to 523 million in 2019 according to the estimates from the Global Burden of Disease Study (1). CVD remains the leading cause of death (1) and is responsible for marked increases in disability-adjusted life years, years of life lost, and healthcare expenditure (3). These point to the urgent need for identifying potentially

* Address reprint requests to: Xue Cai, Department of Nursing Management, Zhongda Hospital, School of Medicine, Southeast University, Dingjiaqiao No.87, Nanjing, 210009, China; Zilin Sun, Department of Endocrinology, Zhongda Hospital; Institute of Diabetes, School of Medicine, Southeast University, Dingjiaqiao No.87, Nanjing, 210009, China. Email: kameyuki@126.com (X. Cai), sunzilin1963@126.com (Z. Sun).

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modifiable factors to reduce or delay the onset of incident CVD, particularly within the context of an elevated lifetime risk for CVD due to an ageing population and improved survival rates (4).

Skeletal muscle controls body movements via muscle contraction and regulates metabolic homeostasis through the release of cytokines and utilization of glucose (5,6). Impairment in its functionality, such as weak muscle strength, has been linked to the development of various diseases including CVD (7–10). For example, in the Prospective Urban-Rural Epidemiology study that enrolled 139,691 participants, weak muscle strength, as reflected by 1 standard deviation (SD) decrease in grip strength, was associated with increased risks of CVD and all-cause mortality by 21 and 37%, respectively, during a 4 year follow-up (8). However, existing data in support of the associations of muscle strength with CVD and all-cause mortality are limited by the fact that muscle strength has been measured only at a single time-point (usually at baseline) (7–11), without accounting for the cumulative exposure over time, where muscle strength may be subject to progressive changes (e.g., due to sedentary behavior or ageing) (12). Moreover, studies concerning the associations of muscle strength with CVD and all-cause mortality (7–11) are often limited to the use of grip strength, which mainly reflects upper limb muscle strength. Other measures, such as chair-rising time that is dependent on the lower limb muscle strength, have not been adequately assessed (13).

The China Health and Retirement Longitudinal Study (CHARLS) assessed muscle strength by both grip strength (normalized by body-weight) and chair-rising time at 3 different time-points within a 4 year period (14). Based on this dataset, we assessed, for the first time, the associations of cumulative muscle strength with risks of CVD (including cardiac diseases and stroke) and all-cause mortality during the subsequent 3 year follow-up in middle-aged and older adults. The secondary aim was to evaluate whether the annual change in muscle strength (assessed by the change-slope), a common approach used to reflect changes in muscle strength over time (15), would exhibit similar associations with risks of CVD and all-cause mortality.

Methods

Study Population

CHARLS is an ongoing nationally representative longitudinal survey of community-dwellers aged >45 years in China (14). It began in 2011–2012 (defined as wave 1) and enrolled a total of 17,705 participants, who were consecutively followed in 2013–2014 (wave 2), 2015 (wave 3), and 2018 (wave 4). Standardized questionnaires were used in each wave to collect information on demographic characteristics, lifestyle factors, and health-related data. The CHARLS protocol was approved by the Institutional Review Board of Peking University, and informed consent was obtained from all participants. This study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Muscle strength, including grip strength and chair-rising time, was assessed in waves 1 to 3, and these data were used to evaluate the cumulative muscle strength (described below). In this context, information obtained in wave 3 was defined as the baseline. Participants were then followed up for approximately 3 years in wave 4, and during this period, the outcomes on CVD and all-cause mortality were assessed (Figure 1). In this study participants were included if they had data available on cumulative muscle strength and reported outcomes on cardiovascular disease or all-cause mortality during follow-up. Participants were excluded if they did not complete all the 3 repeated measurements of muscle strength measurement in waves 1–3. Moreover, participants with CVD at baseline or those who died during follow-up were excluded when analyzing the results on CVD.

