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ORIGINAL RESEARCH

Association Between Muscle Strength and Cystatin C-Based Estimated Glomerular Filtration Rate Among Middle-Aged and Elderly Population: Findings Based on the China Health and Retirement Longitudinal Study (CHARLS), 2015

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Background: Patients with chronic kidney disease (CKD) are prone to muscle strength degeneration. However, the relationship between mild-to-moderate renal insufficiency and low muscle strength remains unclear. As cystatin C is not subject to muscular conditions and is a sensitive serum marker in preclinical renal disease, we aimed to investigate the association between estimated glomerular filtration rate (eGFR) based on cystatin C and muscle strength in the Chinese population.

Methods: This was a cross-sectional study enrolling 12,398 Chinese participants aged above 45 years (5762 men and 6636 women) from the 2015 China Health and Retirement Longitudinal Study. Handgrip strength (HGS) was used to assess muscle strength. Locally weighted scatterplot smoothing (LOWESS) curves were employed to visualize the relationships between eGFR and HGS. Multivariable logistic regression was conducted to analyze the correlation between kidney function and low muscle strength.

Results: Significant differences in HGS by CKD stage were observed in both sexes after adjusting for age and body mass index. LOWESS curves demonstrated concomitant decreases in HGS and kidney function at eGFR levels below 120 mL/min/1.73 m^2 in both sexes. According to multivariate logistic regression, participants with CKD stages 2 (odds ratio [OR]: 1.256, 95% confidence interval [CI]: 1.120–1.409), 3 (OR: 2.725, 95% CI: 2.2585–3.288), and 4–5 (OR: 3.069, 95% CI 1.747–5.392) had higher risk of low muscle strength than those who were normal or had CKD stage 1 after adjusting for demographic and clinical variables.

Conclusion: Our study illustrated that CKD stage was independently associated with low muscle strength in Chinese middle-aged and elderly populations.

Keywords: muscle strength, chronic kidney disease, kidney function, glomerular filtration rate, CHARLS, epidemiology

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Introduction

Muscle strength is an indicator of major health status and clinical outcomes.[1] Low muscle strength has a devastating impact on the quality of life and is linked to higher risks of falls, hospitalizations, morbidity, and mortality.[2] Handgrip strength (HGS) is regarded as a reliable, low-cost, and easy-to-measure indicator of muscle

strength.[3,4] According to several consensus reports, HGS is considered to represent whole-body strength.[5–7] Several factors affect HGS, including age, sex, body mass index (BMI), socioeconomic status, and many chronic diseases. To date, HGS has been shown to be independently associated with hypertension,[8] cardiometabolic health,[9] diabetes,[10] non-alcoholic fatty liver disease,[11] cognitive status,[12] and depression.[13]

Muscle strength degeneration is a common condition in patients with chronic kidney disease (CKD).[14,15] Reduced appetite, accumulation of toxins, metabolic acidosis, inflammation, neuroendocrine abnormalities, vitamin D deficiency, and decreased exercise all contribute to muscle degradation in CKD populations.[14,16] To date, a few studies have addressed the association between kidney function and muscle strength using nationally representative data. Moreover, the correlation between mild-to-moderate renal dysfunction and low muscle strength remains unclear. Considering that muscle strength is a more critical and valuable predictive factor for all-cause mortality than muscle mass,[17] the current study focused on the association between kidney function and muscle strength measured using HGS.

In previous population-based studies, researchers calculated the estimated glomerular filtration rate (eGFR) using serum creatinine, which is produced from the creatine pool in skeletal muscle, thus resulting in inaccuracy. For older adults, skeletal muscle degradation is accompanied by the decline in serum creatinine. Therefore, serum creatinine may overestimate the actual GFR in patients with malnutrition and decreased muscle mass.[18]

Cystatin C is a more reliable biomarker for estimating eGFR since it is not subject to muscle conditions.[19] Furthermore, cystatin C is reportedly a more sensitive serum marker in detecting early renal injury than creatinine.[20] However, a few population-based studies have focused on the association between eGFR based on cystatin C and muscle strength. Herein, we aimed to explore the relationship between eGFR based on cystatin C and muscle strength utilizing data from the 2015 China Health and Retirement Longitudinal Study (CHARLS), which is a nationally representative survey of Chinese adults.

Subjects and Methods

Study Design

The CHARLS is a multistage, cluster-sampling survey focusing on the health and retirement status of the Chinese middle-aged and elderly populations. Detailed information regarding the CHARLS is accessible online (http://charls.pku.edu.cn). A total of 20,967 interviewees were considered for the 2015 wave of the CHARLS. Participants lacking complete blood data, including serum creatinine, serum bicarbonate, cystatin C, uric acid, serum C-reactive protein (CRP), lipid levels, hemoglobin, and glycated hemoglobin (HbA1c) were excluded. Those without body measurements and sociodemographic data, including age, sex, height, weight, waist circumference, HGS, blood pressure, smoking and alcohol consumption, and marital status, were also excluded from the analytical sample. Therefore, of the 12,452 participants meeting the inclusion criteria, those aged ≥45 years were included in the final analysis (n=12,398) (Figure 1).

Study Variables

Handgrip Strength (HGS)

HGS was evaluated using a hydraulic dynamometer (YuejianTM WL-1000 dynamometer). Briefly, participants were required to stand with their arms hanging naturally and squeeze the handles as strongly as possible. Two measurements were performed on each hand. HGS was set as the maximal value of four measurements from both hands.[21,22] HGS values below 30 kg for men and 20 kg for women were defined as low muscle strength.[14,23,24]

Kidney Measurements

The cystatin C-based CKD Epidemiology Collaboration equation[25] was used to calculate eGFR:

$$\text{eGFR (mL/min/1.73m}^2) = 133 \times \min(\text{CysC}/0.8, 1)^{-0.499} \times \max(\text{CysC}/0.8, 1)^{-1.328} \times 0.996^{\text{age}} \times 0.932[\text{if female}]$$

where CysC represents cystatin C measured in mg/dL. We classified eGFR according to the modified Kidney Disease: Improving Global Outcomes categories. Since

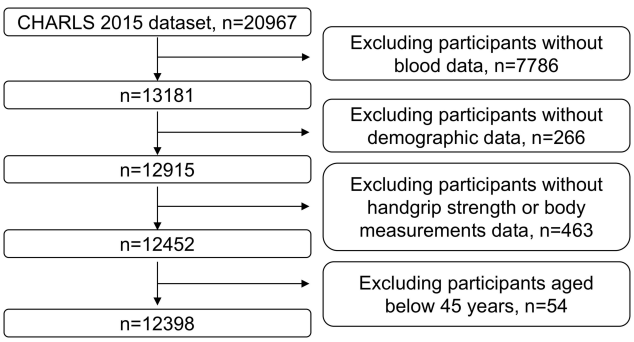

Figure 1 Flow diagram of participants for the study.

there were only 10 participants with eGFRs <15mL/min/1.73 m^2, we merged participants with CKD stages 4 and 5 into one group to avoid weakening statistical power, leaving the following four eGFR groups for analyses: normal and CKD stage 1 (≥90 mL/min/1.73 m^2), CKD stage 2 (60–89.9 mL/min/1.73 m^2), CKD stage 3 (30–59.9 mL/min/1.73 m^2), and CKD stage 4–5 (<30 mL/min/1.73 m^2).

Other Predictive Variables

Demographic data were gathered using self-administered questionnaires. Health-related behaviors, such as tobacco use, alcohol consumption, and medication lists, were also assessed using questionnaires. Hypertension was described as systolic blood pressure (BP)≥130 mmHg and/or diastolic BP≥90 mmHg or the use of antihypertensive drugs. Diabetes was described as HbA1c≥6.5% or hypoglycemic-drug use. Dyslipidemia was described as total cholesterol (TC)≥240 mg/dL, triglyceride (TG)≥200 mg/dL, high-density lipoprotein cholesterol (HDLC)<40 mg/dL, and low-density lipoprotein cholesterol (LDLC)≥160 mg/dL. Obesity was defined as having a BMI≥25 kg/$m.^2$ [26] Abdominal obesity was defined as having a waist circumference >90 cm for men and >85 cm for women.