Cumulative Muscle Strength

The primary exposure was cumulative muscle strength, which includes cumulative grip strength and cumulative chair-rising time. Grip strength and chair-rising time were measured based on standard protocols as previously described (7). In brief, grip strength was assessed by asking participants to squeeze the handgrip dynamometer (YuejianTM WL-1000 dynamometer) as hard as possible and then repeat, and the average of these two readings, using the dominant hand, normalized by body weight (kg/kg), was used for subsequent analysis. Chair-rising time was obtained by recording the time of participants to perform 5 repetitions of sitting-to-standing positions at their fastest pace.

To obtain the cumulative muscle strength over the 4 year period, we denoted X_1, X_2, and X_3 as the muscle strength measured at wave 1, 2, and 3, respectively; and T_1 and T_2 as the time-lengths for waves 1→2 and 2→3, respectively. As X1, X2, and X3 correlated linearly with each other, we calculated cumulative muscle strength as the area under the curve for muscle strength over the duration of the exposure, based on the trapezoid rule (16), as:

$$\text{Cumulative muscle strength} = \frac{(X1 + X2)\times T1}{2} + \frac{(X2 + X3)\times T2}{2}.$$

Since the time-interval for these consecutive waves was approximately 2 years (14), we assigned T_1 and T_2 the value of "2 years" for analysis. We also calculated change-slope of muscle strength over 4 years for each participant, based on a linear model regressing muscle strength in each wave on corresponding time.

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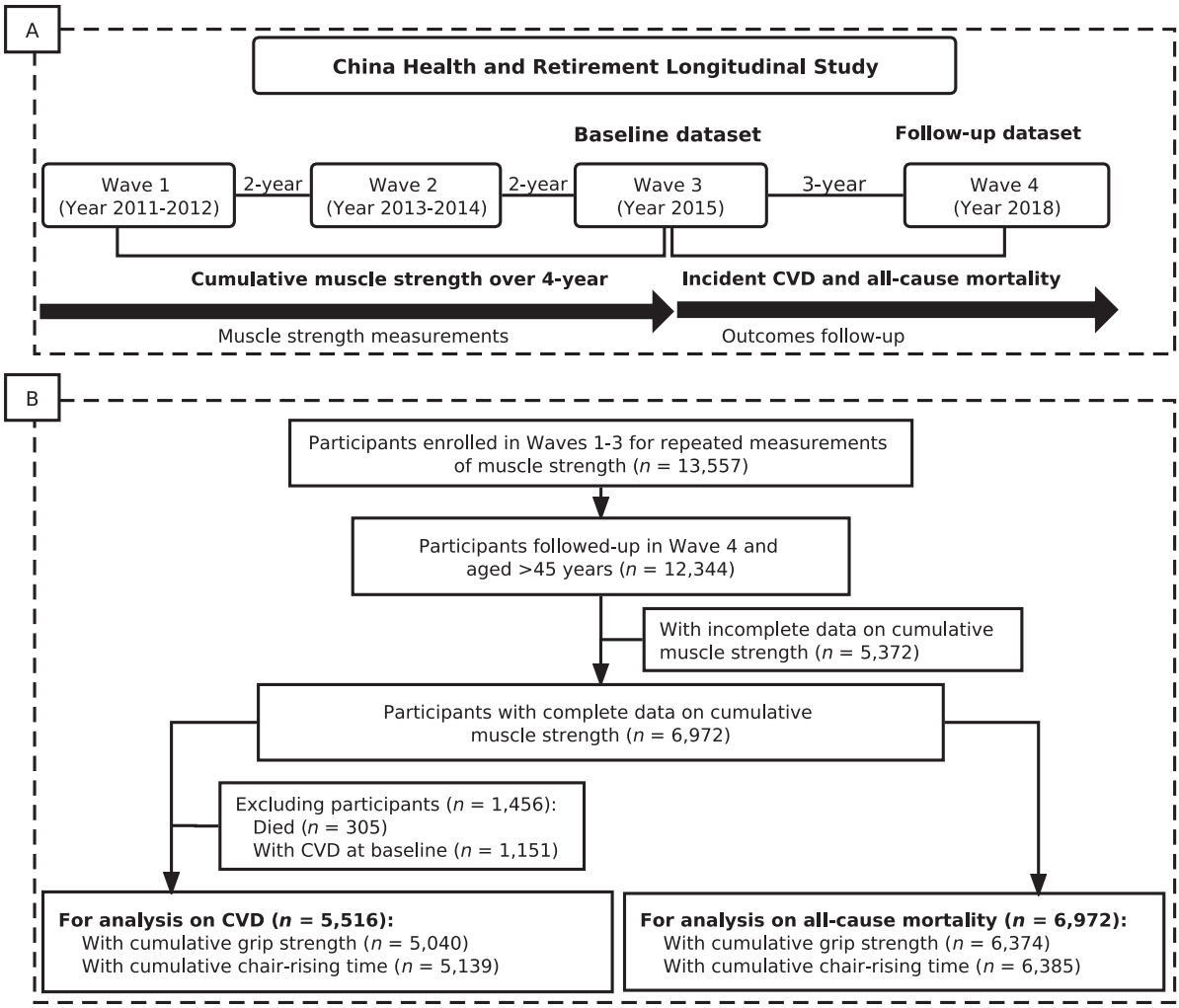