Statistical Analyses

Stata software (version 14.0) was used to construct locally weighted scatterplot smoothing (LOWESS) curves and violin plots. Continuous variables were presented as means±standard deviations and compared using one-way analysis of variance. Categorical variables were analyzed using Pearson's chi-square tests. Logistic regression analysis was performed using odds ratios (ORs) and 95% confidence intervals (CIs) of low muscle strength at different CKD stages. Statistical analyses were performed using IBM SPSS Statistics (version 22.0). A bilateral p-value<0.05 was considered statistically significant.

Results

Characteristics of Participants

A total of 12,398 participants (5762 men and 6636 women) were included in the present study. The distribution of the study population is shown in Table 1. Differences in epidemiologic, clinical, anthropometric, and biochemical factors were assessed according to CKD stage. There were 7239, 4344, 756, and 59 participants in the four eGFR groups. The overall CKD prevalence was 6.6%. The proportion of participants aged above 65 years and prevalence of hypertension and diabetes were higher in those with lower eGFR. In addition, as kidney function declined, systolic BP, uric acid, HbA1c, and CRP levels increased, whereas hemoglobin decreased, accordingly ($p < 0.001$). We created the Supplementary Table 1 comparing several available characteristics between the excluded and included groups. There were 20,453 participates with complete sociodemographic information. Compared with the included participants, the excluded participants were older and with higher proportion of male. The marital status did not differ between the two groups. There were 15,702 participates with anthropometric information. The excluded participates were more likely to have low muscle strength. The prevalence of obesity was also significantly different in the included participates (36.4%, n=12,398) and the excluded participants (32.6%, n=3304).

Prevalence of Low Muscle Strength by eGFR Category and the Correlation Between HGS and eGFR as Continuous Variables

The mean HGS was 37.9 kg (standard deviation [STDEV], 8.8 kg) for men and 25.8 kg (STDEV, 6.7 kg) for women. There was a decreasing trend in the mean HGS levels from CKD stage 1 to stage 4–5 in both men and women ($p < 0.001$) after adjusting for age and BMI (Figure 2). Correlations between eGFR categories and the prevalence of low muscle strength in both sexes were statistically significant ($p < 0.001$ in both; Table 1). The LOWESS curves presented in Figure 3 exhibit the relationship between HGS and kidney function in each sex. There were positive correlations between HGS and kidney function in both sexes when eGFR was below 120 mL/min/1.73 m^2; however, such associations diminished when eGFR exceeded 120 mL/min/1.73 m^2.

ORs for Low Muscle Strength According to CKD Stage

To further remove confounding factors, we used logistic regression analysis to examine the association between CKD stage and low muscle strength (Table 2). In the unadjusted model, the ORs for low muscle strength were significantly greater in CKD stages 2, 3, and especially 4–5 than in the normal and CKD stage 1 group. After adjusting for age, sex, BMI, alcohol consumption, and smoking status, the association between low muscle strength and CKD stage remained statistically significant. On adjusting for serum CRP, uric acid, hemoglobin, TC, HDLC, LDLC, TGs, the presence of hypertension and diabetes mellitus, and marital status, in addition to Model

Table 1 Demographic and Clinical Characteristics of Participants (n=12,398) Grouped by eGFR

Characteristics	Total	eGFR (mL/min/ 1.73 m^2)				p-value
		≥90	60–89	30–59	<30	
Unweighted N	12,398	7239	4344	756	59	
Epidemiologic and clinical						
Age (years)						<0.001
45–55	2562(20.7%)	2293(31.7%)	260(6.0%)	7(1.0%)	2(3.4%)	
55–65	4004(32.3%)	2797(38.6%)	1145(26.4%)	57(7.5%)	5(8.5%)	
≥65	5832(47.0%)	2149(29.7%)	2939(67.6%)	692(91.5%)	52(88.1%)	
Sex						0.601
Men	5762(46.5%)	3216(44.4%)	2117(48.7%)	400(52.9%)	29(49.2%)	
Women	6636(53.5%)	4023(55.6%)	2227(51.3%)	356(47.1%)	30(50.8%)	
Hypertension (%)	6943(56.0%)	3600(49.7%)	2712(62.4%)	577(76.3%)	53(89.8%)	<0.001
Diabetes mellitus (%)	1813(14.6%)	912(12.6%)	698(16.1%)	180(23.8%)	21(35.6%)	0.002
Dyslipidemia (%)	3866(31.1%)	2007 (27.8%)	1532(35.3%)	303(40.1%)	24(40.7%)	0.239
Systolic BP (mmHg)	128.0±19.9	125.3±18.6	131.1±20.5	135.9±22.0	138.7±24.0	<0.001
Diastolic BP (mmHg)	75.7±11.7	75.7±11.6	75.9±11.7	74.4±11.9	74.5±13.4	<0.001
eGFR (mL/min/1.73 m2)	92.0±19.7	105.7±9.4	77.5±7.7	50.0±7.5	22.1±6.6	<0.001
Smoking (%)	4855(39.2%)	2642(36.5%)	1843(42.4%)	346(45.8%)	38(63.3%)	0.003
Drinking (%)	3274(26.4%)	2065(28.5%)	1054(24.3%)	147(19.4%)	8(13.3%)	0.042
Married (%)	10,837(87.4%)	6639(91.7%)	3630(83.6%)	522(69.0%)	45(75.0%)	<0.001
Anthropometric						
Handgrip strength (kg)	31.4±9.8	32.7±9.7	30.3±9.8	26.3±8.6	25.2±9.3	<0.001
Male	37.9±8.8	39.8±8.3	36.6±8.6	30.6±8.2	30.8±8.3	<0.001
Female	25.8±6.7	27.0±6.4	24.3±6.6	21.5±6.2	19.5±6.5	<0.001
Low muscle strength (%)	2125(17.1%)	852(11.8%)	928(21.4%)	319(42.2%)	26(44.0%)	<0.001
Male	979(17.0%)	356(11.1%)	429(20.3%)	183(45.8%)	11(37.9%)	<0.001
Female	1146(17.3%)	496(12.3%)	499(22.4%)	136(38.2%)	15(50.0%)	<0.001
BMI (kg/m^2)	24.0±3.7	24.0±3.5	23.9±3.9	23.7±4.3	23.4±4.3	<0.001
Obesity (%)	4514(36.4%)	2631(36.3%)	1595(36.7%)	273(36.1%)	15(25.4%)	0.309
Abdominal obesity (%)	5782(46.6%)	3261(45.0%)	2120(48.8%)	371(49.1%)	30(50.8%)	0.899
Biochemical						
Serum bicarbonate (mg/dL)	15.5±4.7	14.7±4.1	15.9±4.4	18.5±5.4	32.5±17.2	<0.001
Serum creatinine (mg/dL)	0.80±0.3	0.74±0.2	0.84±0.2	1.17±0.8	2.61±2.1	<0.001
Uric acid (mg/dl)	4.9±1.4	4.6±1.3	5.2±1.4	6.1±1.6	7.4±2.0	<0.001
Cystatin C (mg/l)	0.8±0.2	0.7±0.1	1.0±0.1	1.3±0.2	2.7±1.2	<0.001
Hemoglobin (g/dl)	13.7±1.9	13.8±2.0	13.7±1.9	13.3±2.0	11.7±2.1	<0.001
Total cholesterol (mg/dL)	183.8±36.2	183.6±35.5	184.6±36.8	182.5±38.7	176.1±43.6	<0.001
HDL cholesterol (mg/dL)	51.2±11.5	52.2±11.4	50.1±11.5	47.9±11.4	47.2±12.7	<0.001
LDL cholesterol (mg/dL)	102.2±28.8	101.6±28.0	103.2±29.8	102.5±30.0	96.9±33.5	<0.001
Triglycerides (mg/dL)	142.7±91.1	139.6±92.4	146.8±36.8	150.2±91.4	137.6±68.0	<0.001
Serum CRP (mg/dl)	2.7±5.8	2.3±4.8	3.0±6.4	4.4±7.9	7.8±21.2	<0.001
Glycated Hemoglobin (%)	6.0±1.0	5.9±1.0	6.0±1.0	6.1±1.0	6.1±0.9	<0.001

Notes: Data are shown as means ± standard deviation or numbers (percentages). The p-values were calculated with one-way ANOVA analysis of variance for continuous variables and chi-squared test for categorical variables.