Figure 1. Study design and study flowchart. CVD, cardiovascular disease A. Study design: wave 1 (started in year 2011–2012), wave 2 (in 2013–2014), and wave 3 (in 2015) from the China Health and Retirement Longitudinal Study were used to calculate cumulative muscle strength over 4 years. Incident cardiovascular disease or all-cause mortality was ascertained during a 3 year follow-up (in wave 4). B. Study flowchart: of the participants with available data on cumulative muscle strength, 5,516 were eligible for assessing outcomes on CVD, and 6,972 for outcomes on all-cause mortality.

CVD and All-cause Mortality

The primary outcomes were incident CVD and all-cause mortality. Concordant with prior studies (17,18), incident CVD was identified by inquiring their medical treatments on cardiac diseases and stroke, using validated questionnaires at each wave (Supplementary Table 1). In CHARLS, cardiac diseases were considered a composite outcome of heart attack, coronary heart disease, angina, congestive heart failure, and other heart problems (17). All-cause mortality information was ascertained by exit and verbal autopsy questionnaires (14). The secondary outcomes in this study were incident cardiac diseases and stroke.

Covariates

Covariates included age, sex, history of smoking and alcohol usealcohol use, hypertension, diabetes, and arthritis/rheumatism, and the collection details are listed in Supplementary Table 1. Body weight, height, and blood pressure were measured by trained researchers or nurses. Body mass index (BMI), body shape index (ABSI), and mean arterial pressure (MAP) were calculated accordingly (7,14).

Venous blood samples were collected in the morning, approximately 85% of which were obtained after >8 h fasting. They were shipped by the cold-chain shipping company to the central laboratory at Peking University for storage at –80°C freezers. The whole blood or plasma specimens were used for the measurement of hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), and high-sensitivity C-reactive protein (hs-CRP) at the KingMed Diagnostics laboratory based on the standard assay protocols (19).

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Statistical Analysis

Participant characteristics at baseline in this study are presented as means ± SDs for continuous variables and as percentages for categorical variables. The normality of the continuous variables was inspected visually by QQ-plot. Missing data on the covariates including BMI, ABSI, blood pressure, and blood biomarkers were imputed using the iterative Markov Chain Monte Carlo method under a multivariate normal model. Differences in the baseline characteristics were compared using unpaired *t*-test for continuous variables and χ^2 test for categorical variables. Pearson correlation coefficient (*r*) was used to evaluate the correlations of muscle strength at baseline with cumulative muscle strength and muscle strength change-slope over 4 years.

Although the information about the timing of the incident cases with CVD (including cardiac diseases and stroke) was provided for about 94% of the participants included, it was not released for all-cause mortality. We therefore chose the logistic regression models for consistency to assess their associations with cumulative muscle strength, generating odds ratio (OR) and 95% confidence intervals (CIs). For this, we treated cumulative muscle strength as: (i) a categorical variable in quartiles (*Q1* [bottom], *Q2, Q3*, and *Q4* [top] quartiles), and (ii) a continuous variable presented as per 1 SD (used for the principal analysis). Three models, which included an increasing number of covariates, were employed: model 1 included only the study variable; model 2 was adjusted for age, sex, ABSI, MAP, and lifestyle factors including history of smoking and alcohol use; and model 3 was additionally adjusted for blood biomarkers including TC/HDL, TG, LDL, HbA1c, and hs-CRP (log-transformed). The associations between the change-slope of muscle strength and CVD and all-cause mortality were analyzed in a similar manner.