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein;.

3, the ORs for CKD stages 2, 3, and 4–5 in Model 4 were 1.256 (95% CI 1.120–1.409, $p < 0.001$), 2.725 (95% CI 2.258–3.288, $p < 0.001$), and 3.069 (95% CI 1.747–5.392, $p < 0.001$), respectively.

Discussion

To date, this is the first population-based study to examine the independent association between CKD stage and muscle strength measured using HGS in community-dwelling,

middle-aged and elderly Chinese individuals (≥45 years of age) after adjusting for demographic and clinical variables. We were astonished to discover that mild renal impairment with an eGFR between 60 and 89 mL/min/1.73 m^2 was also a statistically significant risk factor for low muscle strength. It is also the first study to exhibit the association of muscle strength with kidney function in the Chinese population using LOWESS curves. Since our study involved a large Chinese population, our results provide an enhanced understanding of the relationship between kidney function and the prevalence of low muscle strength. The early identification of and interventions mitigating the risk factors for muscle degradation in patients with impaired kidney function potentially decelerate muscle wasting and improve their quality of life. Interventions may include nutritional supplement, drug treatment, and, most importantly, physical activity. Resistance exercise can improve muscle function, increase muscle strength, and reduce the occurrence of low muscle strength.[27,28]

Sarcopenia is a degenerative syndrome that has recently been defined, and it entails a decline in muscle mass and strength.[29] The muscle strength of adults aged above 60 years decreases at a rate between 1.5% and 3.5% every year, and the rate worsens in sedentary elderly people.[30] Sarcopenia can result from the degeneration of aging skeletal muscle or be secondary to malnutrition, lack of exercise, tumor presence, and several chronic diseases. Compared with low muscle mass, low muscle strength is considered the foremost characteristic of sarcopenia, since muscle strength is a superior predictor of frailty, falling, and mortality.[17,31] In our study, we used HGS measured using a handheld dynamometer, which is an objective tool with favorable accuracy in the context of CKD patients, to assess muscle function. When participants undergo HGS tests in the standing position, HGS is also positively correlated with lower body strength and core muscle strength.[14] There are a few findings from the published literature revealing the relationship between HGS and kidney function. A study supported by Korea National Health and Nutrition Examination Survey demonstrated the statistical association between creatinine-based estimated glomerular filtration rate and HGS.[32] Children with CKD were also found to have decreased HGS.[33]

It has been reported that for right-handed people, the HGS in the right hand is usually 10% stronger than that in the left hand.[34] However, it should be noted that 50% left-handed people are weaker in their dominant hand, which may be attributed to the right-handed world.[35] One left-handed person may have to use the right hand more often in daily life and thus, has greater HGS in the right hand. Using only values from the dominant hand may underestimate the HGS of those left-handed people. Hence, we defined the HGS as the maximal value of four measurements from both hands. The variability of HGS measures is influenced by the quality of grip dynamometers. Multiple measurements of HGS may improve the practicability and accuracy, while the measure of HGS usually decreases after repeated muscle contractions. Here we used the maximum measure of four contractions, which is the integration of accuracy and the effect of fatigue. It has been reported that the mean of measures of three contractions does not differ from that of the maximum force of three different contractions.[36]

There are still no globally accepted cut-off values of the absolute HGS. We used the HGS-cut-offs suggested in European Working Group on Sarcopenia in Older People (EWGSOP) published in 2010 (30/20 kg) in our present study, despite the revised version of the EWGSOP (EWGSOP2) published in 2018 recommended new HGS cut-offs (27/16 kg). Recent research found that the new cut-offs of HGS by EWGSOP2 identified very small percentage of the elderly with probable sarcopenia and may lead to underdiagnose sarcopenia.[37] In our study, the number of participants who were identified as low muscle strength was considerably lower with EWGOSP2-recommended (27/16 kg) cut-offs than with the EWGOSP-recommended (30/20 kg) cutoffs (1005 participants, 8.1% versus 2125 participants, 17.1%). To identify the probable sarcopenia in older adults and avoid underdiagnosis, we used cut-offs by EWGSOP (30/20 kg).