Several supplemental analyses were also performed. First, we conducted subgroup analyses to explore the interactions between cumulative muscle strength and sex (men vs. women), age (≥60 vs. <60 years), overweight/obesity (BMI ≥24 vs. <24 kg/m^2), hypertension (with vs. without), and diabetes (with vs. without). Second, we analyzed the outcomes with further adjustment for baseline muscle strength on the basis of model 3. Finally, we evaluated the associations with CVD and all-cause mortality upon the exclusion of participants with missing data on covariates or those with arthritis/rheumatism. All statistical analyses were conducted using Stata14.0 (StataCorp LP, College Station, TX, USA), and a 2-sided *p* value of <0.05 was considered statistically significant.

Table 1. Characteristics of study participants at baseline

	Participants included in the present study	
	For cardiovascular disease outcome[a]	**For all-cause mortality outcome**
No. of participants (*n*)	5,516	6,972
Men (*n*) (%)	2,577 (46.7%)	3,246 (46.6%)
Age (years)	58.2 ± 8.6	58.9 ± 8.8
ABSI	0.07 ± 0.009	0.07 ± 0.009
SBP (mmHg)	129 ± 20	129 ± 20
DBP (mmHg)	75 ± 12	75 ± 12
FPG (mg/dL)[b]	100.7 ± 30.6	100.9 ± 31.1
HbA1c (%)	6.0 ± 1.0	6.0 ± 1.0
HbA1c (mmol/mol)	42 ± 10.9	42 ± 10.9
TC (mg/dL)	185.1 ± 36.5	185.0 ± 37.2
TG (mg/dL)	139.1 ± 88.8	140.4 ± 89.1
HDL (mg/dL)	52.2 ± 12.1	51.8 ± 12.0
LDL (mg/dL)	102.9 ± 28.6	103.0 ± 29.1
TC/HDL	3.7 ± 1.1	3.7 ± 1.0
ln(hs-CRP) (mg/dL)	0.4 ± 1.0	0.4 ± 1.0
Smoking (*n*) (%)[c]	2,388 (43.3%)	3,071 (44.0%)
Alcohol use (*n*) (%)[c]	1,866 (33.8%)	2,266 (32.5%)
History of[c]		
Hypertension (*n*) (%)	2,332 (42.3%)	3,235 (46.4%)
Diabetes (*n*) (%)	829 (15.0%)	1,188 (17.0%)
Arthritis/rheumatism (*n*) (%)	2,049 (37.1%)	2,957 (42.4%)

ABSI, A Body Shape Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein

[a]Participants with cardiovascular disease (at baseline) were excluded

[b]There were 1,444 and 1,797 participants without fasting blood samples at baseline, respectively

[c]They represented participants with the corresponding history.

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Results

Baseline Characteristics

Of the 6,972 participants (Figure 1), 5,516 without CVD at baseline were eligible for analysis on incident CVD outcome (mean age: 58.2 ± 8.6 years, men: 46.7%), and 6,972 for incident all-cause mortality outcome (mean age: 58.9 ± 8.8 years, men: 46.6%; Table 1). Cumulative grip strength over 4 years correlated positively with grip strength at baseline (r = 0.82, p <0.001), but negatively with the change-slope of grip strength (r = –0.05, p <0.001) in the whole population. Similarly, cumulative chair-rising time correlated positively with chair-rising time at baseline (r = 0.69, p <0.001), but negatively with the change-slope of chair-rising time (r = –0.04, p <0.001). Comparisons between participant characteristics at baseline based on the presence or absence of incident CVD and all-cause mortality are shown in Supplementary Tables 2 and 3.