Another novel aspect is the use of cystatin C to calculate eGFR and examine the association between eGFR and HGS, a technique that has not yet been employed in population-based epidemiological studies. Cystatin C, unlike creatinine released from muscle mass, is a cysteine protease inhibitor constantly produced by all nucleated cells. A previous study including 594 Japanese participants showed that muscle weakness was associated with the eGFR calculated using cystatin C instead of that calculated using creatinine.[38] This study further confirms that in the Chinese population, eGFR based on cystatin C is an independent predictor of low muscle strength.

Notwithstanding, this study had certain limitations. First, it was a cross-sectional analysis; hence, we could not illustrate the causal relationship between muscle strength and kidney function, despite adjusting models

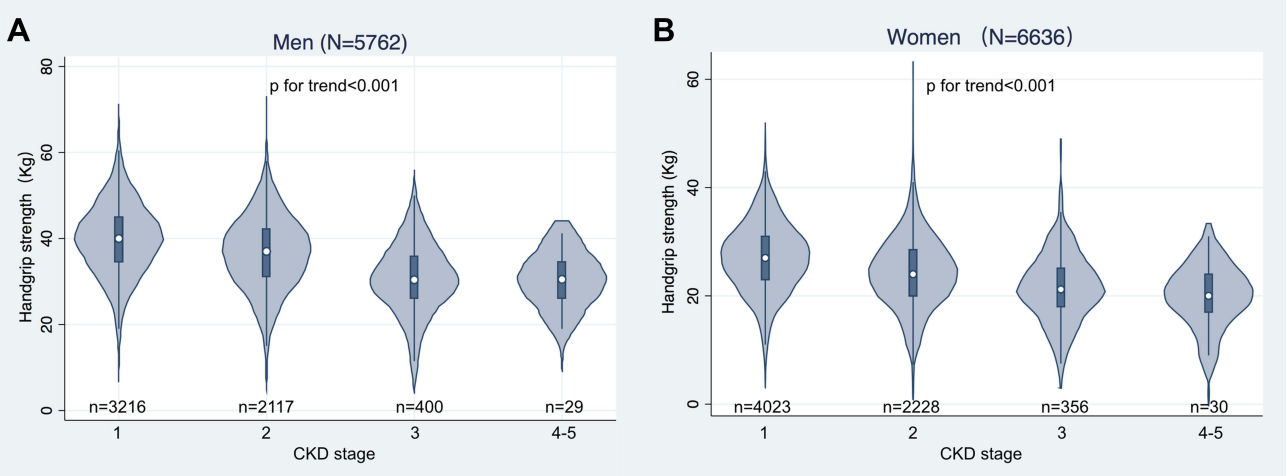

Figure 2 Distribution of handgrip strength by CKD stage in men (**A**) and women (**B**).