Cumulative Muscle Strength and Cardiovascular Disease

Compared with participants who did not develop CVD, those who did showed less cumulative grip strength (2.0 ± 0.5 vs. 2.1 ± 0.5 kg/kg·year, p <0.001, Supplementary Figure 1A) but higher cumulative chair-rising time (43.1 ± 12.6 vs. 39.4 ± 11.0 s year, p <0.001, Supplementary Figure 1B). For cumulative grip strength, the multivariable-adjusted OR for CVD in model 3 was 0.63 (95% CI 0.47–0.85) in the top quartile versus the bottom quartile, and 0.81 (95% CI 0.73–0.91) for each 1 SD increment (Table 2). For cumulative chair-rising time, the corresponding OR was 0.51 (95% CI 0.39–0.67) in the bottom quartile versus the top quartile, and 0.81 (95% CI 0.75–0.88) for each 1 SD decrement. Notably, the decreases in the odds of CVD in relation to cumulative grip strength or cumulative chair-rising time expressed in continuous scales remained significant after further adjustment for their baseline data (Supplementary Table 4). However, nether the change-slope of grip strength nor that of chair-rising time was associated with decreased odds of CVD (Supplementary Table 5).

The magnitudes and patterns of the associations of cumulative grip strength and cumulative chair-rising time with the odds of cardiac diseases or stroke were consistent with that of CVD. For each 1 SD increment in cumulative grip strength, the OR for cardiac diseases and stroke was 0.81 and 0.83, respectively (Supplementary Table 6); and for each 1 SD decrease in cumulative chair-rising time, the corresponding OR was 0.84 and 0.83 (model 3, Supplementary Table 7). Moreover, these associations remained significant for stroke (OR 0.75, 95% CI 0.59–0.97, for 1 SD increment in cumulative grip strength) and cardiac diseases (OR 0.87, 95% CI 0.77–0.98, for 1 SD decrement in cumulative chair-rising time), after further adjustment for their baseline data.

Cumulative Muscle Strength and All-cause Mortality

Compared with participants who did not die during follow-up, those who died showed smaller cumulative grip strength (2.0 ± 0.6 vs. 2.1 ± 0.5 kg/kg·year, p = 0.03, Supplementary Figure 1C) but higher cumulative chair-rising time (45.3 ± 12.3 vs. 40.6 ± 11.6 s·year, p <0.001, Supplementary Figure 1D). For cumulative grip strength, the multivariable-adjusted OR for all-cause mortality was 0.62 (95% CI 0.42–0.93) in the top quartile versus the bot-

Table 2. Cumulative muscle strength and risk of cardiovascular disease[a]

Variables	No. of cases/No. of participants	OR and 95% CIs		
		Model 1	Model 2	Model 3
Cumulative grip strength (kg/kg·year)				
Q1 quartile (<1.7)	212/1,260	1 (Ref.)	1 (Ref.)	1 (Ref.)
Q2 quartile (1.7–2.1)	151/1,260	0.67 (0.54–0.84)	0.73 (0.58–0.92)	0.74 (0.59–0.94)
Q3 quartile (2.3–2.5)	146/1,260	0.65 (0.52–0.81)	0.72 (0.56–0.93)	0.75 (0.58–0.97)
Q4 quartile (>2.5)	117/1,260	0.51 (0.40–0.64)	0.59 (0.44–0.80)	0.63 (0.47–0.85)
p for trend		<0.001	0.001	0.003
Per 1 SD (0.5) increment	626/5,040	0.75 (0.69–0.82)	0.79 (0.71–0.88)	0.81 (0.73–0.91)
Cumulative chair-rising time (sec·year)				
Q1 quartile (<32.6)	103/1,285	0.43 (0.34–0.56)	0.51 (0.39–0.66)	0.51 (0.39–0.67)
Q2 quartile (32.6–38.2)	146/1,289	0.64 (0.51–0.80)	0.71 (0.56–0.90)	0.72 (0.57–0.91)
Q3 quartile (38.2–45.0)	153/1,281	0.67 (0.54–0.84)	0.74 (0.59–0.92)	0.74 (0.59–0.93)
Q4 quartile (>45.0)	215/1,284	1 (Ref.)	1 (Ref.)	1 (Ref.)
p for trend		<0.001	<0.001	<0.001
Per 1 SD (11.3) decrement	617/5,139	0.76 (0.71–0.82)	0.81 (0.75–0.87)	0.81 (0.75–0.88)

OR, odds ratio; CIs, confidence intervals; SD, standard deviation; Model 1: without adjustment; Model 2: adjusted for age, sex, a body shape index, mean artery pressure, and history of smoking and alcohol use; Model 3: adjusted for age, sex, a body shape index, mean artery pressure, history of smoking and alcohol use, total cholesterol/high-density lipoprotein, triglycerides, low-density lipoprotein, hemoglobin A1c, and high-sensitivity C-reactive protein (log-transformed) at baseline

[a]Participants with cardiovascular disease at baseline were excluded.

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Table 3. Cumulative muscle strength and risk of all-cause mortality

Variables	No. of cases/No. of participants	OR and 95% CIs		
		Model 1	Model 2	Model 3
Cumulative grip strength (kg/kg·year)				
Q1 quartile (<1.7)	92/1,594	1 (Ref.)	1 (Ref.)	1 (Ref.)
Q2 quartile (1.7–2.0)	64/1,593	0.68 (0.49–0.95)	0.67 (0.47–0.95)	0.72 (0.51–1.03)
Q3 quartile (2.0–2.4)	65/1,594	0.69 (0.50–0.96)	0.52 (0.35–0.75)	0.55 (0.38–0.81)
Q4 quartile (>2.4)	69/1,593	0.74 (0.54–1.02)	0.57 (0.38–0.85)	0.62 (0.42–0.93)
p for trend		0.07	0.003	0.01
Per 1 SD (0.5) increment	290/6,374	0.89 (0.79–1.00)	0.83 (0.71–0.96)	0.85 (0.73–0.99)
Cumulative chair-rising time (sec·year)				
Q1 quartile (<33.0)	35/1,597	0.35 (0.24–0.52)	0.58 (0.38–0.89)	0.58 (0.38–0.89)
Q2 quartile (33.0–39.0)	42/1,598	0.43 (0.29–0.62)	0.60 (0.41–0.89)	0.60 (0.41–0.89)
Q3 quartile (39.0–46.1)	53/1,595	0.54 (0.38–0.77)	0.66 (0.47–0.95)	0.65 (0.45–0.93)
Q4 quartile (>46.1)	95/1,595	1 (Ref.)	1 (Ref.)	1 (Ref.)
p for trend		<0.001	0.004	0.005
Per 1 SD (11.7) decrement	225/6,385	0.75 (0.68–0.83)	0.87 (0.77–0.97)	0.87 (0.77–0.98)

OR, odds ratio; CIs, confidence intervals; SD, standard deviation; Model 1: without adjustment; Model 2: adjusted for age, sex, a body shape index, mean artery pressure, and history of smoking and alcohol use; Model 3: adjusted for age, sex, a body shape index, mean artery pressure, history of smoking and alcohol use, total cholesterol/high-density lipoprotein, triglycerides, low-density lipoprotein, hemoglobin A1c, and high-sensitivity C-reactive protein (log-transformed) at baseline.

tom quartile, and 0.85 (95% CI 0.73–0.99) for each 1 SD increment (Table 3). For cumulative chair-rising time, the multivariable-adjusted OR was 0.58 (95% CI 0.38–0.89) for the bottom quartile versus the top quartile, and 0.87 (95% CI 0.77–0.98) for each 1 SD decrement. Notably, the decreased odds of all-cause mortality with cumulative grip strength or cumulative chair-rising time between the top and bottom quartiles remained significant after further adjustment for their baseline data (Supplementary Table 8). Nether the change-slope of grip strength nor that of chair-rising time change-slope was associated with decreased odds of all-cause mortality (Supplementary Table 9).