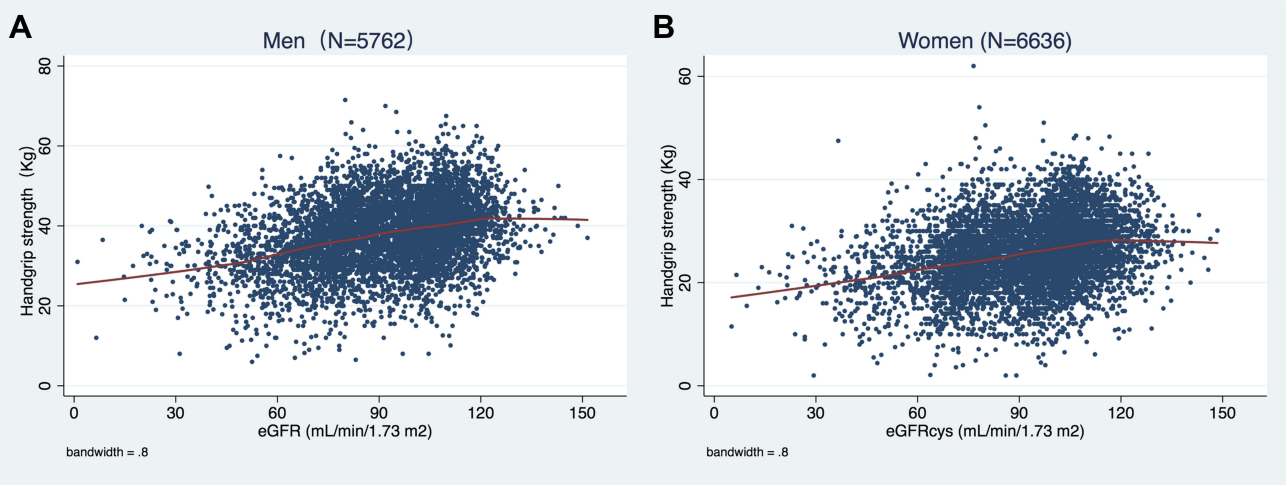

Figure 3 Locally weighted scatterplot smoothing (LOWESS) curves showing associations between handgrip strength and eGFR in men (**A**) and women (**B**).

for numerous variables. Second, the exclusion of participants without complete body measurements and blood data resulted in a reduced sample size, thus weakening statistical power. Third, some clinical variables related to sarcopenia, such as serum albumin, were unavailable in the CHARLS dataset. The lack of urinary albumin rendered CKD diagnosis less accurate. Additionally, we have to narrow the sample due to unavailable anthropometric or biochemical data. Male participates, those who were above 65 years old and those with low muscle strength were underrepresented in the study. Further research supported by a more complete dataset is necessary. The study sampling in the present study was limited to middle-aged and elderly Chinese population. Thus, the generalizability of these findings is limited by the sampling population and the findings may not pertain to more affluent younger adults. Future studies should also pay attention to the broader population. What's more, results based on the single measure of kidney function may be potentially biased. Measurement error is probably existing in our study since measuring devices are often imperfect. Additional validation research is needed to minimize the effects of bias by using the mean of multiple measures.

Conclusions

In the present study, low muscle strength was significantly related to CKD stage among community-dwelling Chinese people. In addition to CKD patients, those with eGFRs between 60 and 89 mL/min/1.73 m^2 also have a relatively high prevalence of low muscle strength compared to those with eGFRs above 90 mL/min/1.73 m^2. These findings

Table 2 Associations Between Level of Kidney Function and Low Muscle Strength

eGFR (mL/min/1.73 m^2)	Low Muscle Strength		
	OR	**95% CI**	**P value**
Model 1			
≥90	(Reference)		
60–89	2.037	1.839–2.255	<0.001
30–59	5.472	4.658–6.429	<0.001
<30	5.733	3.423–9.600	<0.001
P for trend	<0.001		
Model 2			
≥90	(Reference)		
60–89	1.241	1.112–1.385	<0.001
30–59	2.740	2.312–3.247	<0.001
<30	3.066	1.810–5.193	<0.001
P for trend	<0.001		
Model 3			
≥90	(Reference)		
60–89	1.252	1.121–1.399	<0.001
30–59	2.775	2.335–3.299	<0.001
<30	2.945	1.727–5.025	<0.001
P for trend	<0.001		
Model 4			
≥90	(Reference)		
60–89	1.256	1.120–1.409	<0.001
30–59	2.725	2.258–3.288	<0.001
<30	3.069	1.747–5.392	<0.001
P for trend	<0.001		

Notes: Model 1: Unadjusted; Model 2: Adjusted for age (45–55,55–65, and≥65 years old) and sex; Model 3: Adjusted as Model 2 plus BMI, drinking and smoking status; Model 4: Adjusted as Model 3 plus serum CRP, uric acid, hemoglobin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, the presence of hypertension and diabetes mellitus, marital status.

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.

illustrate the relationship between changes in muscle strength and a decline in eGFR, and they have important implications for future studies regarding kidney function and muscle strength.

Ethics Approval

The original CHARLS was approved by the Ethical Review Committee of Peking University, and all participants signed informed consent at the time of participation.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest.

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