Supplemental Analyses

Subgroup analyses showed that the associations of cumulative grip strength and cumulative chair-rising time with the odds of CVD or all-cause mortality were not affected by sex, age, BMI, or the presence of hypertension or diabetes at baseline (all $P_{interaction} \geq 0.09$, Figure 2A, and B). Excluding participants with missing data on covariates or those with arthritis/rheumatism did not influence the outcomes substantially (Supplementary Tables 10, and 11), particularly for CVD.

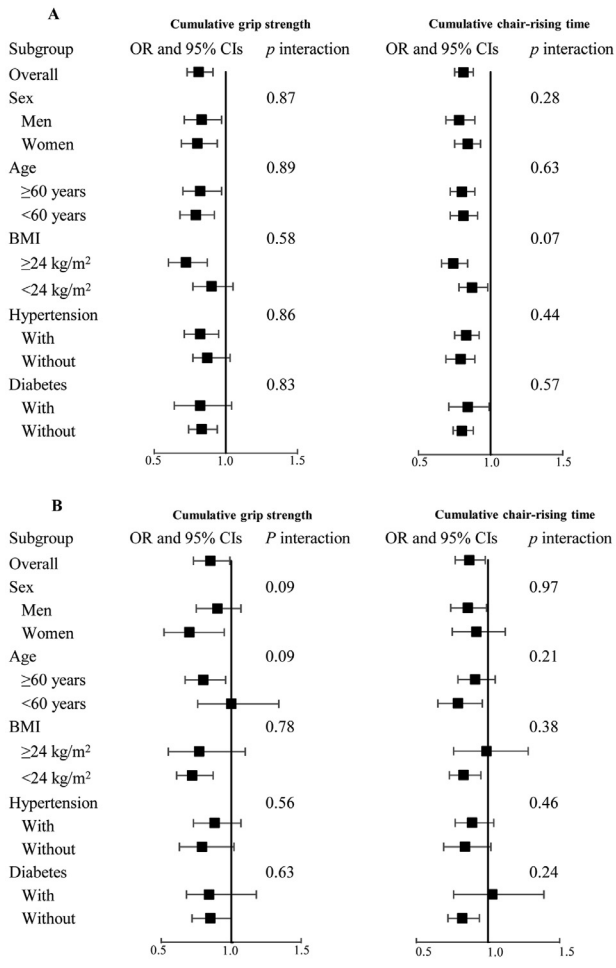

Figure 2. Subgroup analyses. OR, odds ratio; CIs, confidence intervals; BMI, body mass index.

Discussion

Main Findings

In this prospective cohort analysis of middle-aged and older Chinese adults with 3 repeated measurements on muscle strength over 4 years, we found that: (i) increased cumulative muscle strength, as reflected by high cumulative grip strength and low cumulative chair-rising time,

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was associated with decreased risks of CVD and all-cause mortality during a subsequent 3 year follow-up, even after controlling for baseline muscle strength; (ii) increased cumulative muscle strength was also associated with decreased risks of cardiac diseases and stroke; and (iii) the change-slope of muscle strength was not related to risks of CVD or all-cause mortality.

Interpretations

Previous studies have extensively explored the association between muscle strength (principally grip strength) and CVD and all-cause mortality in middle-aged or older adults (8,20,21). A meta-analysis of 42 cohort studies conducted by Wu Y, et al. showed that the risks of CVD and all-cause mortality were 38.7% and 29.1% lower, respectively, in the highest versus the lowest category of grip strength (21). Another meta-analysis of 5 cohort studies by Cooper R, et al. also noted that the risk of all-cause mortality was reduced by 49.0% in the highest versus the lowest quarter of chair-rising time in older adults (13). However, muscle strength reported in these studies was derived from a single measurement only (13,21), and therefore did not take into account the dynamic changes in muscle strength during ageing. Moreover, evidence concerning the association of chair-rising time with CVD is scare (10). Distinct from previous reports, our study introduced, for the first time, the concept of cumulative muscle strength to account for the exposure of muscle strength accumulated within a certain time period. We found that cumulative muscle strength, represented either by cumulative grip strength or cumulative chair-rising time, was associated with decreased risks of CVD and all-cause mortality during follow-up.

We also found that cumulative muscle strength was associated with decreased risk of cardiac diseases and stroke, the latter of which is considered the main cause of CVD mortality in Chinese adults (22). The exact mechanism underlying the inverse association of cumulative muscle strength with CVD and all-cause mortality remains to be investigated. However, cumulative muscle strength showed a strong correlation with muscle strength measured at a single time-point. It is therefore biologically plausible that cumulative muscle strength may share similar pathways as muscle strength in lowering the risk of CVD and all-cause mortality, e.g., through good control of blood pressure and glycemia, and low degree of inflammation (23).

The current evidence on the association between changes in grip strength and CVD and CVD mortality appeared mixed. Liu W, et al. found that low stable grip strength over 8 years based on the trajectory approach was associated with a reduction in the risk of CVD by 53.9% in the U.K. community dwellers (24). Another study involving European older population, however, suggested that changes in grip strength were not associated with the risk of cardiovascular mortality (15). In the current study, we also failed to observe any association between the change-slope of muscle strength over 4 years and the risk of CVD or all-cause mortality. Of note, the inconsistent outcomes between cumulative muscle strength and change-slope of muscle strength on CVD and all-cause mortality were not out of expectation, since their correlations were rather weak as observed in our study. This may, to some extent, suggest the different physiological characteristics for cumulative muscle strength versus change-slope of muscle strength: the former reflects the exposure of the accumulated 'amounts/doses' of muscle strength within a designated time-window to an individual, while the latter refers to the outcome concerning the absolute change in muscle strength over time.

Implications

The observations of our study have some major implications for the prevention of CVD and all-cause mortality. In light of the strong associations between the risk of developing CVD (including cardiac diseases and stroke) and all-cause mortality and cumulative muscle strength, achieving muscle strength at optimal levels and maintaining these optimal levels thereafter or preventing their declines in late life may be a rationale strategy to prevent incident CVD and promote longevity in middle-aged and older adults. Moreover, current clinical health practice related to muscle strength is commonly guided by an occasional measurement of muscle strength (normally at the initial clinical visit). However, our result that the association of cumulative muscle strength with CVD or all-cause mortality remained significant after controlling for baseline muscle strength, highlights the importance of assessing cumulative muscle strength over a single time-point measurement for health guidance. Finally, our study has provided a new approach for assessing the clinically-oriented health benefits of muscle strength, in addition to the frequently used methods such as change-slope (change score) or a single time-point measurement, in population-based epidemiological studies.

Strengths and Limitations

The strengths of our study include a prospective cohort analysis of a nationally representative sample, the repeated measurements of muscle strength assessed by grip strength and chair-rising time at 3 different time-points over 4 years, the robust outcomes as evidenced by supplemental analyses, and novel prospective of using cumulative muscle strength to assess its relationship with clinical outcomes including all-cause mortality-a hard clinical end-point. However, our study has also several limitations. First, due to the observational nature of cohort studies, causality cannot be determined in the present study. Second, our findings might be subject to residual confounders, such as cardiorespi-

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ratory fitness (25) and the adherence to the treatment of CVD-related risk factors (26), which were not measured in the study". Third, cumulative muscle strength in our study was obtained by calculating the area under the curve using 3 repeated measurements of muscle strength from 3 waves based on the trapezoid rule, its accuracy would be further improved if muscle strength was obtained from more than 3 wavs or time-points. Fourth, the unavailability of information on the timing of occurrence of the outcomes, particularly for all-cause mortality in CHARLS, restricted the use of survival analysis methods to analyze the primary outcomes. Finally, our study included only Chinese adults, such that caution should be exercised when generalizing our summary statistics to other populations remains to be explored.

Conclusions

In conclusion, our study provides the first evidence that 4 year cumulative muscle strength, either cumulative grip strength or cumulative chair-rising time, was associated with risks of CVD and all-cause mortality, independent of baseline muscle strength, in middle-aged and older Chinese adults. Our observations support the notion of maintaining optimal muscle strength or preventing muscle strength loss in late life to reduce the onset of CVD and improve the longevity, and offer a new approach for evaluation of health benefits of muscle strength in clinical practice.

Conflict Interest

The authors declare that they do not have competing interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2023.01.002.

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